



EVALUATION OF SET-UP ERRORS AND SET-UP MARGIN IN THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY FOR PELVIC TUMOURS BY USING ELECTRONIC PORTAL IMAGING DEVICE

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ABSTRACT

A set-up error is defined as any deviation between the predetermined and actual treatment positions, and is determined by measuring the displacement of the treatment field position by comparing the treatment image to its reference image. Dose distribution in the target volume is dependent on setup margins. It is important to assess the setup errors for each radiotherapy unit to reduce the treatment errors. The aim of this study was to evaluate the systematic and random setup errors using electronic portal imaging device (EPID) for pelvic tumour patients treated by 3D-CRT (conformal radiotherapy) and also to assess set-up margin. 115 pelvic tumour patients were included in this study in which 1150 portal images were assessed. The displacements between DRR (digitally reconstructed radiograph) and the portal images were measured in the direction of right to lateral, superior to inferior in anterior images by matching rigid bony landmarks. Moreover, the displacements between anterior to posterior and superior to inferior were measured in lateral images. The estimated systematic errors were 0.242, 0.255 cm in right to lateral and superior to inferior direction in anterior images, and 0.227, 0.220 cm in anterior to posterior and superior to inferior in lateral images. The estimated random errors were 0.404, 0.367 cm in right to lateral and superior to inferior in anterior images, 0.313, 0.337 cm in anterior to posterior and superior to inferior in lateral images. The determined margins for CTV to PTV based on ICRU were 0.4711, 0.4465, 0.3870, 0.4026 cm in the order of the above mentioned directions. A 0.5 cm safety margin is suggested for all pelvic tumour patients treated with 3D-CRT in Varian 2300CD linear accelerator unit, Apeksha Hospital, Maharagama.

KEYWORDS: Radiotherapy, 3D-CRT, EPID, Pelvic tumours, Linear accelerator, DRR.

1. INTRODUCTION

Radiotherapy is one of major treatment option in cancer treatment and about 50% of cancer patients receive radiotherapy in radical or palliative intent during their course of treatment (Ramanathan et al., 2022). Radiotherapy uses high-energy radiation to destroy and control the spread of cancer cells. The genetic material (deoxyribonucleic acid, DNA) of cells can be damaged by high-energy radiations and the ability of further division and proliferation can be blocked (Jackson et al., 2009 & Ramanathan, 2021). The rate of repairing and retaining its normal function status of normal cells is usually better than that of cancer cells. Differential cell killing can be induced by high-energy radiation because of this inefficient rate of repair mechanism of cancer cells (Begg et al., 2011).

At present, many newest teletherapy modalities are available such as three-dimensional conformal radiotherapy (3D-CRT), Intensity Modulated Radiotherapy (IMRT), Image Guided Radiotherapy (IGRT), Stereotactic Body Radiation Therapy (SBRT), Stereotactic Radiotherapy (SRT), Stereotactic Radiosurgery (SRS), Particle therapy, etc. (Ramanathan 2017). And, 3D CDT is the most basic modern technique in which 3D anatomic information is used by sophisticated treatment planning system to generate conformal treatment fields sufficient enough to cover the target volume with 3D dose distribution while minimizing the normal tissue irradiation. There are some limitations to achieve the definition of 3D CRT. The knowledge of Clinical Target Volume (CTV) is the major barrier when conforming the radiation dose to the target volume as imaging modalities reveal mostly gross tumour extent only. Possible microscopic extensions also should be included in the target volume to achieve the goals of 3D CRT (Khan and Gibbons, 2014).

The International Commission on Radiation Units and Measurements (ICRU) has provided useful guidelines and the definitions of target volume delineation. The gross demonstrable extent and the location of a malignant and the location of a malignant growth are defined as Gross Tumour Volume (GTV). The Clinical Target Volume (CTV) is acquired by adding a margin around GTV to include the microscopic spread of malignant disease that must be eliminated. The dose

distribution in CTV may deviate from the intended plan due to geometrical uncertainties. ICRU has considered three sources of geometrical uncertainties respectively patient setup variation, organ motion and deformation, and machine-related errors. ICRU recommends two margins (internal margin and setup margin) for avoiding the deviation of CTV coverage due to anatomical and geometrical uncertainties. Internal margin (IM) is added to compensate for the variation due to the movements of internal organs because of their physiological functions (breathing, bladder filling, rectum filling, etc.). The CTV plus IM is called internal target volume (ITV). Setup margin (SM) is added to ITV to compensate for the deviation of intended CTV coverage due to the uncertainties in patient positioning and the alignment of therapeutic beams during the treatment planning and throughout all treatment sessions. The ITV plus SM are together called the planning target volume (PTV) (Landberg et al., 1999).

The set-up error is defined as any deviation between the predetermined and actual treatment position, and is determined by measuring the displacement of the treatment field position by comparing the treatment image to its reference image. Setup errors consist of two components namely systematic and random errors. The systematic component of the setup error describes the errors which occur during the treatment preparation while the errors during the treatment execution are described by the random component. The systemic errors make the dose distribution deviate away from the CTV, and the random errors blur the dose distribution around the CTV (van Herk, 2004). The process of radiotherapy verification helps us to ensure that targeting volume is the same as in the treatment plan (RCR 2008). Because of the possibility to detect and reduce setup errors for a large number of patients, portal imaging to measure set-up errors is the standard practice in a large number of institutions among various types of verification methods. This has made it possible to detect and reduce the setup errors for a large number of patients (Noghreiyani et al., 2019). During the portal imaging, visual comparison between the reference image and the image taken in the treatment position of the patient is performed. The DRR created by the planning system or digitized simulated film produced by a treatment simulator is used as a reference image. This deviation is measured relative to

the isocenter or field borders. The translational uncertainties in the three-dimensional can be detected, and if necessary, the correction can be made according to the correction protocol followed in the institute. The rotational uncertainties can also be detected with modern devices but the possibility of correction is limited according to the available couch movements. The setup error and the geometric PTV margin are interrelated. This margin is defined during the treatment planning process. The margin recipes are formulations that calculated the required PTV margin to provide adequate CTV dose coverage in the presence of errors for specific patient populations (Ecclestone et al., 2012). Several margin recipes have been published by some authors considering the dose coverage probabilities, physical and biological considerations (Landberg et al., 1999, Stroom et al., 1999, van Herk et al., 2000).

Image review at the first fraction of radiotherapy treatment and then periodically is necessary to ensure the treatment accuracy and reproducibility. The limitation of couch positional changes (setup uncertainties), which requires setup review or change before treatment delivery, should be determined for each institution specifically (Goyal et al., 2014). Generating data on its setup accuracy in every department is much better and recommended than using a published margin regarding the setup accuracy (Gupta et al., 2007). The deviation detected by comparing the reference image and treatment position image by using an electronic portal image device (EPID) can be used for evaluating the margin added to the CTV according to the margin recipes published under guidelines provided by ICRU (RCR 2008).

Varian 2300CD is the first linear accelerator installed in 2008 at Apeksha Hospital-Maharagama, which is the main treatment centre for cancer in Sri Lanka. After five years of installation, research was done by Loganathan et al. to evaluate the 3D setup errors of pelvic irradiation using EPID. 100 first two-day pre-treatment portal images of 50 patients have been evaluated and it has been shown that there were significant 3D displacements. The author has suggested that weekly portal images additional to the first two-day pre-treatment portal need to be performed for better treatment delivery. Currently, the workload has doubled that of 2014 at Apeksha

Hospital, Maharagama. The increase in the number of patients will reduce the time spent with a patient. This will cause an increase in the frequency of errors. Even after 10 years of installation, no review had been done about margin calculations. Therefore, it was very important to perform the evaluation of set-up errors and set-up margin due to the age of the machine and higher workload. The aim of the study was to evaluate setup errors and setup margin in 3D-CRT for pelvic tumours by using an electronic portal imaging device.

2. MATERIALS AND METHODS

A retrospective study was conducted among 115 patients treated for pelvic cancer, and all patients completed their course of 3D-CRT treatment during the period from July 2019 to June 2020 in Varian 2300CD linear accelerator unit, Apeksha Hospital, Maharagama. The permission was obtained from the hospital authority to conduct this study. The ethical approval for this study was exempted as there was no involvement with patients' routine treatment steps. The patients aged 18 to 80 years were included in this study. Data were collected from ARIATM oncology information system of Varian Linac.

Generally, radiotherapy is given as fractionated treatment over several weeks, and it is usually given five days per week. Orthogonal images of five fractions were selected from each patient for the assessment including the first two fractions, and other three fractions were randomly selected from the remaining fractions of their course of radiotherapy. Totally, 1190 portal images were assessed using the image review option provided with the ARIATM oncology information system. Each portal image was compared with a digitally reconstructed radiograph (DRR) as a reference image generated by the treatment planning system during the treatment planning process.

DRR is an image generated by the treatment planning system by using imported images from the CT simulator. DRR can be created in any plane other than the image acquisition plane. The quality of DRR can be adjusted up to some extent by the treatment planner, but it mostly depends on CT data. Clear

visualizing of bony anatomy ridges in DRR depends on the quality of the DRR. Clear bony anatomy ridges in DRR helps to give a good comparison result with portal image. DRRs were generated by Varian Eclipse™ treatment planning system in the present study setting. Portal image is an essential tool used to verify the patient set-up with respect to the position of the radiation beam. Isocentrically mounted Varian Portal Vision™ aS1000 electronic portal imaging device was used to acquire electronic portal images (EPI). Typically, a radiation beam with energy 6 MV is used to deliver 1 MU (Monitor Unit) of exposure at 300 MU/min dose rate for the acquisition of portal image. Visual comparison between EPI and DRR is performed by matching clearly visible rigid bony landmarks in the interested area. EPI software gives details of shifts required to correct detected uncertainties. All images are stored in the database automatically for review purposes and can be reviewed using offline image review option in ARIA™ oncology information system as shown in figure 1.

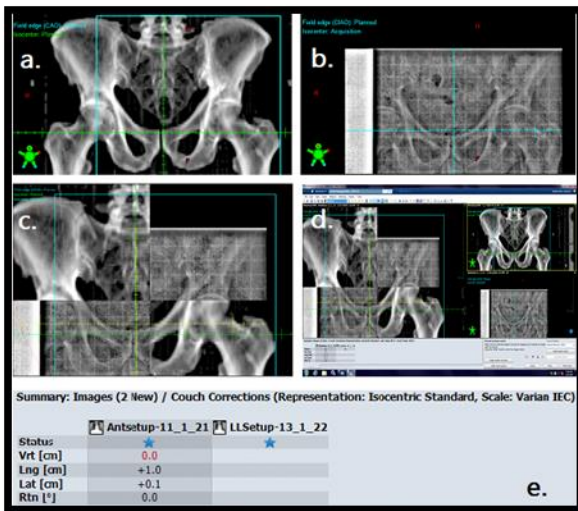


Figure 1: Visual comparison of bony land marks in DRR and EPI by using offline image review option in ARIA™ oncology information system [a- DRR generated by treatment planning system, b- EPI obtained just prior to delivery of treatment, c- superimposed DRR and EPI to correct the deviation with split window tool, d- user interface of offline review option provided with ARIA™ oncology information system, and e- calculated couch

corrections according to the comparison of images a and b].

Displacements between DRR and portal images were estimated in the direction of right to lateral and to superior to inferior using image obtained at 0° gantry angle by matching rigid bony landmarks. Moreover, the displacements were obtained in the direction of anterior to posterior and superior to inferior using a lateral image obtained at 90° gantry angles. Superior, anterior, and left-sided shifts were implied as positive shifts, and inferior, posterior, and right-sided shifts were implied as negative shifts for the analysis of this study. The method used in the report published by the Royal College of Radiologist (RCR, 2008) was used to calculate the individual and population-based random and systemic errors in the direction of right to lateral, superior to inferior from anterior image at gantry angle 0°; anterior to posterior and superior to inferior from lateral image at gantry angle 90° (table 1).

Table 1: Methods demonstrated to calculate population based systematic and random errors. SD stands for standard deviation.

Component	Method of calculation
$m_{\text{individual}}$ (individual systematic error)	Mean setup error for an individual patient
M_{pop} (Overall mean setup error)	Overall mean of population
$\Sigma_{\text{set-up}}$ (Systematic error for population)	SD of the individual mean set-up errors about the overall population mean (M_{pop})
$\sigma_{\text{individual}}$ (Individual random error)	SD of the set-up errors of corresponding individual ($m_{\text{individual}}$)
$\sigma_{\text{set-up}}$ (Population random error)	Mean of all the individual random errors

The CTV to PTV margin calculations were performed according to the popular margin recipe formulae which were published by van Herk et al., 2000, Stroom et al., 1999, and Landberg et al., 1999 (ICRU 62) based on various assumptions shown in

table 2. Calculations and analysis were performed using Microsoft Office Excel (MS Office 2007) spreadsheets and Minitab19 Statistical Software.

Table 2: Formulae used for CTV to PTV margin calculation.

Formulae	Author	Assumptions
$2.5\sum+0.7\sigma$	van Herk et al., 2000	90% of patients in the population receive a minimum cumulative CTV dose of at least 95% of the prescribed dose
$2\sum+0.7\sigma$	Stroom et al., 1999	Average 99% of CTV receives more than or equal to 95% of the prescribed dose
$\sqrt{\sum^2 + \sigma^2}$	Landberg et al., 1999 – ICRU 62	Systemic and random part of set-up error have the same contribution to the dose distribution

3. RESULTS

1190 images of 115 patients were selected for analysis in this study. Details of the patients are listed in Table 3. The majority of patients were female (56.52%) and most of the patients were in the range of 66-80 years (43.48%). Carcinoma in cervix, prostate, rectum, endometrium, anus and bladder were included in this study. All patients were treated in supine position with the support of a head cushion and foot rest.

Table 3: Patients and treatment characteristics.

Characteristics		No. of patients	Percentage
Age (years)	18-30	2	1.74
	30-42	7	6.09
	42-54	17	14.78
	54-66	39	33.91
	66-80	50	43.48
Gender	Male	50	43.48
	Female	65	56.52
Diagnosis	Cervix	32	27.83
	Prostate	37	32.17
	Rectum	8	6.96
	Endometrial	26	22.61
	Anus	1	0.87
	Bladder	11	9.57
Dose (Gy)	Median	50.0	
		51.1	
	Mean	19.8	
	Minimum	72.0	
Fractions	Maximum		
	≤ 10	0	0
	10<&≤20	10	8.70
	20<&≤ 30	100	86.96
	> 30	5	4.35

Measured displacements in ranges for all directions were summarized and are shown in table 4, and those for individual directions are shown in table 5. The distribution of the measured displacement is shown in figure 2 in each direction, right to lateral, superior to inferior using anterior image, anterior to posterior and superior to inferior using lateral image.

Table 4: Summary of displacements in all directions

Range	In all directions
Displacement ≤0.3cm	49.04%
0.3cm < Displacement ≤0.5cm	29.13%
0.5cm < Displacement ≤0.7cm	18.83%
0.7cm < Displacement ≤1cm	2.96%
Displacement > 1cm	0.04%

Table 5: Summary of displacement in individual directions.

Range	R- L(Ant)	S- I(Ant)	A- P(Lat)	S- I(Lat)
Displacement $\leq 0.3\text{cm}$	41.57 %	46.09 %	55.13 %	53.39 %
0.3cm < Displacement $\leq 0.5\text{cm}$	29.57 %	29.22 %	27.30 %	30.43 %
0.5cm < Displacement $\leq 0.7\text{cm}$	24.70 %	21.04 %	16.00 %	13.57 %
0.7cm < Displacement $\leq 1\text{cm}$	4.17%	3.65%	1.39%	2.61%
Displacement $> 1\text{cm}$	0%	0%	0.17%	0%

Table 6: Summarized results of population systematic ($\Sigma_{\text{set-up}}$) and random ($\sigma_{\text{set-up}}$) error, overall mean setup error (M_{pop}), Minimum deviation and Maximum deviation along each direction.

Field	Anterior image		Lateral image	
Direction	R-L	S-I	A-P	S-I
Minimum deviation (cm)	-0.9	-0.9	-1.1	-0.9
Maximum deviation (cm)	0.9	0.9	0.9	0.9
Overall mean (cm)	0.0158	0.0261	-0.0762	0.0313
$\Sigma_{\text{set-up}}$ (cm)	0.242	0.255	0.227	0.220
σ_{setup} (cm)	0.404	0.367	0.313	0.337

Table 7: CTV to PTV margin generated in present study

Recipe	Anterior		Lateral	
	R-L (cm)	S-I (cm)	A-P (cm)	S-I (cm)
$2.5\Sigma + 0.7\sigma$ Van Herk	0.8871	0.8940	0.7868	0.7866
$2\Sigma + 0.7\sigma$ Stroom	0.7663	0.7665	0.6733	0.6764
$\sqrt{\Sigma^2 + \sigma^2}$ ICRU 62	0.4711	0.4465	0.3870	0.4026

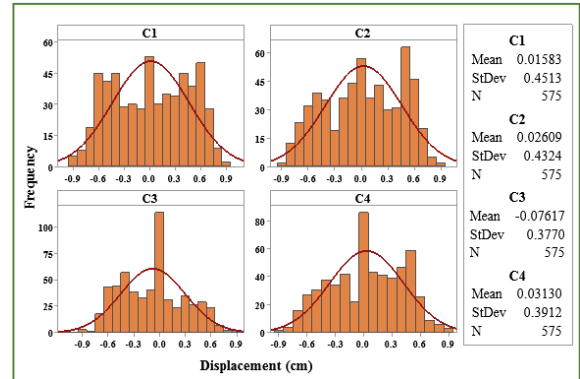


Figure 2: Distribution of measured displacements (C1- right to lateral direction, C2- superior to inferior (from anterior image); C3- anterior to posterior direction, C4- superior to inferior direction (from lateral image).

Population systematic ($\Sigma_{\text{set-up}}$) and random ($\sigma_{\text{set-up}}$) error and overall mean setup error (M_{pop}) were calculated according to the methods shown in Table 1. The mean displacements were 0.0158, 0.0261, 0.0762, and 0.0313 cm in the direction of right to lateral, superior to inferior (anterior), anterior to posterior and superior to inferior (lateral) respectively. Systematic errors were 0.242, 0.255, 0.227, 0.220 cm and random errors were 0.404, 0.367, 0.313, 0.337 cm respectively along the relevant directions (table 6).

The calculated CTV to PTV margin values in the direction of right to lateral and superior to inferior from anterior image, anterior to posterior and superior to inferior from lateral image are shown in table 7.

4. DISCUSSION

The present study setting is a busy radiotherapy centre where an average of 80 patients are treated daily including 3D-CRT, IMRT, and electron beam therapy within 12 to 16 hours by VARIAN 2300CD linear accelerator. Patient positioning is a challenging task as the number of radiotherapy patients is high. Daily image verification is performed for IMRT but portal imaging is performed for the first two days of treatment and weekly portal imaging is followed for 3D-CRT pelvic region treatment. Offline correction

protocol has not been implemented and online correction is carried out if the detected deviation is more than or equal to 0.5 cm in any direction in two orthogonal portal images for 3D-CRT in pelvic region patients. A considerable amount of displacements (78%) were within the tolerance level (<0.5 cm), while nearly one-fourth of all displacements of pelvic cancer patients were out of range.

A comprehensive report published by the Royal College of Radiologists is used for calculating systemic and random errors in this study shown in Table 1. Comparison of systemic error and random error findings in similar studies are tabulated in Table 8 and 9. It shows that results in the present study are well-matched with the previous literature.

Several mathematical models have been published for generating CTV-PTV margins. Assuming equal effect on dose distribution from systemic and random error, International Commission on Radiation Units has published the margin generating formula as $\sqrt{\Sigma^2 + \sigma^2}$, where Σ is the population systemic error and σ is the population random error (Landberg et al., 1999). Incorporation of differential effects on dose distribution over systemic and random errors and using probability matrices and dose-volume histogram respectively, van Herk et al., 2000 and Stroom et al., 1999 have suggested formulae as $2.5\Sigma + 0.7\sigma$ and $2\Sigma + 0.7\sigma$. The calculated margin in the present study is well aligned with the calculated margin in similar studies performed recently by Loganathan et al., 2014 Nigam, Kumar and Balan, 2016 and Noghreiyen et al., 2019 (Table 10).

Table 8: Summary of systematic error reported in four similar studies performed in pelvic radiotherapy and the present study (all values are in cm).

Study	Systematic error			
	R-L	A-P	S-I (Ant.)	S-I (Lat.)
Loganathan et al., 2014	0.2568	0.2698	0.3284	
Nigam et al., 2016	0.3100	0.2700	0.3700	
Swarna K , 2017	0.2404	0.1966	0.5832	
Noghreiyen et al., 2019	0.2364	0.2742	0.4993	0.3859
Present study	0.2416	0.2550	0.2270	0.2203

Table 9: Summary of random error reported in four similar studies performed in pelvic radiotherapy and the present study (all values are in cm).

Study	Random error			
	R-L	A-P	S-I (Ant.)	S-I (Lat.)
Loganathan et al., 2014	0.1628	0.2339	0.1603	
Nigam et al., 2016	0.2500	0.2300	0.2500	
Swarna K , 2017	0.2135	0.1946	0.6191	
Noghreiyen et al., 2019	0.1511	0.1593	0.2747	0.2321
Present study	0.4045	0.3666	0.3134	0.3370

Table 10: Summary of margin calculated in 3 similar studies performed in pelvic radiotherapy and the present study (all values are in cm) according to the recipes published by ICRU 62, Stroom, and Vanherk. [Study 1- Loganathan et al., 2014, study 2- Nigam et al., 2016, and study 3- Noghreiyen et al., 2019].

Recipe	Dir.	Study			
		1	2	3	Present
ICRU	R-L	0.3040	0.4200	0.2805	0.4711
	A-P	0.3570	0.3500	0.3171	0.3870
	S-I (Ant.)	0.3650	0.4400	0.5699	0.4465
	S-I (Lat.)			0.4503	0.4026
Stroom	R-L	0.6270	0.7900	0.5785	0.7663
	A-P	0.7030	0.7000	0.6599	0.6733
	S-I (Ant.)	0.7690	0.9100	1.1909	0.7665
	S-I (Lat.)			0.9342	0.6764
Vanherk	R-L	0.7560	0.9400	0.6967	0.8871
	A-P	0.8380	0.8300	0.7669	0.7868
	S-I (Ant.)	0.9330	1.0900	1.4406	0.8940
	S-I (Lat.)			1.1271	0.7866

The maximum value of the margin generated by mentioned recipes in any direction are highlighted in table 10 and a comparison of these values of similar studies performed recently is shown in Figure

3. It shows that generated margins in the present study are in the range of margins found in the literature.

By applying estimated margins related to the present study, 0.9 cm margin to the CTV ensured that 90% of patients will receive a dose of at least 95% of the prescribed dose according to the assumptions made by van Herk (van Herk et al., 2000). 0.8 cm expansion of the margin to CTV has ensured that 99% CTV is covered by 95% of prescribed dose accordingly (Stroom et al., 1999). According to the ICRU recommendation, 0.5 cm is enough for ensuring the coverage of CTV by prescribed dose assuming systemic and random error effect has equally contributed to margin determination.

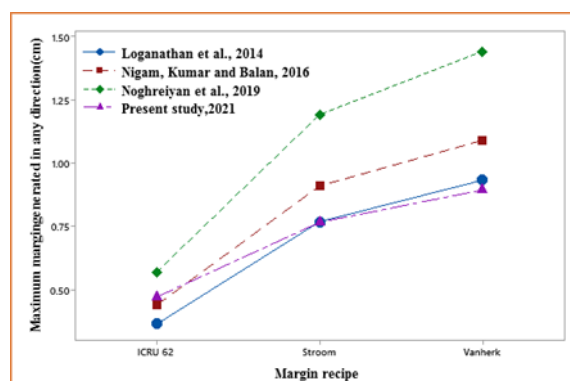


Figure 3: Comparison of maximum margin generated by ICRU 62, Stroom and Vanherk recipes in any direction in three similar studies and present study.

The number of limitations minimizes the ideality of calculated margin values. Internal structural changes cannot be detected on the electronic portal imaging study as the evaluation was based on a visual comparison of the bony anatomy of the portal image reference to the DRR created by TPS. Rotation errors were not evaluated in this study as there is no available facility to re-correct these errors. Error evaluation is only based on two orthogonal portal images. Above mentioned errors were not accounted for in calculating the CTV-PTV margins in the current study. The immobilization technique was the same for all patients and correlation between different techniques was not possible. Calculated

random errors were larger than systemic errors which show that additional attention must be required to reduce random errors during the patient positioning procedure. Inability to involve with the patient positioning procedure was identified as a shortcoming of the current retrospective study.

5. CONCLUSION

Setup errors may vary from institute to institute due to the influence of implemented protocols directly on the systematic and random errors. Determined setup errors of the present study are well matched with the published setup error data corresponding to the pelvic radiotherapy practices. The calculated random errors in the present study were larger than systemic error, which indicates that patient positioning procedures must be carefully handled to minimize day-to-day setup variations.

78.17% of the deviations are within the tolerance limit. The margin which is less than 0.5 cm in all directions produced according to ICRU recommendation is selected as a safety margin among calculated CTV-PTV margin according to three formulae for all patients treated with 3DCRT in the pelvic region.

A deliberate attempt must be taken to evaluate the factors that can potentially impact upon margin to ensure the coverage of target before adopting any published margin recipes. However, the portal imaging study is suggested as a useful tool for monitoring the clinical practice and audit changes introduced by new equipment, technology, and practice.

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