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Uncertainties in prostate localization: A study in a laboratory setting.

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Abstract

Purpose: The main goal of this study is to minimize systematic errors by utilizing linear regression to determine the position of gold seed markers that were implanted in a wax phantom, using EPID images in a controlled laboratory setting.

Materials and Methods: Pairs of orthogonal portal images were generated and carefully examined, while the phantom was subjected to a known displacement in either the lateral or superior-inferior direction. The measured seed displacement was then compared with the average seed displacement determined from the orthogonal EPID images. The accuracy of the inferred seed positions from the portal images was evaluated using linear regression, concordance correlation coefficient (CCC), intraclass correlation coefficients (ICC), and Bland-Altman plots.

Results: The average displacement errors were found to be 3.2 mm, 2.6 mm, 2.4 mm, and 6.7 mm in the lateral left, lateral right, cranio-caudal (inward), and cranio-caudal (outward) directions, respectively.

Conclusion: The results suggest that utilizing linear regression can significantly reduce the systematic errors described in this study and are consistent with previously published findings on setup errors.

Keywords: Linear Regression; Concordance Correlation Coefficient (CCC); Intraclass Correlation Coefficients (ICC); Bland-Altman Plots.

1. Introduction

Prostate carcinoma is the most common cancer among men in the USA, followed by lung cancer. In 2005, there were approximately 232,000 new cases of prostate cancer and 31,000 deaths from the disease [1]. Radiation therapy is commonly used to treat prostate cancer with clinical T1b-T2b, Gleason score ≤ 7, and PSA ≤ 10 ng/mL in addition to surgery, hormone therapy, immunotherapy, and chemotherapy. The goal of radiation therapy is to deliver the highest possible dose to the tumor while minimizing damage to healthy tissue. However, daily uncertainties in patient positioning and prostate location can make it difficult to ensure complete coverage of the tumor.

To address this, daily patient positioning using lasers and skin markings has become a common practice. However, these external tattoos are not as precise as implanted seeds in internal body structures. Therefore, more precise position verification is achieved using embedded seed markers. Several studies have reported errors in the tumor planning target volume (PTV) ranging from 5.5 mm to 8 mm, which can significantly affect the planned and delivered treatment positions [2, 3, 4]. Various solutions, such as CT treatment planning and beam visualization, have proven effective in reducing setup errors [5]. However, to deliver the correct dose to a patient, it is crucial to minimize all potential sources of error.

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One method involves implanting fiducial gold markers in the region of interest, assuming that there is no seed migration. Portal imaging, using orthogonal views, is a widely accepted method for determining the position of the seeds. Several studies have confirmed the effectiveness of this procedure, with displacements ≥ 3 mm reported in a large study conducted by Osei et al. [6]. Setup errors exceeding 5 mm have been reported in 17% of cases [7]. Other studies have analyzed portal images and found standard deviations of 1.4 mm and 1.8 mm in the anterior-posterior (AP) and superior-inferior (SI) directions for bony displacements [8]. Furthermore, prostate motion was analyzed in ten patients, revealing average displacements of 5.8 mm and 3.3 mm in the anterior-posterior (AP) and superior-inferior (SI) directions, respectively.

Moreover, electronic portal imaging device (EPID) setup errors have been found to range from 1.0 to 3.0 mm [9], with a standard deviation of approximately 2 mm. Similar displacement errors were recorded in the left-right (L-R) direction [10]. Minimizing these inter-fraction setup errors is crucial. The purpose of this study is to characterize the degree of prostate delocalization in laboratory settings.

2. Materials and Methods

In this study, the Varian aS500 EPID (Portal Vision, Varian Medical Systems, Palo Alto, CA) was used. The system's advantages and disadvantages have been extensively described elsewhere [11]. One major advantage is the high-frequency imaging provided by portal images, which can be reviewed immediately. Moreover, digital imaging technology enables real-time detection and measurement of setup errors, allowing for patient repositioning before each treatment.

For this examination, a cylindrical plastic container with a diameter of 14 cm and a height of 20 cm was used. The container contained multiple layers of wax, and eleven gold seeds (Alpha Omega Services Inc., Bellflower, CA) were placed between the layers. The seeds had a diameter of 1.2 mm and a length of 2 mm. The phantom was stationary, rigid, and had a flat bottom. The arrangement of the gold seeds is illustrated in Figure 1, with alternating layers of seed placement.

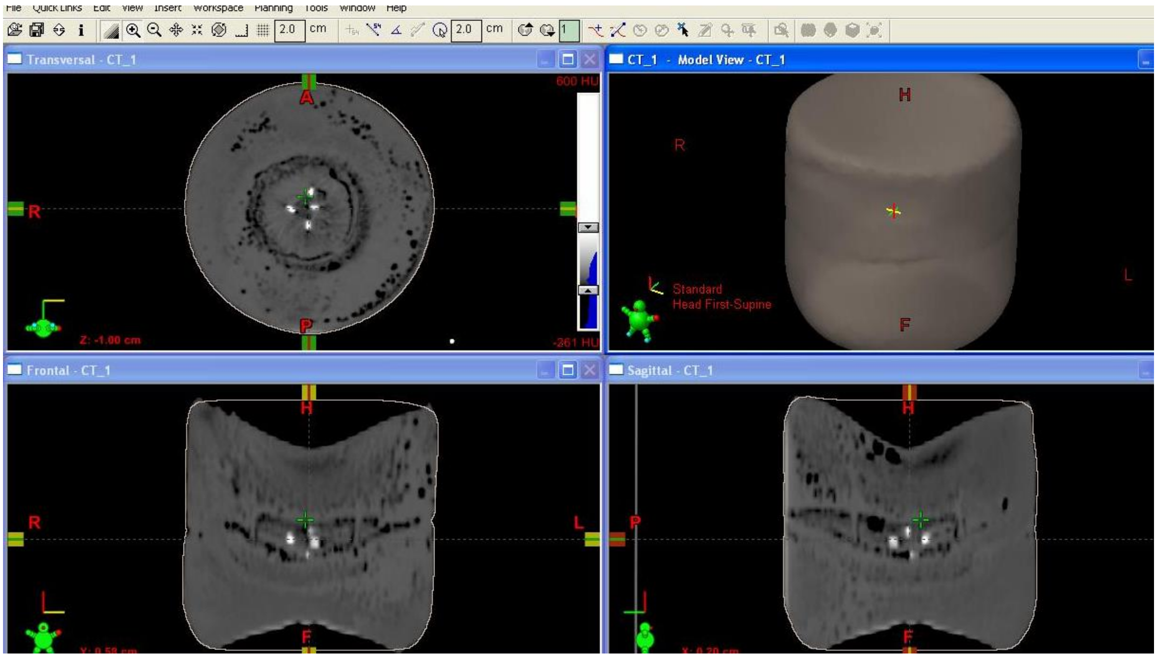


Figure 1 CT images taken after placement of seed in a cylindrical plastic container, built from multiple layers of wax alternating with 11 gold seeds. Digital reconstructed radiograph showing the fiducial markers and the center of mass.

CT scans of the phantom were conducted, with the initial position determined using three laser pointers and skin marks. The CT images were captured in 2 mm slices with a 2 mm separation (couch translation) to improve the reconstruction of digital radiographs (DRR). The full scan consisted of 30 slices, each with 512x512 pixels. The 11 seed markers were identified in the images, and their positions were used to define a contour in the treatment planning software Eclipse (version 15.6.04). A DRR was then generated to visualize the location of each seed relative to the isocenter for each beam port.

The baseline pair of orthogonal images was captured at gantry angles of 0 and 90 degrees. The couch was then moved in a cross-shaped pattern (left, right, toward the gantry, or the target) with translations occurring at 2 mm intervals. Each position was verified using a ruler with a millimeter scale and a digital couch readout. In total, 60 positions were measured, with 15 in each direction, resulting in a total displacement of 30 mm from the center.

The 3D position of each seed was determined by triangulating its projected coordinates in the images captured at 0° and 90° gantry angles. Three independent coordinate systems were used to describe the geometry of the irradiated phantom. The spatial position of each seed was defined relative to the isocenter of the treatment machine, using its center of mass. The recorded positions were analyzed for reliability by calculating intraclass correlation coefficients (ICC), which assess the consistency between two or more quantitative measures [12]. The reproducibility of multiple readings was evaluated using concordance correlation coefficients [13].

2.1. Statistical Analysis

All statistical analyses were conducted using GraphPad Prism (GraphPad Software, La Jolla, CA, USA). Values are presented as mean ± standard deviation (SD), unless otherwise indicated. The relationship between couch shifts and the measured positions was evaluated, and potential confounding factors were identified through regression analysis in each direction. A p-value of less than 0.05 was considered statistically significant. The measured positions were then adjusted using the coefficients of linear regression and assessed for any potential systematic bias.

A Bland-Altman [14] plot was generated to determine the limits of agreement. This method calculates the mean difference, also referred to as "bias," between the two methods of measurement, and the 95% limits of agreement, represented as the mean difference (± 1.96 standard deviations). The 95% limits are expected to encompass 95% of the differences between the two measurement methods.

3. Results

The reference positions of the seeds are listed in Table 1 and depicted in Figure 2. The center of mass coordinates was determined by triangulating from the midpoint of each seed using the portal images.

Table 1 The reference position of the seed with respect to the CT

Seed number	X	Y	Z
1	0.4	-0.2	61.6
2	1.9	-0.7	61.5
3	-0.3	1.1	61.9
4	1.2	-1.4	62.4
5	-0.3	0.5	62.6
6	1.7	-0.5	62.8
8	1.7	0.0	64.3
9	-0.1	1.1	64.5
10	0.6	0.3	65.1
11	0.6	0.3	65.2
Skin	0.6	0.8	63.5

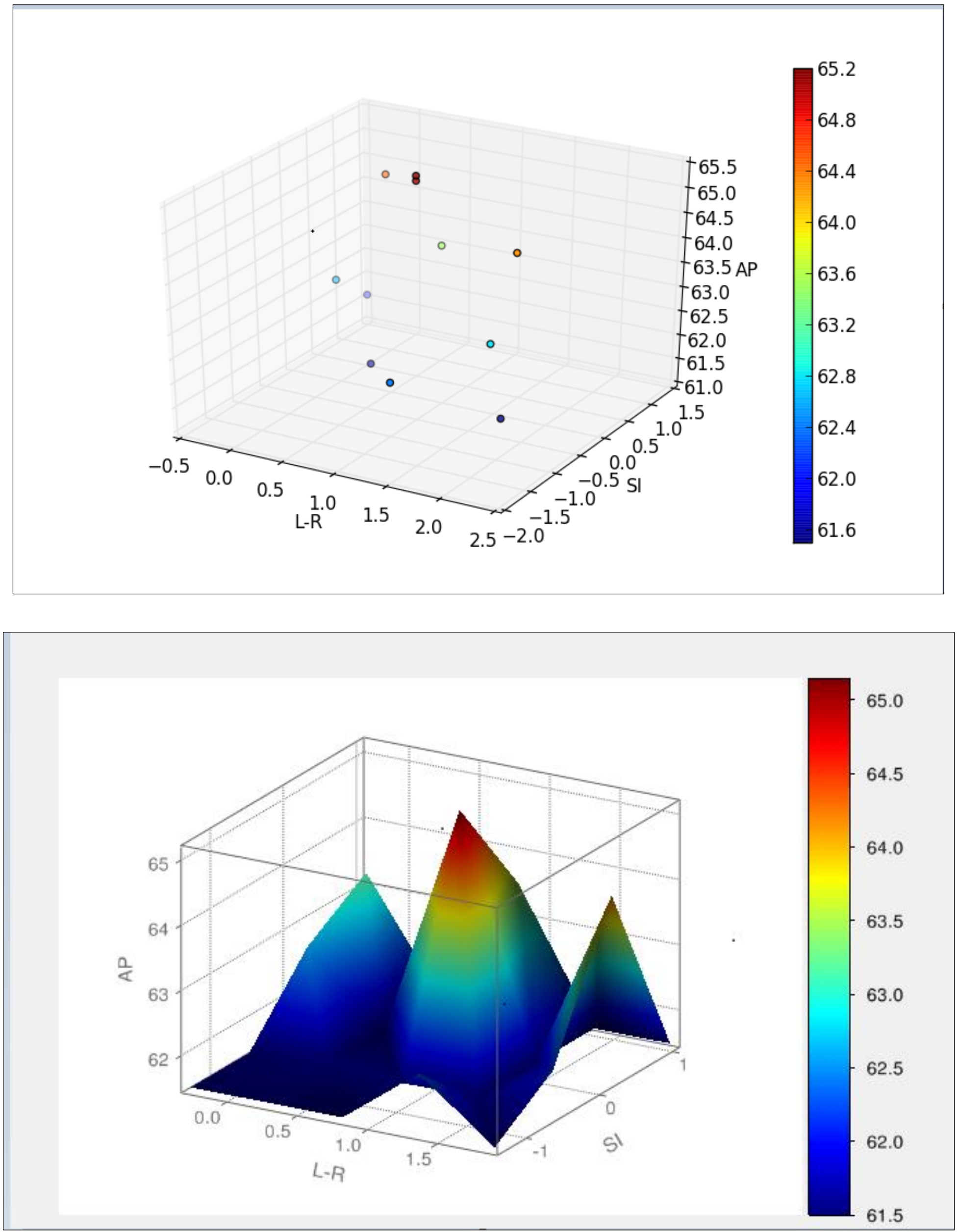


Figure 2 Reference position of seed markers in 3 D model.

The average seed displacement errors (Figure. 3) were 3.2 mm, 2.6 mm, 2.4 mm, and 6.7 mm in the lateral left, lateral right, cranio-caudal (inward), and cranio-caudal (outward) directions, respectively.

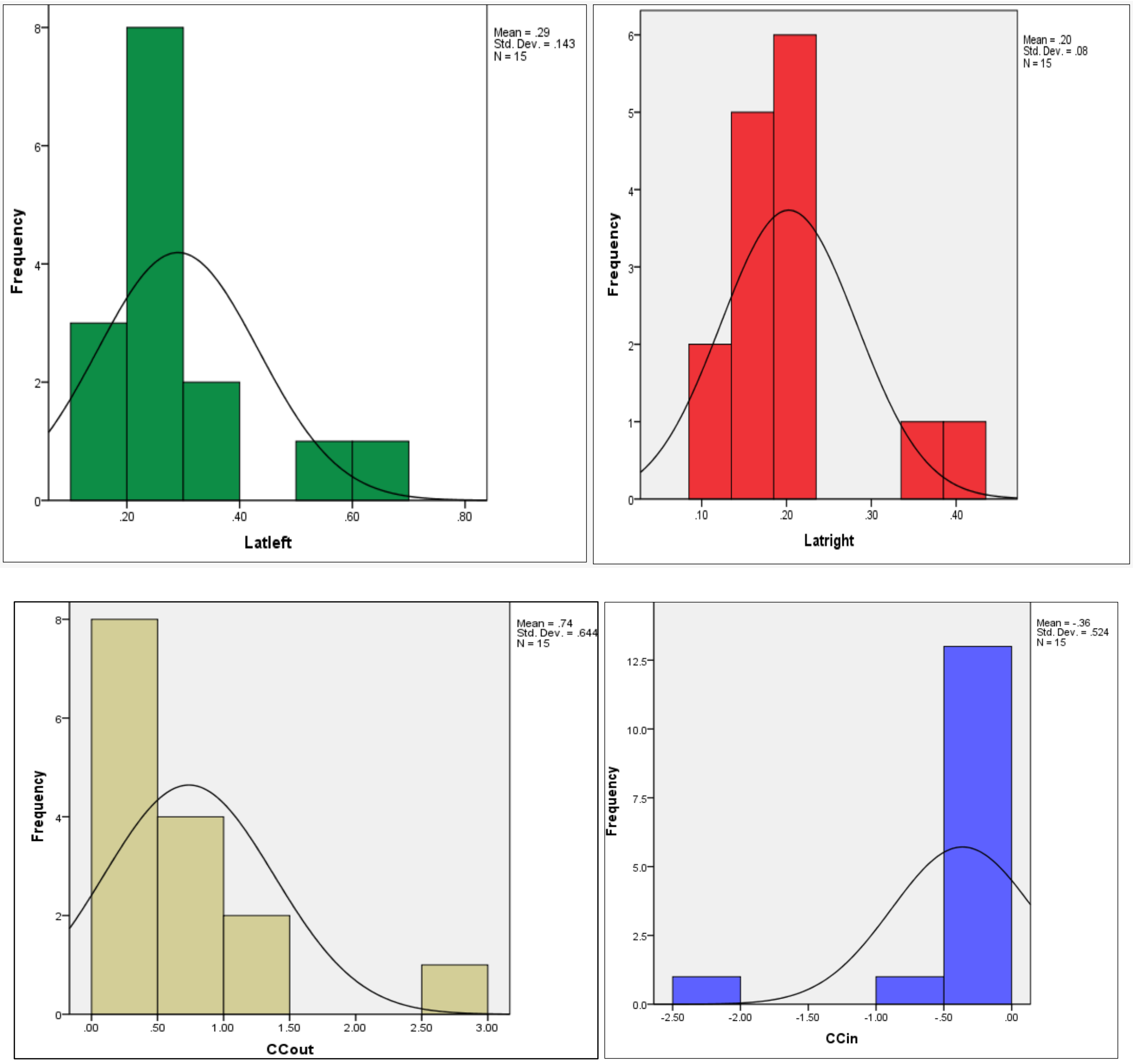
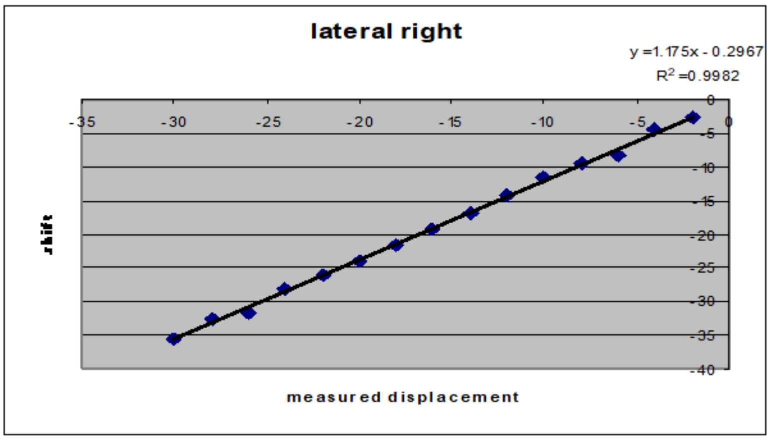
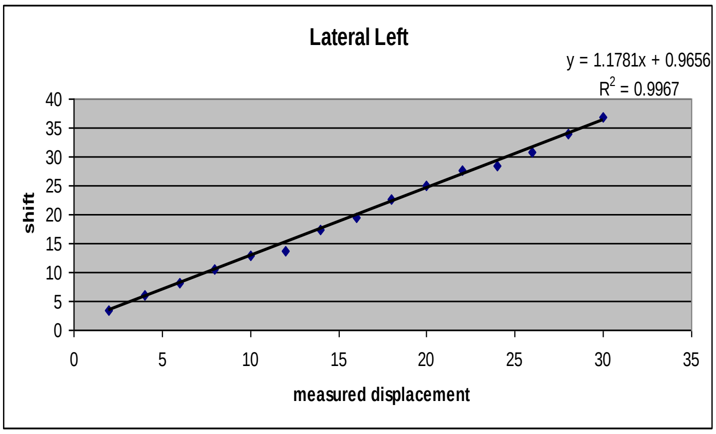
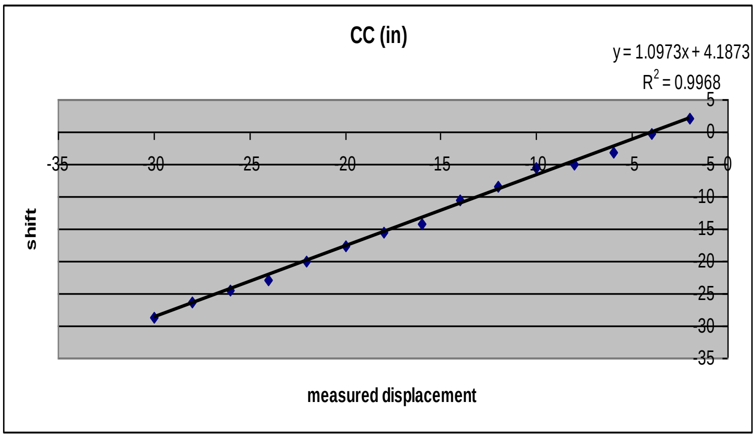


Figure 3 Representation of the systematic errors in Lateral and CC direction for the 11 gold seeds

The linear regression analysis showed a strong correlation between the measured seed displacement and the average seed displacement determined from the orthogonal EPID images, with a concordance correlation coefficient (CCC) of 0.95. The intraclass correlation coefficients (ICC) for seed displacement measurements were found to be above 0.90, indicating excellent reliability (Table. 2).







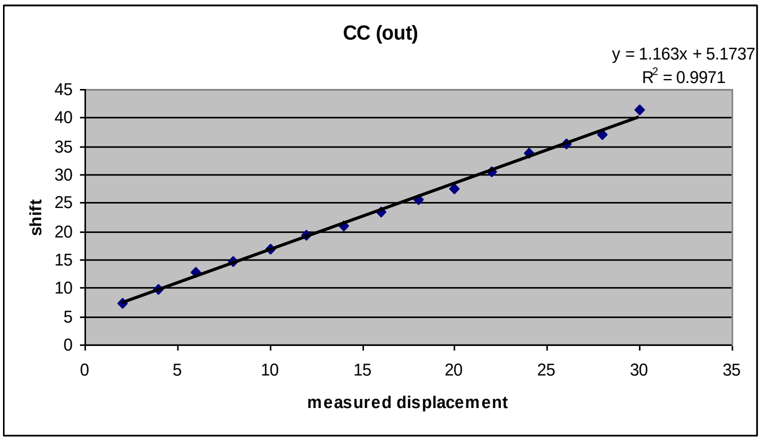


Figure 4 Linear regressions of known phantom shifts vs. the average seed displacement (mm) measured using portal images. From top to bottom, the plots show displacements in the lateral (right), lateral (left), CC (in), and CC (out) directions.

Table 2 Parameters derived from linear regression, Bland and Altman, ICC, and CCC

Direction	Linear Regression			ICC	CCC	Bland and Altman	
	Slope	Intercept	R^2			Lower	Upper
Right Lateral	1.175	-0.2967	0.9982	0.9871	0.9366	-5.2	0.0
Left Lateral	1.1781	0.9656	0.9968	0.9867	0.9122	0.6	5.9
CC (in)	1.0973	4.1873	0.9968	0.9957	0.9555	0.8	4.0
CC (out)	1.163	5.1737	0.9971	0.9887	0.7352	4.2	9.1

Bland-Altman plots demonstrated good agreement between the inferred seed positions from the portal images and the actual seed positions.

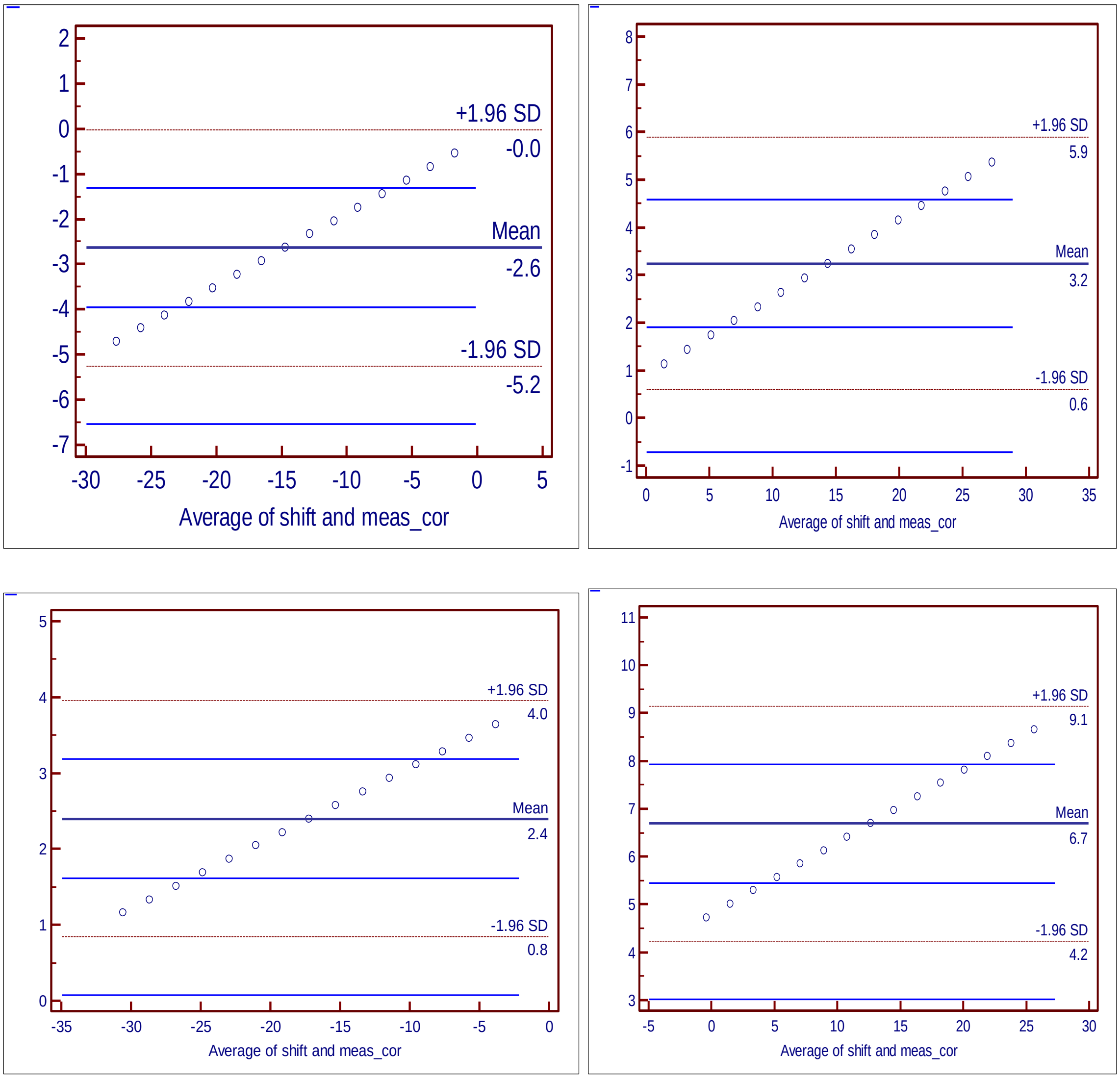


Figure 5 Bland–Altman plots of agreement between phantom shifts and measured displacements in all four directions.

The measured displacements are corrected by their respective linear regressions. The mean of the shift and displacement is plotted on the x-axis, and the differences between the two are plotted on the y-axis. The horizontal dashed lines represent the limits of agreement (each line is drawn 1.96 SD from the mean). The top row of the figure represents the lateral (left) and lateral (right) directions. The bottom row represents CC (in) and CC (out).

4. Discussion

This study aimed to minimize systematic errors in prostate localization by utilizing linear regression and EPID images in a controlled laboratory setting. The results demonstrated that the linear regression analysis helped reduce systematic errors and provided accurate measurements of seed displacement. The average displacement errors observed in this study were consistent with previously published findings [6, 7, 8, 9, 15] highlighting the importance of minimizing setup errors in radiation therapy for prostate cancer.

The use of fiducial gold markers and portal imaging has been proven effective in determining the position of the prostate and reducing setup errors. The EPID system used in this study provided high-resolution images that allowed for real-time detection and measurement of setup errors. The accuracy of the inferred seed positions from the portal images was confirmed using statistical analysis, including linear regression, CCC, ICC, and Bland-Altman plots.

5. Conclusion

In conclusion, this study demonstrated that utilizing linear regression and EPID images can significantly reduce systematic errors in prostate localization. The results highlight the importance of minimizing setup errors in radiation therapy for prostate cancer to ensure accurate delivery of treatment. Further studies can build upon these findings to optimize prostate localization techniques and improve treatment outcomes.

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