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Individualized Nonadaptive Image Guided Radiotherapy (IGRT) In Stage II-III Carcinoma Cervix With Daily Cone Beam Computed Tomography (CBCT): Set Up Error Calculation

Nilesh Mani[1], Harikesh Bahadur Singh[1], Poonam Gupta[2], Ashwani Singh[3], Priyesh[4], Kokila[2]
(Department Of Radiation Oncology, All India Institute Of Medical Sciences-Patna, India)
(Department Of Radiation Oncology, HPPCH- Gorakhpur, India)
(Manipal Hospital, Dwarka, Delhi)
(D.Y Patil Medical College, Kolhapur, Maharashtra)

Abstract:
Background: *The standard of care in stage II-III carcinoma cervix is radical concurrent chemo-radiotherapy followed by brachytherapy. This study aimed to give institutional set up error data calculation and comparative analysis of KV CBCT (Kilovoltage Cone-Beam Computed Tomography) and KV MV (Kilovoltage and Megavoltage) Imaging CBCT.*
Materials and Methods: *A retrospective analysis was performed on patients with histopathologically confirmed FIGO stage II–III squamous cell carcinoma of the cervix treated with definitive IMRT or VMAT. Patient setup errors obtained from online kV-CBCT and MV-CBCT image guidance were retrieved from the treatment planning system and compared. Systematic and random errors were calculated, and age-based subgroup analysis (≤50 vs. >50 years) was performed.*
Results: *Eighteen patients were included in the analysis. No significant differences in setup errors were observed between kV-CBCT and MV-CBCT in the longitudinal, vertical, or lateral directions (all p>0.05). The two imaging modalities demonstrated moderate-to-good agreement intraclass correlation coefficient (ICC: 0.552–0.688), with minimal systematic bias on Bland–Altman analysis. Systematic and random setup errors were low, yielding van Herk planning target volume margins of approximately 3 mm in all translational directions. Although kV-CBCT detected a slightly higher frequency of setup deviations >3 mm, the difference was not significant. Patients aged ≥50 years exhibited significantly greater setup errors on MV-CBCT than those aged <50 years (all p<0.05).*
Conclusion: *kV-CBCT and MV-CBCT demonstrated comparable accuracy for online setup verification in cervical cancer radiotherapy. Both modalities achieved low setup uncertainties, supporting a planning target volume margin of approximately 3 mm, although older patients (≥50 years) showed greater setup deviations on MV-CBCT.*

Keywords: *cervix cancer, image guided radiotherapy, set-up error, non-adaptive, KV-CBCT, MV-CBCT*

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I. Introduction

In the past decade, researchers have made significant progress in treating cervix cancer. Treatment procedures using external radiotherapy require a high degree of precision. There are many sources of error when planning and delivering treatment. Positioning deviations can either be systemic or random. These errors accumulated during treatment sessions, which cause a shift in the cumulative dose distribution[1]. In systemic error, direction and magnitude remain the same in each fraction; this error may cause a fixed part of the target volume to be missing in every fraction. In random error, direction and magnitude vary in each fraction; this resulted in a blurred cumulative dose distribution[2]. The standard of care in stage II-III carcinoma cervix is radical concurrent chemoradiotherapy followed by brachytherapy. Three-dimensional conformal radiotherapy (3D-CRT) remains the standard of care. Intensity modulated radiotherapy (IMRT) in carcinoma is able to achieve better conformity and dose distribution and improve toxicity outcomes and reduce dose to organs at risk (OAR). Image-guided radiotherapy (IGRT) involves imaging the target location and patient setup and corrects for any changes in patient and target position before each treatment session[3]. The use of cone-beam computed tomography (CBCT) for IGRT has become widely available. It provides fast and accurate displacement information of each patient in the translational directions and also rotational directions for some centers with the rotational couch[4]. The planning target volume (PTV) is defined as the safety margin necessary to ensure that the clinical target volume (CTV) receives the prescribed dose. This geometric concept is an indispensable tool for planning and evaluating treatment plans. It includes the CTV, an internal target volume (ITV) margin, and a positioning and repositioning margin. The justification of the PTV margin makes it possible to minimize the effects of geometry (systematic errors) and residual uncertainties (random errors). This study aims to quantify the extent of setup errors and compare setup errors (kv-CBCT and MV-CBCT) and to assess an appropriate margin for PTV in cervix cancer treated by IMRT or volumetric modulated arc therapy (VMAT).

II. Material And Methods

Study Design and Patient Selection

This retrospective observational study included patients with histopathologically confirmed squamous cell carcinoma of the cervix, International Federation of Gynecology and Obstetrics (FIGO) stage II–III, who underwent definitive radical radiotherapy using IMRT or VMAT. Eighteen eligible patients were recruited from medical records meeting the demand of inclusion criteria. Individual setup error data acquired using kilovoltage cone-beam computed tomography (kV-CBCT) and megavoltage cone-beam computed tomography (MV-CBCT) were retrieved retrospectively from the treatment planning and record-and-verify system. Setup error was defined as the displacement between the planned Computed Tomography (CT) and CBCT images in the three translational directions (lateral, longitudinal, and vertical).

Study Hypothesis

The null hypothesis (H_0) stated that no statistically significant difference exists between setup errors measured using kV-CBCT and MV-CBCT during IGRT for cervical cancer. The alternative hypothesis (H_1) proposed that a significant difference exists between the two imaging modalities.

Study Objectives

The primary objective was to compare setup errors measured using kV-CBCT and MV-CBCT in patients with FIGO stage II–III cervical cancer treated with IMRT or VMAT. Secondary objectives included determination of systematic (Σ) and random (σ) setup errors, estimation of planning target volume (PTV) margins using established margin recipes, comparison of setup errors between patients aged <50 years and ≥50 years, and evaluation of the influence of age on setup accuracy.

CT Simulation and Target Delineation

All patients underwent CT simulation in the supine position using a four-clamp pelvic thermoplastic immobilization device. A standardized bladder preparation protocol was followed throughout simulation and treatment. Patients were instructed to empty their bladder, consume 500 ml of water over 10 minutes, and refrain from voiding for 30 minutes before contrast-enhanced CT simulation. A vaginal marker was positioned at the inferior extent of the cervical lesion to facilitate target localization. Planning CT images were acquired from the diaphragm to the mid-thigh using a slice thickness of 3 mm. Patient reference coordinates were established using three orthogonal laser systems, and fiducial markers were placed at the reference points. The CT image dataset was imported into the Monaco treatment planning system for delineation of the gross tumor volume (GTV), clinical target volume (CTV), internal target volume (ITV), planning target volume (PTV), and organs at risk (OARs), including the bladder, rectum, bowel bag, and femoral heads, in accordance with Radiation Therapy Oncology Group (RTOG) contouring guidelines[5].

Treatment Planning

Treatment planning was performed using the Monaco Treatment Planning System. Dose objectives require at least 95% of the planning target volume to receive 95% of the prescribed dose ($D95 \geq 95\%$). Organ-at-risk constraints included bladder volume receiving at least 40 Gy ($V40$) < 75%, rectum $V40 < 85\%$, bowel volume receiving at least 45 Gy ($V45$) ≤ 195 cc, and femoral head maximum dose ≤50 Gy[6].

Image Guidance and Data Collection

Clinical and treatment-related data, including age, histopathology, FIGO stage, prescribed radiation dose, fractionation schedule, and setup error measurements, were collected retrospectively from institutional records. Image guidance was performed using either kV-CBCT or MV-CBCT. CBCT images were acquired daily during the first three treatment fractions and subsequently on a biweekly basis using alternating kV-CBCT and MV-CBCT according to institutional protocol. Image registration was performed by matching CBCT images with the planning CT in the lateral (X), longitudinal (Y), and vertical (Z) directions. Positive setup deviations represented right, anterior, and superior displacements, whereas negative values represented left, posterior, and inferior displacements. All image registrations and setup corrections were performed online by a single experienced observer to minimize interobserver variability.

Calculation of PTV Margins

Planning target volume margins were estimated using the Stroom equation ($2\Sigma + 0.7\sigma$) and the van Herk equation ($2.5\Sigma + 0.7\sigma$), in accordance with the recommendations of the International Commission on Radiation Units and Measurements (ICRU) Report 62[7,8].

Treatment Delivery and Verification

Radiotherapy was delivered using 6-MV, 10-MV, or 15-MV photon beams depending on treatment requirements. Online image verification was performed using daily CBCT during the initial three fractions, followed by biweekly verification with alternating kV-CBCT and MV-CBCT.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 20 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation (SD) or median (range), as appropriate. Setup errors measured by kV-CBCT and MV-CBCT were compared using the paired t-test or Wilcoxon signed-rank test. Agreement between the two imaging modalities was assessed using the intraclass correlation coefficient (ICC) and Bland–Altman analysis. Systematic (Σ) and random (σ) errors were calculated, and PTV margins were estimated using the Stroom and van Herk formulas. Age-group comparisons (<50 vs. ≥ 50 years) were performed using the independent-samples t-test. A two-sided p value < 0.05 was considered statistically significant.

III. Results

A total of 18 patients with carcinoma cervix undergoing image-guided radiotherapy were analysed. In figure 1 (A and B) weekly assessment depicted. The median age was 48 years (range: 36–74 years), with a mean age of 50.6 ± 11.2 years**.**

Figure 1(A): Individual Patient Set up Error (KV CBCT) Weekly Assessment

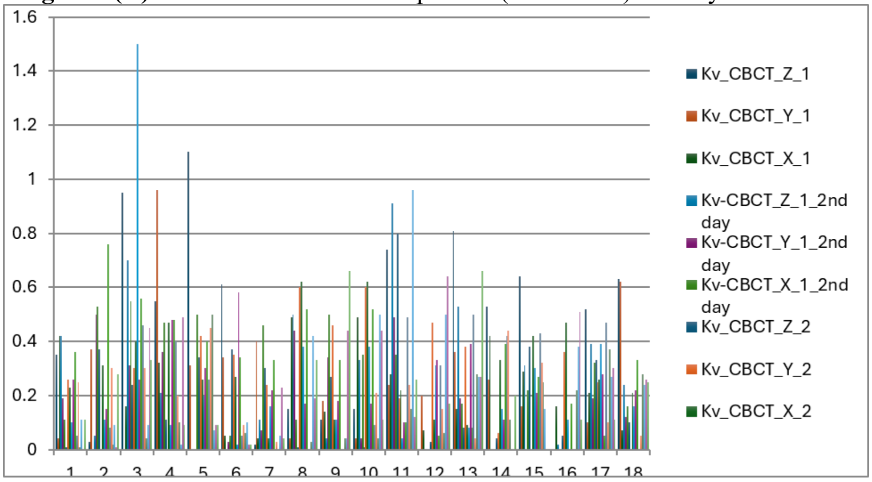
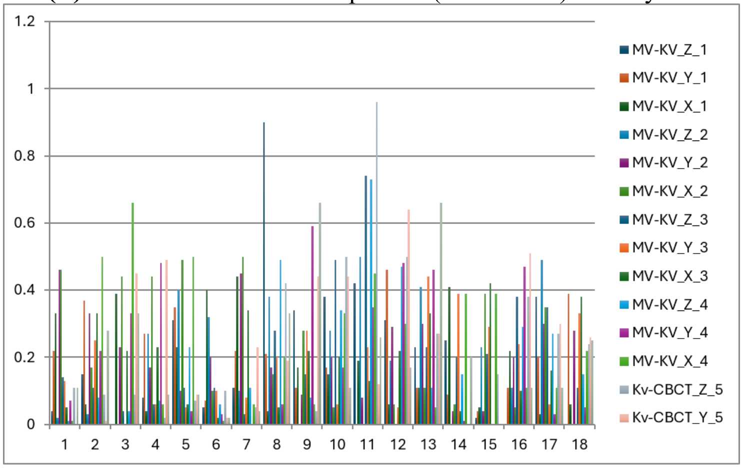
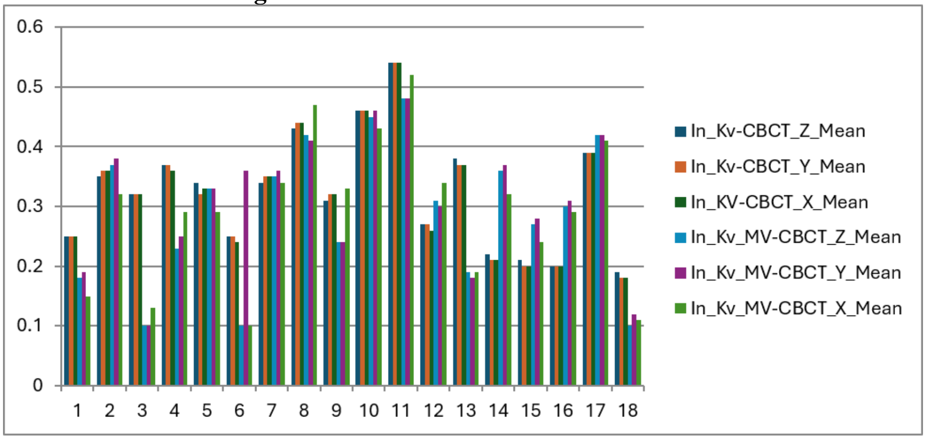


Figure 1(B): Individual Patient Set up Error (MV CBCT) Weekly Assessment



The mean setup deviations measured using kV-CBCT and MC-CBCT described in figure 2.

Figure 2. Mean KV-CBCT and MV-CBCT



Paired comparison of setup deviations measured by kV-CBCT and MV-CBCT demonstrated no statistically significant differences in any translational direction (Table 1). The paired t-test yielded p-values of 0.154, 0.550, and 0.183 for the vertical (Z), longitudinal (Y), and lateral (X) axes, respectively. Similar findings were observed with the non-parametric Wilcoxon signed-rank test (Z: p = 0.177, Y: p = 0.602, X: p = 0.223), confirming good agreement between the two imaging modalities.

Table 1. Comparison of Setup Errors Measured by kV-CBCT and MV-CBCT

Direction	kV-CBCT Mean ± SD (cm)	MV-CBCT Mean ± SD (cm)	Paired t-test p-value	Wilcoxon signed-rank p-value
Vertical (Z)	0.323 ± 0.097	0.289 ± 0.121	0.154	0.177
Longitudinal (Y)	0.322 ± 0.099	0.308 ± 0.111	0.550	0.602
Lateral (X)	0.321 ± 0.100	0.293 ± 0.122	0.183	0.223

Agreement between kV-CBCT and MV-CBCT was assessed using ICC and Bland–Altman analysis. Moderate-to-good agreement was observed, with ICC values of 0.584, 0.552, and 0.688 in the vertical (Z), longitudinal (Y), and lateral (X) axes directions, respectively (Table 2).

Table 2. Intraclass Correlation Coefficient (ICC)

Direction	ICC	Interpretation
Vertical (Z)	0.584	Moderate agreement
Longitudinal (Y)	0.552	Moderate agreement
Lateral (X)	0.688	Good agreement

Bland–Altman analysis demonstrated minimal bias between the two imaging modalities, with mean differences of 0.034 cm (Z), 0.014 cm (Y), and 0.028 cm (X) (Table 3). The corresponding 95% limits of agreement ranged from −0.158 to 0.227 cm, −0.183 to 0.212 cm, and −0.142 to 0.198 cm. The mean differences were small (<0.04 cm in all directions), indicating minimal systematic bias between kV-CBCT and MV-CBCT measurements.

Table 3. Bland–Altman Analysis

Direction	Mean Difference (cm)	95% Lower Limit of Agreement (cm)	95% Upper Limit of Agreement (cm)
Vertical (Z)	0.034	-0.158	0.227
Longitudinal(Y)	0.014	-0.183	0.212
Lateral (X)	0.028	-0.142	0.198

Systematic errors (Σ) were 0.097 cm, 0.099 cm, and 0.100 cm, while random errors (σ) were 0.098 cm, 0.101 cm, and 0.087 cm for the Z, Y, and X directions, respectively. Application of the van Herk formula yielded planning target volume (PTV) margins of 0.31 cm, 0.32 cm, and 0.31 cm, indicating that a margin of approximately 3 mm would adequately compensate for setup uncertainties in all translational directions (Table 4). Using the van Herk formula (PTV Margin= $2.5\ \Sigma + 0.7\sigma$) the required margins were approximately 3.1 mm, 3.2 mm, and 3.1 mm in the longitudinal, vertical, and lateral directions, respectively. Using the age groups (A = <50 years, n=12; B = ≥50 years, n=6), the differences appear substantial. Based on the reported means, SDs, and sample sizes, the approximate Welch's t-test results are described in Table 5. For kV-CBCT, older patients (Group B) showed larger setup deviations, but the differences did not reach statistical significance. For MV-CBCT, older patients demonstrated significantly greater setup errors in all three translational directions. Mean difference (≥50 years, <50 years) in setup error. Larger positive values indicate greater setup variation in older patients.

Table 4. Z(vertical), Y(longitudinal), X(lateral), Systematic Error (Σ), Random Error (σ), and van Herk Margins

Direction	Systematic Error Σ (cm)	Random Error σ (cm)	van Herk Margin (cm)
Vertical (Z)	0.097	0.098	0.310
Longitudinal (Y)	0.099	0.101	0.319
Lateral (X)	0.100	0.087	0.310

Table 5: Group A and Group B comparison (Age-group effect on setup deviation)

Parameter	Group A Mean ± SD	Group B Mean ± SD	t-value	p-value
kV-CBCT Z	0.297 ± 0.0737	0.387 ± 0.1159	-1.79	0.11
kV-CBCT Y	0.293 ± 0.0749	0.383 ± 0.1187	-1.76	0.12
kV-CBCT X	0.292 ± 0.0762	0.385 ± 0.1203	-1.81	0.11
MV-CBCT Z	0.243 ± 0.1111	0.380 ± 0.0883	-2.72	0.017*
MV-CBCT Y	0.271 ± 0.1043	0.382 ± 0.0889	-2.32	0.036*
MV-CBCT X	0.242 ± 0.1042	0.393 ± 0.0931	-3.04	0.009*

*p value≤0.05 (Statistically significant)

Both kV-CBCT and MV-CBCT demonstrated comparable setup accuracy. MV-CBCT showed a trend toward lower random errors and smaller vertical PTV margins, although these differences did not reach statistical significance. The vertical (superior-inferior) direction remained the predominant source of setup uncertainty and should be considered when defining planning target volume margins in cervical cancer IGRT.

IV. Discussion

IGRT has become an integral component of modern radiotherapy for carcinoma cervix because of substantial inter-fraction variations resulting from differences in bladder filling, rectal distension, patient positioning, and internal organ motion. Accurate assessment and correction of setup errors are essential to ensure adequate target coverage while minimizing radiation exposure to surrounding organs at risk. In the present study, no statistically significant differences were observed between kV-CBCT and MV-CBCT-derived setup corrections in the lateral, longitudinal, or vertical directions. The mean differences between the two modalities were small (<0.04 cm in all directions), indicating excellent clinical agreement. Furthermore, moderate-to-good ICC values (0.54–0.70) suggested that both imaging modalities provide comparable information for translational setup verification. The superiority of volumetric image guidance over conventional portal imaging has been well established. CBCT enables visualization of both bony anatomy and soft tissue structures, thereby improving localization accuracy in pelvic malignancies. David A. Jaffray and colleagues first demonstrated the feasibility of cone-beam CT for image-guided radiation therapy, showing improved target localization compared with two-dimensional imaging techniques[9]. The setup uncertainties observed in the current study are comparable to previously reported pelvic radiotherapy series. Jan-Jakob van Herk proposed the widely accepted margin recipe ($2.5\Sigma + 0.7\sigma$), which remains the standard method for calculating PTV margins. Using this approach, the present study demonstrated margins of approximately 3 mm in the lateral and longitudinal directions and 5–6 mm in the vertical direction. These values are consistent with published reports evaluating setup uncertainties in pelvic malignancies. The vertical direction demonstrated the largest setup uncertainty in our cohort. Similar findings have been reported by several investigators evaluating cervical cancer IGRT[10,11]. Variations in bladder and rectal filling contribute substantially to superior-inferior and anteroposterior organ displacement, leading to greater setup variability in the vertical axis. Our findings also demonstrated that random errors exceeded systematic errors in most directions. This observation suggests that day-to-day variations in patient setup and internal organ filling contribute more significantly to overall uncertainty than consistent positioning deviations. Similar results have been reported by investigators evaluating daily and weekly CBCT verification in pelvic cancers, where random errors were identified as the predominant source of setup uncertainty. The agreement observed between kV-CBCT and MV-CBCT is clinically relevant. kV-CBCT generally provides superior soft tissue contrast and lower imaging dose, whereas MV-CBCT offers the advantage of utilizing the treatment beam energy and may be available on systems lacking onboard kV imaging. The absence of significant differences in setup correction measurements suggests that either modality can be used effectively for translational setup verification when appropriate quality assurance procedures are maintained. Several limitations should be acknowledged. First, this was a single-institution retrospective analysis with a relatively small sample size. Second, only translational setup errors were evaluated, whereas rotational errors and deformable organ motion were not assessed. Third, weekly imaging may underestimate inter-fraction variations compared with daily CBCT acquisition. Nevertheless, the study reflects routine clinical practice and provides useful information regarding setup reproducibility in cervical cancer radiotherapy. Overall, the findings indicate that both kV-CBCT and MV-CBCT provide reliable and clinically comparable assessment of setup errors in carcinoma cervix. The calculated PTV margins are within the range reported in the literature and support the continued use of volumetric image guidance to optimize treatment accuracy.

V. Conclusion

This study evaluated interfraction setup uncertainties in patients with carcinoma cervix using kV-CBCT and MV-CBCT image guidance. The calculated systematic and random setup errors were within acceptable clinical limits. The largest setup uncertainty was observed in the vertical direction, likely reflecting day-to-day variations in bladder and rectal filling. Although kV-CBCT offers superior soft tissue visualization, MV-CBCT provided comparable setup correction accuracy and may serve as an effective alternative when kV imaging is unavailable. The use of volumetric image guidance facilitates reduction of setup uncertainties and supports the application of smaller, evidence-based PTV margins, thereby potentially improving treatment precision while minimizing irradiation of surrounding normal tissues.

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