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Invited Paper

The Dosimetric Impact of Individual Setup Errors on Optimized Prostate IMRT Plans

Ehab M. Attalla [1,✉], Mohamed Abdelmajeed[1], Nashaat A. Deiab[1], Wael M. Elshemey[2]

1. National Cancer Institute, Cairo University, Cairo, Egypt.

2. Biophysics Department, Faculty of Science, Cairo University, Cairo, Egypt.

✉ Corresponding author: Prof. Ehab Attalla, National Cancer Institute, Cairo University, Cairo, Egypt. Tel: +20 100 537 3359; E-mail:attalla.ehab@gmail.com

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Abstract

Patient setup errors are well known to affect the accuracy of treatment plans. This work aims at quantifying their effects on the dosimetric outcomes of prostate treatment plans. SIB-IMRT treatment plans are carried out for 12 prostate cancer patients using Monaco TPS. Setup errors of the first three treatment fractions for each case are quantified using kV-CBCT. Accordingly, a plan isocenter is shifted and a recalculated plan is performed. For each of the target volume and the OARs, the dose distribution, the dose-volume metrics, the target homogeneity and the conformity are all quantified for the evaluation of their dosimetric impact. Mean 3D displacement of 3.4 ± 2.5 mm in AP direction, 2.8 ± 1.9 mm in SI direction and 4 ± 1.5 mm in LR direction are reported. A shift difference ≥ 3.0 mm in one or more dimensions occurred in 11 out of the 12 cases (91.66%) while 5 out of 12 cases (41.66%) have a shift difference ≥ 5 mm resulting in an average of 1-2 Gy reduction in the target dose and an average increase in the dose to OARs of 1Gy. There is a pronounced sensitivity of treatment plans to setup errors. The latter have detrimental dosimetric impact on prostate target coverage. KV-CBCT provides reliable IGRT means for defining setup errors in SIB-IMRT. Isocenter verification of setup errors is essential for achieving the approved treatment plan. A daily online correction protocol is suggested for successful elimination of setup errors.

Keywords: Prostate; SIB-IMRT; kV-CBCT; Setup error.

Introduction

Localized prostate cancer is highly prevalent in men (29% of total male cancer and 11% of overall male deadly cancer) [1]. External beam radiation therapy is one of the most commonly used standard treatment options for early and locally-advanced prostate cancer [2]. IMRT is an advanced radiotherapy technique characterized by the ability to provide highly conformal dose distributions to target and improve sparing of normal structures, such as femoral heads, rectum and bladder. IMRT provides significant tumor control and toxicity reduction [3].The steep dose gradients in IMRT dose distribution makes it more sensitive to setup errors [4].

To be effective, however, the implementation of IMRT requires accurate target localization and the selection of appropriate treatment parameters [5]. Employing Simultaneous Integrated Boost (SIB) techniques is preferable for the delivery of highly conformal dose distribution in prostatic cases where doses to initial and boost fields are delivered simultaneously in the same number of fractions [6]. This reduces the overall treatment time and has the potential of escalating the dose to the primary target volume [7].

The uncertainty in prostate patient position during treatment relies on patient setup errors and organ motions. Prostate motion may reach up to 2 cm in the AP direction [8]. On the other hand, setup errors are

usually in the range of 1–3 mm [9]. Most of the clinical studies involving boosting of prostate apply setup verification based on the imaging of patient's bony anatomy [10]. This is specifically applied for the correction of setup variations in AP direction [11]. In SIB, the high-dose region is surrounded by an intermediate dose region in order to limit a possible decrease in the high dose region when a setup error exists. The region of intermediate dose has sharp gradients to a near-zero dose in order to spare nearby OARs, which are potentially more sensitive to setup errors [12].

Several studies have focused on the importance of the evaluation of possible effects of setup errors on prostate patients. Algan et al. [13] stated that the mean V_{95} (Volume of CTV receiving 95% of the prescription dose) values for corrected patient setup rises up to 99.9% compared to the uncorrected one (87.3%).Therefore, it is clear that, the uncorrected isocenter exhibits significant reduction in target coverage.

The calculated PTV margin was less than 5 mm, therefore PTV margin applied in this study provides a sufficient PTV coverage. Daily EPIs (Electronic Portal Images) combined with gold markers implanted into the prostate provide an effective tool for verifying of the prostate position immediately prior to treatment delivery [14].

Landoni et al. [10] re-evaluated original treatment plans after taking setup movements into account. For the cases they investigated, they showed that the mean shifts in the three dimensions were lower than 2 mm. Translations within 2 mm did not significantly affect the Dose Volume Histogram (DVH) shape of the prostate gland and rectal wall. Therefore, it would be recommended to keep the variation in any direction less than 2 mm to avoid violation of margins. Since the dose prescribed to prostate target is constantly higher than the threshold dose for bladder or rectum, reliable position verifications and setup corrections during treatment are of very important, in order to minimize the systematic portion of the setup deviations. Deviations from the planned position during treatment fractions are either systematic (i.e. in the same direction) or random (i.e. in all directions).

The sensitivity to setup errors regarding the target volume is dependent on the quality of the treatment plan while the impact on the critical structures is dependent on the sharpness of the dose gradients outside these critical organs [15]. For highly conformal radiotherapy techniques to be safe, IGRT is essential for isocenter verification and monitoring dose delivery. IGRT holds potential clinical benefits for prostate cancer as well [16].

In this study, SIB-IMRT treatment plans were carried out for 12 prostate cancer patients using Monaco TPS. Patient setup errors for the first three treatment fractions were registered using KV-CBCT. Based on these errors, the average shifts were measured and plans were re-calculated using different isocenter to assess the influence of the dose deviations.

Materials and Methods

This is a retrospective study where anonymous patient records and data were retrieved from the radio-treatment registry of the hospital. Twelve prostate cancers treated using SIB-IMRT techniques were enrolled in this study. In CT simulations, reference markers were placed on the patient skin. CT scan slice thickness was 2.5 mm. The CT images (CT simulator) were transferred to a Work Station in order to delineate targets and OARs by an oncologist. Then images were transferred to Computerized Medical Systems (CMS) Monaco 5.1(St. Louis, MO) TPS through DICOM network. Monaco employed a biological model-based optimization [Equivalent Uniform Dose (EUD)]. A biological cost function theoretically would not be sensitive to hot spot inside the target as hot spots could increase tumor-cell killing and a more inhomogeneous target dose distributions were provided by the biological IMRT plan [17].

The PTV was grown from the prostate CTV with a 7-mm margin in all directions except for nodal CTV and posteriorly where the margin was used to allow a 5-mm. These margins were sufficient to account for the setup uncertainties and to ensure that the prescribed dose was received by the target volume with the least possible amount of irradiation to normal tissue. As known that increasing the number of beams provides better plan quality [18] therefore, the generated plans utilized nine fields that were equally spaced angle around 360° using the Step and Shoot IMRT of Elekta Synergy Linear accelerator (Linac). All plans were normalized to a minimum isodose line encompassing ≥95% of the PTV and above. The applied dose criteria for OARs: rectal tolerance DVH criteria were preferentially V45≤50% or V60≤35% or V70≤20%. Bladder preferences were V60≤ 35% orV70≤ 25%. Femoral head criterion was V50≤5%. The dosimetric impact of setup errors were quantified by comparing the recalculated dose distribution to the original plan.

The prostate and "nodal region" were prescribed 81 Gy and 56 Gy respectively in 35 fractions. The systematic error was defined as the mean displacement between the treatment isocenter and the planning isocenter. The random error was the deviation of each individual position from the mean patient position. Due to the fact that dose distributions are insensitive to random errors

and mainly depend on systematic errors, intensity-modulated strategies aim to reduce systematic errors by monitoring patient errors for the first several fractions [19].Therefore, applying an offset would be highly beneficial to this group of patients as it could reduce systematic errors.

kV-CBCT images were performed on Elekta X-ray Volume Imaging (XVI) system. All treatments were verified by image registration before each treatment fraction. The institute's setup protocol for prostate IMRT cases included first adjustments based on skin markers in the treatment room. Second, the patient's setup verification images were obtained with the Elekta XVI system. Finally, image matching between the CT simulation image and kV-CBCT image was carried out.

In each direction, setup shifts were recorded along three treatment sessions with kV-CBCT. The original plans were calculated on the CT with an empty rectum and bladder with a constant amount of water. Based on the individual setup errors and after taking the average of the first three kV-CBCT shifts, the dose distribution was re-calculated including setup errors. The re-calculated plans (shifted plans) were carried out under the same constraints and the same CT images, and then evaluated relative to the treatment (original) plan. Setup errors can be quantified and detected by precise measurements of the shift between rigid structures such as Pelvic bones. Paired sample t-test was performed for isocenter shifts with respect to the original plan (no shifts) at the statistical significance $p<0.05$ using SPSS.22 software. Data were presented as the mean ± Standard Deviation (SD).

Results

Quantification of patient setup errors

Patient's systematic setup errors were corrected using kV-CBCT volumetric images via manual offline matching depending on the 3D bony anatomy as in Figure 1.Figure 2 (a, b and c) presents the calculated mean shifts for the first three treatment sessions for individual patients.

(a) Antero-posterior (AP) shifts

The mean difference and Standard Deviation (SD) in isocenter shifts as measured by KV-CBCT for the first three fractions in the AP dimension was 3.4 ± 2.5 mm. The percentage of patients who recorded a mean shift > 3 mm or > 5 mm was the same and equal to 25% (3 out of 12).

(b) Supero-inferior (SI) shifts

In the SI dimension, the mean difference in isocenter shifts was 2.8 ± 1.9 mm. The percentage of patients who recorded a mean shift ≥ 3 mm was 16.6% (2 out of 12). No patient shifts were record ≥ 5 mm.

(c) Left-right (LR) shifts

The mean difference in isocenter shifts in the LR dimension was 4 ± 1.5 mm. The percentage of patients who recorded a mean shift ≥ 3 mm was 58.3% (7 of 12) while those recording a mean shift ≥ 5 mm represented 16.6% (2 out of 12).

Impact of patient setup errors on dosimetric outcomes

This study assessed the dosimetric effect of setup variations on targets and normal tissues in prostate cancer patients treated with IMRT using kV-CBCT.

(a) Dose-volume metrics

Figures 3a and 3b illustrate the dose distribution to target volumes and the corresponding DVHs, respectively for a selected patient case. The comparison between the DVHs of original and shifted plans for the target and selected OARs reveals the uniformity of dose to target volumes (PTV81 and PTV56).

Table 1 shows the mean D95, D35, D5 and D_{mean} values for the original and shifted groups of the studied prostate targets and selected OARs. A significant reduction in dose is observed only for the D95 and D_{mean} doses for the shifted plan compared to the original one for PTV81 (472 cGy) and PTV56 (163 cGy), respectively.

(b) Dose conformity and homogeneity

The mean values of Conformity Index (CI) and Homogeneity Index (HI) for original and shifted plans are computed and tabulated for all cases in (Table 2).

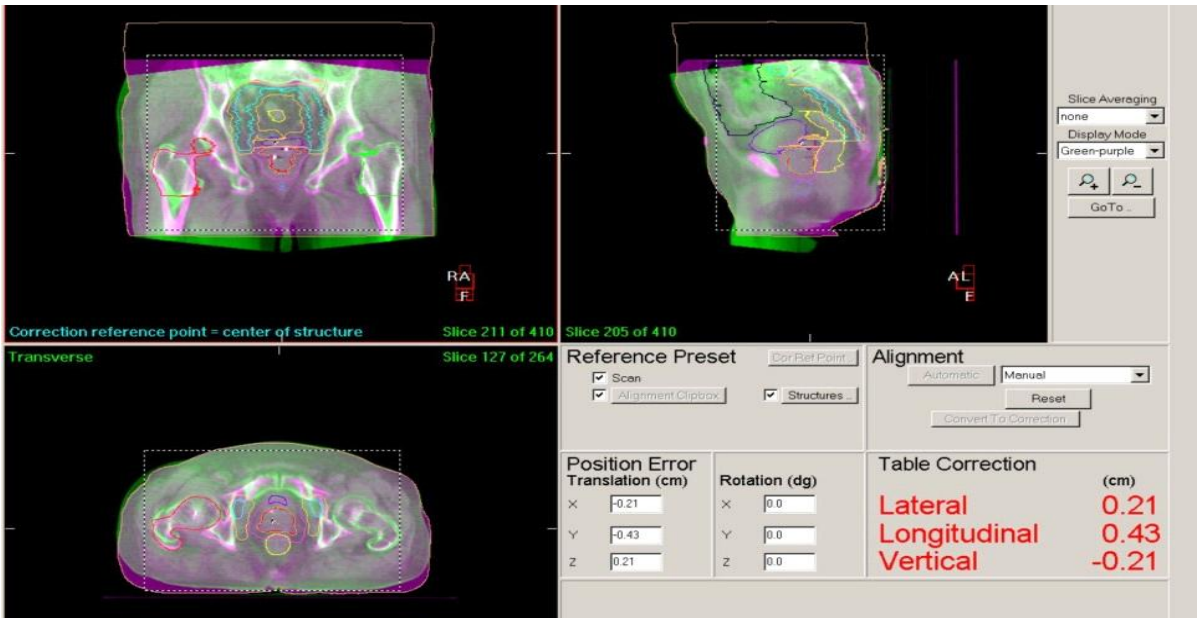

Figure 1. Manual matching using the 3D bony anatomy and implanted fiducial marker via XVI system; (a) axial view (b) Sagittal view and (c) Coronal view.

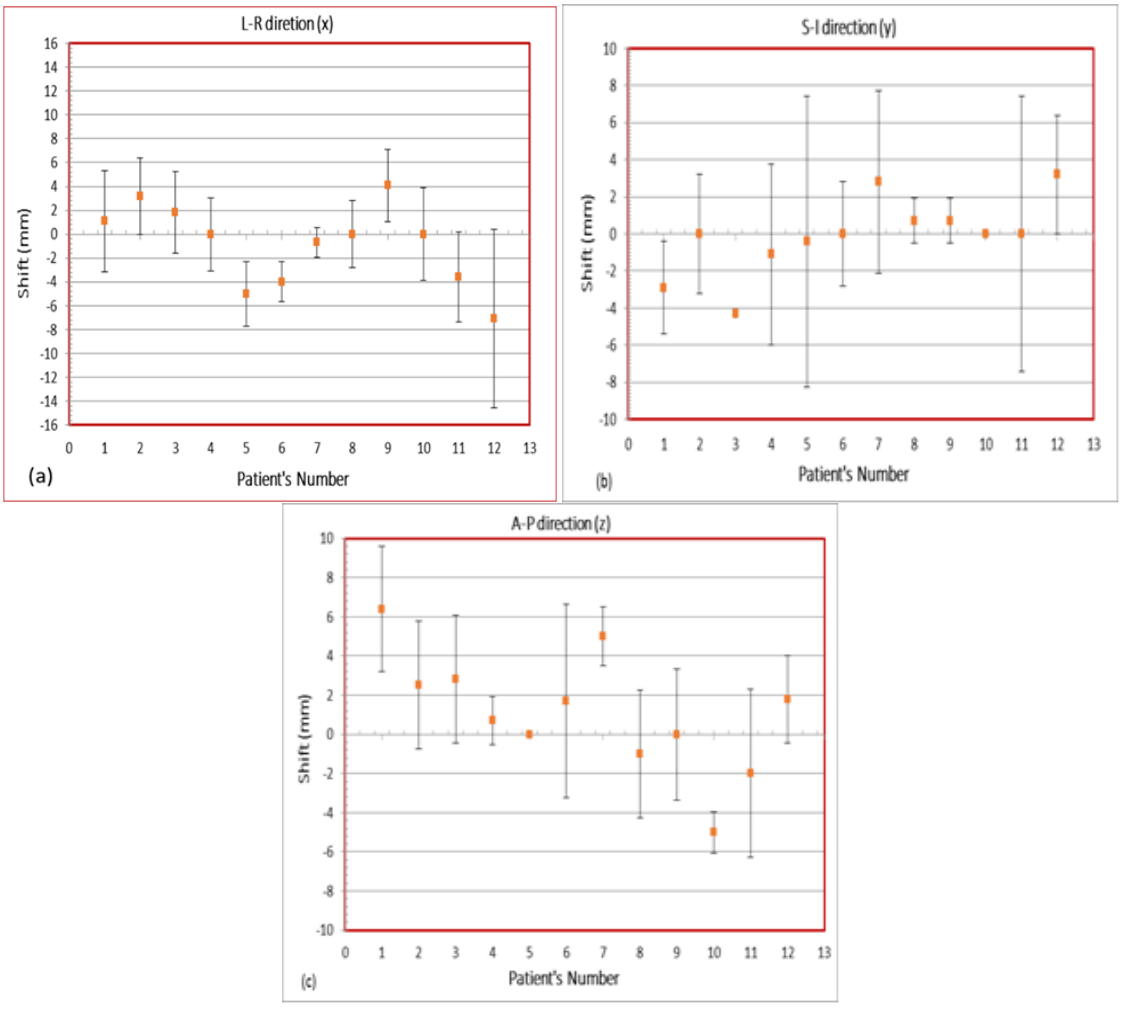

Figure 2. Distribution of setup shifts for each patient in the three directions: (a) Left-Right, (b) Supero-Inferior, and (c) Antero-Posterior.

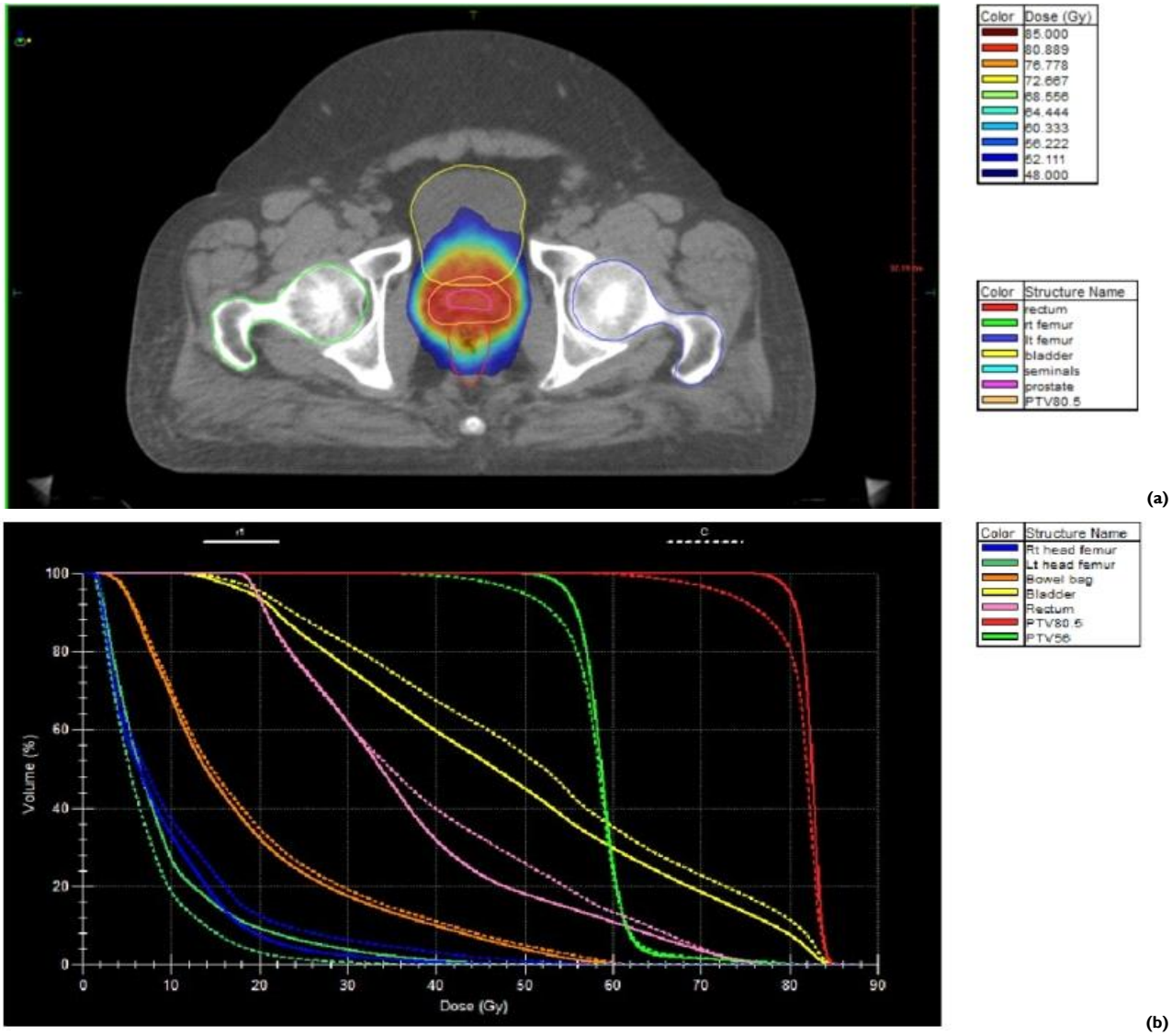

Figure 3. (a) The dose distribution to target volumes and (b) the corresponding DVHs of the targets and OARs for original (solid line) and shifted (dashed line) plans calculated for a single patient.

Table 1. Mean D95, D35, D5 and D_{mean} parameters for the targets (CTV and boost) and OARs within original and shifted plans for studied patients.

Organ-dose parameter		Original	Shifted
D95	Target-81	78.6±1.9[a]	73.9±4.7[b]
	Target-56	54.4±0.7[a]	52.8±1.4[b]
D35	Bladder	51.4±8.2	50.9±10.5
	Rectum	42.0±4.6	41.8±7.8
D5	Rt femur	36.2±11.7	36.7±12.1
	Lt femur	35.9±12.8	35.4±13.2
D_{mean}	Target -81	82.0±1.3[a]	80.7±1.4[b]
	Target -56	58.1±0.5[a]	57.8±0.3[b]
	Bladder	42.6±6.6	42.6±7.7
	Rectum	37.2±3.7	38.5±6.5

Significantly different means (p-value <0.05) are given different symbols. The value after the ± sign is the SD

Table 2. Comparison of the mean CI and HI for the prostate targets in the shifted and original IMRT plans.

Organs	***Conformity index***		***Homogeneity index***	
Prostate	*Original*	*Shifted*	*Original*	*Shifted*
Target-81	0.98±0.02[a]	0.91±0.07[b]	0.1±0.06[a]	0.2±0.03[b]
Target-56	1.02±0.24	0.95±0.03	0.18±0.11[a]	0.26±0.07[b]

Significantly different means (p-value <0.05) are given different symbols. The value after the ± sign is the SD.

Discussion

Setup errors were corrected if they exceeded 2 mm in any direction. A setup error is defined as the displacement of a bony landmark coordinates on the beam from those on the Digitally Reconstructed Radiograph (DRR) [20]. The offline correction method had been proved to successfully reduce systematic errors [21]. Nevertheless, Prasad et al., concluded that daily online imaging and corrections remain the standard image guidance policy for highly conformal radiotherapy of prostate cancer [22].

In this work, the adopted imaging protocol allowed therapists to fully control the image display contrast. In general, patients were imaged once per week unless there was a justified need to acquire more images and were applied an online setup protocol with manual image registration that quantified systematic setup errors of bony anatomy around prostate using kV-CBCT scans from the first three treatment sessions. It was reported that increasing the times of imaging would result in decreasing the PTV margin only by 1-2 mm [23].The evaluated 3D shifts based on KV-CBCT technique in this study showed that 91.66% of the shifts were ≥ 3 mm and 41.66% of the shifts were ≥ 5mm.This was enough to affect the target coverage [24].

Systematic errors in this study are smaller than those reported by Alganet al. [13]. This may be attributed to including inter-fraction organ motions in the work of Algan et al., where they used fiducially markers for each patient. Isocenter shifts reported elsewhere [10, 25] was considerably comparable to the present shifts results.

The maximum acceptable setup error was ±2 mm as it would be difficult to predict if smaller setup errors would have any clinical relevance [26].

The DVH analysis shows that the PTV has a very homogeneous dose distribution (excellent coverage) in all patients in original plans. On the contrary, the shifted plans exhibit a decrease in dose coverage due to isocenter shifts as in Figure 3b. An under dosage of 2-3Gy decrease has been reported for prostate and boost volumes compared to the original treatment plan [16, 27-28].

Algan et al, [13] reported a similar significant dose reduction in D95 of PTV81 for corrected (80.89 Gy) and uncorrected (73.03Gy) plans, respectively. Moreover, Zhu et al. [29] reported 0.3% total reduction in the D95 values after simulation of systematic errors. On the other hand, Hareen et al. [28] found no significant differences in either of D95 or D_{mean} between the original and shifted plans.

They evaluate prostate position after offline imaging of EPIDs. This study assesses setup errors via 3D direction and more accurate position using KV-CBCTs. The change in the isocenter is probably the reason for the reported reduction in the target dose distribution.

Significant reduction in CI (7.1%) is observed in the shifted plans of target 81. An ideal CI approaches a value of 1. In such case, the entire prescription dose is supposed to be delivered to the PTV with no dose to adjacent tissues.

Since HI is a good indicator of a pattern of dose distribution in a target volume, this work calculates HI for target-81 and target-56 using the following equation [30]:

$$\text{Dose homogeneity HI} = D_2 - D_{98} / D_{50}$$

where D_2, D_{50} and D_{98} are the doses covering 2%, 50% and 98% of target volume, respectively.

From table 2, it can be noticed significant increase in the HI for shifted targets (50% and 69% for target-81 and target-56, respectively) compared to original. This indicates a decrease in the homogeneity of dose distribution in shifted targets. Siebers et al. showed that 3 mm systematic errors potentially affected the homogeneity of the dose distribution [31].

According to ICRU-83, the ideal value for HI is equal to zero. The dose distribution in case of target-81, for original and shifted plans, is more homogenous than target-56. This may be attributed to the greater target dose in case of target-81 as shown by Kataria et al. [32].

As a final suggestion, it would be better to use cone-beam computed tomography images as an input file in order to reduce the delivery of additional dose to patients, which is one of our next studies [33].

Conclusions

Prostate SIB-IMRT treatment plans are sensitive to small shifts in patient position. 3D shifts based on KV-CBCT are enough to reduce prostate PTV coverage. In each direction, vector shifts are found to lie within our institutional margin from CTV and consequently PTV provides adequate coverage of CTV. While setup errors have deleterious clinical consequences on target coverage as estimated by dosimetric indices, OAR doses show no significant differences after inclusion of setup errors. KV-CBCT provides comprehensive means for the determination and correction of 3D setup errors. Isocenter verification and correction of daily setup errors are essential for achieving the approved treatment plan. Uncorrected isocenter will probably lead to under dose to prostate volume, thus decreasing local tumor control.

Abbreviations

SI: Supero-inferior; XVI: X-ray Volume Imaging; EUD: Equivalent Uniform Dose; CMS: Computerized Medical Systems; DVH: Dose Volume Histogram; EPI: Electronic Portal Image.

Author Contributions

All authors contributed equally to this study and gave their final approval.

Competing Interests

The authors have declared that no competing interest exists.

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