Technical Note

Dose evaluation of inter- and intra-fraction prostate motion in extremely hypofractionated intensity-modulated proton therapy for prostate cancer

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ARTICLE INFO

Keywords: Intensity-modulated proton therapy
Extreme hypofractionation
Ultra-hypofractionation
Stereotactic body proton therapy
Prostate inter- and intra-fraction motion

ABSTRACT

Inter- and intra-fractional prostate motion can deteriorate the dose distribution in extremely hypofractionated intensity-modulated proton therapy. We used verification CTs and prostate motion data calculated from 1024 intra-fractional prostate motion records to develop a voxel-wise based 4-dimensional method, which had a time resolution of 1 s, to assess the dose impact of prostate motion. An example of 100 fractional simulations revealed that motion had minimal impact on planning dose, the accumulated dose in 95% of the scenarios fulfilled the clinical goals for target coverage (D95 > 37.5 Gy). This method can serve as a complementary measure in clinical setting to guarantee plan quality.

1. Introduction

External beam radiation therapy (EBRT) with photons using mild to moderate hypofractionation is increasingly utilized for patients with high-risk prostate carcinoma (PCa), in whom a lower local control rate and overall survival rate are still reported after definitive-intent treatment compared to low- and intermediate-risk PCa patients [1–7]. Due to the low alpha/beta ratio of PCa, dose escalation with extreme (or ultra-) hypofractionation schemes may theoretically improve local control and reduce treatment time. However, extreme hypofractionation may increase the dose to organs at risk (OARs) and thus increase the incidence of toxicities [8–10].

Intensity-modulated proton therapy (IMPT) can potentially reduce radiation dose to OARs compared to traditional EBRT [11–13]. However, IMPT could be more sensitive to interplay effects due to the time structure (proton beam was chronologically delivered layer by layer) of the beam and inter- and intra-fractional prostate motion, which could decrease target dose coverage [14] resulting in decreased disease control, while increasing dose to OARs and potentially leading to greater toxicity. Therefore, the impact of interplay effects in an extremely hypofractionated intensity-modulated proton therapy (EHIMPT) is important and should be investigated while considering clinical introduction.

In current clinical proton therapy practice, treatment plans are robustly optimized and evaluated for setup and range errors [15]. Although this method is generally more suitable than planning target volume-based plan evaluation, it does not explicitly incorporate the dose impact of inter- and intra-fraction prostate motion during beam delivery.

Some IMPT simulation studies quantified the dose impact of prostate motion by using the prostate motion of individual patients or the worst-case motion scenario [16–19]. However, a more common range of
prostate motion was not investigated to provide evidence for common clinical practice since prostate motion does not have a predictable direction and magnitude [20]. Furthermore, earlier studies [21,22] used the planning computed tomography (pCT) scan to simulate both inter- and intra-fraction prostate motion, neglecting anatomical variations between fractions.

This study aimed to develop a new method for evaluating the impact of inter- and intra-fraction prostate motion on the dose distribution during the delivery of a robustly optimized EHIMPT treatment. This was achieved by utilizing four-dimensional (4D) synthetic computed tomography (sCT) simulations. The method was applied to an example patient anatomy and EHIMPT plan.

2. Materials and methods

2.1. Patient

This study used the CT imaging data (including pCT (Fig. 1A) and five weekly verification CT (vCT) images) of a representative PCa patient (within standardized follow-up program) treated with conventionally fractionated photon therapy (35 × 2.2 Gy). Structures including clinical target volume (CTV), CTV1 (prostate), CTV2 (proximal 2 cm of seminal vesicles) were delineated by an experienced radiation oncologist, and bladder, rectum, anal canal, femoral heads, rectal wall, and skin were delineated by an expert radiotherapy technician and checked by a radiation oncologist. The patient consented for data usage within standardized follow-up program (Medical Ethical Committee permission number: 518/2017).

2.2. Treatment planning

An EHIMPT plan (5 × 7.5 Gy, relative biological effectiveness = 1.1) for this patient was generated in RayStation Research 7.99 (RaySearch Laboratories, Stockholm, Sweden) according to our protocol constraints (Table 1). Every fraction consisted of two lateral beams (90°, 270°). Each beam contained 11 energy layers, delivered in a raster pattern [23]. A phantom (with fiducial markers) treatment plan delivery showed a delivery time for each beam of 16 s. The plan was robustly optimized using a 5 mm setup and 3% range uncertainty. For evaluation purposes, each beam was split into 16 sub-plans, each representing the beam delivery for one second.

2.3. Prostate motion data

Prostate motion data of twenty-six PCa patients treated with conventionally fractionated radiotherapy (without endorectal device) in the Department of Radiation Oncology of the University of Pennsylvania were used [24]. The prostate motion was recorded in real-time at a frequency of 10 Hz in three degrees of freedom using a 4D electromagnetic tracking system (Calypso Medical Technologies, Seattle, WA).

Among 1055 available treatment fractions’ records, all records longer than four-minute treatment time were selected (1024), since the time interval for every fractional treatment would be at least four minutes in our medical center. The 95th percentile of motion range was calculated in each dimension (left right (x), inferior superior (y), and posterior anterior (z)). Every range in each direction yields two opposite 1-dimensional vectors: (0, ±x), (0, ±y), (0, ±z). Equispaced sparse sampling resulted in eight 3-dimensional (3D) motion vectors: (x, y, z), (x, y, -z), (x, -y, z), (x, -y, -z), (-x, y, z), (-x, y, -z), (-x, -y, z), (-x, -y, -z).

Six common motion trajectories were reported by Kupelian et al.

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Fig. 1. (A) Planning CT; (B) Nominal dose distribution; (C) Voxel-wise minimum dose distribution; (D) Example of one fraction with randomized prostate motion and timing; (E) Synthetic CT left lateral beam; (F) synthetic CT right lateral beam; (G) Simulated accumulated dose distribution planning CT; (H) Dose distribution legend. Solid lines delineate the targets’ and organs’ positions before movement, dotted lines delineate the targets’ and organs’ positions after movement.
To the nominal dose (Fig. 1B) and the voxel-wise worst dose (Fig. 1C): plan doses on sCTs were warped back to the vCTs of every fraction, controlling regions of interest (ROIs) for the hybrid deformable image to the institutional procedure for online verification.

### 2.4. Synthetic CT

Five weekly vCTs were used to simulate five fractions of EHIMPT. Each vCT was registered to the pCT based on fiducial markers according to the institutional procedure for online verification.

Each weekly vCT was used to create eight sCTs based on the hybrid 3D motion vectors. The CTVs were translated within the patient anatomy to the motion vector (x, y, z). Next, the CTVs and pelvic bones were set as controlling regions of interest (ROIs) for the hybrid deformable image registration (Anatomically constrained deformation algorithm ANACONDA in RayStation Research 7.99) to obtain the deformation vector fields (DVFs), and created a sCT (Fig. 1E, Fig. 1F) that illustrates the anatomy of corresponding motion scenarios determined as described above. The OARs were delineated at each vCT and were deformed according to the obtained DVFs, so their intra-fraction motion was modeled by the deformation caused by the prostate motion.

### 2.5. Randomization of prostate motion vectors and timing

For each beam, a combination of motion vector and motion initiating time was randomly selected from the 128 combinations (8 motion vectors and 16 initiation time) with a time resolution of 1 s. We conducted 100 fractional simulations, with each motion scenario randomly selected using R (R, Vienna, Austria), to obtain 20 complete treatment simulations. Fig. 1D shows an example of one randomized motion.

### 2.6. Dose accumulation

For each EHIMPT, the sub-plan of every second was calculated on the corresponding sCT. Using the DVFs obtained by ANACONDA, all sub-plan doses on sCTs were warped back to the vCTs of every fraction, and then the five-fraction doses on vCTs were warped and summed to the pCT (Fig. A.1 and A.2 in supplement). The accumulated dose on the pCT (Fig. 1G) represents the simulated accumulated dose of one treatment. Accumulated doses from 20 simulated treatments were compared to the nominal dose (Fig. 1B) and the voxel-wise worst dose (Fig. 1C): voxel-wise minimal dose in CTVs and voxel-wise maximal dose in OARs ([25]).

We chose to simulate the motion with a sudden change in order to observe an obvious dose change ([19]).

### 3. Results

The 95th percentile of prostate motion range were 2.0 mm in lateral direction, 3.2 mm in inferior-superior direction, and 3.9 mm in posterior-anterior directions.

In the 20 simulated treatments, the mean simulated accumulated doses met the dose constraints for CTV1 and CTV2 with D95 % of 37.9 Gy [95 % CI 37.1 – 38.1] and 31.6 Gy [95 % CI 31.5 – 31.8] (Table 1). The worst-case dose (D95 %) to CTV1 in 20 simulated treatments was just below constraint (37.0 Gy). When comparing the mean simulated accumulated dose to nominal dose of CTV1, no difference existed, with 37.9 Gy in the mean simulated accumulated dose and in the nominal dose. However, a difference is reported for D95 % dose of CTV2, with 31.6 Gy in the mean simulated accumulated dose versus 30.3 Gy in the nominal dose (Table 1).

Regarding OAR dose, the mean simulated accumulated dose was lower than the nominal dose in all dose constraints except D0.01 cm³ of the posterior rectal wall and D5cm³ of the rectum. The largest difference was found in the D0.01 cm³ of the posterior rectal wall with 26.8 Gy in the mean simulated accumulated dose and 19.0 Gy in nominal dose (Table 1).

### 4. Discussion

We presented a probability-based motion simulation method for evaluating inter- and intra-fraction motion in robustly optimized EHIMPT. Simulated accumulated doses to the target volumes were adequate in the patient anatomy investigated.

In our analysis we considered both the simulated accumulated dose and the voxel-wise worst dose. Voxel-based worst doses were calculated without considering 4D prostate motion (but only patient setup and CT range errors). Simulations in this study used perfect setup during beam delivery, but included repeated imaging to include inter-fraction motion and synthetic imaging with a 4D resolution of 1 s to include intra-fraction motion. Therefore, our method can be used additional and complementary to the standard robustness evaluation method of proton plans using setup and range errors.

The probability-based motion simulation in our study is based on a randomized procedure applying a range of motion (95 % range derived from 1024 fractions of 26 patients). This was done to simulate a wider range of motion possibilities while excluding the extreme outliers. Other studies ([21,26]) simulated selected motion trajectories that represent extreme motion scenarios, which was less representative. The

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most common prostate motion is a gradual drift, but it has minimal impact to the dose distribution [19]. We chose to simulate the motion trajectory of a sudden intra-fraction prostate motion to observe an obvious dose alteration [25].

In our study, the mean and the minimal dose (worst-case dose) of CTV1-D95 % (prostate) in simulated treatments were 37.9 Gy and 37.0 Gy which are 101.1 % and 98.7 % of the prescribed dose. This is comparable to the results of Su et al. (103.1 % (mean) and 96.7 % (worst-case minimal dose) using uniform scanning proton delivery technique) [21]. Our study showed a small dose variation of 2.4 % between mean and minimum dose, compared to 6.2 % reported by Su et al. which could be due to the use of 5 mm robustness margin compared to 4 mm by Su et al. Besides, simulation of prostate motion reported by Su et al. was less representative for the average PCA patients because of the use of up to 15 mm motion range in one fraction, which rarely occurred [27–29]. Ammazzolaro et al. [22] reported a median (worst) CTV dose drop of 0.5 % (2.8 %) in a 4D intra-fractional prostate motion simulation study, compared to a mean (worst) CTV dose drop of 1.1 % (1.3 %) in our study; the small difference may be caused by the compensation effect of fractionation.

A limitation is that generating sCTs based merely on rigid displacement of the prostate. This problem is inevitable since the Calypso data do not include organ deformation or rotational information. Rotations could result in target dose reduction [30], and severe organ deformation could occur when the prostate moves abruptly [31,32]. At certain instance, the worst-case simulated accumulated dose was even lower than the nominal dose to OARs, a finding consistent with previous studies [16,33]. This occurrence can be attributed to the combined impact of imperfect dose warp, inter-fractional anatomical variation, and the limited representation of deformed OARs in the sCT.

Our study was limited to simulating only one patient’s anatomy and treatment plan. However, the focus was on the implementation of the simulation method. The selected patient had the largest inter-fraction motion among all patients with available vCTs. For patients with possible larger prostate volumes, the amount of energy layers and delivery time increase accordingly (e.g. CTV1 volume increased to 54.9 cm³ needed 13 energy layers per beam).

We will be using the presented probability-based simulation method as an additional tool to the setup and range robustness evaluation of EHIMPT plans to gain more insight and confidence in the robustness of EHIMPT against inter- and intra-fraction prostate motion in a larger group of patients and treatment plans.

In conclusion, this study introduced a new, 4-D simulation method to assess the dose impact of inter- and intra-fraction motion. This method can be used in addition to the robust evaluation method.

CRediT authorship contribution statement

Sen-Quan Feng: Conceptualization, Methodology, Software, Data curation, Writing – original draft, Writing – review & editing, Visualization. Charlotte L. Brouwer: Conceptualization, Methodology, Supervision, Writing – review & editing, Visualization, Project administration. Erik W. Korevaar: Methodology, Writing – review & editing. Neha Vapiwala: Resources, Data curation, Writing – review & editing. Ken Kang-Hsin Wang: Resources, Data curation, Writing – review & editing. Curtindale Deville: Resources, Data curation, Writing – review & editing. Johannes A. Langendijk: Conceptualization, Resources, Supervision, Writing – review & editing, Project administration, Funding acquisition. Stefan Both: Resources, Data curation, Writing – review & editing. Shafak Aluwini: Conceptualization, Resources, Methodology, Supervision, Writing – review & editing, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2023.100474.

References


