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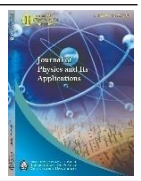

Determination of Planning Target Volume (PTV) Margins Using Redefined Systematic and Random Error Equations from Single-Fraction Verification Data: A Case Study of Cervical Cervic

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ABSTRACT

This study aimed to determine the Planning Target Volume (PTV) margin by redefining the equations for systematic and random errors in a cervical cancer case. The research utilized first-fraction radiotherapy position verification data from 37 cervical cancer patients. These data comprised planned and actual positions, with the difference interpreted as the position shift. The systematic and random error equations proposed by the Royal College of Radiologists (2008) were redefined by adapting them to verification data, which were grouped into several PTV types and treated as daily fractions. The PTV margin was then calculated using formulas by Van Herk (2004), Stroom (2002), and ICRU Report 62. The results showed that the largest systematic and random errors occurred in the vertical and longitudinal directions, measuring 0.83 cm and 1.71 cm, respectively. The PTV margin calculated using the Van Herk method was comparatively larger than those obtained using the other two methods. The percentages of position shifts that exceeded the calculated PTV margins in the vertical, longitudinal, and lateral directions were 16%, 43%, and 35%, respectively. These findings indicate that the redefined equations are capable of compensating for the lack of position shift data across all radiotherapy fractions. The redefined approach can provide a more accurate estimation of PTV margins in cervical cancer treatment using single-fraction verification data.

1. Introduction

The Planning Target Volume (PTV) is a geometrical concept that encompasses the Clinical Target Volume (CTV) with an added margin to account for internal movement and setup variations during radiotherapy [1]. According to ICRU Report No. 50 (1993), CTV is defined as the Gross Tumor Volume (GTV) plus the presumed macroscopic tumor [2]. In practice, geometric uncertainties are involved in delineating the GTV, including limited imaging modality resolution, intraobserver variability, differences in observer interpretation, and differing or ambiguous guidelines leading to target volume delineation. If there is uncertainty in target volume delineation during planning, this uncertainty will similarly impact the entire treatment fraction. Thus, target volume delineation uncertainty is considered one of the systematic errors [3]. ICRU Reports No. 50 and 62 ultimately recommend creating the PTV by adding a margin around the CTV. This compensates for incorporating organ position uncertainties in the treatment planning process [2][4].

The PTV margin can be calculated using formulations proposed by Van Herk [3], Stroom [5], and those outline in ICRU Report 64 [4]. The Van Herk method assumes that at least 95% of the prescribed radiation dose should adequately cover the Clinical Target Volume (CTV) in 90% of patients in 90% of all treated patients to ensure the effectiveness of radiation therapy [3]. This analytical solution calculates the necessary margin to achieve perfect conformity so that the dose received by the CTV closely matches the planned dose while minimizing the dose to surrounding healthy tissue. The PTV margin calculation using the Van Herk (2004) method is derived from the calculation of systematic (Σ) and random (σ) errors, as shown in Equation 1.

$$Margin\ PTV = 2{,}5\Sigma + 0{,}7\sigma \quad (1)$$

The Stroom (2002) method is a development of the Van Herk (2004) method for fringe doses due to the limited number of beams. This modification ensures

that even with fewer radiation beams, the dose reaching the CTV remains aligned with the therapeutic goals while the dose to healthy tissue is minimized [5]. The PTV margin equation for the Stroom (2002) method is shown in Equation 2.

$$Margin\ PTV = 2\Sigma + 0{,}7\sigma \quad (2)$$

The ICRU Report No. 62 (1999) method PTV Margin Equation is shown by equation 3.

$$Margin\ PTV = \Sigma + 0{,}7\sigma \quad (3)$$

The PTV margins above were obtained after calculating the systematic error (Σ) and random error (σ), multiplied by factors of 0.7 for random errors and 2.5, 2, and 1 for the systematic errors in theVan Herk, Stroom, and ICRU Report No. 62 methods, respectively. To determine the values of systematic error (Σ) and random error (σ), calculations of individual mean setup error, overall population mean setup error, population systematic error, individual random error, and population random error are required [6].

Individual mean set-up error ($\boldsymbol{m_{individual}}$) is the average set-up error for a single patient. The calculation is done by summing the set-up errors by position shifts (Δ_n) for each radiation fraction and dividing by the number of radiation fractions (n). The $\boldsymbol{m_{individual}}$ is shown in Equation 4.

$$\boldsymbol{m_{individual}} = \frac{\Delta_1+\Delta_2+\Delta_3+\cdots+\Delta_n}{n} \quad (4)$$

Position shift (Δ_n) is the value obtained from the calculation of the difference between geometric verification data for the same patient for each fraction, which is the actual data ($x_{ai,j,k}$) minus the planning data ($x_{pi,j,k}$).

The overall mean set-up error ($\boldsymbol{M_{Pop}}$) is the mean for the group of patients analyzed and should ideally be zero. A significant deviation from zero indicates a fundamental error common in this patient group that requires further correction. This parameter is a strong indicator of the effectiveness of specific treatment techniques and is often overlooked. The equation is the same as Equation 4, with the mean for each patient ($\boldsymbol{m_1, m_2, m_{13}, \ldots, m_P}$) summed and the total divided by the number of patients in the group analyzed (P). $\boldsymbol{M_{Pop}}$ is shown in Equation 5.

$$\boldsymbol{M_{Pop}} = \frac{m_1+m_2+m_3+\cdots+m_P}{P} \quad (5)$$

The systematic error for the population ($\sum_{set-up}$) is defined as the standard deviation (SD) of the individual set-up errors relative to the overall population mean, as Equation 2. The mean for each patient is calculated using Equation 4. The resultant sum is divided by the number of patients minus one, and the square root of that value yields $\sum_{set-up}$, as shown in Equation 6.

$$\sum_{set-up} = \frac{\sqrt{(m_1-M_{Pop})^2+(m_2-M_{Pop})^2+(m_3-M_{Pop})^2+\cdots+(m_p-M_{Pop})^2}}{(P-1)} \quad (6)$$

For each individual, the interfractional random daily set-up error ($\sigma_{individual}$) is calculated as the standard deviation (SD) of the set-up errors relative to the individual mean value (m) according to Equation 4. This calculation involves summing the squares of the differences between the set-up errors and the mean for each image. The total sum is then divided by the number of images minus one, and the square root of this value is taken to obtain the $\sigma_{individual}$ value, as shown in Equation 7.

$$\sigma_{population} = \frac{\sqrt{(\Delta_1-m_1)^2+(\Delta_2-m_2)^2+(\Delta_3-m_3)^2+\cdots+(\Delta_n-m_P)^2}}{(n-1)} \quad (7)$$

The population random errors are calculated as the average of all individual random errors ($\sigma_1, \sigma_2, \sigma_3, \ldots, \sigma_P$). This equation presumes that the number of images obtained per patient is the same, or that any differences in the number of images will have a negligible impact on the final outcome, as shown in Equation 8.

$$\sigma_{set-up} = \frac{\sigma_1+\sigma_2+\sigma_3+\cdots+\sigma_P}{P} \quad (8)$$

The five equations require a significant amount of image repetition data, particularly position shift data (Δ_n), obtained from position verification for each radiation fraction to monitor variations in target position and organ motion. As known, cervix cancer treatment involves 25-30 radiation fractions [7]. It is necessary to repeat geometric verification for each fraction to obtain the PTV margin, ensuring that the administered dose corresponds to changes in target size [8].

The issue of repeating geometric verification for each radiation fraction during treatment is rarely carried out in some Radiotherapy Installations, including at RSP Universitas Andalas. This activity is only conducted for the first fraction of radiation due to the high number of patients in the treatment queue, resulting in an increased patient budget. Therefore, the calculation of systematic and random errors using the geometric verification method for each radiation fraction is rarely performed. However, in many radiotherapy centers, especially those with high patient volume, daily geometric verification for each treatment fraction is often not performed due to time and resource constraints. This leads to challenges in accurately calculating PTV margins based on conventional methods that require multiple verification data points.

Therefore, the researchers attempted to redefine the variables in the equation. The Royal College of Radiologist (2008) equation proposed and adapted it to the cervix cancer patient position data available at the Radiation Oncology Installation of Universitas Andalas Teaching Hospital. This aims to enable the calculation of the PTV margin even with only one verification data per patient and to remain optimal in maintaining the dose to adhere to the ICRU Report 50 (1993) guidelines, which recommend 95%-107% to minimize adverse effects on healthy tissues surrounding the target area [2].

2. Methods

This study was conducted using a retrospective observational design based on single-fraction geometric verification data obtained from 37 cervical cancer patients treated at the Radiation Oncology Unit of Universitas Andalas Teaching Hospital.

Patient position data is static data that depicts the position and layout of the patient table during treatment. This data consists of planning position data ($\mathbf{x}_{pi,j,k}$) and actual position data ($\mathbf{x}_{ai,j,k}$). Planning data ($\mathbf{x}_{pi,j,k}$) is obtained from CT-Simulator results in the form of images reconstructed in the Treatment Planning System (TPS) known as Digitally Reconstructed Radiograph (DRR) images. Meanwhile, actual data ($\mathbf{x}_{ai,j,k}$) is obtained from EPID verification results [9].

This study utilizes 31 sets of patient position data ($\mathbf{x}_{i,j,k}$), each consisting of planning data ($\mathbf{x}_{pi,j,k}$) and actual data ($\mathbf{x}_{ai,j,k}$) obtained from the first fraction. The positional shift data (Δ_n) resulting from the disparity between the position data ($\mathbf{x}_{i,j,k}$) is used as the initial data in calculating systematic errors (Σ), random errors (σ), and PTV margins.

Patient data was classified according to the type of PTV instead of the displacement data for each radiation fraction to be adjusted with the equations to be used, considering that each patient's data includes one displacement data (Δ_n). This is because the calculation of individual mean error (m) requires many displacement data (Δ_n) for each radiation fraction. Therefore, the data is replaced with multiple displacement data for each patient in the same type of PTV. In this study, the patients' PTVs used are Combined PTV, High PTV, and PTV 50. This change in definition is based on the margin PTV values obtained applying to all patients. The determination of the PTV name depends on biological conditions, cancer stage, and the dose given to the PTV. Thus, it can be ensured that the same PTV will receive the same treatment.

After data classification, the positional shift values are determined by calculating the difference between planning data ($\mathbf{x}_{pi,j,k}$) and actual data ($\mathbf{x}_{ai,j,k}$). These positional shift data are then used as the initial data in calculating systematic errors (Σ) and random errors (σ) and determining the PTV margin values. This adjustment allows for the utilization of available single-fraction data to estimate setup variations while maintaining clinical relevance by grouping patients with similar treatment characteristics.

To calculate the PTV margin, certain variables in equations 4-8 must be redefined according to new definitions, as presented in Table 1.

Table 1: Refefined Variables

Previous Variable		Subsequent Variable	
(Δ_n)	Patient Position Shifts in Each Radiation Fraction	(Δ_n)	Patient Position Shifts During the First Radiation Fraction Across Patient Groups with the Same PTV Type
$(m_{individual})$	Average Position Shift Per Patient	(m)	Average Position Shift for a Group of Patients
(M_{Pop})	Average of $m_{individual}$ for all Patients	(M)	Average of m for all Patients Group
$(\sum_{set-up})$	Standard Deviation of $m_{individual}$ Relative of M_{Pop}	$(\boldsymbol{\Sigma})$	Standard Deviation of m relative to M
$(\sigma_{individual})$	Standard Deviation of Δ_n Relative to M_{Pop}	(σ_{Pop})	Standard Deviation of Δ_n Relative to M
(σ_{set-up})	Average of the Overall $\sigma_{individual}$	(σ)	Average of the Overall σ

Consequently, the equations for calculating systematic and random errors are redefined as follows:

Population systematic error (m) is the sum of all position shifts in the first fraction (Δ_n) of irradiation from all patients in one type of PTV divided by the number of patients (n) or the average value of the obtained shifts. m is the redefined form of Equation 4 in the form shown by Equation 9.

$$m = \frac{\Delta_1+\Delta_2+\Delta_3+\cdots+\Delta_n}{n} \quad (9)$$

The group mean systematic error (M) is the sum of population systematic errors ($m_{population}$) divided by the number of PTV types (P). M is the redefined form of Equation 5 as shown by Equation 10.

$$M = \frac{m_1+m_2+m_3+\cdots+m_P}{P} \quad (10)$$

The systematic error ($\sum$) is the standard deviation of systematic errors relative to the group mean systematic error (M). $\sum$ is the redefined form of Equation 6 as indicated by Equation 11.

$$\sum = \frac{\sqrt{(m_1-M)^2+(m_2-M)^2+(m_3-M)^2+\cdots+(m_P-M)^2}}{(P-1)} \quad (11)$$

The population random error (σ_{pop}) is the population standard deviation for one type of PTV from one cancer case. σ_{pop} is the redefined form of Equation 7 as indicated by Equation 12.

$$\sigma_{pop} = \frac{\sqrt{(\Delta_1-m_1)^2+(\Delta_2-m_2)^2+(\Delta_3-m_3)^2+\cdots+(\Delta_n-m_P)^2}}{(n-1)} \quad (12)$$

The random error (σ) is the sum of population random errors from all PTV groups divided by the number of PTV types. σ is the redefined form of Equation 8 as indicated by Equation 13.

$$\sigma = \frac{\sigma_{pop1}+\sigma_{pop2}+\sigma_{pop3}+\cdots+\sigma_{popP}}{P} \quad (13)$$

After obtaining the values of systematic error (Σ) and random error (σ), the PTV margins in the vertical (i), longitudinal (j), and lateral (k) directions are determined using three calculation methods: Van Herk (2004) (Equation 1), Stroom (2002) (Equation 2), and ICRU *Report* No. 62 (Equation 3). All

statistical calculations and margin estimations were performed using Microsoft Excel 2019, with manual derivation based on the redefined equations.

3. Result and discussion

The patient position shift data (Δ_n) is obtained from the difference between the planning data ($\mathbf{x}_{pi,j,k}$) and the actual data ($\mathbf{x}_{ai,j,k}$) from the verification of the first fraction. The position data is categorized into several types of PTV. The results of data categorization and position shift values can be seen in Table 2.

Table 2: Results of Position Shift Data Grouping Based on PTV Types

Patients	PTV Types	Shift (Δ) (cm)		
		Vertical (i)	Longitudinal (j)	Lateral (k)
1	Combined	-1,60	-4,70	-1,30
2		-2,30	4,00	0,40
3		-0,70	3,50	0,60
4		2,30	-1,70	0,10
5		2,40	-0,90	-0,10
6		-1,40	0,70	0,00
7		0,50	-1,00	-0,60
8		-1,40	-3,60	0,30
9		4,10	-2,10	-0,50
10		-2,80	2,60	-0,20
11		0,40	-2,40	0,40
12		-2,50	0,30	1,00
13		-1,10	2,90	0,40
14		-0,20	2,30	-1,50
15		1,20	-2,20	-0,80
16		0,20	2,30	0,40
17		0,80	1,50	0,00
18		1,00	-3,10	0,40
19		1,40	-0,80	0,30
20		0,10	0,90	-0,90
21	High	2,30	-2,80	-0,20
22		0,00	-0,50	0,70
23		-1,80	0,70	0,00
24		0,40	1,50	-0,40
25		1,30	-0,70	-0,40
26		1,60	-2,00	-0,10
27		-1,70	0,10	-0,30
28		-0,30	-0,20	-0,30
29		0,40	-0,20	-0,20
30		-4,10	-0,80	-0,60
31	Intermediate	1,70	-1,70	0,60
32		3,60	4,50	-1,10
33	Pelvis High	5,30	0,40	-0,50
34		-1,10	-0,50	0,00
35		4,10	1,30	0,00
36	ThL	2,50	3,20	0,00
37		4,20	-3,10	0,20

After grouping the data as shown in Table 2, the largest displacement values in the vertical direction (i) are found in the Combined PTV group, which are -3.1 cm towards the negative direction from the isocenter point and 1.9 cm towards the positive direction from the isocenter point. Meanwhile, the largest displacement values in the longitudinal direction (j) are found in the Combined PTV group, which are 14.3 cm towards the positive direction from the isocenter point and -2.9 cm towards the negative direction from the isocenter point. In the lateral direction (k), the largest displacement values are found in the Combined PTV group, which are 3.9 cm towards the positive direction from the isocenter point and -1.5 cm towards the negative direction from the isocenter point. The obtained displacement values are quite significant. This is because the difference in the isocenter used in the planning data

acquisition process ($x_{pi,j,k}$) and the actual data acquisition ($x_{ai,j,k}$).

Based on the calculations performed using the equations redefined in Equations 9 to 13, the calculation results are obtained as shown in Table 3.

Table 3a: Results of Systematic (Σ) and Random Error (σ) Calculation in the Vertical Direction (i)

PTV	Systematic Errors (cm)			Random Errors (cm)	
	$m_{population}$	M	$\sum$	σ_{pop}	σ
Combined	-0,25			0,67	
High	0,08			0,37	
Intermediate	2,65	1,64	0,83	1,34	1,52
Pelvic	2,10			4,53	
th	3,60			0,67	

Table 3b: Results of Systematic (Σ) and Random Error (σ) Calculation in the Longitudinal Direction (j)

PTV	Systematic Errors (cm)			Random Errors (cm)	
	$m_{population}$	M	$\sum$	σ_{pop}	σ
Combined	-0,44			0,83	
High	-0,06			0,43	
Intermediate	1,40	0,26	0,36	4,38	1,71
Pelvic	-0,05			0,64	
th	0,47			2,29	

Table 3c: Results of Systematic (Σ) and Random Error (σ) Calculation in the Lateral Direction (k)

PTV	Systematic Errors (cm)			Random Errors (cm)	
	$m_{population}$	M	$\sum$	σ_{pop}	σ
Combined	0,01			0,18	
High	-0,19			0,13	
Intermediate	-0,25	-0,12	0,08	1,20	0,39
Pelvic	-0,25			0,35	
th	0,07			0,08	

Based on Table 2, the results obtained are not significantly different from the study conducted by Ariani (2014) and Mutmainnah (2022) using the calculation method from Equation 4 to Equation 8, which were not redefined, resulting in systematic error (∑) bigger than random error (σ) [10][7]. The largest systematic and random errors by Ariani (2014)'s study were found on the z-axis or vertical direction, measuring 0.59 cm and 0.38 cm, respectively [10]. The largest systematic and random error by Mutmainnah (2022) were found on the x-axis or lateral direction, measuring 0.63 cm for systematic error and 0.42 cm for random error on the x-axis (lateral direction) and z-axis (vertical direction) [7]. However, in this study, the largest systematic error (∑) was found on the z-axis vertical direction, measuring 0.68 cm, and the largest random error (σ) was found in the y-axis or longitudinal direction, measuring 1.69 cm. This is because the obtained displacement values are also significant. However, if the position shift data values are small, then the systematic and random error values obtained would also be small.

Those values are still preferable compared to not performing PTV calculations at all. Thus, the redefined equations for systematic and random errors can be applied in calculations using data from a single fraction displacement. Discrepancies in values obtained compared to previous studies are unavoidable. Organ motion and differences in technology and methodology across modalities lead to differences in accuracy, precision, and result variation [11]. Furthermore, the diverse conditions of PTV in each patient also contribute to variations in systematic and random error values [12]. Therefore, utilizing Equations 9 through 13 for calculations can save time and budget for patients.

The values of systematic error (∑) and random error (σ) are then utilized in calculating the PTV margin in cases of cervix cancer. Determining the PTV margin aims to evaluate and calibrate the radiation therapy system comprehensively.

Based on the calculation of systematic error (∑) and random error (σ), the margin values for three calculation methods in the vertical, longitudinal, and lateral directions are obtained using Equations 6, 7, and 8.

Based on Table 3, the PTV margin values in the vertical, longitudinal, and lateral directions were obtained using three calculation methods. The PTV margin with the Van Herk method yielded sizes of 3.14 cm, 2.72 cm, and 1.89 cm, while with the Stroom method, sizes of 2.09 cm, 1. 91 cm, and 1.59 cm were obtained. Meanwhile, using the ICRU Report 62 method, margin sizes were 0.96 cm, 0.60 cm, and 0.27 cm.

The ANOVA analysis of the relationship between PTV margins in cervix cancer using the Van Herk, Stroom, and ICRU Report 62 methods yielded results indicating a P-value of 0.7325 (> 0.05) for the vertical direction, 0.6783 (> 0.05) for the longitudinal direction, and 0.9821 (> 0.05) for the lateral direction. The Tukey HSD/Tukey Kramer test results showed that there were no significant

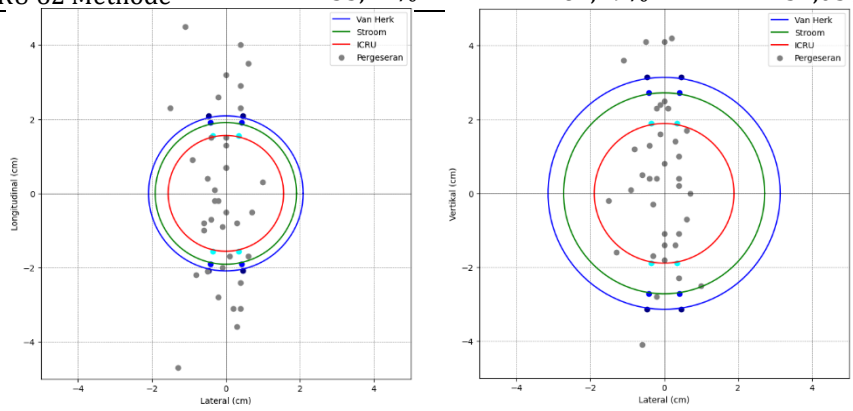
differences in the average PTV margins for each direction (P-value > 0.05). Thus, the distribution of PTV margin values is uniform in all directions.

Table 4: Calculation Results of PTV Margins

	Vertical (cm)	Longitudinal (cm)	Lateral (cm)	Standart Deviation (cm)
Systematic Error (∑)	0,83	0,36	0,08	0,31
Random Error (σ)	1,52	1,71	0,39	0,58
PTV Margin Van Herk Method	3,14	2,09	0,46	1,10
PTV Margin Stroom Method	2,72	1,91	0,42	0,95
PTV Margin ICRU Report 62 Method	1,89	1,56	0,35	0,66

Table 5: Percentage of Shifts Outside the PTV Margin

PTV Margin	Percentage of Shifts Outside the PTV Margin		
	Vertical	Longitudinal	Lateral
Van Herk Method	16,22%	43,24%	35,14%
Stroom Method	18,92%	54,84%	35,14%
ICRU 62 Methode	35,14%	61,29%	54,05%



(a) (b)

Fig. 1: Relationship between Patient Position Shifts and PTV Margin Using Van Herk, Stroom, and ICRU Methods in the (a) Lateral (X) and Longitudinal (Y) Directions, (b) Lateral (X) and Vertical (Z) Directions

The PTV margins obtained using Stroom and ICRU Report 62 formulas are smaller compared to Van Herk method. Based on Table 4, the PTV margin using the Van Herk method has a low percentage of shifts outside the margin: 16,22% in the vertical direction, 43,24% longitudinally, and 35,14% laterally [3]. The PTV margin values obtained from each method are different due to the varying systematic error (∑) multiplication factors in each formula, leading to different margin values for each method. The PTV margin, which depends on setup deviations, is not always the same for all institutions due to differences in positioning methods, therapy application techniques, and QA standards [10].

The percentage of shifts indicates that the Van Herk PTV margin is recommended, provided the position shift values do not exceed the PTV margin calculated using the Van Herk equation, shown in Figure 1. This recommendation should be supported by PTV delineation in the TPS Eclipse software to ensure clear visualization of the PTV margin. This approach helps to maximize the PTV dose while minimizing the dose to the Organ at Risk [13].

The significant variation in the shifts obtained results in relatively large PTV margins in each direction. Which indicated that a PTV margin of more than 1 cm suggests that the systematic and random errors in this study are still quite substantial [10].

One of the most likely factors causing the significant shifts between planning and actual conditions is the difference in the isocenter. Additionally, random errors between patients are also unavoidable, leading to PTV margins for cervix cancer patients ranging from 0.35 cm to 3.14 cm.

4. Conclusion

This study demonstrated that the redefinition of systematic and random error equations enables the determination of Planning Target Volume (PTV) margins using a single verification dataset. The largest systematic error (Σ) was identified in the vertical direction (0.83 cm), while the greatest random error (σ) occurred in the longitudinal direction (1.71 cm).

Among the three calculation methods, the Van Herk approach yielded the largest PTV margins, resulting in better coverage with fewer position shifts falling outside the defined margins: 16.22% (vertical), 43.24% (longitudinal), and 35.14% (lateral). These findings indicate that the redefined error equations can effectively estimate PTV margins in the absence of multi-fractional data, making them a practical solution in clinical environments with limited imaging resources.

Compared to conventional methods, the redefined approach remains consistent in error estimation and provides adequate safety margins for cervical cancer radiotherapy planning. The integration of these equations with treatment planning systems is recommended to enhance the accuracy and efficiency of radiation delivery while maintaining adherence to clinical dose constraints.

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