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ORIGINAL ARTICLE

Optimal Clinical Target Volume to Planning Target Volume Physical Margins for Prostate Cancer Radiotherapy: Practical Issues Related to Online Correction Based on Onboard Imaging

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ABSTRACT

Clinical target volume to planning target volume (CTV-PTV) margins was determined during prostate radiotherapy using image guided radiation therapy for correcting of setup errors. Three gold markers were implanted into the prostate glands of 10 patients. An online system of an electronic portal imaging device provided real time displacement analysis in 3-dimensional systems between the planned and actual daily positions of the seeds. Descriptive statistics (mean and standard deviation) were used to describe the inter-fractional motion results. The total displacement of the population in the left-right, superior-inferior, and anterior-posterior directions were 1.75, 2.07, and 2.71 mm for systematic errors and 5.67, 6.15, and 6.05 mm for random errors before correction and 0.67, 1.21, 1.35 mm and 2.37, 3.00, 3.02 mm after correction, respectively. The average CTV-PTV margins in these directions were 8.3, 9.5, and 11.0 mm before correction and 3.3, 5.1, and 5.5 mm after correction, respectively. The average treatment duration increased by 5 min compared to the matched control group. Using EPID and implanted fiducial marker is an effective way to reduce CTV-PTV margins.

Keywords; *Gold Markers, Image Guided Radiation Therapy, Online Corrections, Prostate Cancer, Setup Errors*

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INTRODUCTION

Radiotherapy plays a major role in the treatment of localized prostate cancer, and there is evidence that higher doses of radiation can increase biochemical control rates, especially for patients in intermediate and high-risk groups [1, 2]. Safely increasing the radiation dose administered to the prostate gland is limited by the radiation toxicity effects on the healthy tissue, particularly the rectum [3].

In radiation therapy, it is necessary to ascertain that the tumour volume is treated as planned and a correct radiation dose has been delivered to the target tissue. Therefore, maintaining the suitable target coverage while minimizing normal tissue toxicity is a challenge, this significantly influences selecting clinical target volume to planning target volume (CTV-PTV) margins.

Setup errors and CTV-PTV geometric margins are interrelated. However, despite systematic errors from various sources, a safe CTV-PTV margin is needed for ensuring adequate dose coverage. The CTV-PTV margin may be altered depending on the number of contributing errors that can be detected and corrected during a treatment course [4]. For instance, these key issues can be addressed by using image-guided technology and implanted fiducial gold markers.

In the present study, we determined the optimal CTV-PTV margin size with a focus on patient setup errors and organ motions, for prostate cancer patients using image guided radiation therapy (IGRT) in our radiation therapy department. In general, there may be some differences in the amount of CTV-PTV margins base on their errors between centres, but determining a safe margin is essential with high priority for implementing any form of conformal radiotherapy [5].

This work was performed for the first time by using an electronic portal imaging device (EPID) and implanted gold markers in our country (Iran). Recently, we are progressing from 2-dimensional (2D) to 3-dimensional (3D) treatment planning and started intensity modulated radiation therapy (IMRT). We successfully implemented an IGRT system for localizing the position of the prostate gland during 3D conformal radiotherapy and IMRT [6].

In this study, we used the online correction method for precisely evaluating a treatment in the presence of geometric errors with a known probability distribution. This method explicitly accounts for systematic and random errors in determining the CTV-PTV margin. All of the analysis was performed on realistic treatment plans.

MATERIALS AND METHODS

Patient Preparation

Ten patients with localized prostate carcinoma (T1c-T3bN0M0) provided written informed consent to participate in a prospective study that was approved by Iran Medical University Research Ethics Committee. Ten sets of three gold seeds which provided for implanting within the prostate glands as fiducial markers manufactured by CIVCo and Alpha-Omega Services Inc. (US Companies). The age of the patients ranged from 57 to 80 years (mean, 71.6 years), initial prostate-speci c antigen level of 5.9–16.4 ng/mL (mean, 11.3 ng/mL), and Gleason scores of 6–8. All patients received neoadjuvant hormonal therapy.

Three gold ducial markers were inserted by an interventional radiologist under local anaesthetic. The aim was to implant two seeds at the base, and one at the apex of the prostate. The duration of seed implantation by the radiologist was about 20 min from the time patients entered the implantation room to when they exited the room. The patients tolerated the procedure well with no recorded complications. A 7-day-long course of oral Cipro oxacin antibiotic and Metronidazole were also prescribed.

Treatment Planning Procedure

Computed Tomography (CT) planning was performed 5–7 days after the gold seed insertion to allow any periprostatic edema to settle. The patients were asked to comply with the department standard protocol of having a comfortably full bladder for simulation before each treatment. For bowel preparation, the patients were instructed to have a light dinner the night before simulation and also during each treatment, as mentioned in the protocol; if possible, they were encouraged to empty their bowels. Patients were positioned supine without any fixation devices on the simulation CT couch; skin tattoos over bony landmarks were used as the external reference points for aligning the treatment elds. Axial images were obtained using a 16-slice helical CT scanner with 5-mm slice thickness and 2-mm reconstruction protocol from the midpoint of the sacroiliac joints to 2 cm inferior of the pubic rami. The prostate as the clinical target volume and bladder and rectum (ischial tuberosities to the rectosigmoid exure) were outlined on each axial image by using the TIGRT LinaTech Treatment Planning System (TPS)(Sunnyvale; USA).

A 5-field IMRT technique with 15˚, 55˚, 110˚, 260˚, and 330˚ was used for prostate treatment planning. The plan was prepared in accordance with International Commission on Radiation Units and Measurements (ICRU) 50 guidance (planning target volume to receive 95–107% dose). The monitor units from the daily pre-treatment localization portal images were included as components of the delivered dose. Digitally reconstructed radiographs (DRRs) of each eld were generated. Nine patients were treated with doses of 80 Gy in 40 fractions and one patient received 78 Gy in 39 fractions by using a 2-phase technique (first phase 28 fractions with 200 cGy per fractions to treat prostate and seminal vesicle and second phase 11-12 fractions for treating prostate only or prostate plus 1cm of seminal vesicle depending to the clinical staging as a subsequent boost) (7) with CTV-PTV margins of 1 cm on each side, except 0.7 cm posterior.

Plans were produced for treatment on Primus Series Oncology Systems [Siemens Company (Berlin; Germany)] linear accelerators at beam energy of 15 MV. Field shaping was achieved in all cases using external multi-leaf collimators with a leaf width of 0.5–1 cm at the isocenter from the centre to the edge of the field.

A commercially available software system [Theraview classic 5.1, Cablon Medical B.V. (Leusden; Netherland)] was used in combination with implanted ducial markers within the prostate gland and

standard portal imaging equipment. This software system quanti es the differences between the planned and actual daily positions of the intraprostatic markers (centre to centre of the related marker automatically), reporting the couch translational movements required for realigning the patient.
In each fraction, portal images at two nearly orthogonal angles (with 5 monitor units each) were acquired using a camera-based portal imaging system. The DRRs of the planned eld positions were used for assisting the identi cation of the relative gold marker positions on the portal images. The markers were visualized using the Theraview portal imaging software and its marker enhancement option.
The software program reconstructed the 3D positions of the gold markers from different beam's eye views (BEVs). The discrepancies of the markers positions (prostate surrogate) between the plans and daily images were calculated (from centre of the makers in DRRs to centre of related markers in EPIs) and corrected 3-dimensionally for each fraction. Displacement data were automatically recorded within the Theraview software and the action level was 3 mm (8). The DRR and portal images, as well as gold markers at 15˚ BEV, are shown in Figure 1.

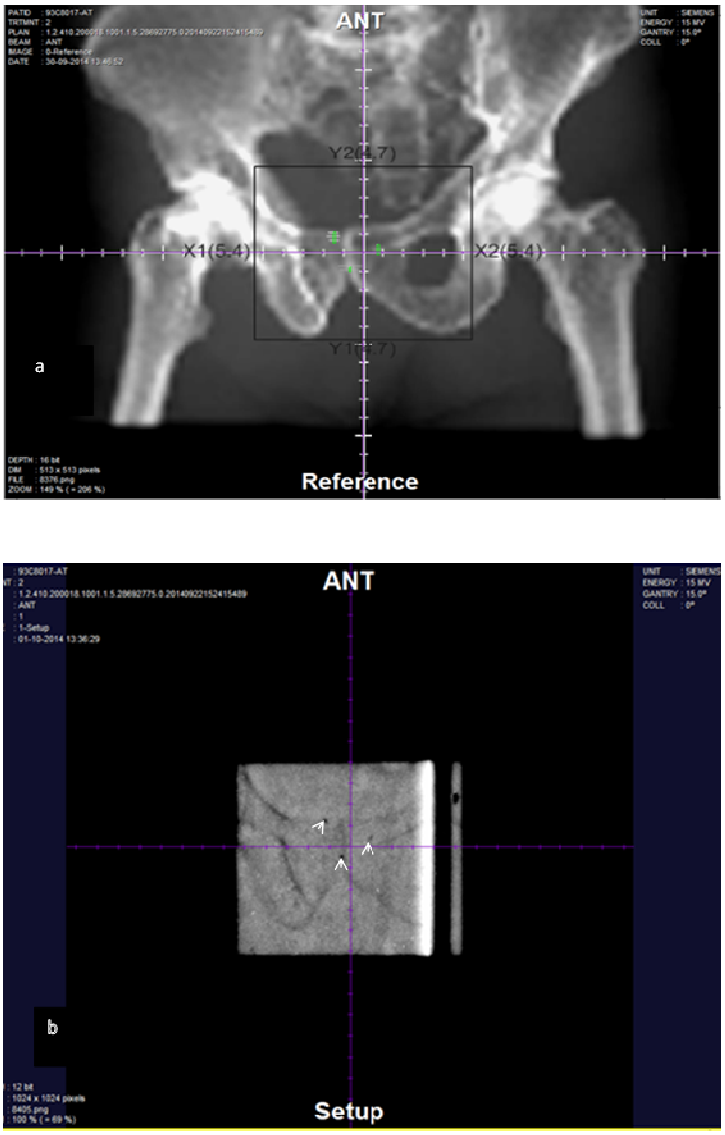

Figure 1: (a) The digitally reconstructed radiographic image (reference) of prostate with implanted fiducial gold markers (green shade) and (b) the portal image of the same beam's eye view at 15˚ (arrow heads indicate the gold markers in the portal image)

RESULTS

Data from 10 patients and 315 fractions of radiotherapy (average of 63 measurements for each patient in two sessions [i.e., before and after setup corrections]) were analysed in this study.

Descriptive statistics [mean and standard deviation (SD)] were used for describing the inter-fractional motion observed in individual patients. The population systematic error for setup and organ motion for the group of patients was calculated as the SD of the distribution of average setup displacements per patient. The random error for setup and organ motion was calculated as the average of the individual variances (4).

The variations of a typical patient's setup errors in the left-right (LR), anterior-posterior (AP), and superior- inferior (SI) directions for 35 fractions before and after correction are shown in Figure 2.

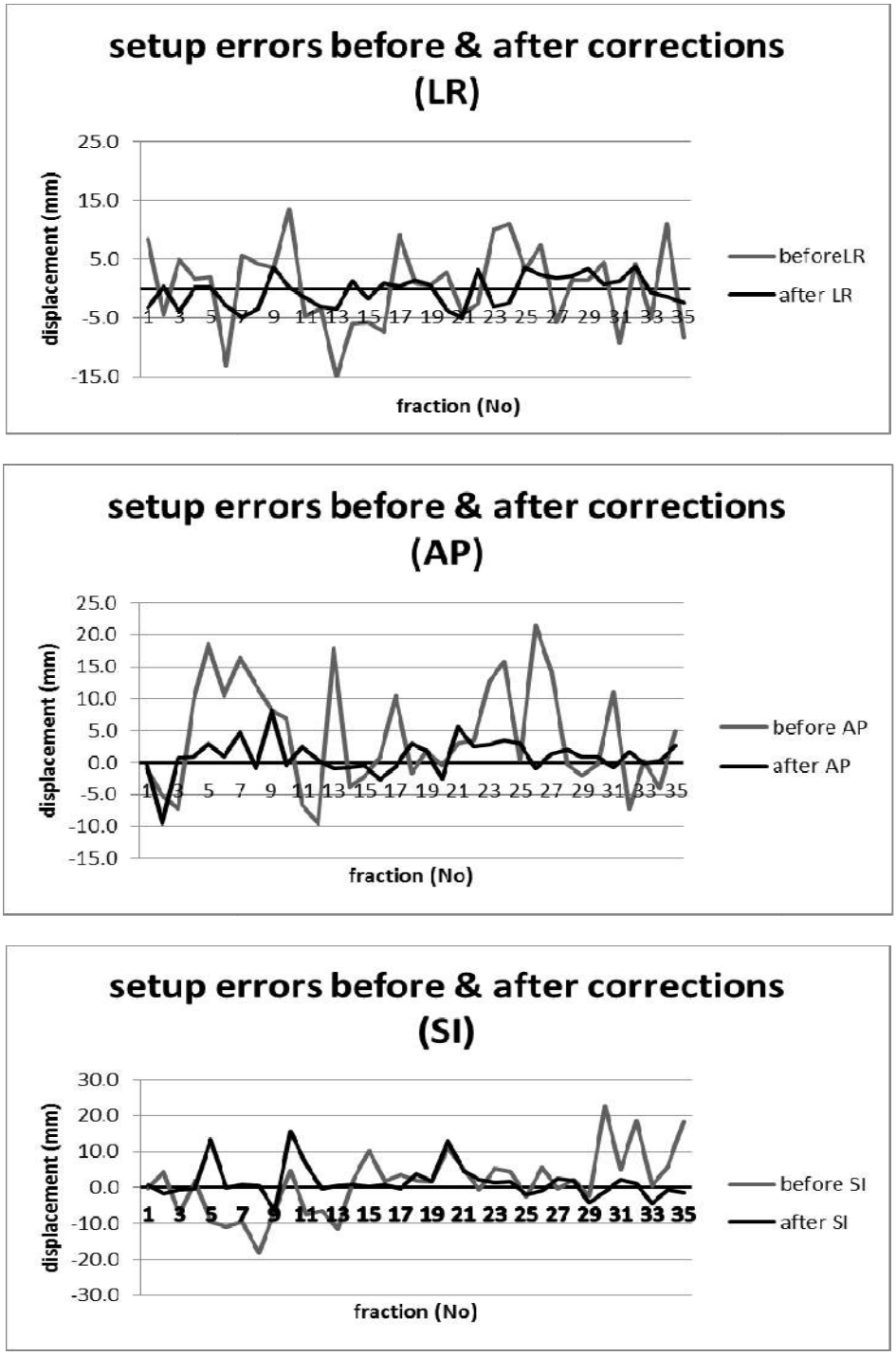

Figure 2: Setup variations of a typical patient during 35 fractions in the (a) left-right (LR), (b) anterior posterior (AP), and (c) superior-inferior (SI) directions before and after correction

An overview of prostate treatment uncertainties (mean and SD) obtained in this study for each patient (before correction) is shown in Table 1.

Table 1: Overview of prostate treatment uncertainties (mean and standard deviation) for each patient in this study obtained at the Pars Hospital Cancer Institute (before correction)

patient	Systematic errors (mm)			Random errors (mm)		
	LR*	AP†	SI‡	LR*	AP†	SI‡
1	0.51	4.26	1.24	6.94	8.34	8.63
2	-1.46	-1.17	2.44	5.18	6.63	7.66
3	-2.44	-3.22	1.67	3.55	4.81	4.25
4	-1.25	2.11	3.45	4.38	5.87	7.02
5	-0.59	-1.06	1.85	5.35	4.97	4.77
6	0.05	0.51	0.98	4.84	5.84	5.45
7	3.94	-5.46	7.73	5.76	7.38	8.82
8	0.74	0.16	3.29	4.99	3.96	5.53
9	-0.88	0.32	0.37	6.70	4.63	3.27
10	-1.11	-1.89	2.94	8.97	8.07	6.12

*LR, left-right; † AP, anterior-posterior; ‡ SI, superior-inferior

Average population displacements for both systematic and random errors before and after correction are listed in Table 2.

Table 2: Overall population means, systematic (Σ_{pop}) and random (σ_{pop}) errors in each direction before and after correction

	Σ_{pop} setup/motion (mm)			σ_{pop} setup/motion (mm)			Mean systematic errors		
	LR	AP	SI	LR	AP	SI	LR	AP	SI
Before correction	1.75	2.71	2.07	5.67	6.05	6.15	0.24	-0.54	2.60
After correction	0.67	1.35	1.21	2.37	3.02	3.00	0.01	-0.30	0.63

*LR, left-right; † AP, anterior-posterior; ‡ SI, superior-inferior

Based on the above data, the average values for CTV-PTV margins in the three directions (i.e., LR, AP and SI) were 8.3, 11.0, and 9.5 mm before online correction and 3.3, 5.5, and 5.1 mm after correction, respectively, according to the formula $2.5\Sigma + 0.7\sigma$ (Σ and σ represents the systematic and random errors, respectively) (9).

The range of CTV-PTV margin alterations in the study population along each of the three directions (i.e., LR, AP, and SI) is shown in Table 3. The mean range of CTV-PTV margin alterations in the LR, AP, and SI directions were -11.75–15.21, -11.45–14.08, and -9.99–15.65 before correction and -4.32–4.44, -7.30–5.81, and -5.66–4.49 after correction, respectively (negative values indicate posterior, inferior or left displacement). The broad range of displacement in the AP direction after correction could be anticipated due to rectal movement by feces or gas, which displaces the prostate gland (10-11).

Table 3: The range of clinical target volume to planning target volume margin alterations in the study population along each of the left-right (LR), anterior-posterior (AP), and superior-inferior (SI) directions

Mean	LR (mm)		AP (mm)		SI (mm)	
Before correction	-11.75	15.21	-11.45	14.08	-9.99	15.65
After correction	-4.32	4.44	-7.3	5.81	-5.66	4.49

The treatment duration for these patients with online setup correction, compared with the matched treatment, was increased by 5 min.

DISCUSSION

Prostate IGRT is one of the well-documented techniques (the research published in North America, Belgium, and Netherlands) of both inter-fractional motion and setup variations that can occur during prostate cancer radiotherapy. These variations can be detected using IGRT [12–14]. In this research, the EPID and implanted fiducial gold markers were used for measuring prostate displacement in three directions (i.e., LR, AP, and SI).

We observed a translational motion, mainly in the AP, SI direction, of the prostate and seminal vesicles with mean of -0.54 ± 2.71 mm and 2.6 ± 2.07 mm, respectively. Zelefsky et al, [15] showed the mean

displacement of -1.2 ± 2:9 mm and -0.5 ± 3.3 in the AP and SI directions respectively in their study which is very similar to our finding. These results were also compatible with the ndings of other researchers [16–19]. In addition to errors that vary from patient to patient or from fraction to fraction, movements can also occur within a single fraction. In particular, respiratory and peristaltic motions have a time scale that is shorter than the delivery time of a single fraction [18]. A deviation from zero was often observed in the calculated means and SDs of each patient that could be due to imprecision of the equipment (i.e., lasers), procedure [18], and especially involuntary movement in elderly patients.

The systematic errors calculated from the inter-fractional translational data (1.75, 2.07 and 2.71 mm in the LR, SI and AP directions, respectively.) were very near to those reported in previously published study (2.2, 2.9 and 4.8 mm in the LR, SI and AP directions, respectively.), but the random errors were more significant (5.67, 6.15 and 6.05 mm in comparison with 2.2, 2.9 and 3.5 mm in the LR, SI and AP directions, respectively.) obtained from Van der Heide et al, study [20]. The later could be due to the longer time taken to enter the treatment room and correct the couch position, and absence of the immobilization devices. Ideally, the time duration between online verification and treatment should be as short as possible (several minutes) for reducing the variation that may occur because of patient movement during this time. Beyond this, the obtained data may no longer represent the patient's true position during the therapy [4]. The effect of random and systematic errors on the dose is different [8]. Random errors blur the dose distribution, [21] whereas systematic errors shift the cumulative dose distribution relative to the target.

PTV margins obtained from our study in the LR, AP, and SI directions were 8.3, 11.0, and 9.5 mm, respectively, and were in a good agreement with the current standard of a 10-mm isotropic margin in most United Kingdom protocols [22]. If the errors for setup variability (including systematic and random errors) and organ motions were corrected by using an online veri cation protocol, the PTV margins in the LR, AP, and SI directions could be reduced to 3.3, 5.5, and 5.1 mm, respectively. However, although an online correction protocol will minimize these errors, it will not eliminate them, and many other sources of uncertainty remain. The sources of uncertainty include the effect of intra-fractional motion [23, 24], rotational motion [25, 26], which we did not measure in our study, the accuracy of prostate delineation on computed tomography (CT) or magnetic resonance imaging [27], and the detection accuracy of gold markers [3]. If none of these errors are measured, a PTV margin reduction based on inter-fraction translational error could lead to the missing of the CTV, and preventing such situations is the primary goal of IGRT.

There are relatively few reports about the increase in treatment duration and the potential effect on department workload [3]. Chung et al. reported that the treatment duration from the rst image to the last beam increases from 6.1 to 8.7 min, if the radiographers had to re-enter the room to apply corrections [28]. On that study no comparison with the controls was performed. In our study, the treatment duration increased by 5 min from the time of acquiring the first image to re-entering the treatment room and applying the corrections. If this was to be applied to all of our prostate patients, the daily workload would increase by 1 h and 40 min. However, this practice will still be useful compared to the reduction of normal tissue dose, especially in the rectum.

CONCLUSIONS

The implementation of the proposed image-guided system and online setup corrections can reduce CTV-PTV margins, leading to the reduction in the number of normal tissue complications for the same dosage or the same complications for normal tissue with higher tumour control probability. In general, there may be some differences in the amount of CTV-PTV margins base on their errors between centres, but determining a safe margin is essential with high priority for implementing any form of conformal radiotherapy [5]. At present calculation of setup margin on the base of previously mention equation seems enough but considering different biological factors of every patients for doing adaptive individualized radiotherapy are essential.

No additional linear accelerator modi cation was required and standard imaging devices could be used. In spite of the increased treatment duration, the advantage and benefits of the proposed procedure were very valuable.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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