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Evaluation of set-up errors and estimation of set-up margin during external beam radiation therapy of prostate cancer using electronic portal imaging device (EPID)

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Original Article

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Abstract

Aim: In radiation therapy, accurate dose distribution in target volume requires accurate treatment setup. The set-up errors are unwanted and inherent in the treatment process. By achieving these errors, a set-up margin (SM) of clinical target volume (CTV) to planning target volume (PTV) can be determined. In the current study, systematic and random set-up errors that occurred during prostate cancer radiotherapy were measured by an electronic portal imaging device (EPID). The obtained values were used to propose the optimum CTV-to-PTV margin in prostate cancer radiotherapy.

Materials and methods: A total of 21 patients with prostate cancer treated with external beam radiation therapy (EBRT) participated in this study. A total of 280 portal images were acquired during 12 months. Gross, population systematic (Σ) and random (σ) errors were obtained based on the portal images in Anterior–Posterior (AP), Medio-Lateral (ML) and Superior–Inferior (SI) directions. The SM of CTV to PTV were then calculated and compared by using the formulas presented by the International Commission on Radiation Units and Measurements (ICRU) 62, Stroom and Heijmen and Van Herk et al.

Results: The findings showed that the population systematic errors during prostate cancer radiotherapy in AP, ML and SI directions were 1·40, 1·95 and 1·94 mm, respectively. The population random errors in AP, ML and SI directions were 2·09, 1·85 and 2·29 mm, respectively. The SM of CTV to PTV calculated in accordance with the formula of ICRU 62 in AP, ML and SI directions were 2·51, 2·68 and 3·00 mm, respectively. And according to Stroom and Heijmen, formula were 4·23, 5·19 and 5·48 mm, respectively. And Van Herk et al. formula were 4·96, 6·17 and 6·45 mm, respectively.

Findings: The SM of CTV to PTV in all directions, based on the formulas of ICRU 62, Stroom and Heijmen and van Herk et al., were equal to 2·73, 4·98 and 5·86 mm, respectively; these values were obtained by averaging the margins in all directions.

Introduction

Prostate cancer, after lung cancer, is considered as the second most common cancer among men worldwide.[1] There are several therapeutic modalities for this malignancy including radical prostatectomy, radiotherapy and hormonal therapy.[2–4] It has been proven that different therapeutic techniques of external beam radiotherapy (EBRT) can be applied as a standard modality for prostate cancer treatment.[5,6] The main goal of three-dimensional conformal radiation therapy (3DCRT), as an EBRT technique, is to deliver conformal dose distribution to the target volume while minimising radiation dose to surrounding normal tissues.[7]

Accurate dose distribution in target volume requires accurate treatment setup.[8] The set-up errors are unwanted and inherent in the treatment process. The set-up errors are defined as the difference between the actual and planned position of radiation fields delivered to the patient.[9] Deviations from planned radiation geometry during radiotherapeutic treatment could be considered as a gross and/or random and/or systematic error.[10,11] The gross error is a major unacceptable error in the patient's setup such as incorrect patient, field size, shape or orientation. In this case, there is the possibility of underdose to part of the clinical target volume (CTV) and/or an overdose in the surrounding normal tissues[10]; hence, these errors must be corrected before the start of the treatment course. The systematic error has a constant direction and magnitude in all fractions of a treatment course, which could be referred to one patient or to the treatment population. These errors could occur at the start of the treatment session or during the treatment course. The mechanical inaccuracies in medical devices can lead to the systematic errors such as inaccurate setting of the external laser

system, variations in machine efficiency, performance problems in the collimator system. The random error can have different directions and magnitudes in each treatment session and these errors could refer to the individual patient or to the treatment population. The random errors can be due to changes in the shape of target, the patient position and block shields between the treatment sessions and/or during delivery of the radiation dose in a treatment session.[10,12] Stroom and Heijmen[11] discussed the importance of the correct distinction between systematic and random errors.

The International Commission on Radiation Units and Measurements (ICRU) in Reports 50 and 62[13] has proposed the establishment of a set-up margin (SM) to account for uncertainties in the patient positioning and beam alignments in the entire course of treatment. The SM is a function of the set-up errors and discounts the uncertainties in the variation of patient positioning, mechanical uncertainties of the equipment, human factor, etc., as well as it increases the chance of the prescription dose being delivered to the intended volume. The CTV-to-planning target volume (PTV) margin depends on various factors such as set-up errors in the patient's treatment session. In addition, Stroom and Heijmen[11] and Van Herk et al.[14] have proposed formulas for the determination of CTV-to-PTV margin.

The set-up errors can be detected during the verification process. Appropriate evaluation of the patient's setup includes comparing the portal image acquired in the treatment room with the reference image. The data of reference images can be extracted from radiographic films, digitally reconstructed radiographs (DRRs), simulator images, ultrasound or 3D patient models (such as CT scan data). The portal images can be taken in the treatment room. In recent years, electronic portal imaging devices (EPIDs) have been widely used in the clinic to detect and manage geometric errors in the radiotherapeutic treatment.[15]

In prostate cancer radiotherapy, a large area of the pelvis is irradiated; therefore, preservation of radio-sensitive organs around the treatment area such as rectum and bladder are essential.[16] The accurate setup of patients can result to deliver the prescribed dose to the target volume and the lowest possible dose to the surrounding normal tissues. Considering the importance of the subject, we investigated the gross, systematic and random set-up errors during the prostate cancer patients.

It is noteworthy that the estimation of set-up errors for each certain tumoural region undergone radiotherapy is necessary for each radiotherapy centre; hence, our aim in this study is to estimate the gross (if any), random and systematic errors occurring during the setup of prostate cancer patients treated in our center at three directions X [Medio-Lateral (ML)], Y [Superior–Inferior (SI)], Z [Anterior–Posterior-(AP)] using EPID, and to propose the optimum CTV-to-PTV margin in prostate cancer patients.

Materials and Methods

A total of 21 patients with prostate cancer referred to Radiotherapy Center, Yazd, Iran was included in this study. All the patients were treated as whole pelvic radiotherapy (WPRT) technique to treat prostate gland, seminal vesicle and pelvic lymph nodes. Patients were randomly selected and there were no restrictions on their selection. Exclusion criteria were set-up error, which is more than the action level on set-up day. The action level determined as displacement greater than 10 mm.

Simulation process

The patients were simulated with a dual-slice GE CT scan (GE Healthcare, USA) located in the radiotherapy centre. All patients were simulated with constant tube potential (130 kVp), mean (standard deviation) tube current time 150 (30) mAs, slice thickness 5 mm and pitch of 1·5. Before conducting the simulations, the patients were asked to completely discharge the rectum and bladder, and drink two glasses of water (at least 10 minutes before the simulation). This process helps to keep the volume of rectum and bladder similar each day and improves treatment reproducibility. All patients were on a flat table with knee support, in supine position under CT scan and treatment, with arms on the chest. In order to comply with the principles of radiation protection and the principle of *As Low As Reasonably Achievable*(ALARA),[17] CT scan borders were limited to the intended treatment area.

Treatment planning process and therapeutic regimen of patients

All of the patients were planned with Prowess version 5·2 (Prowess Inc., Concord, CA, USA) treatment planning system (TPS) with gantry angles of 0° (AP), 180° [posterior-anterior (PA)], 270° [right lateral (RLAT)] and 90° [left lateral (LLAT)]. Conventional WPRT borders include **AP-PA fields**; Inferior border: often 1 cm below the ischial tuberosities, Superior border: bottom of the L5 vertebral, Lateral border: 1·5–2 cm to either side of the lateral bony pelvis; **Lateral fields;** Inferior and Superior borders: same as AP view, Anterior border: anterior of the pubis symphysis, Posterior border: S2–S3 intervertebral space. However, the treatment fields were adjusted according to the physician's contour.

The patients were irradiated in the first phase by 18 MV photon beams from a Siemens Oncor linear accelerator (Linac) (Siemens Medical Systems, Concord, CA, USA) with a total dose of 45 Gy in 25 fractions (1·8 Gy per fraction). The therapeutic region included prostate gland, seminal vesicle and involved lymph nodes, which were contoured by the radiation oncologist. The radiation dose delivery was conducted with 41 multileaf collimator (MLC) pairs.

Portal images

The OPTIVUE 500 EPID installed on the Linac was used to achieve the portal images. The EPID has a 41×41 cm^2 active detector area, spatial resolution of 0·33 lines per millimetre (lp/mm), maximum acquisition rate of 3·5 frames per second (FPS) and a matrix size of 512×512 pixels. The portal images were prepared on the basis of the protocol proposed by the Royal College of Radiologists (RCR).[10] The EPID images were taken before the 1st, 2nd, 3rd, 6th, 11th, 16th and 21st treatment sessions with 2 monitor units (MU). In total, 280 EPID images were acquired during the 12-month study. Portal images were assessed in AP, ML and SI directions.

There are two approaches to analyse images taken from the EPID, online treatment verification and offline mode. In online treatment verification, the reference images are compared with the images taken in the treatment room and the set-up discrepancies correct them before the treatment is delivered. In the offline mode, the corrections are applied on the next treatment day.[18] In this study, due to a large number of patients in the centre, we used the offline method, except on the first day of treatment.

In all the steps mentioned below, the value of the displacement error greater than 10 mm was considered as gross error. In the first fraction, the images were acquired and reviewed online against the reference images. If the errors were more than the gross error, the

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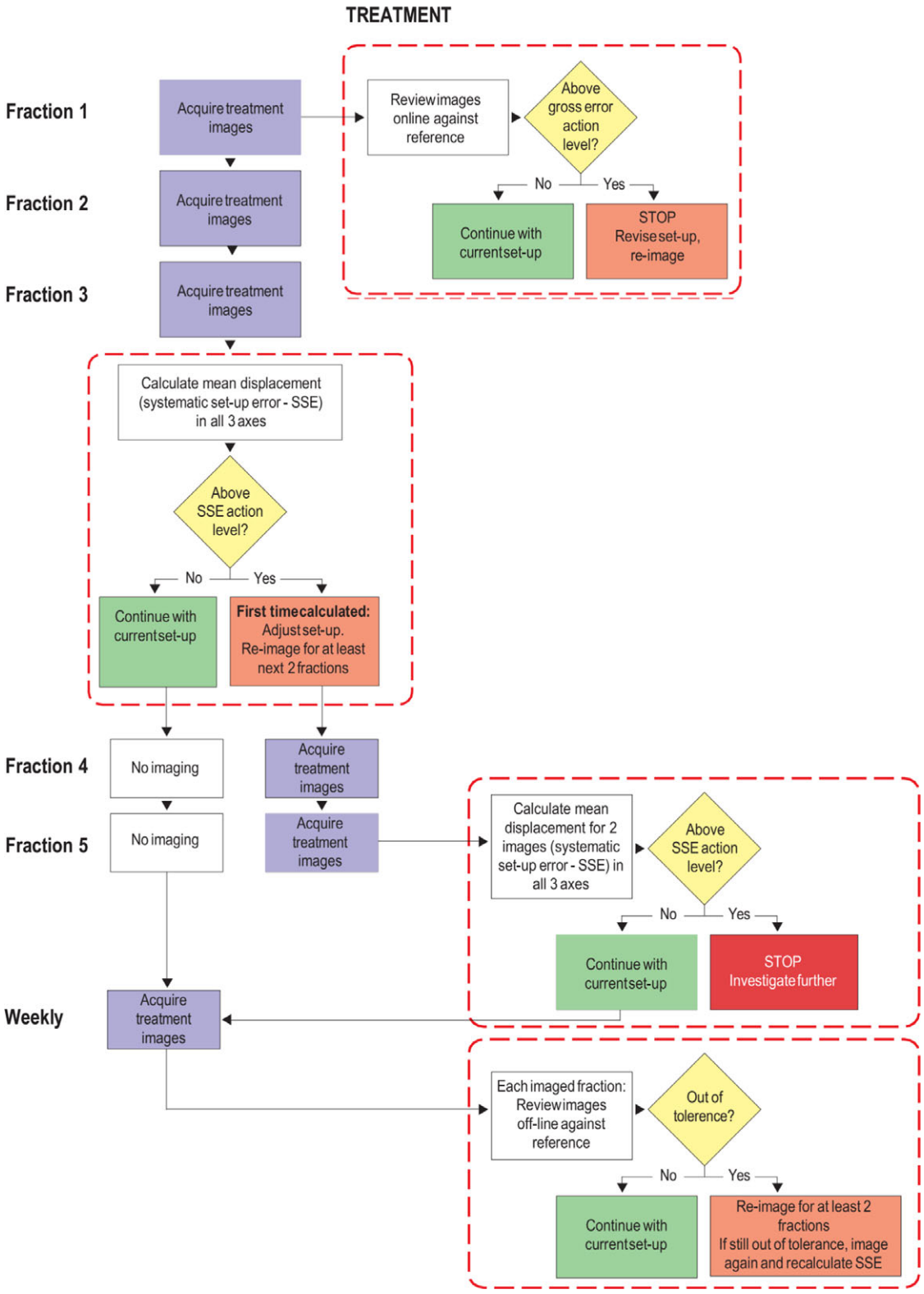

Figure 1. Flowchart of the image verification process. It has reproduced in its entirety with permission.[10]

treatment was stopped, and the patient was omitted from the research process and referred to the medical physics department for re-simulation and replanning procedure, otherwise, the treatment process was continued with the current setup. The acquired portal images in second and third fractions were compared with the reference images. If the set-up errors were more than the gross error, imaging was repeated in the next two fractions, otherwise, the treatment process was continued with the current setup. Then, imaging was repeated weekly with the above criteria. The flowchart of the process is shown in Figure 1.[10]

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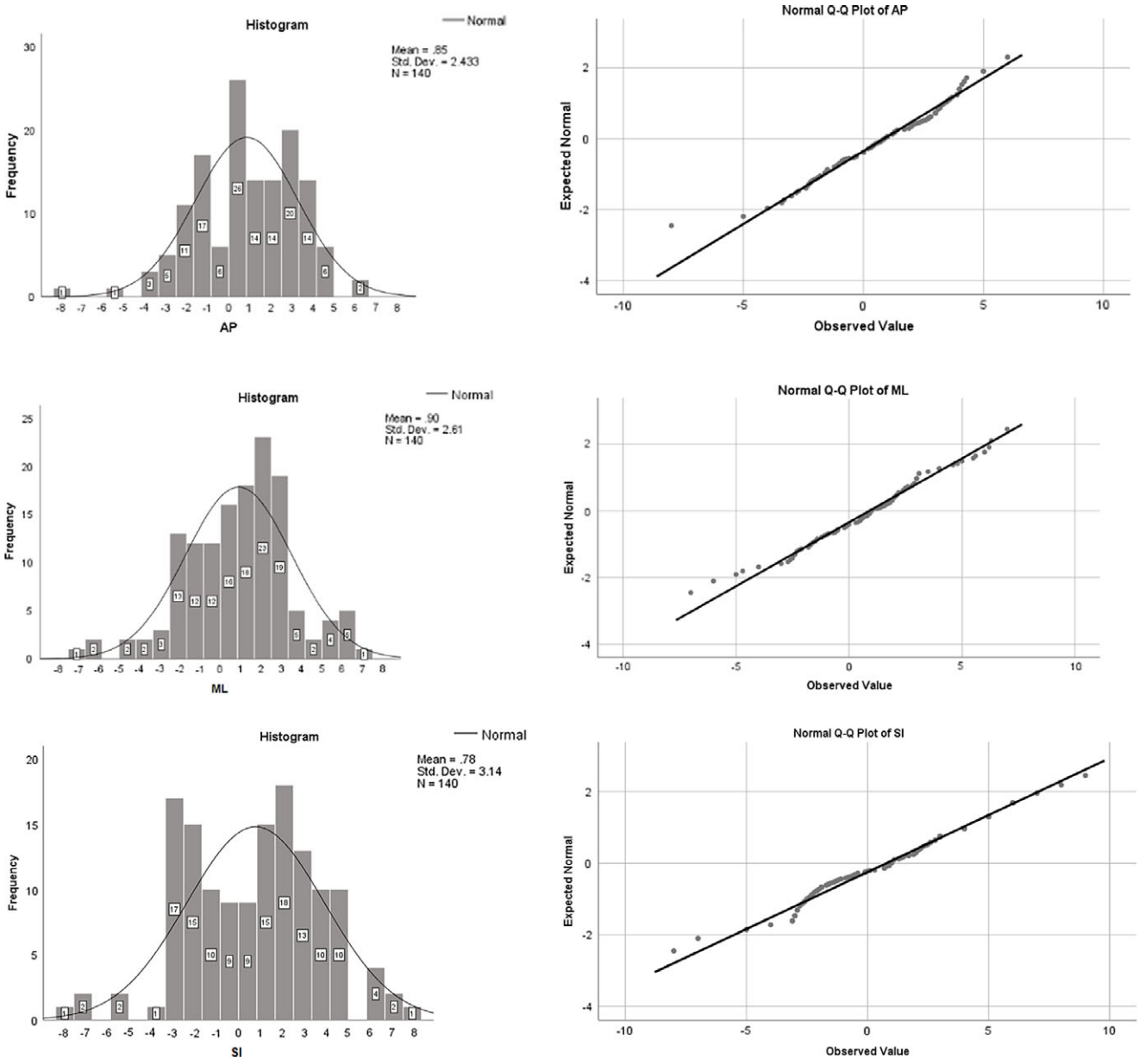

Figure 2. Q–Q plots and histogram of the patient set-up error in each direction.

CTV-to-PTV margin

In the present study, the SMs of CTV to PTV were calculated from mathematic formulas presented by ICRU 62 ($\mathrm{sqrt}\Sigma^2 + \sigma^2$),[13] Stroom and Heijmen ($2\Sigma + 0{\cdot}7\sigma$)[11] and Van Herk et al. ($2{\cdot}5\Sigma + 0{\cdot}7\sigma$).[14] Systematic error for the individual patients is defined as the mean deviation of a patient positioning from the isocentre. The population systematic error ($\Sigma_{\mathrm{systematic}}$) is defined as the distribution of the mean errors of all patients, which are expressed as the standard deviation of the distribution of mean errors for each individual patient. Random error for the individual patient is the standard deviation of the mean of displacement in each treatment fraction. The population random error (σ_{random}) is defined as the mean of the individual random errors.

Statistical Analysis

Normality tests were done using the Shapiro–Wilk test and Q–Q plot. The *p*-value greater than 0·05 assumed as the normal distribution.

Results

The study was performed on 21 patients with prostate cancer for 12 months. Of the 21 patients, 1 patient was excluded from the research process with a set-up error of more than 10 mm in the first session of the treatment process.

All data in AP, ML and SI directions were normal distributions. Figure 2 indicates Q–Q plots and histogram of the patient set-up error in each direction.

The highest and lowest displacement values along the AP direction were 7 and 0 mm, respectively, (ranged from −7 to +7 mm) as well as the average displacement along this axis was 0·9 mm. The highest and lowest displacement values along the ML direction were 9 and 0 mm, respectively, (ranged from −8 to 9 mm) as well as the average displacement in the direction of this axis was 0·8 mm. The highest and lowest displacement values along the SI direction were −8 and 0 mm, respectively, (ranged from −8 to 6 mm) as well as the average displacement along this axis was 0·9 mm. Figures 3a, b, and c and 4a, b, and c show

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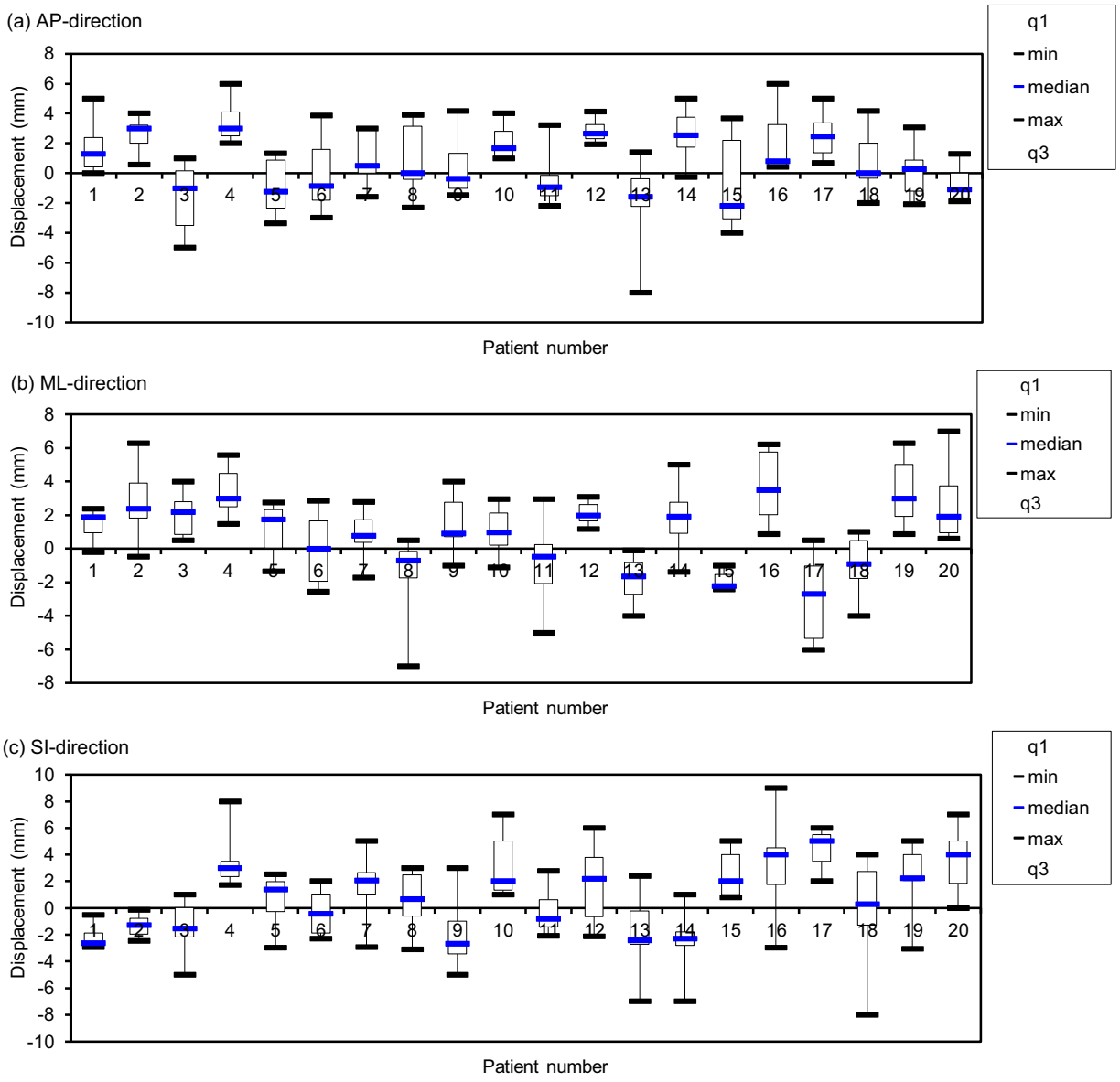

Figure 3. The distribution of the prostate set-up displacement at (a) AP direction, (b) ML direction and (c) SI direction for each individual patient. Midlines indicate median values. The q1 and q3 indicate the first and third quartiles, respectively.

the distribution of displacement values in all three directions for each patient (AP, ML and SI directions).

The population systematic errors (Σ) obtained in the AP, ML and SI directions were 1·40, 1·95, 1·94 and mm, respectively. The population random errors (σ) calculated in the AP, ML and SI directions were 2·09, 1·85 and 2·29 mm, respectively.

As shown in Table 1, the SMs of CTV to PTV resulted from ICRU 62 recommendation[13] in AP, ML and SI directions were 2·51, 2·68 and 3·00 mm, respectively. Moreover, according to the formula presented by Stroom and Heijmen,[11] the corresponding values of SMs were 4·26, 5·19 and 5·48, mm, as well as the SMs, obtained from the formula presented by Van Herk et al.[14] were 4·96, 6·17, 6·45 mm.

Discussion

Each radiotherapy centre using complex treatment techniques requires to assess the patient set-up errors for each specific tumour site. The SMs can be calculated by the formulas presented in the literature; in this regard, obtaining the random and systematic set-up errors is necessary. In the present study, the magnitude of the systematic and random set-up errors in prostate cancer patients treated with 3DCRT was estimated by EPID. The SMs of CTV to PTV were calculated for these patients in the AP, ML and SI directions.

The importance of the correct distinction between the systematic and random set-up errors has been proven. It was reported that the effect of systematic set-up errors is almost three times more important than the random set-up errors. Our results (Figure 3) indicated that along the *ML* direction, 80% and 95% of the displacements from the isocentre had the values less than 3 mm and less than 5 mm, respectively. For the *SI direction*, 78 and 90% of the displacements had values less than 3 mm and less than 5 mm, respectively. For the *Ap direction*, 76 and 98% of the displacements had values less than 3 mm and less than 5 mm, respectively (Figure 3).

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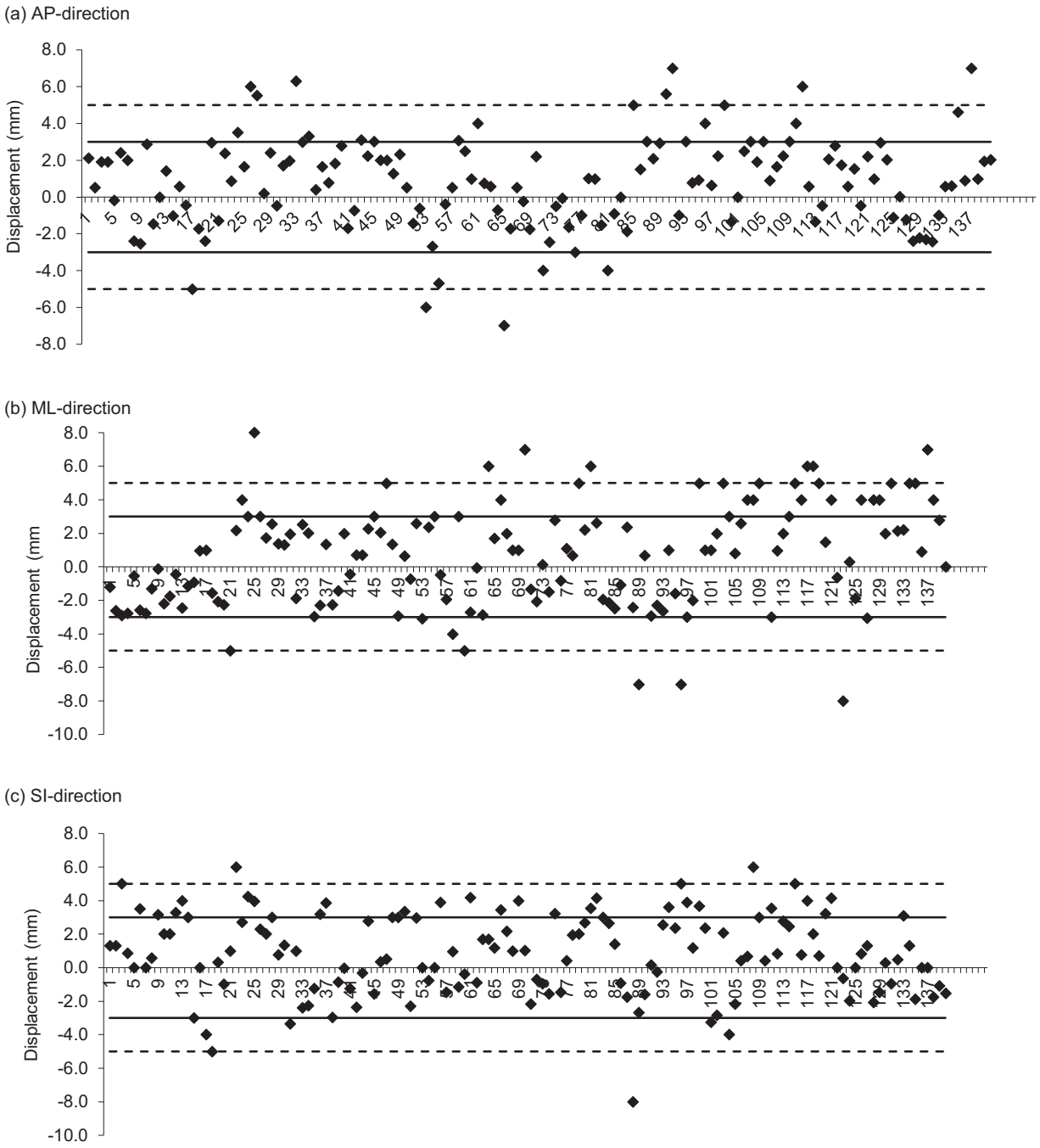

Figure 4. Distribution of displacements from the isocentre for 20 prostate patients. (a) AP direction, (b) ML direction and (c) SI direction. The dashed lines indicate ± 5 mm. The solid lines indicate ± 3 mm.

Krageli[19] investigated the set-up error and its effect on margin and radiation field size in prostate cancer EBRT. He reported the random errors of 5·1, 4·1 and 4·9 mm for lateral, craniocaudal and anteroposterior axis, respectively, as their reported values were more than those obtained in our study (2·09 mm (*AP* direction), 1·85 mm (*ML* direction) and 2·29 mm (*SI* direction)). However, the systematic errors calculated in our study for AP, ML and SI directions (1·40, 1·95 and 1·94 mm, respectively) were higher than those reported by Kragelj[19] (0·57, 0·17 and 0·87 mm, respectively). In another study, Rudat[20] reported the random set-up errors of 3·1, 5·4 and 4·9 mm along the lateral, craniocaudal and anteroposterior, respectively, which were more than those calculated in our study.

Knowing the magnitude of the SM in the cancer radiotherapy is important, because there are healthy organs surrounding the target volume that should be preserved. Hence, the SMs should be optimised to prevent the irradiation of normal tissues and better coverage of target volume. Various mathematical equations have been proposed to estimate the SM of CTV to PTV. In the current study, the CTV-to-PTV margins for prostate cancer patients treated with 3DCRT were estimated with three formulas proposed by the ICRU 62,[13] Stroom and Heijmen[11] and van Herk et al.[14] The SMs in all

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Table 1. Population systematic errors (Σ), random errors (σ) and SMs of CTV to PTV (mm)

	Population systematics and random errors (mm)		CTV-to-PTV margins (mm)		
Direction	Systematic error (Σ)	Random error (σ)	ICRU 62	Stroom and Heijmen	Van Herk
Anterior–Posterior (AP)	1·40	2·09	2·51	4·26	4·96
Medio-Lateral (ML)	1·95	1·85	2·68	5·19	6·17
Superior–Inferior (SI)	1·94	2·29	3·00	5·48	6·45

Table 2. Population systematic (Σ) and random (σ) set-up errors occurred during cancer radiotherapy and SMs of CTV to PTV (mm) reported by some researchers

Study	Σ (mm)	σ (mm)	SM (mm)	
Suzuki et al.[21]	0·7–1·3	0·7–1·6	5 mm margin for PTV and 3 mm for PRV	
Gupta et al.[9]	0·96–1·2	1·94–2·48	<5 mm CTV–PTV margin in all directions	
Strbac and Jokic[22]	1·77–1·86	1·77–1·86	<6·1 mm CTV–PTV left–right directions,	
			<5·1 mm CTV–PTV caudocranial direction,	
			<4·8 mm CTV–PTV dorsoventral direction.	
Vejdani Noghreiyan et al.[23]	2·36–4·99	1·51–2·74	<5·78 mm CTV–PTV left–right directions,	
			<9·34 mm CTV–PTV caudocranial direction,	
			<6·59 mm CTV–PTV dorsoventral direction.	
Present study	1·40–1·95	1·85–2·29	ICRP 62 formula	Anterior–Posterior (AP) 2·51 mm
				Medio-Lateral (ML) 2·68 mm
				Superior–Inferior (SI) 3·00 mm
			Stroom and Heijmen formula	Anterior–Posterior (AP) 4·26 mm
				Medio-Lateral (ML) 5·19 mm
				Superior–Inferior (SI) 5·48 mm
			Van Herk et al. formula	Anterior–Posterior (AP) 4·96 mm
				Medio-Lateral (ML) 6·17 mm
				Superior–Inferior (SI) 6·45 mm

directions, in accordance with the above-mentioned formulas, was equal to 2·73, 4·98 and 5·86 mm, respectively; these values were obtained by averaging the margins in three directions. Therefore, in our centre, these SMs should be added to the CTV for full coverage of the target volume. Table 2 compares our findings related to the population systematic errors, random errors and displacements with other studies.

Conclusion

In this study, systematic and random set-up errors that occurred during prostate cancer radiotherapy were measured by EPID. Furthermore, the SMs of CTV to PTV were calculated.

The results demonstrated that the population systematic errors in AP, ML, SI directions were 1·40, 1·95 and 1·94 mm, respectively, and the corresponding values for random set-up errors were 2·09, 1·85 and 2·29 mm. Furthermore, the SMs of CTV to PTV in all directions, in accordance with the formulas of ICRU 62,[13] Stroom and Heijmen[11] and van Herk et al.,[14] were equal to 2·73 and 4·98, and 5·86 mm, respectively. These values were obtained by averaging the margins in all directions. Prior to this, we used 10 mm as CTV-to-PTV margin in all directions except posteriorly, where it was 5 mm (to reduce the rectal dose), as recommended by Khan et al.[24] The authors are intending to investigate and compare different treatment plans with different SM values to find the optimal SM for prostate patients, in terms of coverage of target volume and dose of organs at risk (OARs).

Further investigations can be performed to determine the systematic and random errors as well as the determination of CTV-to-PTV margins for other tumoural areas undergone radiotherapy. Also, investigation of the causes of the set-up errors and an attempt to eliminate or mitigate these errors can be considered as a future study.

Limitation

Due to a large number of patients in the centre, it was not possible and feasible to take corrective actions on the day of treatment when observing a set-up error (except on the first day of treatment).

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Author contributions. Daryoush Khoramian designed and directed the project; Daryoush Khoramian, Soroush Sistani and Bagher Farhood performed the measurements and manuscript preparation.

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Conflicts of Interest. The authors declare that they have no conflicts of interest.

Ethical standard. The project was part of the radiotherapy quality assurance (QA) program.

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