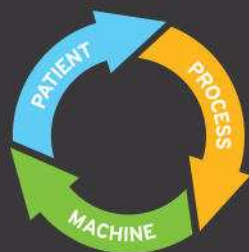


SunCHECK™ YOUR NEW INTEGRATED PLATFORM FOR QA



PATIENT QA
MACHINE QA
DEVICES & DATA
ONE WORKFLOW.



Fast online replanning for interfraction rotation correction in prostate radiotherapy

Charis Kontaxis,^{a)} Gijsbert H. Bol, Linda G. W. Kerkmeijer, Jan J. W. Lagendijk, and Bas W. Raaymakers

Department of Radiotherapy, University Medical Center Utrecht, Heidelberglaan 100, Utrecht 3584CX, The Netherlands

(Received 19 March 2017; revised 5 June 2017; accepted for publication 6 July 2017; published 9 August 2017)

Purpose: To enable fast online replanning for prostate radiotherapy with the inclusion of interfraction rotations and translations and investigate the possibility for margin reduction via this regime.

Methods: Online daily replanning for a 35-fraction treatment for five prostate cases is simulated while accounting for anatomical transformations derived from fiducial marker data available in our clinic. Two online replanning strategies were simulated, compensating for: (a) rotation-only in combination with a couch shift and (b) both translation and rotation without a couch shift. They were compared against our current clinical protocol consisting of a single offline plan used over all fractions with daily couch repositioning (translations only). For every patient, the above methods were generated for several planning margins (0–8 mm with 2 mm increments) in order to assess the performance of online replanning in terms of target coverage and investigate the possible dosimetric benefit for the organs at risk. The daily DVHs for each treatment strategy were used for evaluation and the non tumor integral dose (NTID) for the different margins was calculated in order to quantify the overall reduction of the delivered energy to the patient.

Results: Our system is able to generate a daily automated prostate plan in less than 2 min. For every patient, the daily treatment plans produce similar dose distributions to the original approved plan (average CTV D99 relative difference: 0.2%). The inclusion of both shifts and rotations can be effectively compensated via replanning among all planning margins (average CTV D99 difference: 0.01 Gy between the two replanning regimes). Online replanning is able to maintain target coverage among all margins, while — as expected — the conventional treatment plan is increasingly affected by the interfraction rotations as the margins shrink (average CTV D99 decrease: 0.2 Gy at 8 mm to 2.9 Gy at 0 mm margin). The possible gain in total delivered energy to the patient was quantified by the decreased NTID ranging from 12.6% at 6 mm to 32.9% at 0 mm.

Conclusions: We demonstrate that fast daily replanning can be utilized to account for daily rotations and translations based on the daily positioning protocol. A daily plan can be generated from scratch in less than 2 min making it suitable for online application. Given the large magnitude of prostate rotation around the LR axis, online correction for daily rotations can be beneficial even for the clinical 8 mm margin and could be utilized for treatments with small margin reduction mainly limited then by anatomical deformations and intrafraction motion. Our online replanning pipeline can be used in future treatments with online MR guidance that can lead to further safe reduction of the planning margins. © 2017 The Authors. *Medical Physics* published by Wiley Periodicals, Inc. on behalf of American Association of Physicists in Medicine. [https://doi.org/10.1002/mp.12467]

Key words: fast plan adaptation, IMRT, interfraction rotation correction, online daily replanning, prostate radiotherapy

1. INTRODUCTION

To enable better dose conformality, dose escalation, and organ at risk (OAR) sparing, there is a continuous effort to improve image-guided radiotherapy (IGRT) in prostate cancer.^{1–3}

In the clinical setting, fiducial markers, implanted in the prostate, are being used to provide online information of the prostate position.^{4,5} During every treatment fraction, prior to radiation delivery, an electronic portal imaging device (EPID) acquires the latest position of the markers and thus provides the rigid translation and rotation transformation.

Daily online position verification based on the translational part of this transformation has been employed by

shifting the treatment couch prior to radiation delivery in order to reduce the systematic and random positioning errors.^{6,7} Moreover, couch rotation of limited angles has been employed to partially correct for the registered prostate rotations.⁸

The magnitude of these rotations can be significant, reaching a systematic mean of 3 degrees with systematic and random standard deviations (SD) of approximately 5 degrees around the left–right (LR) axis.⁹ These rotations undergo large variations and their dosimetric impact on the target dose can be quite significant without the use of appropriate planning volume target (PTV) margins.^{10,11}

The use of replanning software is able to fully account for these changes in an online clinical setting. This software

should be able to generate clinical acceptable plans in a very short time period in order to avoid the time-dependent intrafraction prostate motion that could occur between patient positioning and radiation delivery.^{12,13}

In this work we present an online daily replanning application by simulating a 35-fraction prostate treatment, accounting for both translational and rotational components of interfraction motion as recorded by the implanted prostate fiducial markers. For every case, we simulate the whole treatment for several decreasing PTV and boost volume margins (EBV) and compare it against a conventional static plan in terms of target coverage and high dose OAR sparing. We investigate the feasibility and the possible benefits of online replanning for rotational correction by enabling margin reduction and healthy tissue sparing.

2. MATERIALS AND METHODS

We simulated online daily replanning utilizing our research planning platform (Section 2.A) for five prostate patients previously treated in our clinic. The available daily prostate translations and rotations for these patients, based on implanted fiducial markers, were used to generate the daily anatomies for the replanning (Section 2.B.1). Two replanning regimes were developed, based on the underlying transformation used to generate the daily anatomy (Section 2.B.2) and were compared to the current clinical approach of using a single pretreatment plan over the course of the 35-fraction treatment (Section 2.B.2). Finally, the same experiments were performed for a set of decreasing planning margins in order to assess the pipeline's ability to ensure target convergence and possibly spare healthy tissue (Section 2.B.2).

2.A. Planning system

In our previous work¹⁴ we have presented the adaptive sequencer (ASEQ), a novel treatment planning methodology for online IMRT applications suitable for both current clinic and hybrid MRI-linear accelerator machines. ASEQ is an adaptive sequencing strategy which iteratively converges to an ideal dose distribution that fulfills all clinical constraints. We have showed that ASEQ can be successfully used to generate clinical-grade plans, when combined with a segment weight optimization (SWO). We have recently reimplemented ASEQ and integrated it in our new MRI-linac treatment planning system (MRLTP) that enables fast online replanning.

MRLTP incorporates all the necessary optimization modules including beamlet generation (dose contribution of each beamlet to every anatomical voxel in Gy/MU), fluence optimization, and fluence map segmentation. The dose engine in use is the research version of the GPU-based Monte Carlo dose (GPUMCD, Elekta AB).¹⁵ Our fluence optimizer utilizes a quasi-Newton method for the inverse dose optimization problem.¹⁶ The optimization uses minimum and maximum dose prescription per voxel/structure along with weights to penalize under- and overdosage, respectively. MRLTP's prescription file also follows a similar format

including the volume of interest (VOI) and dose/weights used to drive the initial optimization that produces the ideal dose distribution which fulfills the clinical constraints.

MRLTP includes several planning pipelines utilizing ASEQ (e.g., conventional SWO plan, daily replanning etc.). It is compatible with anatomical changes described by both rigid transformations and three-dimensional (3D) deformation vector fields (DVF) in order to facilitate different adaptation strategies.

In this work the daily replanning pipeline shown in Fig. 1 is used to simulate the prostate adaptive treatments in which during every treatment fraction: the daily anatomy is loaded, the beamlet data corresponding to this anatomy are calculated and an ASEQ replan (followed by a SWO) is generated targeting the fraction's anatomy.

All plans were made for an Elekta Versa HD 10 MV linear accelerator with an Elekta Agility MLC. The dose grid resolution was $3 \times 3 \times 3 \text{ mm}^3$ and the beamlet size $5 \times 5 \text{ mm}^2$. The Monte Carlo uncertainty for GPUMCD was set to 3% for both beamlet and segment calculations. The following gantry angles were used: 40° , 100° , 180° , 260° , and 320° . All plans were calculated using 50 segments prior to SWO.

The development and experiments of this work were performed on a system with a dual Intel^{reg} Xeon[®] E5-2670 v3, 64 GB RAM and two NVIDIA[®] GTX Titan X cards dedicated to the GPUMCD dose engine, comparable in specs with the current industry standard for a treatment planning computer system.

2.B. Experiments

2.B.1. Anatomy

Marker data: Five prostate cases previously treated in our clinic during 35-fractions were used for these experiments. Three gold markers were implanted in the prostate of the patient prior to the planning CT. Then, for every case, a rigid transformation including shift and rotation per fraction was

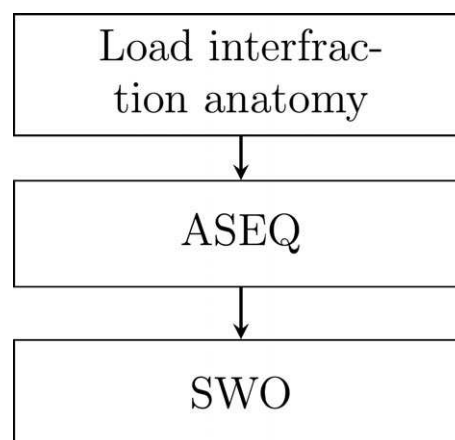


FIG. 1. MRLTP interfraction pipeline.

available from the online setup correction protocol used during the treatment based on fiducial markers.

For every fraction during the previous clinical treatment of the patients, the online determined position of the marker set was used to correct the patient position. This online correction excluded any rotations and consisted of a couch translation according to the registered transformation of the markers compared to their baseline position in the planning CT. Table I shows the average magnitude and SD for the translation and rotational components of the included cases during the 35-fractions relative to the planning marker coordinates. Their combined average and SD rotational magnitude is 5.7 (5.0), 1.4 (1.2), 2.3 (1.7) degrees in LR, anterior–posterior (AP), and superior–inferior (SI) directions respectively, in line with what has been reported in literature.^{9,17} Cases 4 and 5 are indicative of larger and smaller magnitudes respectively.

Daily anatomy generation: For replanning the original anatomy was rigidly transformed^{8,18} based on the daily marker set. The original body volume from the pretreatment CT was maintained while the targets along with the bladder and rectum were transformed according to the daily recorded transformations. More specifically, the CT densities of the original body volume were maintained while the daily transformed VOIs were assigned to water. In this way, the bulk of the bony anatomy is preserved and taken into account during replanning while the uniform assignment of the internal structures enables the unbiased calculation and evaluation of the daily dose distributions.

Planning VOIs: The targets consisted of the prostate including the tumor [boost volume (BV)] and the clinical target volume (CTV) which included both the prostate body and seminal vesicles. The CTV to PTV margin clinically used was 8 mm isotropically. The same margin was clinically used to form the EBV by expanding the BV isotropically while excluding any overlap with the seminal vesicles and the OARs. The PTV and EBV were prescribed with 70 and 77 Gy, respectively. Table II shows the clinical planning constraints and Table III shows the PTV and EBV target volumes for each margin.

2.B.2. Replanning

For every patient a conventional plan based on the planning CT (REF) was generated which satisfied the clinical constraints (Table II).

Replanning regimes: Subsequently, for each treatment fraction, two online replanning regimes were simulated depending on the transformation used to generate the daily anatomy: (a) replanning targeting the rotated-only patient anatomy based on the daily rotations where a couch

TABLE I. Mean magnitude and SD of marker translation (mm) and rotations (degrees) per component LR (SD), AP (SD), SI (SD).

Case	Translation	Rotation
1	1.4 (1.0), 3.4 (2.3), 1.7 (1.6)	5.0 (4.8), 1.1 (1.1), 3.6 (1.7)
2	1.8 (1.3), 2.4 (1.7), 1.8 (1.3)	4.8 (2.3), 1.2 (0.8), 1.2 (0.8)
3	3.5 (2.6), 3.3 (1.9), 1.8 (1.1)	5.3 (3.7), 1.1 (0.7), 1.6 (1.0)
4	1.9 (1.3), 2.8 (2.2), 1.8 (1.3)	10.9 (6.4), 2.7 (1.4), 3.9 (1.5)
5	1.7 (1.5), 3.0 (2.3), 3.0 (1.8)	2.5 (1.4), 0.7 (0.4), 1.1 (0.9)

TABLE II. Prostate planning constraints.

VOI	Constraints
PTV	99% vol \geq 66.50 Gy
EBV	99% vol \geq 73.15 Gy
Rectum	50% vol \leq 50 Gy 5% vol \leq 72 Gy
Bladder	10% vol \leq 50 Gy 1 cm ³ vol \leq 80 Gy
Sphincter	mean \leq 38 Gy

correction is necessary to account for the daily shifts (DYN_R) and (b) replanning targeting the patient anatomy which was transformed using both daily rotations and translations without the need of an external couch correction (DYN_RT).

Motion affected reference plans: In order to assess the effect of the motion in the static plans, all REF plans were delivered on the transformed patient anatomy that included only the recorded rotations (REF_R). By excluding the recorded shifts we simulate the current clinical treatment, where a couch shift is performed prior to radiation delivery in order to account for the daily translational error. Thus, REF_R forms the ground truth motion affected dose distributions generated by the conventional treatment.

Margin: The above 35-fraction treatment was simulated for several CTV to PTV and BV to EBV margins including: 8 (clinical), 6, 4, 2 and 0 mm, in order to investigate the smallest achievable margin at which dynamic replanning ensures proper CTV and BV coverage and how would the reference plan at these margins perform when delivered to the daily anatomy.

Method Evaluation: For every patient, one REF, 35 DYN_R and 35 DYN_RT full prostate plans were generated for each one of the different margin sets. Moreover, the REF plan was recalculated on each daily anatomy leading to 35 REF_R dose distributions per margin set. Among the different margin sets, a total of 530 dose distributions/dose volume histograms (DVH) per patient were used for the evaluation.

For the evaluation of the results the D99 points (dose delivered to 99% of the volume) for the PTV, CTV, EBV, BV structures, as well as the Bladder and Rectum V72 points (percentage of the volume that received more than 72 Gy) were extracted from the DVHs. By these points we can evaluate the target and critical OARs in the high-dose region close to the target.

Moreover, the non-tumor integral dose (NTID) was calculated for all REF plans to evaluate how the margin decrease affects the overall delivered energy to the patient. The integral dose (ID) for a VOI i of uniform density ρ_i , consisting of equally sized voxels with total volume V_i and average delivered dose \bar{D}_i , can be calculated using Eq. (1).¹⁹ The non-tumor VOI was generated by subtracting the CTV from the body volume and was assigned with a uniform density of 1 g/cm^3 .

$$ID_i = \rho_i V_i \bar{D}_i \quad (1)$$

Automated plan generation: Regarding user interaction, for every patient — margin combination, the MRLTP prescription was manually tweaked in order to achieve the clinical constraints for the initial REF plan. Subsequently the full 35-fraction treatment was simulated in a fully automated way by using the same prescription file for all dynamic replans.

3. RESULTS

3.A. Daily replanning

Having generated all the datasets and extracted the DVH points described in Section 2.B.2, the average values per treatment fraction among the different cases were calculated. Figure 2 shows the REF 8 mm DVH summed among all patients.

3.A.1. Replanning strategies DYN_R and DYN_RT

We first compared the two dynamic replanning regimes to establish the effect of the included shifts. For every structure the average difference over all planned fractions between

TABLE III. Volume Sizes (cm^3).

Case	8 mm	6 mm	4 mm	2 mm	0 mm
1 PTV	168.5	124.4	109	78	54
1 EBV	89.4	70.4	64.5	51.6	40
2 PTV	169.7	124.8	113	82.4	58.8
1 EBV	93.9	80	74	61.4	48.2
3 PTV	143	106.6	90.6	66.5	48.9
1 EBV	82	68.3	61.7	50.1	40.6
4 PTV	161.2	117.4	103.6	73.7	49.2
1 EBV	90.5	72.8	66	50.8	36.6
5 PTV	146.9	104.2	92.9	64.4	42.4
1 EBV	69.2	56	51.2	41.1	31.4
Mean PTV	157.9	115.5	101.8	73	50.7
Mean EBV	85	69.5	63.5	51	39.4

DYN_R and DYN_RT was calculated (Table IV). The differences show that the two regimes produce very similar dose distributions among the 35 fractions. More specifically the CTV and BV had average differences of 0.01 Gy and -0.02 Gy respectively among the different planning margins. Bladder and rectum had a V72 average difference of -0.02% and -0.01% respectively. DYN_RT can compensate for both shifts and rotations, without affecting the resulting dose distributions and thus a physical couch shift is not necessary as the full transformation can be accounted for in the online replanning prior to radiation delivery. Consequently, DYN_RT was selected for the rest of our analyses to represent the replanning capabilities of our pipeline.

3.A.2. Evaluation of replanning DYN_RT and reference plans

Figures 3 and 4 show boxplots of the complete 35-fraction datasets. Medians are visualized with horizontal red lines and means with blue circles. For each VOI and margin set, one boxplot for the respective REF, DYN_RT, and REF_R is plotted. This allows a direct comparison between the several regimes and margins sets simultaneously. For every structure the average difference over all planned fractions between REF, DYN_RT and REF_R was calculated.

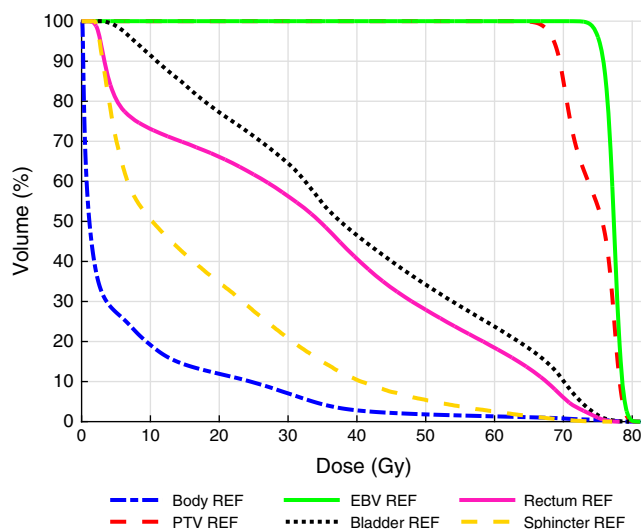


FIG. 2. REF DVH among 35-fractions averaged over all cases. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE IV. Mean differences DYN_RT - DYN_R (D99 in Gy and V72 in volume %).

Case	8 mm	6 mm	4 mm	2 mm	0 mm
PTV D99	0.06	-0.06	-0.12	-0.12	-
EBV D99	-0.11	-0.06	-0.01	-0.13	-
CTV D99	0.05	0.03	0.07	-0.05	-0.06
BV D99	-0.02	0.01	-0.04	-0.02	-0.04
Bladder V72	-0.05	-0.0004	-0.07	0.03	0.003
Rectum V72	0.06	-0.05	-0.02	0.0007	-0.03

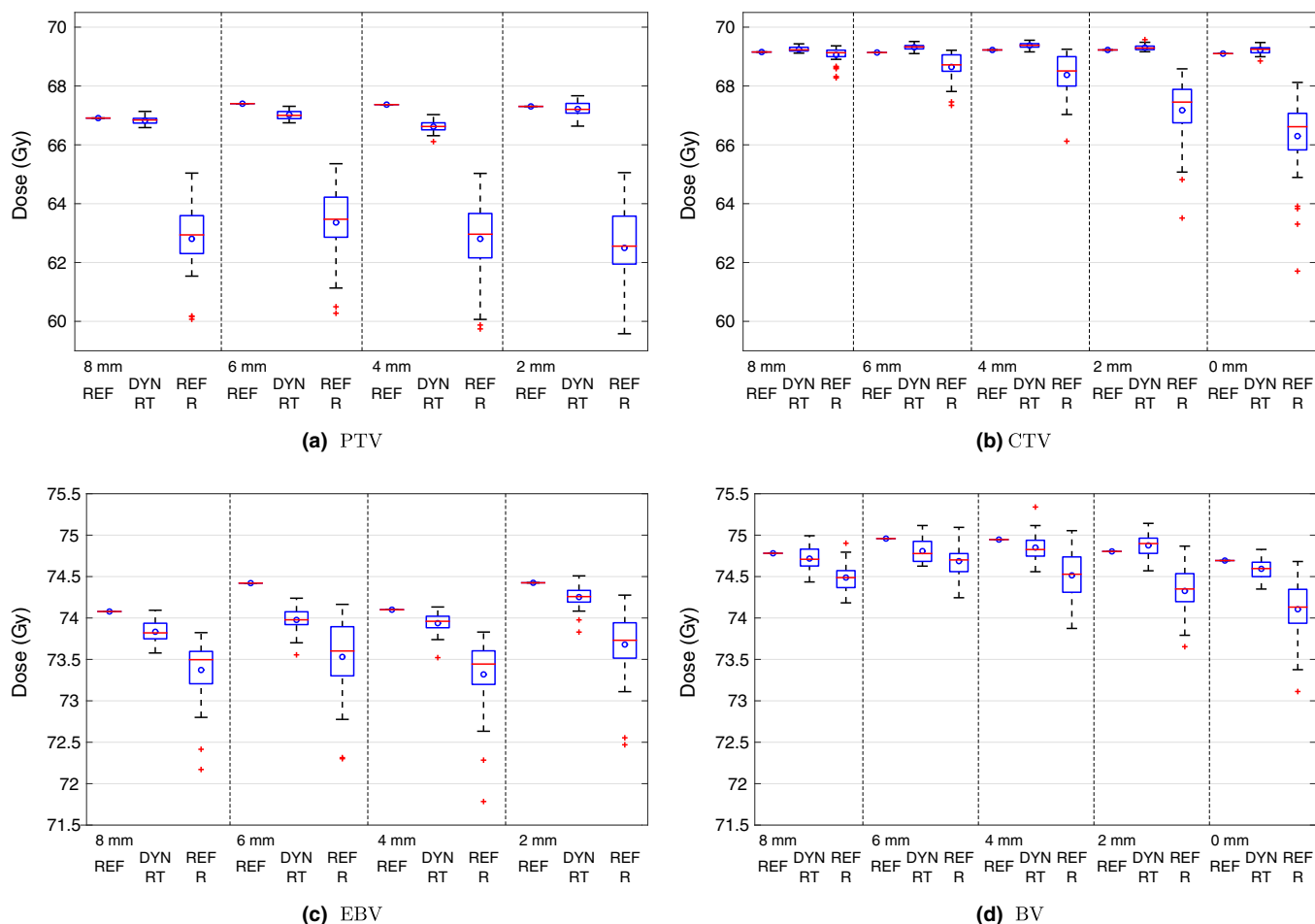


FIG. 3. Boxplots of the target DVH D99 points comparing REF, DYN_RT, and REF_R averaged among all cases. [Color figure can be viewed at wileyonlinelibrary.com]

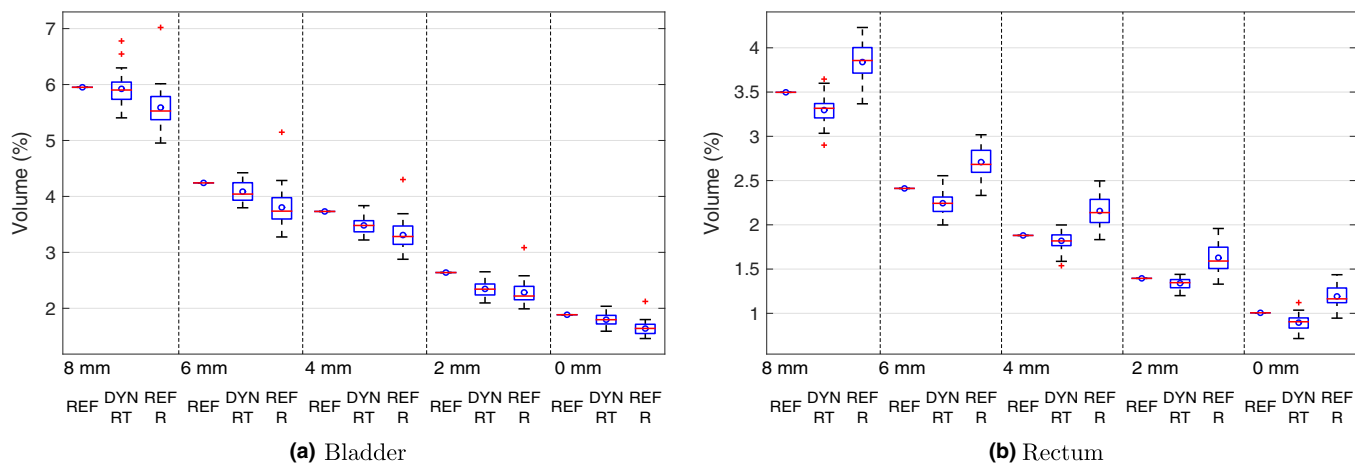


FIG. 4. Boxplots of the OAR DVH V72 points comparing REF, DYN_RT, and REF_R averaged among all cases. [Color figure can be viewed at wileyonlinelibrary.com]

REF vs. DYN_RT: Compared to the REF plans, DYN_RT stays very close to the intended clinical dose distributions of the patients, while sparing the high-dose regions of the critical OARs. CTV and BV points yield differences of -0.1 and 0.1 Gy on average, while bladder and rectum V72 are

decreased by 0.2% and 0.1% on average among the different margins.

REF_R vs. DYN_RT: We then established how DYN_RT compares to the motion affected REF plans (REF_R).

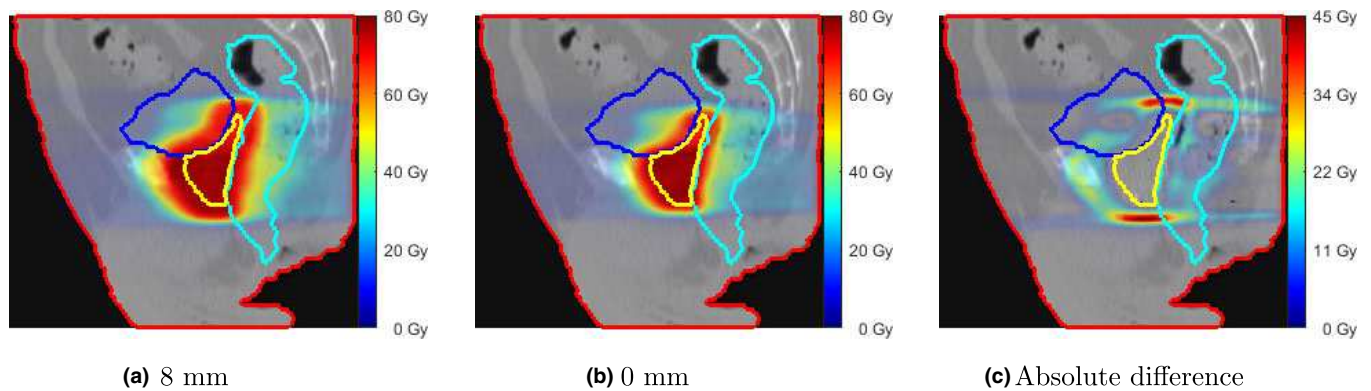


FIG. 5. Dose comparison of the central sagittal CTV slice for the REF 8 and 0 mm plans (bladder, CTV, and rectum, respectively, are visualized in the AP direction). [Color figure can be viewed at wileyonlinelibrary.com]

TABLE V. NTID per case (J).

Case	8 mm	6 mm	4 mm	2 mm	0 mm
1	139.7	123.9	118.6	104.8	99.7
2	136.8	119.9	116.3	98.2	91
3	138.2	122.5	114.6	101.1	94.7
4	134.2	116.4	113.9	98.2	86.2
5	113.2	96.1	92	78.5	73
Mean	132.5	115.8	111	96.2	88.9

TABLE VI. SWO plan MRLTP timings (seconds).

Case	Dose influence	Process anatomy	Single iteration	SWO	Full plan
1	22.2	5.6	1.5	12.8	121.2
2	22.2	6	1.3	10.1	107.8
3	21.9	5.8	1.3	6.9	102.8
4	21	5.2	1.3	12.4	111.6
5	19.6	4.9	1.2	10.3	98.4
Mean	21.4	5.5	1.3	10.5	108.4

Regarding the targets (Fig. 3), DYN_RT consistently generates higher dose coverage among all margins. Even at the standard clinical 8 mm margin, DYN_RT leads to an average 0.2 Gy increase in both BV and CTV. As the margins are decreased, DYN_RT continues to provide the expected coverage while REF_R is increasingly affected by the interfraction rotation. While a decrease in the PTV and EBV structures is to be expected, CTV also experiences high underdosage in all margins < 8 mm, ranging from 0.7 to 2.9 Gy (1% –4.2%) and BV coverage drops by an average of 0.4 Gy.

As far as the OARs are concerned (Fig. 4), Bladder V72 is similar in both DYN_RT and REF_R (average difference 0.2%), while staying very close to the original REF plan in both regimes. Rectum V72 is consistently decreased by the DYN_RT regime with a difference ranging from 0.3%–0.5% compared to the REF_R.

Margin decrease via DYN_RT: DYN_RT maintains equal coverage among the different margins. By comparing the 6, 4, 2, and 0 mm results to the clinical 8 mm margin, we establish that the CTV and BV coverage is unaffected (average difference -0.06 Gy for both), while bladder and rectum V72 progressively decrease along with the margin reaching a difference of 4.1% and 2.4%, respectively at the 0 mm.

The possible benefit of margin reduction can also be quantified by evaluating the NTID delivered by each respective REF plan. Table V shows the NTID values of all cases across the different margins. The relative reduction of the mean

integral dose among all cases compared to the 8 mm margin is 12.6%, 16.2%, 27.4%, and 32.9% at 6, 4, 2, and 0 mm margins, respectively. This decrease is to be expected due to the reduction of PTV volume reported in Table III, where the corresponding percentages of relative decrease in irradiated volume compared to the 8 mm PTV are 26.8%, 35.5%, 53.8% and 67.9% at 6, 4, 2 and 0 mm respectively. This effect can also be qualitatively observed in Fig. 5 which shows the central CTV sagittal dose slice from the REF 8 and 0 mm plans as well as the absolute dose difference between the two.

3.B. Timings

In this section we present timings of the daily replanning pipeline. Table VI shows timings of the SWO plans (Fig. 1) for each one of the included cases using the clinical 8 mm margins.

The presented timings show that online daily replanning is already achievable by generating from scratch a new prostate plan consisting of 50 segments in 108.4 s on average, with an average ASEQ iteration calculating a new segment in around 1.3 s.

4. DISCUSSION

We have simulated a 35-fraction prostate treatment during which a daily replan is made targeting the fraction anatomy according to marker transformations available from previously treated patients in our clinic. The major advantage of

daily replanning would be the inclusion of rotations into the optimization, which are often not corrected for in the clinical workflow. An average daily rotation of $5.7 (\pm 5.0)$ degrees around the LR axis was observed in our sample following the values reported in literature.^{9,17} Rotations of these magnitudes have been shown that can have a significant dosimetric effect and thus limit further reduction of the planning margins.^{10,11}

4.A. Online replanning performance

The utilization of daily full replanning is able to address beam related effects and generate optimal dose coverage/OAR sparing given the daily anatomy but its long computational times have restricted online application. Several methods have been proposed in an effort to partly substitute daily replanning within the online time requirements, from updating the multi-leaf collimator (MLC) leaf positions²⁰ and adjusting gantry/mlc angle¹⁸ to a combination of an offline preshifted plan library with online correction for the beam unflattening effect and target changes.²¹ In this work we present a system that enables full replanning for prostate in less than 2 minutes making it compatible with clinical application.

4.B. Clinical workflow — Online application

Under the daily replanning framework presented in this work, our pipeline could also be used to utilize rigid transformations extracted by different modalities/systems including Cone Beam CT (CBCT) and the Varian Calypso® implantable Beacon® transponders.

An important aspect of online replanning that could hamper online application is the plan evaluation procedure of the daily automated plans. In our pipeline all 35-fractions for every patient are calculated in an automated fashion using the same prescription file which was configured once before the calculations. By using the same internal constraints the resulting dose distributions of the DYN_RT regime stay very close to the original approved REF plans among all fractions (Figs. 3,4) and thus can simplify the daily plan evaluation which could then be performed by recalculating the new online plan in a secondary external dose engine prior to radiation delivery.

Furthermore, our pipeline is able to include both shifts and rotations in the replanning without affecting the resulting plans (Table IV), which means that an external couch correction could be excluded from the clinical protocol. Instead, the patient would be positioned on the table and the calculated translation and rotation would be directly fed into the planning system for replanning.

4.C. Planning margin

4.C.1. Contributing factors

The selection of the clinical planning margins depends on several factors that include prostate/OAR deformations, marker localization, and contouring uncertainty²². The anatomical

deformations can be a product of the prostate volume change during radiotherapy, the relative motion between prostate and seminal vesicles, and the motion of the surrounding structures e.g., changes in bladder/rectal filling. Moreover, the possible intrafraction motion should also be characterized and considered during the margin calculation phase. It has been suggested that for prostate a margin of 2 mm is necessary to account for the intrafraction motion alone.²³

4.C.2. Rigid motion

Following the workflow in our clinic, clinical fiducial marker data were used to provide the online rigid daily transformations for the prostate. Given that this motion information is limited to the target and its vicinity as well as the fact that the prostate rotations around the LR axis are correlated to the rectal volume,²⁴ we applied the transformation to the target and OARs^{8,18} while maintaining the original body volume. We then evaluated only the high dose regions of the OARs as described by the V72 DVH point in the clinical protocol while the targets were analyzed by using the D99 points to provide a strict dose coverage evaluation.

Under this rigid motion assumption, we show that by accounting for daily rotations in the replanning phase, better target coverage is achieved while the volume of the rectum in the high-dose region is decreased among all margins, including the current clinical 8 mm. As can be observed in Fig. 3 and 4 the prostate D99 is higher by 0.2 Gy and the rectum V72 reduced by 0.5% on average when comparing the DYN_RT to the REF_R results for the 8 mm margin. We are now working towards introducing the online replanning pipeline in our clinic under the current clinical protocol used in this work.

Moreover, while replanning ensures target coverage and OAR sparing as the planning margins decrease, the actual margin reduction is limited by the treatment uncertainties covered in Section 4.C.1. Given all these considerations, CTV to PTV margins of 4 mm have already been clinically introduced in our clinic in the FLAME-trial which consisted of a 35-fraction treatment with integrated gross tumor volume (GTV) 95 Gy boost while only correcting for daily rotations based on fiducial markers of up to 3 degrees around AP/LR axis and 6 degrees around SI axis by changing the gantry/table/collimator angle.²⁵

4.D. Hybrid MRI-linear accelerators

The online applicability of our system makes it also suitable for the new generation of hybrid radiotherapy machines like the MR-linac²⁶ which will be able to provide the patient 3D anatomical changes during treatment. Under this context — given the online intrafraction MRI — both intrafraction motion and anatomical deformations (Section 4.C.1) will be available via deformable image registration (DIR) and can be taken into account during replanning, allowing for safe margin reduction. It has already been suggested that given online MRI imaging in combination with DIR and adaptive planning strategies the prostate CTV to PTV margins could be further reduced to $\leq 3 \text{ mm}^3$.

In our previous work²⁷ we have shown that ASEQ can be used for intrafraction plan adaptation under the presence of a magnetic field based on the incoming motion information described by 3D DVFs. The current implementation of our system was designed to efficiently handle DVFs and enables very fast plan adaptation that will be required in these future treatment scenarios. In that context the thorough validation of the DIR methods and resulting DVFs that describe the underlying motion is then critical for the application of such pipelines. We are currently investigating the utilization of MRLTP in hypofractionated MRI-guided prostate treatments for daily replanning and evaluation of its possible clinical benefits.

5. CONCLUSION

We have presented a replanning pipeline for online daily rotational correction based on fiducial marker data in a 35-fraction prostate treatment and investigated its effects for a varied set of planning margins. A full prostate plan can be calculated in less than 2 min and for every patient the daily plans are generated in a fully automated fashion leading to very similar dose distributions to the pretreatment plans allowing for simplified daily plan evaluation and acceptance procedures. We showed that online replanning is able to accommodate for both shifts and rotations without requiring an extra couch correction. We demonstrated that daily replanning ensures the intended target coverage and OAR sparing over all margin sets, while the conventional plans are increasingly affected by daily rotations. Fully accounting for the daily translations and rotations can lead to higher target coverage and OAR sparing even at the current clinical margin of 8 mm and enables margin reduction mainly constrained by the anatomical deformations and intrafraction motion. Our pipeline can also be utilized in future MRI-guided treatments for daily online replanning enabling further margin reduction.

ACKNOWLEDGMENTS

This line of research has been partly financially supported by Elekta AB, Stockholm, Sweden. The authors thank Elekta AB, Stockholm, Sweden for providing some of their research software tools.

CONFLICT OF INTEREST

The authors have no relevant conflicts of interest to disclose.

^{a)}Author to whom correspondence should be addressed. Electronic mail: c.kontaxis@umcutrecht.nl.

REFERENCES

- Al-Mamgani A, Van Putten WL, Heemsbergen WD, et al. Update of Dutch multicenter dose-escalation trial of radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys.* 2008;72:980–988.
- Zelevsky MJ, Yamada Y, Fuks Z, et al. Long-term results of conformal radiotherapy for prostate cancer: impact of dose escalation on biochemical tumor control and distant metastases-free survival outcomes. *Int J Radiat Oncol Biol Phys.* 2008;71:1028–1033.
- McPartlin AJ, Li XA, Kershaw LE, et al. MRI-guided prostate adaptive radiotherapy: a systematic review. *Radiother Oncol.* 2016;119:371–380.
- Balter JM, Lam KL, Sandler HM, Littles JF, Bree RL, Ten Haken RKT. Automated localization of the prostate at the time of treatment using implanted radiopaque markers: technical feasibility. *Int J Radiat Oncol Biol Phys.* 1995;33:1281–1286.
- Dehnad H, Nederveen AJ, Van der Heide UA, Van Moorselaar RJA, Hofman P, Lagendijk JJW. Clinical feasibility study for the use of implanted gold seeds in the prostate as reliable positioning markers during megavoltage irradiation. *Radiother Oncol.* 2003;67:295–302.
- Litzenberg D, Dawson LA, Sandler H, et al. Daily prostate targeting using implanted radiopaque markers. *Int J Radiat Oncol Biol Phys.* 2002;52:699–703.
- Beaulieu L, Girouard LM, Aubin S, et al. Performing daily prostate targeting with a standard V-EPID and an automated radio-opaque marker detection algorithm. *Radiother Oncol.* 2004;73:61–64.
- Van Herten YRJ, Van de Kamer JB, Van Wieringen N, Pieters BR, Bel A. Dosimetric evaluation of prostate rotations and their correction by couch rotations. *Radiother Oncol.* 2008;88:156–162.
- De Boer HCJ, Van Os MJH, Jansen PP, Heijmen BJM. Application of the no action level (NAL) protocol to correct for prostate motion based on electronic portal imaging of implanted markers. *Int J Radiat Oncol Biol Phys.* 2005;61:969–983.
- Amro H, Hamstra DA, Mcshan DL, et al. The dosimetric impact of prostate rotations during electromagnetically guided external-beam radiation therapy. *Int J Radiat Oncol Biol Phys.* 2013;85:230–236.
- Shang Q, Olsen LJS, Stephans K, Tendulkar R, Xia P. Prostate rotation detected from implanted markers can affect dose coverage and cannot be simply dismissed. *J Appl Clin Med Phys.* 2013;14:177–191.
- Both S, Wang KK, Plastaras JP, et al. Real-time study of prostate intrafraction motion during external beam radiotherapy with daily endorectal balloon. *Int J Radiat Oncol Biol Phys.* 2011;81:1302–1309.
- Cramer AK, Haile AG, Ognjenovic S, et al. Real-time prostate motion assessment: image-guidance and the temporal dependence of intra-fraction motion. *BMC Med Phys.* 2013;13:4.
- Kontaxis C, Bol GH, Lagendijk JJW, Raaymakers BW. Towards adaptive IMRT sequencing for the MR-linac. *Phys Med Biol.* 2015;60:2493.
- Hisoigny S, Ozell B, Bouchard H, Despres P. GPUMCD: a new GPU-oriented Monte Carlo dose calculation platform. *Med Phys.* 2011;38:754–764.
- Ziegenhein P, Kamerling CP, Bangert M, Kunkel J, Oelfke U. Performance-optimized clinical IMRT planning on modern CPUs. *Phys Med Biol.* 2013;58:3705.
- Aubry JF, Beaulieu L, Girouard LM, et al. Measurements of intrafraction motion and interfraction and intrafraction rotation of prostate by three-dimensional analysis of daily portal imaging with radiopaque markers. *Int J Radiat Oncol Biol Phys.* 2004;60:30–39.
- Rijkhorst EJ, Van Herk M, Lebesque JV, Sonke JJ. Strategy for online correction of rotational organ motion for intensity-modulated radiotherapy of prostate cancer. *Int J Radiat Oncol Biol Phys.* 2007;69:1608–1617.
- D'Souza WD, Rosen II. Nontumor integral dose variation in conventional radiotherapy treatment planning. *Med Phys.* 2003;30:2065–2071.
- Court LE, Dong L, Lee AK, et al. An automatic CT-guided adaptive radiation therapy technique by online modification of multileaf collimator leaf positions for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2005;62:154–163.
- Ahunbay EE, Ates O, Li XA. An online replanning method using warm start optimization and aperture morphing for flattening-filter-free beams. *Med Phys.* 2016;43:4575–4584.
- Nichol AM, Brock KK, Lockwood GA, et al. A magnetic resonance imaging study of prostate deformation relative to implanted gold fiducial markers. *Int J Radiat Oncol Biol Phys.* 2007;67:48–56.
- Kotte ANTIJ, Hofman P, Lagendijk JJW, Van Vulpen M, Van der Heide UA. Intrafraction motion of the prostate during external-beam radiation therapy: analysis of 427 patients with implanted fiducial markers. *Int J Radiat Oncol Biol Phys.* 2007;69:419–425.

24. Hoogeman MS, Van Herk M, De Bois J, Lebesque JV. Strategies to reduce the systematic error due to tumor and rectum motion in radiotherapy of prostate cancer. *Radiother Oncol.* 2005;74:177–185.
25. Lips IM, Van der Heide UA, Haustermans K, et al. Single blind randomized Phase III trial to investigate the benefit of a focal lesion ablative microboost in prostate cancer (FLAME-trial): study protocol for a randomized controlled trial. *Trials.* 2011;12:255.
26. Lagendijk JJW, Raaymakers BW, Van Vulpen M. The magnetic resonance imaging linac system. *Semin Radiat Oncol.* 2014;24:207–209.
27. Kontaxis C, Bol GH, Lagendijk JJW, Raaymakers BW. A new methodology for inter- and intrafraction plan adaptation for the MR-linac. *Phys Med Biol.* 2015;60:7485.