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The Importance of Organ-Specific Setup Uncertainties Assessment for Determination of the Planning Target Volume Margin in Prostate and Cervical Cancer Using Electronic Portal Imaging Device (EPID)

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ABSTRACT

Introduction: The setup uncertainty is a significant issue in radiotherapy that affects the accuracy of the delivered dose to the clinical target volume (CTV). To ensure that the target receives an adequate dose despite setup errors, a setup margin is defined around the CTV to determine the planning target volume (PTV). This study aims to develop a protocol for determining the CTV-to-PTV margin specific to the needs of each radiotherapy department, with a focus on the cervix and prostate.

Material and Methods: A total of 300 portal images from 25 cervical cancer patients and 25 prostate cancer patients were aligned with Digitally Reconstructed Radiographs (DRRs). Population errors, both systematic (Σ) and random (σ), were calculated, and the necessary CTV-to-PTV setup margins in the lateral, longitudinal, and vertical directions were estimated using the formulas recommended by the International Commission on Radiation Units and Measurements (ICRU-62), Stroom, and Van Herk.

Results: The systematic and random errors fell within the ranges of 2.54-2.91 mm and 1.73-2.11 mm for the cervix, and 2.09-2.35 mm and 1.64-2.0 mm for the prostate. The average margins, as per the ICRU 62, Stroom, and Van-Herk formulas, were 3.27, 6.03, and 7.36 mm for the cervix, and 2.87, 2.60, and 6.22 mm for the prostate, respectively

Conclusion: The utilization of calculated margins to delineate the PTV will ensure that the CTV receives an adequate dose. The author recommends organ-specific margins in research, rather than using overall margins, based on the differences between prostate and cervix margins.

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Introduction

The main goal of contemporary conformal radiotherapy is to consistently deliver optimal coverage and dosage to the gross tumor volume (GTV) and planning target volume (PTV) while minimizing radiation of organs at risk (OARs). A crucial aspect in achieving this goal is to ensure accurate, consistent, and reproducible delivery of radiation doses both physically (in terms of dose distribution) and geometrically (in three-dimensional space), to cancer targets [1,2]. The accuracy of delivering doses to cancer targets is constrained by uncertainties in various treatment parameters. Uncertainty is a parameter that characterizes the range of values when a specific measurement is repeatedly performed. These uncertainties at each stage can have an impact on subsequent steps and lead to errors in dose delivery, which refer to discrepancies between the intended dose distribution specified in a treatment plan and the actual dose distribution given to a patient during a course of treatment sessions. The movements of internal organs due to physiological functions and the repositioning of the patient during daily setup are major sources of error. [3-7]. Potential reasons for the setup errors include: 1. Incorrect patient positioning in terms of anatomy and rotation; 2. Incorrect size, shape, and orientation of the treatment field; 3. Incorrect determination of the isocenter [8,9]. Setup errors in all directions are classified into two main

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categories: (1) Systematic errors, which are consistent deviations that recur in the same direction across all treatment sessions. These can result from mechanical issues in medical equipment, such as misalignment of the external laser system, inconsistencies in machine performance, or malfunctions in the collimator system. (2) Random errors, which vary from day to day and differ among patients. These are associated with treatment delivery and may arise from factors such as inaccurate patient positioning, improper placement of shielding blocks, or variations in beam alignment [8–11]. The International Commission on Radiation Units and Measurements (ICRU), in Report 62 [3], recommends applying two types of safety margins from the Clinical Target Volume (CTV) to the PTV to ensure accurate radiation dose delivery to the CTV: (1) Internal Margin (IM) – accounts for internal organ motion caused by physiological activities such as breathing, bladder filling, and rectal changes. When the IM is added to the CTV, the resulting volume is known as the Internal Target Volume (ITV). (2) Setup Margin (SM) – added to the ITV to compensate for uncertainties in patient positioning and beam alignment during both treatment planning and delivery. The combination of ITV and SM defines the PTV. In addition to ICRU recommendations, formulas for calculating the CTV-to-PTV setup margin have been proposed by Stroom and Heijmen [4], as well as Van Herk et al. [5]. Accurately estimating setup errors is crucial for each radiotherapy center to define appropriate margins for specific tumor sites. These errors should be assessed prior to the start of treatment. Setup errors can be identified during verification by comparing treatment portal images—such as those from an Electronic Portal Imaging Device (EPID)—with reference images like Digitally Reconstructed Radiographs (DRRs) [9,12–15].

This study aims to assess both systematic and random setup errors using EPID and DRR methods, and to propose the most suitable organ-specific CTV-to-PTV margins along with acceptable limits for setup inaccuracies in patients with cervical and prostate cancer. Instead of applying a single, region-wide margin—such as one for the entire pelvis where both organs are situated—these margins will be customized for each individual organ. The research is centered on patients receiving Three-Dimensional Conformal Radiotherapy (3D-CRT).

Materials and Methods

Patient selection

This study was approved by the Ethics Committee of Mashhad University of Medical Sciences. (IR.MUMS.MEDICAL.REC.1401.150). The study protocol complies with the Declaration of Helsinki. Fifty patients with pelvic cancer who underwent 3D-CRT at the Imam Reza Hospital's Radiation Oncology Center in Mashhad, Iran, were chosen. Among them, 25 were male and had prostate cancer, while 25 were female and had cervical cancer. The selection of these patients was random and unrestricted. All these patients received treatment with whole pelvic radiotherapy, including treatment for their lymph nodes.

Treatment Simulation

All patients underwent scanning using a 16-slice CT scanner (Neusoft Medical System Co., Shenyang, China) at 120 kVp, with a slice thickness of 5 mm, while lying in the supine position with their arms crossed over their chests. Additionally, three radiopaque markers were placed under laser beam guidance during the CT planning stage. It is important to note that these markers were either tattooed on the patient's body or on the patient's thermoplastic device to ensure stability throughout the entire treatment course.

Treatment Planning

CT images were imported into the Isogray treatment planning system (Dosisoft, Cachan, France), where treatment plans were developed for all patients. The DRRs were created to serve as reference images. An oncologist delineated the target volumes and OARs by contouring. Treatments were delivered using 6, 10, and 15 MV photon beams from an Elekta Precise linear accelerator (Stockholm, Sweden), which featured an amorphous silicon (a-Si) EPID and multi-leaf collimators (MLCs) with 40 leaves on each side. The prescribed dose to the PTV was 50.4 Gy, administered in 28 fractions of 1.8 Gy each, using gantry angles of 0°,90°, 180°, and 270°.

Treatment Verification

Before each treatment session, patients were positioned using their immobilization devices, and tattoo markers were aligned with sagittal, coronal, and transverse lasers in the treatment room. Pre-treatment orthogonal portal images were captured for each patient using the amorphous silicon (a-Si) EPID, featuring a 41×41 cm^2 detector with a resolution of 1024×1024 pixels. Images were acquired at gantry angles of 0° and 90° (corresponding to anterior-posterior and lateral views) using a 6 MV X-ray beam, with 3 monitor units (MU) and a dose rate of 50 MU/min per field. For each patient, portal images were obtained before treatment during the first three consecutive radiation sessions. A total of 300 portal images were obtained from 50 patients, consisting of 150 images in the anteroposterior direction and 150 images in the lateral direction. The portal images from EPID were compared (referred to as registration) with DRRs as the reference images using the MOSAIQ software (100 Mathilda Pi, Sunnyvale, CA 94086, U.S.A). Displacements in each anterior and lateral projection were estimated along three major axes: X (Right-Left: RL) laterally, Y (Superior–Inferior: SI) longitudinally, and Z (Anterior–Posterior: AP) vertically, by aligning rigid bony landmarks. The iliac crest and pubic symphysis were used as reference landmarks for AP images, while the sacrum and coccyx bones were used for lateral projections (Figure 1). The observed translational displacements were categorized as negative for posterior, inferior, and left-sided shifts, and positive for anterior, superior, and right-sided shifts. A displacement error exceeding 10 mm was excluded from the study.

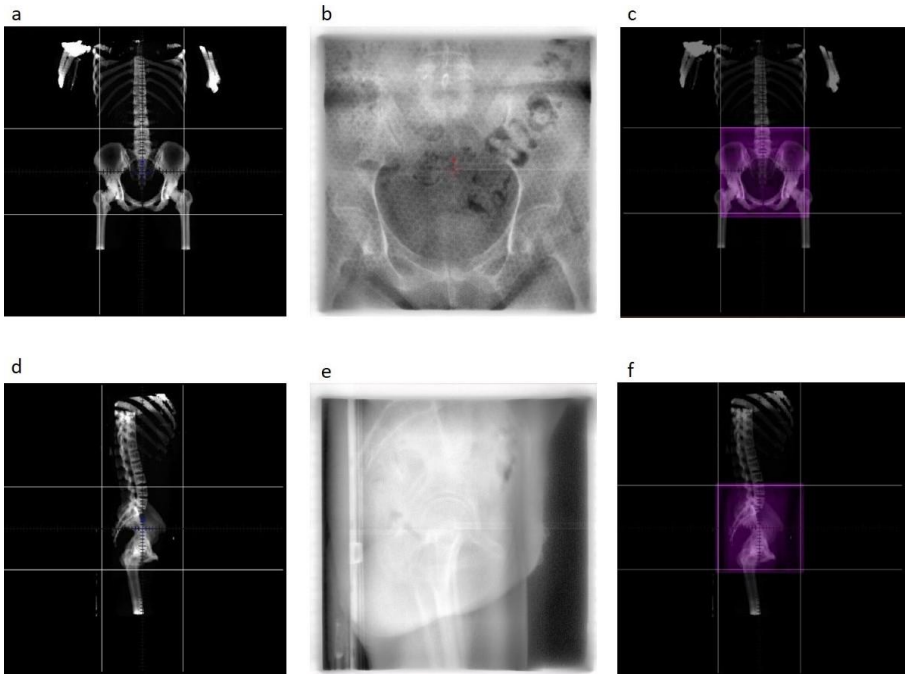

Figure 1. Offline setup verification using MOSAIQ software; (a) Anterior-posterior Digitally Reconstructed Radiograph(DRR), (b) Anterior-posterior EPID, (c) Anterior-posterior registration of the DRR and EPID to obtain deviation, (d) Lateral DRR, (e) Lateral EPID, (f) Lateral registration of the DRR and EPID.

Statistical Analysis

The displacement between the DRR and EPID was determined as a combination of random and systematic errors, denoted as setup deviation ($\mu_{(EPID - DRR)}$), which was assessed in all patients through translocations in three translational directions separately. The random errors occurring day to day in each setup position were represented by σ, while Σ represented the systematic errors defined as the average setup deviation per patient.

Individual mean setup error

Individual mean setup error (m_{ind}) for an individual patient given by [16]:

$$m_{ind} = \frac{\sum_{i=1}^{n} \mu_{(EPID-DRR)_i}}{n} \quad (1)$$

Where $\mu_{(EPID-DRR)_i}$ represents the setup error (displacement between the EPID and DRR) for each imaged fraction, and n denotes the number of imaged fractions (n).

Individual random error

A patient-specific inter-fractional random (daily) setup error (σ_{ind}) is the standard deviation (SD) of the setup error of the corresponding mean individual value (m_{ind}) obtained from equation (1) in the specified direction. It is calculated using the following formula [16,17]:

$$\sigma_{ind} = \sqrt{\frac{\sum_{i=1}^{n}(\mu_{(EPID-DRR)_i} - m_{ind})^2}{n-1}} \quad (2)$$

Population random error

The population random error (σ_{setup}) is determined by averaging all the individual random errors. This is calculated as [16,17]:

$$\sigma_{setup} = \frac{\sum_{p=1}^{p} \sigma_{ind}}{p} \quad (3)$$

Where (p) represents the number of patients.

Overall population mean setup error

The equation to calculate the overall population mean setup error (M_{pop}) follows as [16,17]:

$$M_{pop} = \frac{\sum_{p=1}^{p} (m_{ind})_p}{p} \quad (4)$$

Population systematic error

The population systematic setup error (Σ_{setup}) in a given direction is defined as SD of the individual mean setup errors (m_{ind}) relative to the overall population mean (M_{pop}), and it is computed using the following formula [16,17]:

$$\Sigma_{setup} = \sqrt{\frac{\sum_{p=1}^{p} (m_{ind} - M_{pop})^2}{(p-1)}} \quad (5)$$

Calculation of CTV-to-PTV Margin

The setup margins from the CTV to the PTV were determined based on systematic and random errors, using the formulas recommended by ICRU-62 [3], Stroom et al. [4], and Van Herk et al. [5].

ICRU-62 formula: $\sqrt{\Sigma^2 + \sigma^2}$

Stroom et al. formula: $2\Sigma+0.7\sigma$

Van Herk et al. formula: $2.5\Sigma+0.7\sigma$

Results

A research study involved 50 patients (25 with prostate issues and 25 with cervix issues), and 300 EPIDs were captured. The EPID images were compared to the DRR reference images, and the displacements were measured. One patient was excluded from the study due to a setup error exceeding 10 mm. Statistical analysis was conducted on the recorded displacements, leading to the identification of systematic and random errors, as well as an appropriate margin for CTV-to-PTV using suggested formulas. All analyses were divided into three categories: cervix, prostate, and pelvis. The pelvic analysis was comprehensive, encompassing all data related to the prostate and cervix. The comparative distribution of the setup displacements for the cervical, prostate, and pelvic areas in the RL, SI, and AP directions are illustrated in Figure 2 and Table 1.

Using Equations (1 and 2), the individual mean setup error (m_{ind}) and individual random error (σi_{nd}) in the RL, SI, and AP directions for the cervix and prostate in the pelvic area were obtained and are indicated in Figure 3. Patient numbers 1 to 25 are for each cervix chart and patients 26 to 50 are for prostate. Using Equations (3, 4, and 5), the mean setup error (M_{pop}), population systematic setup error (Σ_{setup}), and population random setup error (σ_{setup}) were computed. Based on these setup errors, the CTV-to-PTV margins were calculated using the methods proposed by ICRU-62, Stroom, and Van Herk. Table 1 presents the frequency of displacements, systematic and random errors, and the resulting CTV-to-PTV margins for the cervix, prostate, and pelvis in the RL, SI, and AP directions, along with the overall average (mean of RL, SI, and AP). An analysis was conducted comparing the cervix, prostate, and pelvic regions in the RL, SI, and AP directions, as well as the overall average. This comparison involved evaluating systematic error, random error, and the calculated margin size using three different formulas. The findings from these comparisons are displayed in Figure 4. In specific organs and pelvis, the systematic error exceeds the random error in all directions (RL, SI, AP). Specifically, for the pelvis, the systematic error is greater than that of the prostate and less than that of the cervix in all directions. The random error for the pelvis is greater than that of the prostate and less than that of the cervix in all directions, except in the RL direction, where it is less than that of the prostate and greater than that of the cervix. The most significant systematic error measures 2.91 mm, while the smallest is 2.09 mm, both in the SI direction and associated with the cervix and the prostate, respectively. The largest random error is 2.11 mm, linked to the cervix, and the smallest is 1.64 mm, related to the prostate, occurring in the SI and AP directions. The CTV-to-PTV margin sizes were calculated using the ICRU-62, Stroom, and Van-Herk formulas. The PTV margin calculated using the Van-Herk formula exceeds that of the Stroom formula in all directions and overall average, and the Stroom formula is greater than the ICRU-62 formula.

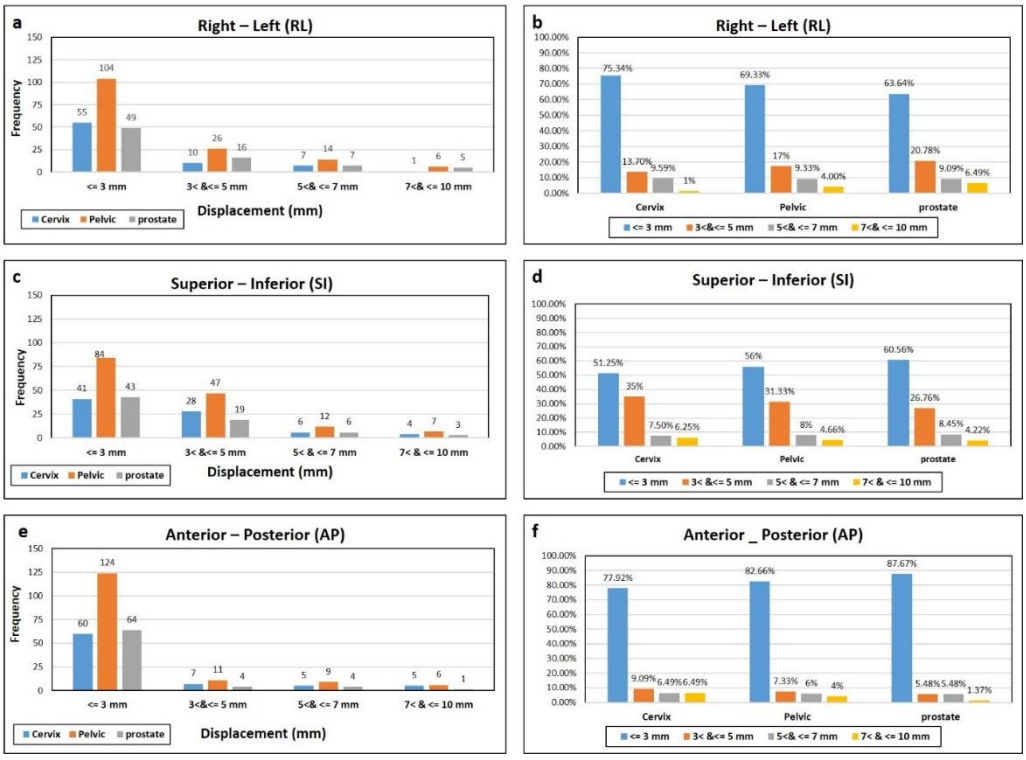

Figure 2. The comparative distribution of displacement for the cervical, prostate, and pelvic areas in the (a, b) Right-Left (RL), (c,d) Superior-Inferior (SI), and (e,f) Anterior-Posterior (AP) directions.

Table 1. The frequency of displacement, systematic and random errors, and calculated CTV-to-PTV margin for the cervix, prostate, and pelvis.

Location	Displacement, Setup Error &Margins		X: Right-Left (RL)	Y: Superior -Inferior (SI)	Z: Anterior -Posterior (AP)
Cervix	Displacement (%)	≤3mm	75.34%	51.90%	77.92%
		>3mm to ≤5mm	13.70%	35%	9.09%
		>5mm to ≤7mm	9.59%	7.59%	6.49%
		>7mm to ≤10 mm	1%	5.06%	6.49%
	Errors (mm)	Systematic Error (Σ)	2.55	2.91	2.54
		Random Error (σ)	1.73	2.11	1.88
	CTV-to-PTV Setup Margin (mm)	ICRU62	3.08	3.59	3.15
		Stroom	5.80	6.52	5.78
		Van- Herk	7.07	7.97	7.05
Prostate	Displacement (%)	≤3mm	63.64%	60.56%	87.67%
		>3mm to ≤5mm	20.78%	26.76%	5.48%
		>5mm to ≤7mm	9.09%	8.45%	5.48%
		>7mm to ≤10 mm	6.49%	4.23%	1.37%
	Errors (mm)	Systematic Error (Σ)	2.19	2.09	2.35
		Random Error (σ)	2.04	1.84	1.64
	CTV-to-PTV Setup Margin (mm)	ICRU62	2.99	2.78	2.86
		Stroom	5.08	5.88	5.84
		Van-Herk	6.17	5.92	6.57
Pelvic (general)	Displacement (%)	≤3mm	69.33%	56.33%	82.66%
		>3mm to ≤5mm	17%	31.33%	7.33%
		>5mm to ≤7mm	9.33%	8%	6%
		>7mm to ≤10 mm	4.00%	4.67%	4%
	Errors (mm)	Systematic Error (Σ)	2.38	2.60	2.45
		Random Error (σ)	1.89	1.96	1.75
	CTV-to-PTV Setup Margin (mm)	ICRU62	3.03	3.25	3.0
		Stroom	5.46	5.90	5.60
		Van-Herk	6.65	7.20	6.82

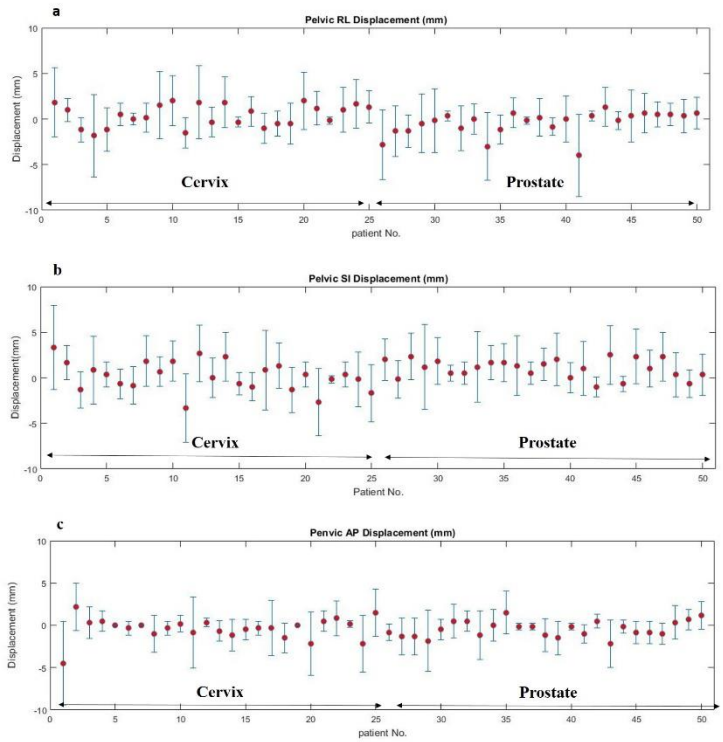

Figure 3. The individual mean ± standard deviation (SD) for (a) RL (b)SI, and (c) AP for the cervix and prostate in pelvis area. Patient numbers 1 to 25 are for each cervix chart and patients 26 to 50 are for prostate.

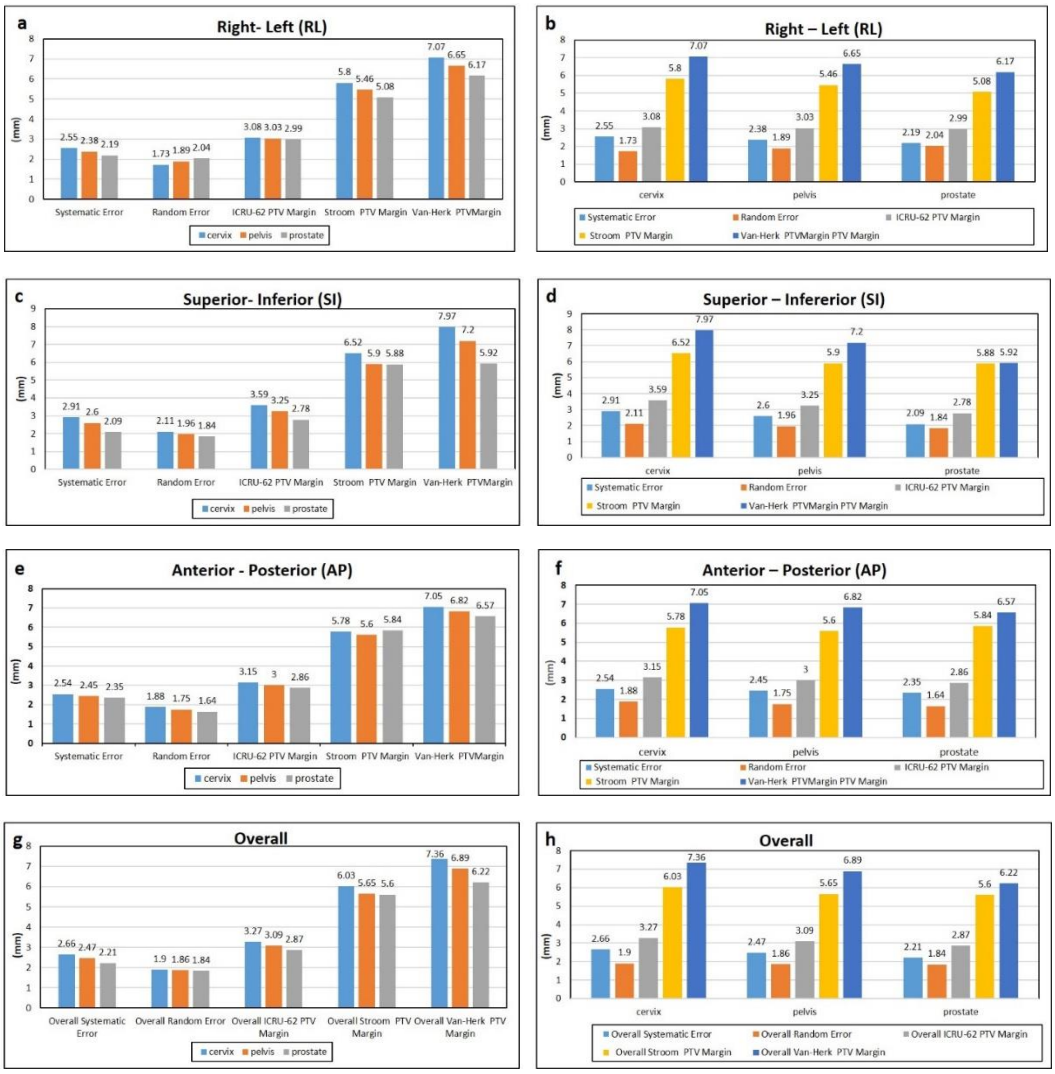

Figure 4. The comparison between systematic error, random error, and the calculated margin size using three formulas in the in the (a, b) RL, (c, d) SI, (e, f) AP directions, and (g, h) overall (the average of RL, SI, and AP), for the cervical, prostate, and pelvic areas

The margin calculated for the pelvic PTV with all three formulas in all three directions overall average is greater than that for the prostate and less than that for the cervix, except for the margin calculated with the Stroom formula in the AP direction, which is less than the prostate and greater than the cervix. The largest calculated margin is 7.97 mm, which is associated with the cervix and calculated using the Van-Herk formula in the SI direction, while the smallest margin is 2.86 mm, related to the prostate, and calculated using the ICRU-62 formula in the AP direction.

Discussion

Patient setup error is a significant issue in radiotherapy that can result in the incorrect delivery of the prescribed dose to the target tissue. These errors can be either systematic or random. Systematic errors lead to larger dosimetric effects compared to random errors and cause a shift in the cumulative dose distribution relative to the target. Random uncertainties cause the target dose distribution to become blurred. [6,7]. It is important to assess both systematic and random errors in each radiotherapy center for various body regions, including the pelvis, thorax, head and neck, and brain, to determine the appropriate safety setup margin (SM) around CTV. This is crucial for ensuring that the target tissue receives the prescribed dose while minimizing unnecessary radiation to surrounding healthy tissues [12-14]. Various mathematical models, such as ICRU-62, Stroom, and Van Herk formulas, have been proposed to calculate the CTV-to-PTV setup margin [3-5]. While the ICRU in Report 62 assumes an equal impact of systematic and random errors, the Stroom, and Van-Herk formulas are assigned different weight factors for the systematic and random errors to account for the varying effects on dose distribution.

Many studies have been conducted to determine the appropriate SM for the CTV in different centers around the world, focusing on the pelvic region and its associated organs, including the cervix, prostate, rectum, and others [13-26].

Table 2. The comparison of systematic and random errors, and calculated CTV-to-PTV margin for the cervix, prostate, and pelvis between the present study and other studies.

Location	Study	Setup Error &Margins		X: Right -Left (RL)	Y: Superior -Inferior (SI)	Z: Anterior -Posterior (AP)
Cervix	Present study	Errors (mm)	Systematic Error (Σ)	2.55	2.91	2.54
			Random Error (σ)	1.73	2.11	1.88
		CTV-to-PTV Setup Margin (mm)	ICRU62	3.08	3.59	3.15
			Stroom	5.80	6.52	5.78
			Van-Herk	7.07	7.97	7.05
	Nigam et al.[18]	Errors (mm)	Systematic Error (Σ)	3.1	3.7	2.7
			Random Error (σ)	2.5	2.5	2.3
		CTV-to-PTV Setup Margin (mm)	ICRU62	4.2	4.4	3.5
			Stroom	7.9	9.1	7.0
			Van-Herk	9.4	10.9	8.3
	Laursen et al.[19]	Errors (mm)	Systematic Error (Σ)	2.9	2.6	3.6
			Random Error (σ)	3.2	2.4	3.6
		CTV-to-PTV Setup Margin (mm)	ICRU62	*	*	*
			Stroom	*	*	*
			Van-Herk	9.6	8.2	11.6
	Patni et al.[20]	Errors (mm)	Systematic Error (Σ)	1.9	3.5	2.0
			Random Error (σ)	1.3	2.3	1.2
		CTV-to-PTV Setup Margin (mm)	ICRU62	*	*	*
			Stroom	*	*	*
			Van-Herk	5.66	10.36	5.84
Prostate	Present study	Errors (mm)	Systematic Error (Σ)	2.19	2.09	2.35
			Random Error (σ)	2.04	1.84	1.64
		CTV-to-PTV Setup Margin (mm)	ICRU62	2.99	2.78	2.86
			Stroom	5.08	5.88	5.84
			Van-Herk	6.17	5.92	6.57
	Khoramian et al.[13]	Errors (mm)	Systematic Error (Σ)	1.95	1.94	1.40
			Random Error (σ)	1.85	2.29	2.09
		CTV-to-PTV Setup Margin (mm)	ICRU62	2.68	3.0	2.51
			Stroom	5.19	5.48	4.26
			Van-Herk	6.17	6.45	4.96
	Osei et al. [17]	Errors (mm)	Systematic Error (Σ)	1.4	2.6	2.2
			Random Error (σ)	1.3	1.3	1.6
		CTV-to-PTV Setup Margin (mm)	ICRU62	*	*	*
			Stroom	*	*	*
			Van-Herk	4.41	7.41	6.62
	Kragelj [21]	Errors (mm)	Systematic Error (Σ)	2.9	2.3	2.5
			Random Error (σ)	4.3	3.5	4.2
		CTV-to-PTV Setup Margin (mm)	ICRU62	*	*	*
			Stroom	*	*	*
			Van-Herk	10.26	8.2	9.19
Pelvic (overall)	Present study	Errors (mm)	Systematic Error (Σ)	2.38	2.60	2.45
			Random Error (σ)	1.89	1.96	1.75
		CTV-to-PTV Setup Margin (mm)	ICRU62	3.03	3.25	3.0
			Stroom	5.46	5.90	5.60
			Van-Herk	6.65	7.20	6.82
	Thasanthan et al. [22]	Errors (mm)	Systematic Error (Σ)	2.56	3.28	2.69
			Random Error (σ)	1.62	1.60	2.33
		CTV-to-PTV Setup Margin (mm)	ICRU62	3.04	3.65	3.57
			Stroom	6.27	7.69	7.33
			Van-Herk	7.56	9.33	8.36
	Amaoui et al. [23]	Errors (mm)	Systematic Error (Σ)	2.01	1.20	1.39
			Random Error (σ)	2.90	1.26	1.66
		CTV-to-PTV Setup Margin (mm)	ICRU62	*	*	*
			Stroom	*	*	*
			Van-Herk	7.11	3.90	4.69
	Ramanathan et al. [14]	Errors (mm)	Systematic Error (Σ)	2.42	2.55	2.27
			Random Error (σ)	4.04	3.67	3.13
		CTV-to-PTV Setup Margin (mm)	ICRU62	4.47	4.46	3.87
			Stroom	7.66	7.66	6.73
			Van-Herk	8.87	8.94	7.86

Since the calculations for the SM in a specific body region need to be performed uniquely at each center, this work was also carried out at our center. The results of this study are presented in Table 2 in comparison with other studies [13,14,17-23].

Our data is consistent with the results of similar studies. The variability in data may differ among institutions, influenced by factors such as the treatment site, type of imaging device, immobilization equipment, precision of treatment lasers, patient positioning, patient cooperation, clinical staff expertise, and the duration of the setup process. [27].

The Stroom formula indicates that, on average, over 99% of the CTV receives at least 95% of the prescribed dose. Van Herk's method used this criterion to calculate margins so that at least 90% of patients received a cumulative CTV dose of at least 95% of the prescription dose [3,4]. By using these formulas to determine margins, we can ensure that the CTV receives an adequate dose. The study's findings on margins are given to radiation oncologists for incorporation into the CTV margins for PTV delineation. It's important to note that this study does not cover other elements of the CTV-to-PTV margins, such as the IM due to internal organ movement and the potential impact of rotational errors. This is because portal imaging in the LAT and AP directions does not allow for their assessment. These factors, alongside uncertainties related to target volume definition and observer variability, should be explored in their dedicated studies.

In our study, the smallest margin determined using the Stroom formula was 5.08 mm. Considering that the margins obtained using Van-Herk's formula are larger than Stroom when the target with the smallest margin calculated by Stroom receives a sufficient dose, it will definitely receive a sufficient dose within the margin calculated by Van-Herk. This value should be established as a standard at our radiotherapy center and be used as a threshold in the offline adaptive radiotherapy protocol. This protocol was applied when displacements of over 5.08 mm in any direction between EPID and DRR were detected. If setup deviations were within 5.08 mm in all directions, no action was taken, and portal imaging was repeated weekly during treatment. However, if displacements exceeded 5.08 mm in any direction, adjustments were made.

In certain studies, it has been observed that, rather than focusing on a specific organ (such as the prostate, cervix, or rectum) to establish the CTV-to-PTV setup margin, the emphasis is placed on the whole area such as the pelvis [14-16,22-24]. However, the findings of this study indicate that for the pelvis, the systematic and random errors are greater than those of the prostate and less than those of the cervix. The margin calculated for the pelvic CTV-to-PTV using all three formulas, is greater than that for the prostate and less than that for the cervix. Consequently, assigning a general pelvic margin to the prostate is excessive, while it is insufficient for the cervix. This results in healthy tissues around the prostate CTV receiving excessive radiation and the CTV in cervix not receiving an adequate dose.

Conclusion

This research was conducted to address the needs of each radiotherapy department in establishing a protocol for determining the CTV-to-PTV safety margin in a particular organ, as well as the threshold for offline correction for the cervix and prostate. An overall assessment of the pelvis (including the cervix and prostate) revealed that the setup error and margins in the pelvis are consistently greater than those in the prostate and less than those in the cervix. Therefore, applying the general pelvic margin results in the target tissue in the cervix not receiving a sufficient dose, while healthy tissues around the target tissue in the prostate receive an additional dose, and a threshold value of 5.08 mm was established for offline correction, which determines whether to proceed with treatment or make adjustments to the patient's setup. The author suggests organ-specific margins, rather than determining general margins.

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References

1. Hamilton CS, Ebert MA. Volumetric uncertainty in radiotherapy. Clinical Oncology. 2005;17(6):456-64.
2. Strbac B, Jokic VS. Evaluation of set-up errors in head and neck radiotherapy using electronic portal imaging. Physica Medica. 2013;29(5):531-6.
3. Wambersie A, Landgerg T. ICRU report 62: prescribing, recording andreporting photon beam therapy. Bethesda, MD: ICRU Publ., 1999.
4. Stroom JC, Heijmen BJ. Geometrical uncertainties, radiotherapy planning margins, and the ICRU-62 report. Radiotherapy and oncology. 2002; 64(1):75-83
5. Van Herk M, Remeijer P, Rasch C, Lebesque JV. The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy. International Journal of Radiation Oncology* Biology* Physics. 2000; 47(4):1121-35.
6. Van Dyk J, Battista JJ, Bauman GS. Accuracy and uncertainty considerations in modern radiation oncology. The modern technology of radiation oncology. 2013; 3:361-412.
7. Van Herk M. Errors and margins in radiotherapy. InSeminars in radiation oncology. 2004; 144(1):52-46.
8. .Matsopoulos GK, Asvestas PA, Delibasis KK, Kouloulias V, Uzunoglu N, Karaiskos P, et al. Registration of electronic portal images for patient set-up verification. Physics in Medicine & Biology. 2004; 49(14):3279.
9. Anjam SM, Banaee N, Rahmani H, Nedaie HA. Determination of geometric accuracy of radiotherapy fields by port film and DRR using Matlab graphical user interface. Medical &

biological engineering & computing. 2019; 57:259-69.
10. Ahmadi E, Eskandari A, Mohammadi M, Naji M, Naseri S, Gholamhosseinian H. Evaluation of Interfractional Setup Uncertainties and Calculation of Adequate CTV-PTV Margin for Head and Neck Radiotherapy using Electronic Portal Imaging Device. Journal of Biomedical Physics and Engineering. 2025;15(1):5.
11. Bagheri, A., Momennezhad, M., Nasseri, S., Eskandari, A., Saatchian, E., Naji, M., Mohammadi, M. Y. Evaluation of Dose Distribution at the Level of Electronic Portal Imaging Device using Treatment Planning System. *Journal of Biomedical Physics and Engineering*, 2024; (): -. doi: 10.31661/jbpe.v0i0.2312-1700
12. Hashemi SM, Bahreyni MH, Mohammadi M, Nasseri S, Bayani S, Gholamhosseinian H, et al. An Empirical Transmitted EPID Dosimetry Method using a Back-Projection Algorithm. Journal of biomedical physics & engineering. 2019; 9(5):551.
13. Khoramian D, Sistani S, Farhood B. 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). Journal of Radiotherapy in Practice. 2022;21(4):493-500.
14. Ramanathan V, Gunarathne K, Sampath DC, Rizwy MM. Evaluation of Set-Up Errors and Set-Up Margin in Three-Dimensional Conformal Radiotherapy for Pelvic Tumours by Using Electronic Portal Imaging Device. KDU Journal of Multidisciplinary Studies. 2022; 4(2).
15. Kasabašić M, Faj D, Belaj N, Faj Z, Tomaš I. Implementing of the offline setup correction protocol in pelvic radiotherapy: safety margins and number of images. Radiology and Oncology. 2007; 41(1):48-55.
16. Pramanik S, Ray DK, Bera S, Choudhury A, Iqbal A, Mondal S,et al. Analysis of setup uncertainties and determine the variation of the clinical target volume (CTV) to planning target volume (PTV) margin for various tumor sites treated with three-dimensional IGRT couch using KV-CBCT. Journal of Radiation Oncology. 2020; 9:25-35.
17. Osei EK, Jiang R, Barnett R, Fleming K, Panjwani D. Evaluation of daily online set-up errors and organ displacement uncertainty during conformal radiation treatment of the prostate. The British journal of radiology. 2009;82(973):49-61.
18. Nigam J, Kumar P, Balan U. Set up errors and recommended safety margins in the pelvic radiotherapy fields of cancer cervix patients: an institutional experience. jms. 2016; 1:7125.
19. Laursen LV, Elstrøm UV, Vestergaard A, Muren LP, Petersen JB, Lindegaard JC, et al. Residual rotational set-up errors after daily cone-beam CT image guided radiotherapy of locally advanced cervical cancer. Radiotherapy and Oncology. 2012; 105(2):220-5.
20. Patni N, Burela N, Pasricha R, Goyal J, Soni TP, Kumar TS, et al. Assessment of three-dimensional setup errors in image-guided pelvic radiotherapy for uterine and cervical cancer using kilovoltage cone-beam computed tomography and its effect on planning target volume margins. Journal of Cancer Research and Therapeutics. 2017; 13(1):131-6.
21. Kragelj B. Setup error and its effect on safety margin in conformal radiotherapy of the prostate. Radiology and Oncology. 2005; 39(3).
22. Thasanthan L, Piyasena WR, Croos AM, Dhanushia R, Narayanan PP. Assessment of three-dimensional set-up errors in pelvic radiation therapy. J Cancer Prev Curr Res. 2014;1(2):00009.
23. Amaoui B, Hadaoui A, Mouhssine D, Semghouli S. Evaluation of setup errors in conformal radiotherapy for pelvic tumours: Case of the Regional Center of Oncology, Agadir. Radiation Medicine and Protection. 2020;1(2):99-102.
24. Laaksomaa M, Kapanen M, Tulijoki T, Peltola S, Hyödynmaa S, Kellokumpu-Lehtinen PL. Evaluation of overall setup accuracy and adequate setup margins in pelvic image-guided radiotherapy: comparison of the male and female patients. Medical Dosimetry. 2014; 39(1):74-8.
25. McGary JE, Grant III W. A clinical evaluation of setup errors for a prostate immobilization system. Journal of Applied Clinical Medical Physics. 2000;1(4):138-47.
26. Zhang X, Shan GP, Liu JP, Wang BB. Margin evaluation of translational and rotational set-up errors in intensity-modulated radiotherapy for cervical cancer. SpringerPlus. 2016; 5:1-9.
27. Molana S, Arbabi F, Sanei M, Hashemi E, Tajvidi M, Rostami A, et al. Evaluation of patient setup accuracy and determination of optimal setup margin for external beam radiation therapy using electronic portal imaging device. Canc Therapy & Oncol Int J. 2018;11(2):48-55.