Evaluation of safety margins for cone beam CT-based adaptive prostate radiotherapy

Florian Dupont[1,2], David Dechambre[3] & Edmond Sterpin[1,4,5]

[1]UCLouvain, Center of Molecular Imaging, Radiotherapy and Oncology (MIRO), Brussels, Belgium;

[2]Cliniques Universitaires Saint-Luc (CUSL), Nuclear Medicine department, Brussels, Belgium;

[3]Cliniques Universitaires Saint-Luc (CUSL), Radiotherapy department, Brussels, Belgium;

[4]KU Leuven, Department of Oncology, Laboratory of experimental radiotherapy, Leuven, Belgium;

[5]Particle Therapy Interuniversity Center Leuven (ParTICLe), Leuven, Belgium

Corresponding author: Florian Dupont (florian.dupont@saintluc.uclouvain.be)

Nuclear medicine department

Cliniques Universitaires Saint-Luc (CUSL)

10 Avenue Hippocrate

1200 Brussels, Belgium

Highlights

- Adaptive radiotherapy induces randomness in delineation process
- Computation of relevant delineation uncertainty is achievable for rigid volume
- The method allows to reduce PTV margins for prostate Adaptive Radiotherapy

Abstract

Adaptive radiotherapy is characterized by the use of a daily imaging system, such as CBCT (Cone-Beam Computed Tomography) images to re-optimize the treatment based on the daily anatomy and position of the patient. By systematically re-delineating the Clinical Target Volume (CTV) at each fraction, target delineation uncertainty features a random component instead of a pure systematic. The goal of this work is to identify the random and systematic contributions of the delineation error and compute a new relevant Planning Target Volume (PTV) safety margin.

169 radiotherapy sessions from 10 prostate cancer patients treated on the Varian ETHOS treatment system have been analyzed. Intra-patient and inter-patient delineation variabilities were computed in six directions, by considering the prostate as a rigid, non-rotating volume. By doing so, we were able to directly compare the delineations done by the physicians on daily CBCT images with the initial delineation done on the CT-sim and MRI, and sort them by direction using the polar coordinates of the points. The computed variabilities were then used to compute a PTV margin based on Van Herk margin recipe.

The total margin computed with random and systematic delineation uncertainties was of 2.7, 2.4, 5.6, 4.8, 4.9 and 3.6 *mm* in the left, right, anterior, posterior, cranial and caudal directions, respectively.

According to our results, the gain offered by the separation of the delineation uncertainty into systematic and random contributions due to the adaptive delineation process justifies a reduction of the PTV margin down to 3 to 5 *mm* in every direction.

Keywords: Adaptive radiotherapy, margins, delineation

1 Introduction

External beam radiotherapy treatment delivery entails uncertainties [1, 2] that can affect the coverage of the target and therefore the treatment outcome [3, 4]. In order to account for them, a margin is added to the clinical target volumes (CTV) to create planning target volumes (PTV). This margin depends on the uncertainties that we are dealing with, and can be computed using safety margin recipes, for instance the so-called Van Herk formula [5]. This recipe is based on the separation of systematic uncertainties, that affect the treatment as a whole, and the random uncertainties, that affect each fraction independently.

CBCT-based image-guided radiation therapy (IGRT) reduces patient's and organ's motion uncertainties [6, 7] by allowing a more accurate positioning of the target before each fraction. The target delineation, however, remains the same for the whole treatment. It means that an error linked to it is fully systematic and will therefore greatly affect the final PTV margin [8].

The development of CBCT-based online adaptive solutions have recently changed this statement. This technology aims to ensure the dose coverage of the target, while optimizing the preservation of healthy tissues, by allowing a reoptimization of the treatment before each fraction based on the current patient's position and anatomy [9]. The delineation of the target and the organs at risk (OAR) is therefore modified every day [10], which introduces a random component in the delineation uncertainty.

Recent publications have shown that a good CTV coverage (> 95%) can be achieved with reduced PTV margins in prostate Online Adaptive Radiotherapy (OART) by simulating treatments with isotropic 4 *mm* margins [11] or non-isotropic 3 *mm* posterior, 5 *mm* left/right/anterior, and 7 *mm* superior/inferior margins [12]. This method, however, does not consider the delineation uncertainty but only the intra-fraction motion. Margin reductions down to 3 to 5 *mm* have also been successfully implemented in Magnetic Resonance guided Radiotherapy (MRgRT) [13, 14, 15], but these results cannot be immediately transposed to CBCT-

based OART, as the entire radiotherapy workflow is different and as well as the expected delineation error between MRI and CBCT.

Several methods have proven useful to evaluate contouring variations, such as dice coefficient, Hausdorff's distance or Center of Mass (COM) distance [16, 17]. However only helpful as to provide one single evaluation parameter of the accuracy of a contouring technique, they do not allow directional analysis of the variations between contours compatible with the PTV margins formula. An accurate method to perform such directional analysis has been presented by Remeijer et al. [18] and consists in a comparison of the spherical coordinates of the points of the contours.

The aim of this work is to propose a methodology to compute the systematic and random contributions of the delineation uncertainty in CBCT-based online adaptive radiotherapy, and use them to compute a relevant PTV margin for the particular case of prostate OART.

2 Materials and Methods

2.1 Patient Data

We included data from 169 radiotherapy sessions delivered to 10 prostate cancer patients treated between August 2021 and April 2022 with adaptive radiotherapy using the Varian ETHOS system (Varian Medical Systems, Palo Alto, CA) in the CUSL (Cliniques Universitaires Saint-Luc). All patients were treated under a moderately hypofractionnated ART protocol (20x3Gy or 28x2.5Gy in case of concomitant lymph nodes treatment). The reference contours of the CTV (defined as the entire prostate) and the Organs at Risk (OAR) were made by a physician on a planning CT scan with the help of an MRI. Before each fraction, a CBCT of the patient is acquired and a synthetic CT is created by deformable image registration with the simulation CT. The influencers (organs that have an influence on the CTV shape and position, i.e., the bladder and rectum) are auto-contoured on the CBCT by the AI-based auto-contouring integrated in the Ethos system. These structures are reviewed by a physician and modified if needed before being used by the system to perform a structure-based deformation and mapping of the CTV. The resulting contours are finally reviewed by the same physician and a second CBCT is acquired just before the fraction's delivery in order to ensure that the anatomy has not changed during the adaptation process.

The data analyzed was the initial CTV contours delineated on the CT-sim and the reviewed CTV contours on the CBCT.

The use of patients' data has been approved by the ethics committee of Saint-Luc hospital (approval number: 2019/16SEP/402).

2.2 Estimation of delineation uncertainties

For every patient, the DICOM RTSTRUCT files containing the delineation of the CTV in the simulation CT and in all of the daily CBCTs have been collected. Their differences have been computed using a homemade script using *Python* (v3.9). The method used is based on the work of Remeijer et al. [18] to quantify the 3D variations of the delineated volume. Their method was chosen here because it is an effective way to quantify both the systematic and the random volume variations in all six directions of space for nearly spherical CTV volumes. Moreover, the outcomes are immediately computed in a form that is compatible with the Van Herk margin recipe [5].

The workflow to compute the delineation uncertainty is described in Figure 1. First, the COM of each structure is computed in order to express the coordinates of each point of the structure relative to its center (1). The points' coordinates are converted into spherical ones (2), and the radial distances are interpolated into a predefined mesh of azimuthal and polar angles (3). Finally, the results are segmented into six areas corresponding to the six directions (right, left, anterior, posterior, cranial and caudal) and the mean difference is computed for each part. The six areas are defined as all the points situated between +45° and -45° relative to the axis pointing in the considered direction (4). For each patient, the script returns the mean variation in every direction and the standard deviation between the different sessions. Given this information, we can find the systematic standard deviation Σ by computing the standard deviation of the means of the patients and the random standard deviation σ by computing the root mean square of the individual standard deviations.

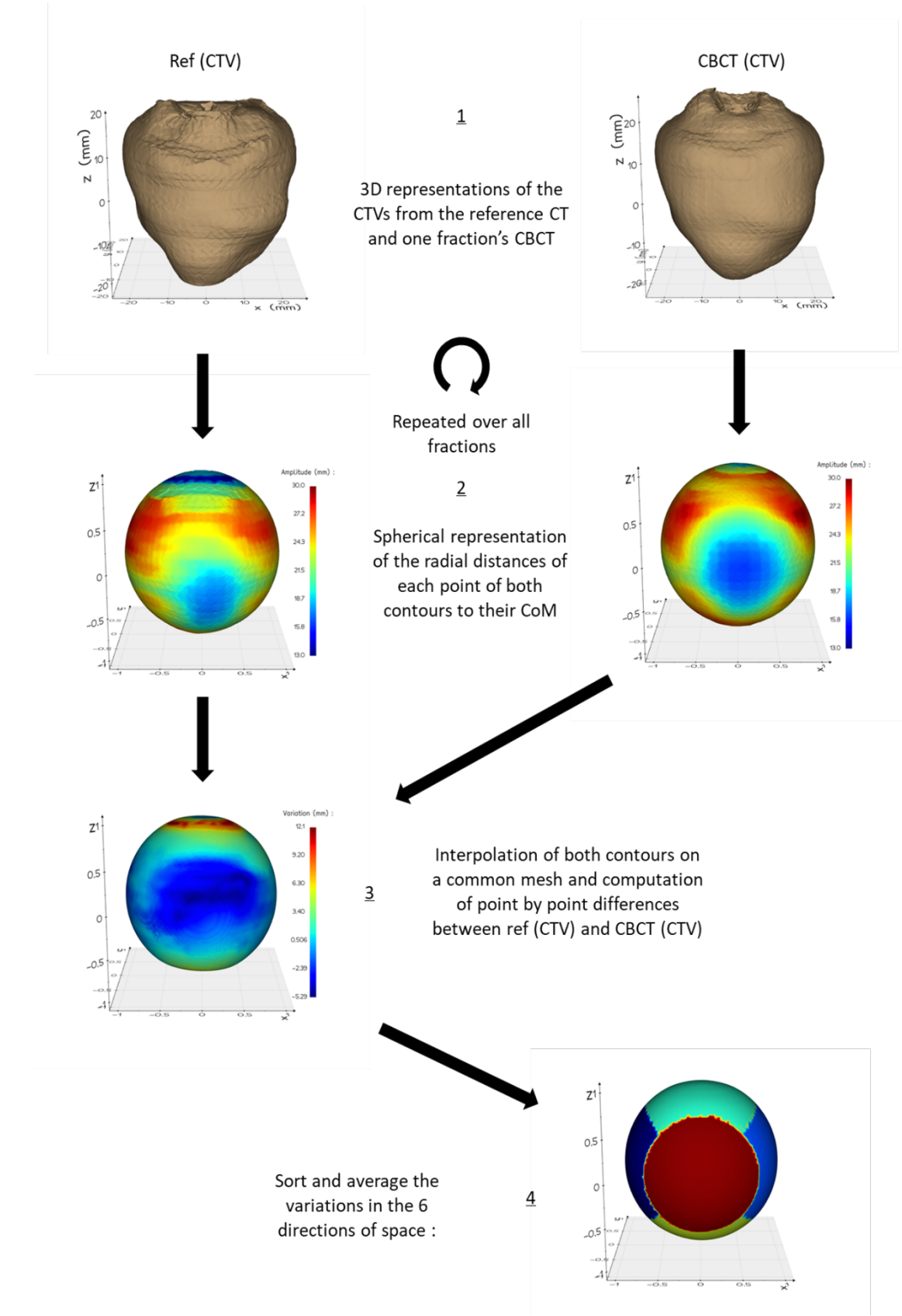

Figure 1 : Main steps of the workflow to compute the mean and standard deviation of the delineation's variations over one patient' radiotherapy treatment.

To be able to extract single values for the random and systematic contributions of the delineation uncertainty, some assumptions had to be made. The first one is that the movements of the prostate are only translational, and there are no rotations of any kind. The second one is that there are no variations of the shape of the prostate through the treatment [19]. The last one is that for every patient, the delineation done by the physicians on the CT-sim with the help of an MRI is used as a reference. These assumptions allow a matching of all the contours in a common coordinate system to compare their shapes point by point.

2.3 Computation of the PTV margin and clinical evaluation

Once the delineation uncertainties are computed in all directions, a total PTV margin is computed using the Van Herk method [5], by adding an isotropic penumbra of 2.8 *mm* [20] and a systematic setup error of 0.3 *mm* (maximum measured offset between CBCT and treatment isocenters on the ETHOS system at the radiotherapy department of the CUSL). The intrafraction systematic and random motion errors are computed using data from McPartlin et al. [21], which give a systematic contribution of 0.4, 0.7 and 0.6 *mm* and a random contribution of 0.7, 1.1 and 1.1 *mm* for the LR, AP and CC directions, respectively. Another margin was computed with the same parameters except for the delineation uncertainty, for which we take systematic variations of 1.7, 2 and 2.5 *mm* for the LR, AP and CC directions, respectively, from Rasch et al. [22].

An estimation of the potential benefits in term of dose savings was computed by simulating a prostate adaptive radiotherapy treatment on a randomly selected patient using the ETHOS Emulator with the margin computed and with the commonly reported 7 *mm* isotropic margins [23, 24, 25]. The same adaptive dose planning procedure is used for both simulations, with the same RTIntent (sequence of planning objectives ordered by clinical importance) and optimized by the Ethos intelligent optimizer. The dose distributions for the bladder and the rectum are compared and the CTV coverages are checked to ensure equivalent plan quality.

3 Results

The results for the delineation uncertainties are given in Table 1. The systematic error is calculated as the standard deviation of the mean variations over all patients and the random contribution as the root mean square of the standard deviations.

Delineation uncertainty (*mm*)						
	Left	Right	Anterior	Posterior	Cranial	Caudal
Systematic uncertainty	0.7	0.6	1.5	1.5	1.3	0.8
Random uncertainty	1.2	1.0	2.1	1.3	1.9	1.6

Table 1: Summary table of the delineation uncertainty. The systematic error is calculated as the standard deviation of the mean variations over all patients and the random contribution as the root mean square of the standard deviations.

The PTV margins derived from this delineation uncertainty are shown in Figure 2, side by side with the reference margin, computed with fully systematic delineation uncertainty.

The dose saving has been evaluated by simulating the adaptive treatment on one randomly chosen patient with the 7 *mm* isotropic PTV margin and anisotropic margins of 3 *mm* in LR, 4 *mm* in caudal and 5 *mm* in cranial and AP directions. This last margin is referred to as adapted margin in the remainder of this work.

The CTV coverage is equivalent with both margins. The V40[1] in the bladder and in the rectum are reduced by 20.3% and 23.7%, respectively, with the adapted margin, compared with the 7 *mm* isotropic margin.

An example of the DVH (Dose Volume Histogram) for one fraction is given in Figure 3.

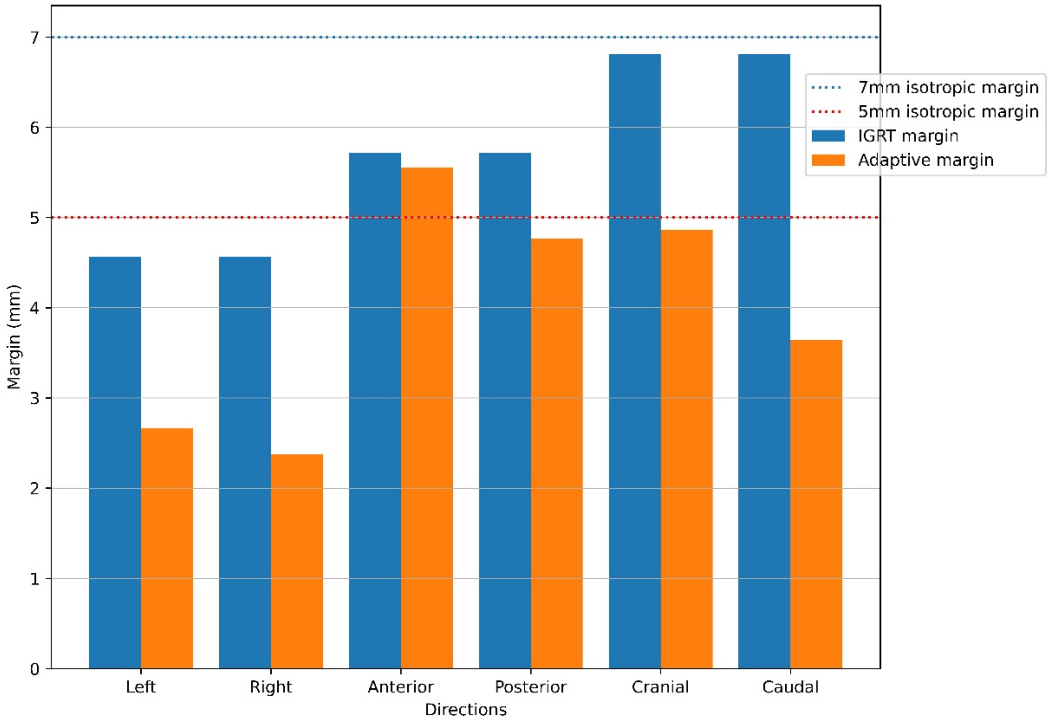

Figure 2: Comparison of the margins computed. The IGRT margin is the margin calculated by considering the delineation uncertainty as purely systematic, and the Adaptive margin is the one considering the delineation uncertainty as partially random.

[1] Vx for an organ is defined as the percentage of the volume of this organ undergoing more than x Gy.

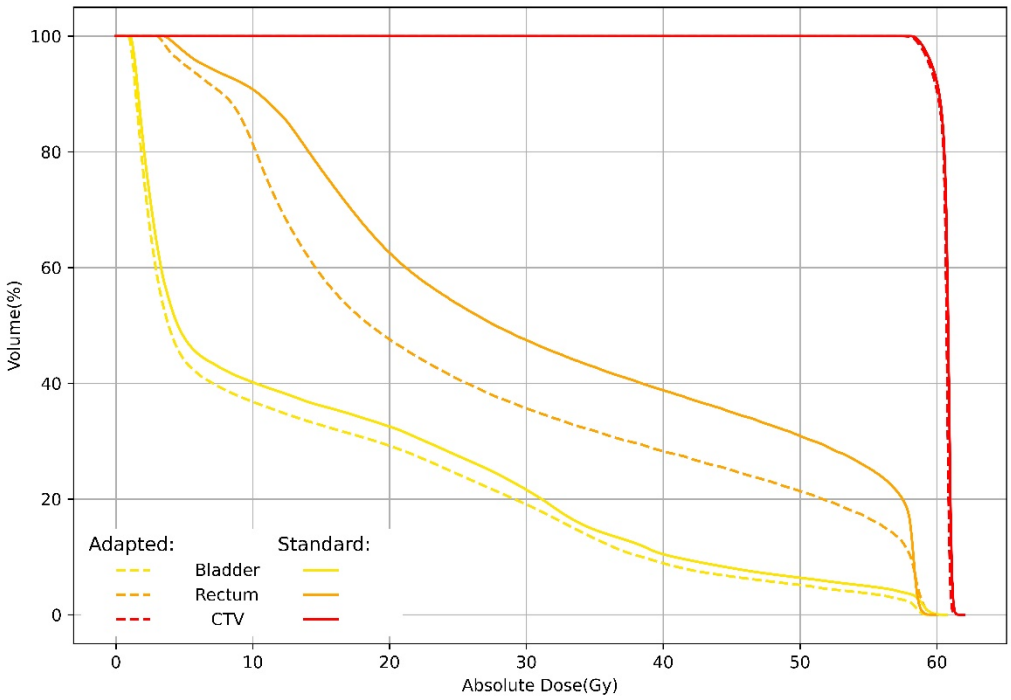

Figure 3: Dose-volume histogram of one fraction, presenting the CTV (in red), the rectum (in orange) and the bladder (in yellow) for the treatment with adapted margin (dashed lines) and with standard 7 mm isotropic margin (solid lines). The dose axis has been rescaled to reflect the total treatment dose.

4 Discussion

CBCT-based adaptive radiotherapy requires redefining the target for each fraction, allowing to consider the delineation uncertainty to be partly random and not fully systematic. This technology being quite recent, there is still a lack of literature on the topic. Moreover, to our knowledge, there is no study calculating a proper delineation uncertainty in the context of online adaptive radiotherapy treatment. Doing so usually requires substantial resources, such as a pool of physicians, delineating the same patient several times. With this new methodology, the only resource needed is the daily delineation of the target by a physician, which is already realized in clinical adaptive radiotherapy routine.

To compute delineation uncertainties compatible with the Van Herk margin recipe, some assumptions had to be made, that will be justified in this section. The first one is that the prostate only undergoes translations, which means that the potential rotations are neglected. These rotations have been quantified by many studies, with inter-fractions' standard deviations of 2° to 4°, according to Van Herk et al. [1] and more recently Graf et al. [26]. Thanks to the nearly spherical shape of the prostate, these relatively small rotations will not significantly affect the calculated margin, except maybe in the region of the apex, which is the least spherical part of the prostate, and hence with the highest relative impact on the computed delineation uncertainty.

The second assumption is that the shape of the prostate does not change. According to Deurloo et al. [27], the variations of the shape of the prostate is small compared to the intra-observer variability. The largest

variations have been observed in the anterior and posterior parts of the prostate, with 0.8 *mm* and 0.9 *mm* of averaged variations, respectively. Recent data from MRgRT shows larger volume variations in the CC direction during moderately hypofractionated radiotherapy due to prostate swelling [28], with a median dimension increase of 2.3 *mm* (which results in a 1.15 *mm* increase in cranial and caudal directions). This systematic volume increase was, however, not observed in our dataset (we observe a standard deviation of 7% in the delineated volumes, with no specific trend). It is therefore safer not to include it in the margin computation. The random shape correction only contributes to a reduction of the total margin, since it is taken into account in the delineation uncertainty computation, despite being corrected by the system during the adaptation. The shape variation should therefore be quadratically subtracted from the computed delineation uncertainty to find the true error. Propagated to the total margin, this correction reduces the margin by 0.1 *mm* and 0.2 *mm* in the anterior and posterior directions, respectively. For the other directions, the variations are smaller, or even unmeasurable, due to much larger intra-observer variability. This contribution can therefore clearly be neglected.

The two above assumptions may seem like an irrelevant simplification, given the fact that the point of OART is precisely to consider the translations, rotations and changes of shape of the patient's daily anatomy. Nevertheless, as the shape variations and the rotations are not dissociable from the delineation variations with only one set of delineation per anatomy, we choose to consider a conservative scenario where everything is considered as uncertainty and used to compute the margin.

As explained previously, the method to compute the delineation uncertainty involves interpolating the radial distances of the contour's point into a predefined set of polar and azimuthal coordinates. This process is only possible if the polar and azimuthal coordinates of every point of the contour are unique. Otherwise, some parts of the contour may be superimposed, and a single projected point may be associated with several different radial distances, which would induce errors in the computation. It is not an issue for contours with convex or nearly convex shapes, as the prostate, but it would be if the method were used on more complex elements.

Finally, we believe that using the CT-sim's delineation as a reference to calculate the uncertainties in delineation is reasonable. This delineation, which is carried out by a skilled physician using an MRI, is the closest approximation to a gold standard when there are no in situ observations available. Furthermore, a potential error on the initial delineation would contribute to the computed systematic delineation uncertainty, as it is calculated using the mean variation between all fractions' prostate contours and the simulation's delineation. Therefore, we consider it a valid approach.

Our results show, as expected, that the systematic error in an adaptive radiotherapy workflow is significantly smaller than the isotropic error of 2.5 *mm* proposed by Van Herk [29] that was used until now in IGRT-based workflow, with values ranging from 0.6 *mm* to 1.5 *mm*. It is also smaller than the 1.7 *mm*, 2 *mm* and 2.5 *mm* errors for LR, AP and CC directions, respectively, found by Rasch et al. [22], but in accordance with the interobserver delineation variability in MRI found by Pathmanathan et al. [30] (0.7-1 *mm* of mean contour distances) and the systematic contouring uncertainty from Nichol et al. [31] (0.8 *mm*). This reduction of the systematic margin comes at the cost of a new contribution to the random margin that was not present before.

The total delineation uncertainty, computed as the quadratic sum of the random and systematic contributions, is in the same range as what can be found in the literature [16]. The only significant reductions compared to the results from Rasch et al. [22] are in the right and caudal directions. The small differences observed strengthen the relevance of the assumptions made for the computation.

Thanks to the fact that the random contributions have overall a lower impact on the final margin than the systematic ones when computed with the Van Herk margin recipe, the new delineation uncertainty measured in this work allows to reduce significantly the PTV margin for every direction. The benefits are particularly large in the LR and CC directions, with reductions up to 58%, and lighter but still positive in the AP direction.

Separating the delineation uncertainty into systematic and random contributions could affect the PTV margins used in adaptive radiotherapy of any target. However, the method developed here suffers some restrictions. In particular, the seminal vesicles, which are often treated along with the prostate, do not meet the criteria to use the method [32]. A more general technique should therefore be developed to consider rotations, volume changes and complex shapes. A solution for that could be to ask several physicians to delineate the volume on each CBCT to establish a "daily ground truth" as the median of all the contours. The method can then be used to compare each fraction's delineation to the fraction's ground truth and determine the delineation uncertainty. The non-convex issue can also be fixed by splitting the volumes into smaller convex ones.

The impact on the dose distribution evaluated by simulation shows important dose savings for the OAR (ranging from 11 to 35%), especially in the high dose regions (V48, V50 and V56.8), which are reduced by at least 25%. Even though our study considered only the practical aspect of margin reduction, a hint on its impact has been provided to the reader. We believe that this improvement will translate in clinical benefits as it has already been shown in MRI-guided adaptive radiotherapy [15], but the analysis should be performed on a wider range of patients to generalize the observation.

5 Conclusion

A method was developed to compute custom adaptive radiotherapy PTV margin that consider separately the random and the systematic contributions of the previously fully systematic delineation uncertainty for rigid, non-rotating volumes.

The application of this method to the particular case of the treatment of prostate cancers in the radiotherapy department of the CUSL has a major impact on the total PTV margin by reducing it to 2.7, 2.4, 5.6, 4.8, 4.9 and 3.6 *mm* in the left, right, anterior, posterior, cranial and caudal directions, respectively.

Due to the assumptions that have been made through this work, this method is still restricted to the computation of margins for specific types of tumors, like the prostate, with negligible rotations and minor changes of shape. Nevertheless, the separation of the delineation uncertainty into random and systematic contributions opens the path for margin reduction in adaptive radiotherapy for various tumor types and localizations.

6 Declaration of interest

The authors have no conflict of interest in connection with the paper.

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