Novel Anisotropic Margin Calculation Based On the Cumulative Frequency Distribution of Uncertainties in the Clinical Target Volume

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Abstract

Objective: The purpose of this study was to determine the PTV margins from the cumulative frequency of uncertainties of the clinical target volume (CTV) position obtained using hybrid-image guided radiotherapy (H-IGRT) with volumetric-modulated arc therapy (VMAT).

Materials and Methods: Study participants were 22 patients with intermediate-risk prostate cancer who underwent VMAT. All patients were treated using the following image-guided (IG) procedure: 1) no-correction skin mark setup (no-IG); 2) bony anatomy registration with 2D-imaging (2D-IG); and 3) organ registration using CBCT images (3D-IG). The systematic (Σ) and random (σ) errors were obtained from the no-IG, 2D-IG, and 3D-IG registration images of 198 fractions. The PTV margin was computed using the cumulative frequency distribution of the actual position errors of the CTV, and which was compared with the formulation by $M_{PTV} = 2.5 \Sigma + 0.7 \sigma$.

Results: The margin size of 3D IG procedure was as follows: 3D-IG: 7.6, 5.4, and 3.5 mm for the AP, SI, and LR axes, respectively. Using $M_{PTV} = 2.5 \Sigma + 0.7 \sigma$, $3D-IG$: 4.2, 3.7, and 1.3 mm for the AP, SI, and LR axes, respectively. In $M_{PTV} = \alpha \Sigma + \beta \sigma$, the coefficients $\alpha$ and $\beta$ were $\alpha = 3.4, 2.3, and 4.6$ and $\beta = 2.9, 3.0, and 3.0$ for AP, SI, and LR, respectively.

Conclusion: The margin size ($M_{PTV}$) calculated by our modified formulation based on the margin direction satisfied 99% of the prescription dose coverage in each direction and a minimum of 95% of the dose coverage to the CTV for all patients using H-IGRT.

Keywords: Hybrid image-guided radiotherapy; Planning target volume margin; Prostate cancer; CTV position uncertainty

Introduction

Online image guided radiotherapy (IGRT) is used for prostate registration for prostate cancer patients [1-5]. At our hospital, online correction via a three-step setup protocol with hybrid-image guided radiotherapy (H-IGRT) is conducted, i.e., two-dimensional (2D)/three-dimensional (3D) and 3D/3D registrations are performed using H-IGRT. Our IGRT protocol preferentially uses organ registration relative to the anterior rectal wall, which corrects for almost all systematic errors; however, several random errors remain. Setup correction protocols may reduce geometric treatment uncertainties and the clinical target volume (CTV) to-planning target volume (PTV) margins. Therefore, a novel approach is required for PTV margin calculations ($M_{PTV}$) in H-IGRT that accounts for small systematic uncertainty, random uncertainty and target registration residual error (TRE) depend on H-IGRT system, in contrast to the more general formulation by van Herk et al., i.e., $M_{PTV} = 2.5 \Sigma + 0.7 \sigma$, which accounts for the population systematic uncertainty $\Sigma$ and random uncertainty $\sigma$. This formula ($M_{PTV}$) was computed with statistical procedure using systematic and random uncertainties of CTV position [6]. Furthermore, the coefficients of the model parameters were numerically calculated under a spherically symmetric condition thereby leading to an isotropic margin perpendicular to a spherical tumor surface. However, did not consider about residual error to be TRE in case of using IGRT. For example, as TRE arise due to deformation of prostate and/or seminal vesicles even if the registration at CTV using image guidance with CBCT. The purpose of this study was to determine the PTV margins from the cumulative frequency of CTV uncertainties include TRE obtained by an H-IGRT system.

Materials and Methods

Patients and treatment plan

Twenty-two intermediate-risk prostate cancer patients who were treated using VMAT between 2012 and 2013 were included in this study. All patients were immobilized in a position using a vacuum cushion (Vac-Lok; MedTech, Orange City, IA, USA). Computed tomography (CT) scans were acquired with 2.5 mm slice thicknesses using a 16-detector row CT scanner (Optima CT580W; GE Medical Systems, Waukesha, WI, USA) from the lower abdomen to 50.0 mm below the ischial tuberosity. The initial reference markers and associated skin marks were placed at the time of CT simulation.

CTV was defined as the entire prostate and the proximal 15.0 mm of the seminal vesicles. PTV was generated by adding an 8.0 mm margin to CTV in all dimensions except posteriorly, where a 5.0 mm margin was used. Contouring of the organ at risk (OAR) included the rectum, bladder, femoral heads, penile bulb, and small bowel, defined according to the Radiation Therapy Oncology Group (RTOG) pelvic...
normal tissue contouring guidelines [7]. The total prescription dose was 78.0 Gy to the PTV at 2.0 Gy per fraction. Dose normalization was set to the PTV mean dose. The treatment plans were generated using single-arc VMAT (358 degrees; 74 sec per rotation). All treatment plans were developed using Eclipse® version 10.0 planning software (Varian Medical Systems, Palo Alto, CA, USA) for 10 MV photon irradiation. The dose was calculated using the Analytical Anisotropic Algorithm in Eclipse®.

To verify leaf motion of each beam or specific patient’s plans, various quality assurance tests were conducted [8,9]. Once the VMAT plan was developed and approved, CT simulation datasets were imported into the ExacTrac® X-ray 6D system (BrainLab AG, Feldkirchen, Germany) for 2D/3D registration using digital reconstructed radiographs (DRRs) of 2D oblique images to the planning CT images [10]. The CT simulation datasets were also imported into the ARIA record and verification system (Varian Medical Systems, Palo Alto, CA, USA) for 3D/3D registration using CBCT images and planning CT images [11,12]. VMAT was delivered using linear accelerators equipped with a high-definition multi-leaf collimator (HD-MLC); spatial resolution: 2.5 mm at the isocenter; Novalis TX; BrainLab AG, Feldkirchen, Germany). The daily treatment time, including image registration from the final image acquisition until the end of irradiation, was 4 to 6 min. Before each fractionation, the bladder and rectum volume were prepared in the same way as at the time of CT simulation.

**IGRT strategy for prostate cancer at our hospital**

Figure 1 shows a diagram of the IGRT procedure used in this study. The H-IGRT system consisted of an ExacTrac® X-ray 6D system and linear accelerator equipped with CBCT. All patients were treated using the step-by-step IG procedures involving no-correction skin mark setup (no image guidance; no-IG), bony anatomy 3D registration using 2D images from ExacTrac® X-ray 6D system (2D image guidance; 2D-IG), and 3D organ registration using CBCT images (2D image guidance; 2D-IG).

Firstly, the no-IG procedure was used to align the skin mark with the lasers. However, setup residual error of the CTV arose due to geometrical constraints associated with the bony anatomy [11,13]. Also, a systematic pitching error (maximum: 2.0 mm) was present due to the difference between the flexibility of the CT couch and that of

![Figure 1: Hybrid image-guided radiotherapy (H-IGRT) strategy used in our institute. The solid arrowheads represent the pre-treatment procedure for IGRT error detection, and the dotted arrowheads correspond to the post-treatment procedure for IGRT error detection.](image-url)
the linear accelerator treatment couch. Therefore, as a next step, the 2D-IG procedure using the ExacTrac® X-ray 6D system was used to correct for the setup residual error of the bony anatomy and systematic pitching error of the linear accelerator treatment couch. At the same time, the inter-fractional setup error was calculated by the BrainLab iterative rigid registration process, which uses mutual information as a similarity measure for its calculation [10,11]. Subsequently, inter-fractional organ motion error was corrected using 3D-IG, with priority given to the anterior rectal wall while simultaneously ensuring that the portion of the rectum overlapping the PTV is excluded.

Uncertainty component of the CTV for each image guidance procedure

Inter- and intra-fractional variations in the CTV positions relative to the treatment beam were represented as systematic (Σ) or random (σ) uncertainties which were calculated based on components of each CTV in the Table 1, respectively. Σ is the standard deviation of the overall means per patient (M), σ is the overall standard deviation of the population, and Σ and σ uncertainties were calculated from 2D- and 3D-IG image data. The authors evaluated a total of 396 image sets for inter-fractional variation (198 fractions) and a total of 288 image sets for intra-fractional variation (144 fractions) in the CTV position for the 22 patients.

Inter-fractional systematic (Σ\textsubscript{inter-treat}) and random (σ\textsubscript{inter-treat}) setup uncertainties of the bony anatomy were calculated from bony anatomy registration data obtained from 2D-IG images (Figure 1).

The CTV position error associated with our setup was categorized into inter- and intra-fractional bony anatomy error (CTV\textsubscript{inter-setup} and CTV\textsubscript{intra-setup}) [14]. Inter-fractional organ motion systematic (Σ\textsubscript{inter-org}) and random (σ\textsubscript{inter-org}) uncertainties of the CTV were calculated between the planning CTV position and the CTV position after 2D-IG bony anatomy registration, which was obtained by preregistration of the 3D-IG images; these CTV uncertainty components were defined as CTV\textsubscript{inter-org}. Note that Σ\textsubscript{inter-org} and σ\textsubscript{inter-org} include the position error due to deformation [15-17]. Although Σ\textsubscript{inter-org} and σ\textsubscript{inter-org} were corrected using 3D-IG, inter-fractional residual systematic (Σ\textsubscript{inter-treat}) and random (σ\textsubscript{inter-treat}) uncertainties of the CTV remained due to the anterior rectal wall reference with 3D-IG. Consequently, Σ\textsubscript{inter-treat} and σ\textsubscript{inter-treat} were calculated using the difference between the planning CTV position and the final CTV position used for treatment in the hybrid image guidance (CTV\textsubscript{inter-treat}); i.e., the final CTV position after the no-IG, 2D-IG, and 3D-IG procedures. As described above, 3D-IG was performed with preferential registration given to the anterior rectal wall in this study. Therefore, CTV\textsubscript{inter-treat} was included in the deformation error of the CTV due to rectal deformation and/or filling as well as inter-fractional prostate motion error (Figure 2).

The intra-fractional setup random uncertainty (σ\textsubscript{intra-treat}) was calculated from the pre- and post-treatment setup error position of the bony anatomy. Systematic (Σ\textsubscript{intra-treat}) and random (σ\textsubscript{intra-treat}) uncertainties for intra-fractional organ motion were calculated from the position error during the CTV\textsubscript{intra-treat} fraction (CTV\textsubscript{intra-treat} - CTV\textsubscript{intra-treat}), Σ\textsubscript{intra-treat} and σ\textsubscript{intra-treat} were calculated using image sets of pre- and post-treatment registration of 16 of 22 patients. These intra-fractional uncertainties were obtained using 2D- and 3D-IG images immediately after irradiation.

2D-IG and 3D-IG procedures all included only translational motion errors related to displacement; rotational angle errors were excluded from evaluation in this study. These five uncertainty components (referred to as CTV\textsubscript{all}) were included in the residual uncertainty from 3D-IG in addition to the CTV uncertainty reported in the International Committee on Radiation Units (ICRU) Report-62 [18]. The coordinates of CTV\textsubscript{all} centre were obtained using the isocenter automatic setting function for the PTV. To minimize inter-observer variation, the contouring of organs for definition of the centroid coordinates was performed by a single physicist.

Overall systematic (Σ\textsubscript{all}) and random (σ\textsubscript{all}) uncertainties

The no-IG, 2D-IG, and 3D-IG procedures all had different overall systematic (Σ\textsubscript{all}) and random (σ\textsubscript{all}) uncertainty components for the CTV, as shown in Table 1. Σ\textsubscript{all} and σ\textsubscript{all} of each IGRT were calculated using the root-sum-square (RSS) of the components of CTV\textsubscript{all}, as shown in Table 1. Σ\textsubscript{all} and σ\textsubscript{all} of these uncertainty components are listed in Table 2; the values for Σ\textsubscript{all} and σ\textsubscript{all} are represented as Gaussian uncertainties.

### Table 1: Uncertainty components of the clinical target volume (CTV) variation with respect to the planning target volume (PTV) margin design.

<table>
<thead>
<tr>
<th>No IGRT</th>
<th>2D-IGRT</th>
<th>3D-IGRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTV\textsubscript{inter-setup}</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CTV\textsubscript{inter-organ}</td>
<td>CTV\textsubscript{inter-organ}</td>
<td>CTV\textsubscript{inter-treat}</td>
</tr>
<tr>
<td>CTV\textsubscript{intra-treat}</td>
<td>CTV\textsubscript{intra-treat}</td>
<td>CTV\textsubscript{intra-treat}</td>
</tr>
<tr>
<td>CTV\textsubscript{inter-treat}</td>
<td>CTV\textsubscript{inter-treat}</td>
<td>CTV\textsubscript{inter-treat}</td>
</tr>
</tbody>
</table>

Abbreviations: Please refer to Figure 1.

<table>
<thead>
<tr>
<th>Component</th>
<th>AP (mm)</th>
<th>SI (mm)</th>
<th>LR (mm)</th>
<th>M\textsubscript{mean}</th>
<th>AP (mm)</th>
<th>SI (mm)</th>
<th>LR (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M\textsubscript{intra-treat}</td>
<td>-0.3</td>
<td>0.8</td>
<td>1.4</td>
<td>M\textsubscript{mean}</td>
<td>-0.9</td>
<td>-0.7</td>
<td>0.0</td>
</tr>
<tr>
<td>Σ\textsubscript{intra-treat}</td>
<td>2.0</td>
<td>1.2</td>
<td>1.6</td>
<td>Σ\textsubscript{mean}</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>σ\textsubscript{intra-treat}</td>
<td>0.6</td>
<td>0.3</td>
<td>0.4</td>
<td>σ\textsubscript{mean}</td>
<td>0.7</td>
<td>0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>M\textsubscript{inter-org}</td>
<td>1.6</td>
<td>0.4</td>
<td>0.2</td>
<td>M\textsubscript{mean}</td>
<td>0.9</td>
<td>-1.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Σ\textsubscript{inter-org}</td>
<td>2.1</td>
<td>1.2</td>
<td>0.3</td>
<td>Σ\textsubscript{mean}</td>
<td>1.1</td>
<td>1.2</td>
<td>0.4</td>
</tr>
<tr>
<td>σ\textsubscript{inter-org}</td>
<td>0.4</td>
<td>0.3</td>
<td>0.2</td>
<td>σ\textsubscript{mean}</td>
<td>0.5</td>
<td>0.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Abbreviations: M: the overall mean of the mean patient-specific error across all patients; Σ: systematic uncertainty, overall standard deviation across all patients of the mean patient-specific error; σ: random uncertainty, standard deviation of the patient-specific standard deviation. AP: anterior–posterior direction; SI: superior–inferior direction; LR: left–right direction.

### Table 2: Systematic (Σ) and random (σ) uncertainties of each CTV acquired from 2D- and 3D-IG data using the proposed H-IGRT strategy.
The anisotropic PTV margins can be calculated using the formula

\[ M_{PTV\text{\scriptsize{vector}}} = \alpha \Sigma + \beta \sigma, \]

where \( m_1, m_3 \) are required to describe the margin size of the CTV position uncertainty, computed using cumulative frequency distribution, the tolerance level for the PTV margin calculation (M = 2.5 \( \Sigma + 0.7 \sigma \)) [6].

**Design of the equation to calculate the anisotropic PTV margins for H-IGRT**

The anisotropic PTV margins can be calculated using the formula

\[ M_{PTV\text{\scriptsize{vector}}} = \alpha \Sigma + \beta \sigma, \]

where \( m_1, m_3 \) are required to describe the margin size of the CTV position uncertainty, computed using cumulative frequency distributions of \( m_1 \); CTV_{inter-setup}; m_2; CTV_{intra-organ}; m_3; CTV_{intra-trait}; and m_4; CTV_{intra-trait} (Figure 1). The uncertainties with respect to the PTV margin for each IG procedure are listed in Table 1. To compare the margin size with our results, the no-IG, 2D-IG, and 3D-IG PTV margins were calculated using the margin formula of van Herk et al. (M = 2.5 \( \Sigma + 0.7 \sigma \)) [6].

**Results**

**Systematic (\( \Sigma \)) and random (\( \sigma \)) uncertainties of CTV\_\text{all}**

The systematic (\( \Sigma \)) and random (\( \sigma \)) uncertainties of CTV for each IG condition are shown in Figure 1. The uncertainty components of the CTV position error with respect to the PTV margin are shown in Table 1. \( \Sigma \), \( \sigma \), and the mean of these uncertainty components are listed in Table 2; the values for \( \Sigma \) and \( \sigma \) are represented as Gaussian distributions. The uncertainty of the CTV position for each IG procedure increased in the order AP, SI, and LR for both \( \Sigma \) and \( \sigma \). According to van Herk et al., \( \Sigma \) for each dimension was larger than \( \sigma \) [6], similar to our results, with \( \Sigma > \sigma \) overall (Table 2).

\[ \Sigma_{\text{all}} \text{ and } \sigma_{\text{all}} \text{ were computed using Eqs. (1) – (3). For the H-IGRT strategy proposed in this study, systematic and random errors were revised progressively over the IG procedure (no-IG, 2D-IG, and 3D-IG); hence, } \Sigma_{\text{all}} \text{ and } \sigma_{\text{all}} \text{ were relatively small after the completion of 3D-IG (Table 3).} \]

Although \( \Sigma_{\text{all}} \text{ and } \sigma_{\text{all}} \text{ for the SI and LR directions for 2D-IG and 3D-IG showed the same results, the individual uncertainty components differed, as shown in Table 1. As described above, the authors adopted...
the anterior rectal wall registration for the 3D-IG procedure. Therefore, despite prior rectal preparation, rectal filling had an impact on CTV position in 3D-IG; specifically, the LR value was greater than that for 2D-IG.

Comparison of the PTV margin sizes using the theoretical formula and actual distributions of the variations in CTV position in our H-IGRT strategy

The cumulative dose frequency distributions of CTV position errors were obtained using inter- and intra-fractional error for CTV$_{\text{ICV}}$. The curves of the cumulative dose frequency distributions were computed using polynomial regression ($R^2 > 0.99$) fitting (Figure 3).

The approximate expressions shown in Figure 3 were then used to compute the PTV margin size within tolerance levels of 80, 90, 95 and 99% for the five components (Table 5). Among the individual components, CTV$_{\text{inter-setup}}$ had the greatest influence on PTV margin size, followed by CTV$_{\text{inter-treat}}$, CTV$_{\text{inter-organ}}$, CTV$_{\text{intra-setup}}$, CTV$_{\text{intra-treat}}$ and CTV$_{\text{intra-organ}}$ (Table 4). Intra-fractional organ motion and intra-fractional setup uncertainty values (CTV$_{\text{intra-setup}}$ and CTV$_{\text{intra-treat}}$) were similar to others in the literature [20,21]. The maximum position error of the CTV was in the AP direction of CTV$_{\text{intra-treat}}$ (>9.0 mm, 99% confidence level).

The PTV margins (No-PTV margin, 2D-PTV margin and 3D-PTV margin) were computed using the RSS of the uncertainties in the AP direction of CTV$_{\text{ICV}}$. The PTV margin size required for the H-IGRT was 7.6, 5.4, and 3.3 mm AP; 4.3 mm SI; and 3.3 mm AP (2D-IG); 4.3 mm SI; and 3.3 mm AP (3D-IG). Using van Herk’s formula, both the 2D- and 3D-PTV margins in the LR direction were 1.3 mm; these sizes are not suitable for clinical use.

Design of an anisotropic PTV margin for H-IGRT

In this study, $\alpha$ and $\beta$ in the equation ($M_{\text{PTV}} = \alpha \Sigma_{\text{error}} + \beta \sigma_{\text{error}}$) were derived for the calculation of the anisotropic PTV margin via H-IGRT.
\[ \Sigma_{\text{vol}} \text{ and } \sigma_{\text{vol}} \text{ were obtained from the uncertainties for } CTV_{\text{vol}} \text{ shown in Table 3. } M_{\text{PTV}} \text{ for a prescription dose of } 95\% \text{ to the CTV was determined using the cumulative frequency distributions of } CTV_{\text{vol}} \text{ shown in Table 6. Accordingly, } \alpha \text{ and } \beta \text{ in this equation were computed using a least squares matrix operations (Table 7). } \Sigma_{\text{vol}} \text{ and } \sigma_{\text{vol}} \text{ were reduced during the H-IGRT procedure (Figure 1) due to the progressive corrections that occurred for each process (no-IG, 2D-IG, and 3D-IG). Consequently, for adequate anisotropic PTV margin size calculations, } \alpha \text{ ranged from 2.3–5.5 and } \beta \text{ was 2.8–3.0 (Table 7).} \]

**Discussion**

The authors performed online correction using H-IGRT to all fractions for prostate cancer patients undergoing VMAT. The H-IGRT strategy corrected for the systematic and random errors of CTV. The systematic \( (\Sigma_{\text{vol}}) \text{ and random uncertainties (} \sigma_{\text{vol}} \text{), according to the each IG correction protocol were computed with image data sets acquired for inter- and intra-fractional errors of CTV (Tables 1 and 2). Additionally, the proposed PTV margin calculation considered not only inter-fractional prostate movement which was acquired from each IGRT procedure but also a TRE that arise with No-IG, 2D- and 3D-IG.

CTV position exhibits anisotropic variation; thus, the PTV margin size calculation must consider all three dimensions for a minimum dose of more than 95% to the CTV. The CTV is generally expanded with a “rolling ball” algorithm [19] as a spherically symmetric condition in treatment planning for prostate cancer. In this instance, each PTV margin direction should be kept within 98.5% tolerance for a minimum dose of >95% to the CTV. Using the proposed H-IGRT strategy, the 3D-PTV margin size was 7.6, 5.4, and 3.5 mm in the AP, SI, and LR directions, respectively (Table 5), whereas the current PTV margin in the current study (8.0 mm in all dimensions, except posteriorly, where it was 5.0 mm) were barely reduced. Since the authors are adopting anterior rectal wall registration, rectal side margin will be enough at 5.0 mm.

With regard to daily variations in prostate position, several authors described prostate movement of 6.0–20.0 mm in each direction by inter-fractional organ motion or deformation [22-24]; inter-fractional organ motions are larger than intra-fractional motions [25]. Thus, without online IGRT procedures, safety margins of 10.0 mm for the AP and SI directions and 8.0 mm in the LR direction around the prostate have been recommended [1,2]. Hurkmans et al. and Rudat et al. [1,2] computed the PTV margin from actual inter-fractional setup uncertainty; safety margins of 8.0 mm (LR) and 10.0 mm (AP and SI) were reported for prostate cancer patients. Smitsman et al. and Meijer et al. [17,26] considered inter-fractional organ motion uncertainty and residual error of the seminal vesicles in their margin design.

In the present study, the PTV margin size was calculated using the cumulative frequency distributions of inter- and intra-fractional variations and TRE, which included the seminal vesicles in the CTV. The margin of the no-IG (only skin mark setup) were 12.6, 7.3, and 5.9 mm for the AP, SI, and LR directions, respectively, calculated using the cumulative frequency distribution of \( CTV_{\text{vol}} \). \( \Sigma_{\text{vol}} \text{ and } \sigma_{\text{vol}} \text{ were substituted into van Herk et al.'s formula } (M = 2.5 \Sigma_{\text{vol}}+0.7 \sigma_{\text{vol}}). \) and the PTV margin was calculated again, revealing margins of 8.3, 5.0, and 4.4 mm for the AP, SI, and LR directions, respectively. The maximum difference between those results and ours was observed in the AP direction. Also, the 2D- and 3D-PTV margins using van Herk et al. were 1.7–3.4 mm smaller than our results (Table 6). Meijer et al. [26] computed the PTV margin size using a model-based deformable image registration and online IGRT, and compared their results with van Herk et al. [6], whose values were reportedly smaller by a maximum of 3.0, 2.0, and 2.0 mm in the AP, SI, and LR directions, respectively. Coverage in each direction of the CTV computed using the margin size formula proposed by van Herk et al. was no more than 80–95%, with 3D coverage limited to 51–86% (Tables 5 and 6).

Engels et al. [27] analysed the correlation of the PTV margin size and impact on the five-year freedom from biochemical failure (FFBF) in IGRT for prostate cancer. The PTV margins of 5.0, 4.0, and 3.0 mm (AP, SI, and LR, respectively) were compared with an isotropic PTV margin of 6.0 mm in all directions; PTV margins of 6.0 mm in all directions indicated a five-year FFBF percentage of 96%, compared with 74% for the tighter PTV margin group. In our results, the PTV margin sizes with \( M_{\text{PTV}}=2.5 \Sigma+0.7 \sigma \) were 4.2, 3.7 and 1.3 mm (in the AP, SI, and LR directions, respectively); thus, the PTV margin may be inadequate if van Herk et al.'s formula is used for H-IGRT. Given this margin size, the coverage would range from 51 to 86% for the 3D CTV. Hence, the authors concluded that the use of the \( M_{\text{PTV}}=2.5 \Sigma+0.7 \sigma \) formula for prostate cancer may be inadequate.

Van Herk et al. assumed that organ movement could be represented by a normal probability distribution; the margin recipe was represented with one formula for all directions for the PTV calculation. In contrast, our recipe offers greater flexibility in that it can accommodate random variation using a cumulative distribution function, because uncertainty of CTV position of the respective direction has a certain variance and distribution. Additionally, H-IGRT can cover variations in the CTV position for each vector, using our recipe, by correcting for nearly all associated systematic errors. More specifically, assuming that \( \Sigma \) is zero by use of the H-IGRT system, and then the calculation for the PTV margin size considers only the random uncertainty (\( \sigma \)), which is simply multiplied by a coefficient value, ranges from 2.8–3.0 to the \( \sigma \). In this study, the proposed method considered equations for the PTV margin calculation for No-IG and 3D-IGRT in three axes, AP, SI, and LR.

**Conclusion**

H-IGRT was corrected for systematic and random errors of the CTV for almost all fractions. The margin size (\( M_{\text{PTV}} \)) was calculated

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**Table 5:** Anisotropy of the PTV margin size computed using the frequency distributions of the CTV position variation.

<table>
<thead>
<tr>
<th>Percentage of the CTV position within tolerance</th>
<th>No-PTV margin (mm)</th>
<th>2D-PTV margin (mm)</th>
<th>3D-PTV margin (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AP</td>
<td>SI</td>
<td>LR</td>
</tr>
<tr>
<td>80%</td>
<td>6.6</td>
<td>2.4</td>
<td>4.0</td>
</tr>
<tr>
<td>90%</td>
<td>8.7</td>
<td>3.9</td>
<td>4.8</td>
</tr>
<tr>
<td>95%</td>
<td>10.2</td>
<td>5.8</td>
<td>5.5</td>
</tr>
<tr>
<td>99%</td>
<td>12.6</td>
<td>7.3</td>
<td>5.9</td>
</tr>
</tbody>
</table>

\( M_{\text{PTV}}= \sum (m_i^2 + m_j^2 + m_k^2 + m_{ijk}^2). \) \( M_{\text{PTVcorrected}} \) is the margin size in each direction. \( m_i-m_n \) are listed in Table 4.
using a novel formula that accounted for the anisotropy of the organ considered (the prostate); the recipe satisfied a 99% prescription dose in three directions (AP, SI, and LR). Moreover, using the H-IGRT procedure, the minimum dose to the CTV was 95% of the prescribed dose over three dimensions for all prostate cancer patients.

**Acknowledgment**

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### Table 6: Comparison of the PTV margin size using the formula given by van Herk et al. \((M_{\text{PTV}} = \alpha \sum + \beta \alpha)\) and the actual distributions of the CTV position using the proposed H-IGRT strategy.

<table>
<thead>
<tr>
<th>No-PTV margin</th>
<th>2D-PTV margin</th>
<th>3D-PTV margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha)</td>
<td>(\beta)</td>
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**References**


