Iranian Journal of Medical Physics

ijmp.mums.ac.ir

Comparison of Setup Errors in Prostate Cancer Radiotherapy: MV EPID vs. kV CBCT

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ARTICLE INFO

Article type:
Original Paper

Article history:
Received: Aug 08, 2025
Accepted: Nov 04, 2025

Keywords:
Prostatic Neoplasms
Radiotherapy
Image-Guided
Cone-Beam Computed Tomography
Electronic Portal Imaging
Patient Positioning

ABSTRACT

Introduction: Accurate patient setup is essential for precise dose delivery in prostate radiotherapy. This study quantified random and systematic setup errors using MV EPID and kV CBCT verification techniques to identify the modality associated with minimal setup errors and to determine appropriate planning target volume (PTV) margins.

Material and Methods: Setup errors along the X (left–right, LR), Y (superior–inferior, SI), and Z (anterior–posterior, AP) axes were retrospectively extracted from archived electronic records for 100 prostate cancer patients treated between 2015 and 2023. Fifty (50) patients had positions verified using MV EPID and 50 using kV CBCT techniques. Setup errors were compared using an independent samples t-test with a significance threshold of $p < 0.05$. PTV margins were calculated using Van Herk's formula.

Results: For kV CBCT, random errors were 0.8 (LR), 3.0 (SI), and 1.5 mm (AP), and systematic errors were 0.1, 0.4, and 0.2 mm, respectively. For MV EPID, corresponding random errors were 0.5 (LR), 14.1 (SI), and 8.6 mm (AP), and systematic errors were 0.1, 2.0, and 1.2 mm. No statistically significant difference was found along the LR axis ($p = 0.0630$), but significant differences were observed along the SI and AP axes ($p = 0.0022$ and $p = 0.0001$). Calculated PTV margins for kV CBCT were 0.9 (LR), 3.2 (SI), and 1.6 mm (AP), whereas for MV EPID, these were 0.5 (LR), 14.8 (SI), and 9.0 mm (AP). kV CBCT demonstrated superior setup accuracy with reduced margins.

Conclusion: kV CBCT demonstrated superior setup accuracy, enabling tighter PTV margins and reduced normal tissue exposure. Its use is recommended for hypofractionated prostate cancer radiotherapy.

► *Please cite this article as:*
Setlhapelo EM, Nyathi M. Comparison of Setup Errors in Prostate Cancer Radiotherapy: MV EPID vs. kV CBCT. Iran J Med Phys 2026; 23 (1): 59-68. 10.22038/ijmp.2025.81930.2438.

Introduction

Prostate cancer is a major global health concern [1], and the second most diagnosed malignancy among men [1]. Radiotherapy is a standard treatment for localized disease [2], with conformal techniques designed to deliver adequate dose coverage to the planning target volume (PTV) [3], while sparing surrounding normal tissues [2,4]. The PTV includes the clinical target volume (CTV) and a margin that accounts for treatment uncertainties. The CTV includes the gross tumor volume (GTV). The GTV encompasses a gross palpable or visual malignant mass and a volume of tissue that accounts for the microscopic extension of the malignancy [4,5]. Modern techniques such as intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) are highly sensitive to these uncertainties, which result from prostate motion and patient setup errors [2,4,5].

Prostate motion refers to positional changes between planning and treatment, whereas setup errors describe discrepancies between planned and actual treatment geometry [1,6]. These are classified as random or systematic. Random errors vary between fractions and may lead to target underdosing and increased dose to organs at risk (OAR), while systematic errors are consistent deviations throughout treatment and may affect individual patients or the entire cohort [1,3,7]. The International Atomic Energy Agency (IAEA) has defined acceptable limits for these uncertainties, emphasizing the need for effective verification and correction strategies [8]. These permissible values are summarized in Table 1 [8].

Table 1. Geometric uncertainty values in the radiotherapy process

Source	Systematic uncertainties	Random uncertainties	Reduced by
Organ motion	1–50 mm	1–50 mm	Markers, repeat CT
Setup	1–5 mm	1–5 mm	In-room imaging

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Figure 1. Elekta linear accelerator (LINAC) equipped with MV EPID arm opposite the gantry and kV CBCT arm perpendicular to the gantry at CMJAH.

Image-guided radiotherapy (IGRT) is widely used to reduce positioning uncertainties and enable smaller PTV margins [8,9]. Patient positioning is commonly verified using megavoltage electronic portal imaging device (MV EPID) or kilovoltage cone-beam computed tomography (kV CBCT) imaging. MV EPID is cost-effective and suitable for bony anatomy alignment, whereas kV CBCT provides superior soft tissue contrast and more accurate target localization [10,11]. The On-Board Imager™ (OBI) system integrates both modalities for enhanced visualization of the prostate [12,13]. However, kV CBCT is associated with longer treatment times, higher patient dose, and increased cost, creating a trade-off between accuracy and resource utilization [14,15]. Fiducial markers may further enhance precision and reduce inter-fractional variation [16,17].

Patient positioning during radiotherapy can be assessed by evaluating inter-fractional variations. This is typically achieved by comparing MV X-ray images acquired with an EPID [10, 18, 19] to reference kV X-ray images obtained from computed tomography (CT) simulation or digitally reconstructed radiographs (DRRs) [20]. Owing to the limited spatial resolution of MV-based imaging, several investigators have combined MV EPID with volumetric kV CBCT techniques to enhance the precision of setup verification and improve overall treatment accuracy [11, 21]. The OBI system is commonly used for this purpose. It consists of an X-ray tube and a kV flat-panel imager mounted on the treatment machine gantry using robotic arms capable of operating along three axes of motion (Figure 1).

The objective of this study was to estimate random and systematic errors occurring during the setup of prostate cancer patients treated at a tertiary hospital in the X (left-right, LR), Y (superior-inferior, SI), and Z (anterior-posterior, AP) directions, using MV EPID and kV CBCT techniques, and to determine which of the two techniques would result in minimal setup errors and more appropriate PTV margins for clinical application.

Materials and Methods

Study design

Corrected setup error data representing patient displacement along the LR (X), SI (Y), and AP (Z) axes were retrospectively extracted from archived electronic health records at the Radiation Oncology Academic Hospital. Data from 100 prostate cancer patients (>45 years) treated between 2015 and 2023 were analysed, with 50 patients verified using MV EPID and 50 using kV CBCT techniques. The mean age of patients in the MV EPID group was 63.2 ± 7.6 years, while the mean age of the kV CBCT cohort was 72.1 ± 6.2 years at the time of radiotherapy.

Treatment modalities and setup position verification techniques

Setup positions before and after image-guided corrections were recorded along the left–right (LR), superior–inferior (SI), and anterior–posterior (AP) axes. For patients treated with MV EPID, verification imaging was performed on the first treatment day and again at mid-course, whereas patients in the kV CBCT cohort underwent daily verification imaging. All patients were positioned supine. Immobilization using knee and foot supports was applied where clinically indicated, while a subset of patients predominantly within the MV EPID cohort was treated without formal immobilization devices. CT simulation was performed with a slice thickness of 3 mm.

CT Simulation and Patient Preparation

Scan range and prescribed dose

For all patient cohorts CT simulation extended from the first lumbar vertebra (L1) to the mid-femora region. In the MV EPID group, prescribed doses ranged from 45 Gy to 66 Gy delivered in 15–33 fractions, with dose per fraction ranging between 2 and 3 Gy. In the kV

CBCT group, prescribed doses were 57 Gy and 60 Gy delivered in 19 and 20 fractions respectively, with a uniform dose of 3 Gy per fraction.

Bladder and Bowel Preparation Protocol

Patients were instructed to take laxatives the night before CT simulation. On the day of scanning, patients emptied their bladder and rectum prior to consuming 1 litre of water one hour before the procedure to ensure consistent bladder filling. This preparation protocol was maintained throughout the treatment course to minimise organ motion and variability.

Overall Radiotherapy Process

The overall radiotherapy process involves various processes and steps, including CT simulation, planning, verification and delivery [15,22]. Figure 2 presents the entire process summarized in a flow chart.

Setup Error Determination and Image Registration

Setup error per fraction was calculated by comparing planned positions with actual treatment positions from verification images relative to DRRs. Manual image registration was performed using anatomical landmarks or regions of interest. Deviations from the isocentre in LR, SI and AP directions were defined as setup errors and recorded in millimetres (mm) in the electronic health record system. These data were used for subsequent analysis and presentation in relevant tables and figures.

Data Analysis

Random and Systematic Setup Error Calculation Formalism

Random and systematic setup errors were calculated following the standard radiotherapy margin formalism described by van Herk and colleagues [23-25]. where $i = 1,2,\ldots,N$index patients, and $j = 1,2,\ldots,F_i$index fractions for patient i. Here, $F_i$is the total number of fractions delivered to patient i, which varied according to individual treatment prescriptions, and d_{ij}represents the setup displacement for patient $i$at fraction j. All calculations were performed independently for the x-, y-, and z-axes.

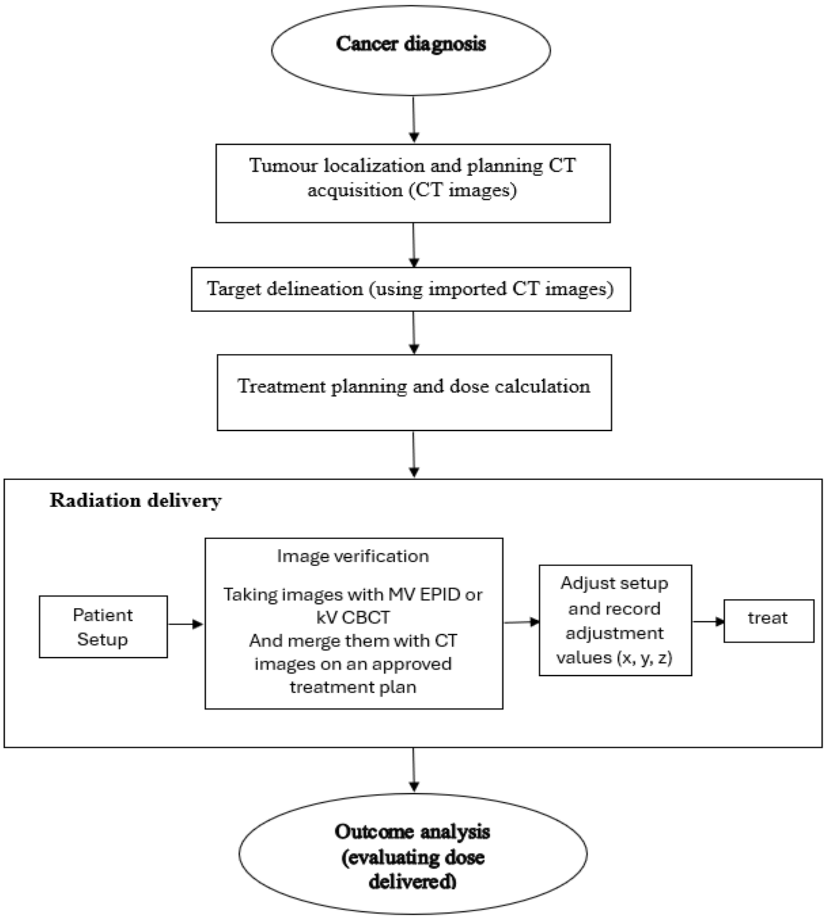

Figure 2. Flowchart for overall radiotherapy process.

The mean setup error was calculated using Equation (1) [8, 20,25]

$$m_i = \frac{1}{F_i} \sum_{j=1}^{F_i} d_{ij} \quad (1)$$

This value represents the average setup displacement for patient $i$along a given axis.

The Random error (σ_i) for patient (i) was calculated using Equation (2) [8, 20,25,26] which represents the fraction-to-fraction variation for that patient

$$\sigma_i = \sqrt{\frac{1}{F_i - 1} \sum_{j=1}^{F_i} (d_{ij} - m_i)^2} \quad (2)$$

This represents the fraction-to-fraction variation for that patient.

The population Random setup error (σ), (RSE) was calculated using Equation (3) [8,25,26]

$$\sigma = \sqrt{\frac{1}{N} \sum_{i=1}^{N} {\sigma_i}^2} \quad (3)$$

This is the most used expression in radiotherapy margin studies and represents the average intra-patient variation.

The population Systematic setup error (Σ), (SSE) was calculated using Equation (4) [8,25,26]

$$\Sigma = \sqrt{\frac{1}{N-1} \sum_{i=1}^{N} (m_i - \overline{m})^2} \quad (4)$$

Were

$$OMS = \overline{m} = \frac{1}{N} \sum_{i=1}^{N} m_i \quad (5)$$

And Σ describes the spread of the patient mean shifts and represents inter-patient variability. The mean translational deviation ($\overline{m}$) corresponds to the average displacement across all patients in each principal direction for the given treatment group [23,25,26]. This value ($\overline{m}$) represents the Overall Mean Setup (OMS) error [8].

PTV Margins Calculation Formalism

PTV margins were calculated using the van Herk formula, which ensures 95% CTV dose coverage in 90% of the treated population by accounting for systematic and random setup errors [25,26]:

$$m_{PTV} = 2.5 \sum_{setup} + 0.7\sigma_{setup} \quad (6)$$

Systematic error was defined as the mean displacement per patient, while random error was the standard deviation of displacements. The population systematic error (Σ) was calculated as the standard deviation of individual patient means, and the population random error (σ) as the root mean square of individual random errors [22,25,26].

Statistical Analysis

Microsoft Excel 365 (Microsoft Corporation, Redmond, WA, USA) was used for descriptive analysis, graph plotting, and calculation of overall means, as well as random and systematic setup errors. A significance level of $p < 0.05$ was adopted. A Student's t-test was performed to determine whether statistically significant differences existed between the two imaging techniques across all principal axes (i.e., LR, SI, and AP directions).

Ethics Approval

Ethical approval was obtained from the Research Ethics Committee of Sefako Makgatho Health Sciences University (SMU) and the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (Wits). The study complied with the Declaration of Helsinki and its subsequent amendments.

Results

A total of 1920 treatment fractions from 100 prostate cancer patients were analysed (50 MV EPID, 50 kV CBCT). Random and systematic setup errors were calculated for the LR(X), SI(Y), and AP(Z) axes and compared using a significance level of $p < 0.05$.

Setup Errors

Overall ranges of setup errors are presented in Table 2. Negative values indicate posterior, left, and inferior shifts, while positive values indicate anterior, right, and superior shifts.

Table 2. The overall range of setup variation for both patient groups in the right left -lateral (LR)s, superior inferior (SI), and anterior – posterior (AP) directions

Patient group	LR: mm	SI: mm	AP: mm
MV EPID: 3DCRT	-1.5 + 1.1	-78 + 6.7	-0.7 + 23.6
kV CBCT: IMRT/VMAT	-1.6 + 1.6	-6.8 + 4.3	-2.3 + 4.3

Individual Systematic Setup Errors and Frequency Distributions

Figures 3a–3c and 5a–5c present the individual systematic setup errors for the fifty (50) MV EPID and 50 kV CBCT patients along the X-, Y-, and Z-axes, respectively. These scatter plots illustrate the per-patient variation in setup accuracy for both imaging modalities. Correspondingly, Figures 4a–4c and 6a–6c display the frequency distributions of these systematic errors, showing the most common ranges of deviation and highlighting overall reproducibility patterns. Together, these visualisations provide insight into setup behaviour across both modalities, enabling comparison of variability and the consistency of patient positioning along each anatomical axis.

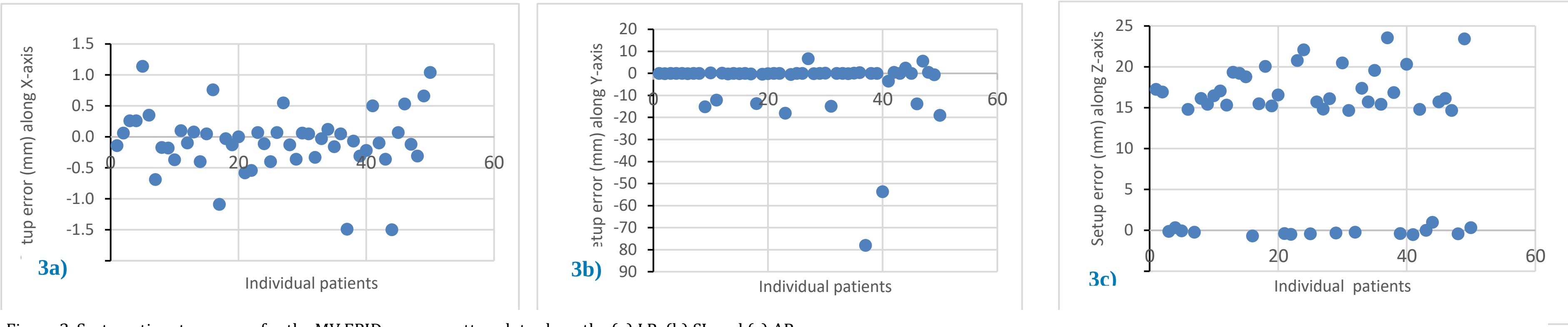

Figure 3. Systematic setup errors for the MV EPID group: scatter plots along the (a) LR, (b) SI, and (c) AP axes.

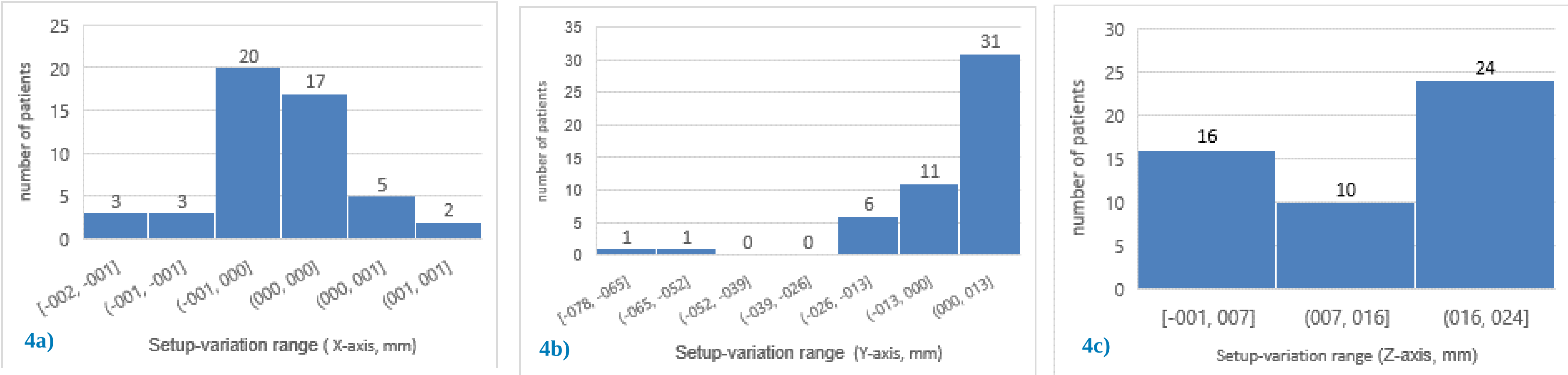

Figure 4. Frequency distributions of systematic setup errors for the MV EPID group along the (a) LR, (b) SI, and (c) AP axes.

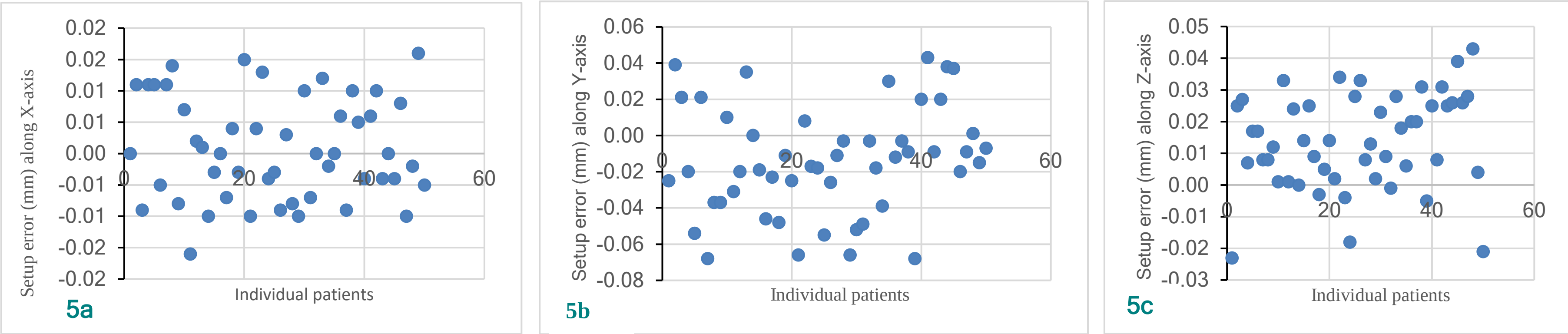

Figure 5. Systematic setup errors for the kV CBCT group: scatter plots along the (a) LR, (b) SI, and (c) AP axes.

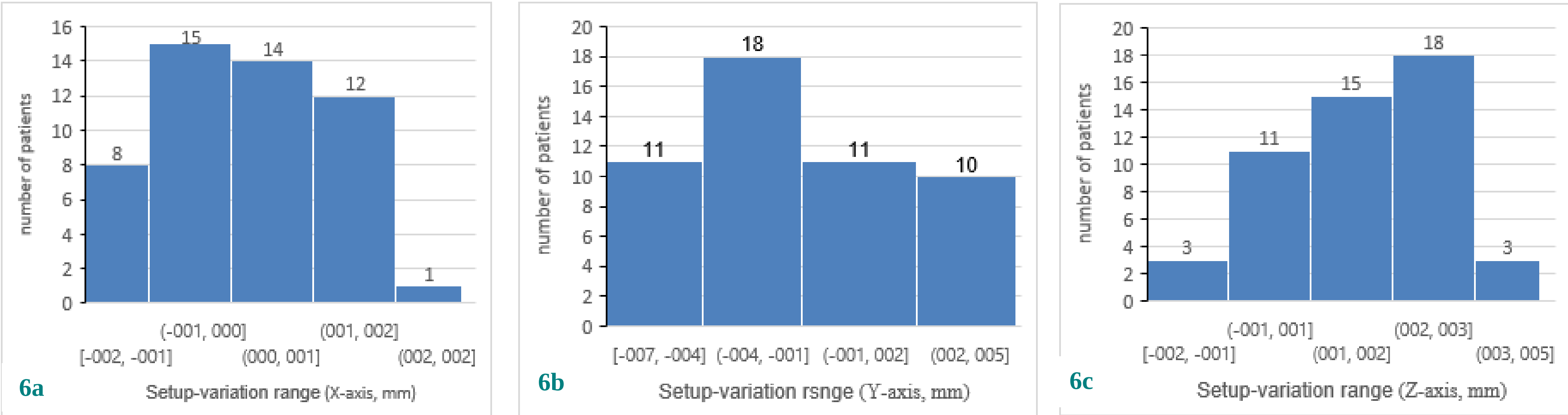

Figure 6. Frequency distributions of systematic setup errors for the kV CBCT group along the (a) LR, (b) SI, and (c) AP axes.

Figures 3a–3c show scatter plots of systematic setup errors for the MV EPID group. Neutral positioning was rare, occurring in one patient on the X- and Z-axes. Most patients demonstrated negative shifts along the X-axis (28/50) and a strong positive trend along the Z-axis (37/50), while the Y-axis showed predominantly neutral positioning (32/50). Histograms in Figures 4a–4c indicate clustering of values around near-zero for the X-axis, wider dispersion along the Y-axis, and pronounced positive displacement along the Z-axis, with most patients falling within higher positive ranges.

For the kV CBCT group (Figures 5a–5c), scatter plots similarly revealed a dominant positive trend along the Z-axis (42/50), while the X- and Y-axes showed more balanced distributions of positive and negative shifts. Corresponding histograms (Figures 6a–6c) demonstrated tighter clustering of values compared to MV EPID, particularly along the Z-axis, confirming improved setup consistency.

Overall, both modalities showed the greatest and most consistent displacement along the Z-axis, indicating that vertical alignment remains the most critical factor for accurate patient positioning, with kV CBCT demonstrating more controlled and reproducible setup patterns than MV EPID.

Overall Mean, Random and Systematic Errors

Figure 7 presents overall mean setup error (OMS), random setup errors (RSE), and systematic setup errors (SSE). MV EPID demonstrated higher error magnitudes across all axes compared to kV CBCT, particularly in the SI and AP directions. LR deviations were minimal for both techniques.

Comparison of MV EPID and kV CBCT

kV CBCT significantly reduced both random and systematic setup errors compared to MV EPID across all axes (Figure 8). Although MV EPID is more efficient and delivers a lower imaging dose, it requires more frequent verification to achieve comparable positioning accuracy.

Correlation, Variance and P-values

Table 3 summarises correlation, variance and statistical significance between the two modalities. Statistically significant differences were observed in the SI ($p = 0.0022$) and AP ($p = 0.0001$) directions, while no significant difference was found for the LR axis ($p = 0.0630$).

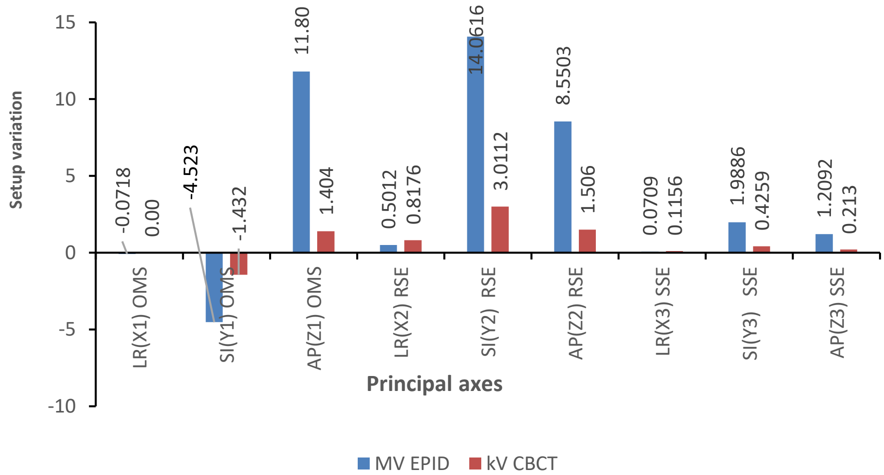

Figure 7. Setup position variations for MV EPID and kV CBCT

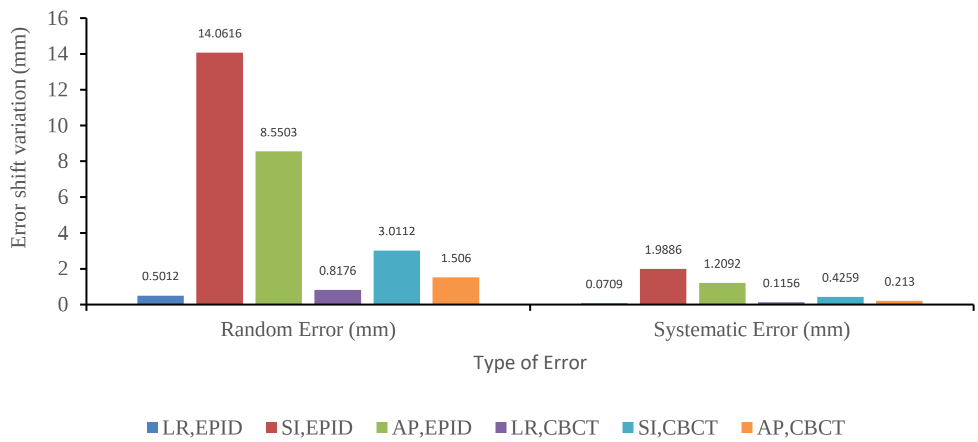

Figure 8. Comparison of calculated random and systematic setup error variations for MV EPID versus kV CBCT techniques

Table 3. Calculated correlation, p – value, and variance from MV EPID and kV CBCT data.

	MV EPID vs. kV CBCT		
Principal axes	LREPID&CBCT	SIEPID&CBCT	APEPID&CBCT
Correlation	0.26	-0.06	-0.06
Variance	0.46	103.40	37.69
p-values ($p < 0.05$)	0.0630	0.0022	0.0001

PTV margin comparison

Using Van Herk's formula, calculated PTV margins for kV CBCT were 0.9 mm (LR), 3.2 mm (SI), and 1.6 mm (AP), compared to 0.5 mm, 14.8 mm, and 9.0 mm respectively for MV EPID. Given that the institution currently applies a uniform 10 mm margin, these findings demonstrate that kV CBCT allows for substantially reduced PTV margins while maintaining setup accuracy.

Discussion

This study compared MV EPID and kV CBCT imaging verification techniques in prostate cancer radiotherapy. MV EPID verification was performed at treatment initiation and mid-course, whereas kV CBCT was performed daily, allowing more consistent correction of interfraction positioning errors. Previous studies have shown that MV EPID, particularly when used with implanted fiducial markers, can estimate prostate positional variation during treatment [23,27,28]. Hanley et al. [23] recommended daily verification when random errors predominate and periodic verification when systematic errors dominate. In this study, random errors exceeded systematic errors in both modalities, supporting the rationale for daily verification—consistent with the use of kV CBCT.

Overall, kV CBCT demonstrated consistently superior setup accuracy compared to MV EPID, in agreement with previous studies by Greer et al. [18], McNair et al. [19], and Mahdavi et al. [15]. However, this observed superiority should be interpreted with caution, as it may be partially confounded by differences in treatment technique. Specifically, the kV CBCT cohort was treated using IMRT/VMAT workflows, which are typically associated with stricter setup verification, tighter planning margins, and more rigorous image-guidance protocols than those commonly applied in 3D-CRT. As such, the observed differences in setup accuracy likely reflect a combination of imaging modality and associated clinical workflow rather than imaging modality alone

These results highlight the advantage of volumetric imaging in improving soft-tissue localization and reducing setup variability. The higher longitudinal (SI-axis) variability observed in the MV EPID cohort was anticipated, as patients treated without immobilization devices are more susceptible to day-to-day anatomical and positional variation [11,29]. Because MV EPID relies solely on bony anatomy and provides limited soft-tissue contrast, it is inherently more vulnerable to discrepancies arising from organ filling and deformation.

Within the MV EPID dataset, two unusually large SI-axis deviations were identified. These values were verified against the original electronic treatment records and confirmed as accurate clinical measurements. Both cases corresponded to fractions in which patients presented with substantial bladder or rectal filling variations well-established contributors to large SI displacement in prostate radiotherapy [11,29-31]. MV EPID-based alignment, which does not visualize soft-tissue structures, can register these internal anatomical changes as large positional errors [10,32]. Although infrequent, such deviations are clinically plausible and reflect real-world IGRT performance rather than technical artefacts. They were therefore retained in the analysis. Sensitivity checks confirmed that although they widened the distribution, they did not alter the overall conclusion that kV CBCT provides more stable and reproducible interfraction positioning [18,32,33].

Figures 3a–3c and 4a–4c demonstrated that the Z-axis showed the most consistent positive displacement trend in the MV EPID group, with Figures 5a–5c and 6a–6c exhibiting a similar pattern in the kV CBCT group. This finding reinforces the need for precise vertical alignment during prostate setup, even with advanced imaging technologies, as vertical prostate drift remains a common pattern of anatomical motion [29,31].

The reduced setup errors observed with kV CBCT can be attributed to its superior ability to visualize both bony and soft-tissue anatomy in three dimensions, unlike the low-contrast, two-dimensional MV EPID images [10,33]. All setup errors observed with kV CBCT remained within IAEA-recommended tolerances [8], supporting its reliability for daily IGRT. These results align with prior research demonstrating improved target coverage and sparing of organs at risk when CBCT-based verification is used [30-35].

Clinically, kV CBCT offers additional advantages, including the potential for reduced PTV margins, lower irradiation of surrounding normal tissues, and improved dosimetric accuracy [28]. It also enables adaptive radiotherapy by allowing clinicians to visualize changes in tumour and organ geometry throughout treatment [32,36]. However, this comes at the cost of higher cumulative imaging dose and increased operational expenses. Pelvic CBCT typically delivers 1.7–5.5 cGy per scan [37], whereas MV EPID contributes only 0.2–0.6 mGy per exposure [38]. In resource-limited settings, these practical considerations may limit routine daily CBCT use despite its clear benefits.

Several limitations must be acknowledged. The retrospective, single-center study design and relatively small cohort limit generalisability. Additional potential sources of bias include exclusion of younger patients, variation in imaging protocols over an eight-year period, and inherent differences between treatment modalities (3D-CRT for MV EPID vs. IMRT/VMAT for CBCT). Manual image registration introduces possible inter-observer variability, which could influence measurement consistency. Furthermore, the uniform bowel and bladder preparation protocol may not fully account for day-to-day organ motion variation.

Future work should include multi-center studies with larger cohorts to improve external validity. Prospective comparisons of patient-reported outcomes between MV EPID-guided 3D-CRT and CBCT-guided IMRT/VMAT would further clarify clinical benefits. Additionally, comprehensive dosimetric analyses linking setup errors to PTV coverage would enhance margin optimisation strategies.

Overall, the results demonstrate that kV CBCT provides superior accuracy, reproducibility, and clinical reliability for prostate IGRT. Its enhanced ability to control interfraction variability supports its preferential use, particularly in hypofractionated and high-precision radiotherapy protocols, while recognising the economic and operational considerations that may influence its implementation.

Conclusion

kV CBCT demonstrated clear advantages over MV EPID in the setup of prostate cancer patients, offering improved positioning accuracy and the potential to minimise radiation exposure to adjacent normal tissues. This enhanced precision supports the use of tighter PTV margins and may contribute to improved treatment safety and outcomes. Based on these findings, routine implementation of kV CBCT is recommended, particularly for hypofractionated regimens where high positioning precision is essential.

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