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Scientific Article

First-in-Men Online Adaptive Robotic Stereotactic Body Radiation Therapy: Toward Ultrahypofractionation for High-Risk Prostate Cancer Patients

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Purpose: Ultrahypofractionation presents challenges for a subset of high-risk prostate cancer patients due to the large planning target volume (PTV) margin required for the seminal vesicles. Online adaptive radiation therapy could potentially reduce this margin. This paper focuses on the development, preclinical validation, and clinical testing of online adaptive robotic stereotactic body radiation therapy for this patient group.

Methods and Materials: An online adaptive workflow was developed for the CyberKnife with integrated in-room CT-on-rails. Preclinical validation involved comparing deep learning–based auto-contouring with deformable or rigid contour propagation in terms of subsequent editing time. A fast treatment planning method was implemented and compared with the conventional method in terms of optimization time and adherence to planning constraints. Clinical testing was conducted in the first study patients of the UPRATE trial, which investigates the feasibility of seminal vesicle PTV margin reduction in low-volume metastasized prostate cancer patients. Treatment time and patient experience were recorded.

Results: Rigid registration for prostate and deep-learning auto-contouring for seminal vesicles and organs at risk were selected based on editing time and robustness for anatomic changes. The fast treatment planning method reduced the optimization time from 10 to 3.5 minutes (P = .005). No significant differences in dose parameters were observed compared with the conventional plans. During clinical testing, 53 of 60 fast treatment plans adhered to the planning constraints, and all 60 were clinically accepted and delivered. The average total treatment time was 67.7 minutes, showing a downward trend. The treatment was well-experienced overall.

Conclusions: Online adaptive stereotactic body radiation therapy using CyberKnife with integrated CT-on-rails is clinically feasible for prostate cancer patients with seminal vesicles included in the target volume. The UPRATE trial outcome will reveal the extent to which online adaptation can reduce the PTV margin of the seminal vesicles.

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Introduction

The low α/β ratio for prostate cancer (PCa)[1,2] suggests a fractionation sensitivity difference (tumor/normal tissue) that might favor (ultra)hypofractionation.[3] Ultrahypofractionation for low- and intermediate-risk PCa has been shown to be noninferior regarding failure-free survival[4] and toxicity.[5] However, ultrahypofractionation is challenging for a subset of high-risk PCa patients, in which the entire seminal vesicles (SVs) are included in the target volume.[6] The range of motion of the SVs is substantial and largely uncorrelated to the prostate; therefore, a planning target volume (PTV) margin in the order of 8 mm is commonly added in the treatment of SVs.[7-10] This large PTV margin, together with high fraction doses, could result in an unacceptable dose to the main organs at risk (OARs), ie, the rectum, bladder, and/or bowel, and thereby to an unacceptable risk of genitourinary and gastrointestinal toxicity.[11] To safely treat SVs with ultrahypofractionation, strategies to reduce the PTV margin are required.

A recent systematic review of relevant literature regarding SV motion showed that efforts to reduce this motion, such as strict drinking or dietary instructions to influence bladder or rectal volume, lacked effectiveness.[12] Similarly, the use of rectal spacers seemed to have a limited effect on the reduction of SV motion.[13] Additionally, it showed that the intrafraction component of the PTV margin is approximately 5 mm. Hence, eliminating the interfraction component from the PTV margin by using online adaptive radiation therapy (ART) could be a way to safely treat SVs with ultrahypofractionation. Studies have shown the potential of online ART to correct for interfraction motion.[14,15] Online ART using daily plan adaptation is a technique that is becoming more widely available in the clinic. Solutions based on magnetic resonance imaging (MRI)[16-18] or cone beam computed tomography (CBCT)[19] have both been shown to adequately treat the prostate with ultrahypofractionation. The MRI-based solution exhibits long fraction times of approximately 45 to 60 minutes[16-18] and uses gating,[16,20] multileaf collimator tracking in a trial setting,[21] or subfractionation[18] to mitigate intrafraction prostate motion. The CBCT solutions have shorter treatment times, averaging around 20 minutes,[19] but lack intrafraction motion compensation.

At our institute, a trial has started (UPRATE-trial; EMC21-0540; clinicaltrials.gov: NCT05361902), approved by the medical ethics committee at Erasmus MC, in which a combination of online daily replanning using an in-room computed tomography (CT) scanner on rails, and intrafraction fiducial tracking, as available on the CyberKnife system using 2-dimensional kilo voltage (KV) imaging,[22] is used. This trial aims to prove the feasibility of reducing the SVs' PTV margin from 8 to 5 mm. To this end, patients with low-volume metastasized PCa, as described in the STAMPEDE trial,[23] are included and treated with 6 weekly fractions of 600 cGy. When the UPRATE trial turns out to be successful, the next step would be to apply this 5 mm PTV margin around the SV in the curative setting for high-risk patients using a higher, curative total dose. At our institute, in low-volume metastasized PCa patients with tumor invasion in the SVs, the entire or the base of the SVs are included in the target volume at the discretion of the treating physician. This is in contrast to the STAMPEDE trial patients, where the SVs were not included in the target volume. The technical feasibility of online adaptive stereotactic body radiation therapy (SBRT) on the CyberKnife has been demonstrated before.[24] This paper describes the development and preclinical validation of the online adaptive SBRT workflow on the CyberKnife for the UPRATE trial. Furthermore, the first-in-men clinical treatments of the first 10 trial patients are reported to focus on fraction duration and patient experience.

Methods and Materials

Patient and treatment characteristics

The online adaptive workflow of the UPRATE trial has been developed and tested on 10 previously treated PCa patients, each with 1 planning CT scan and 3 repeat CT scans and target volumes, including the entire SVs. The workflow's clinical testing was carried out on the first 10 patients with low-volume metastasized PCa, who received treatment as part of the UPRATE trial. Exclusion criteria, as per UPRATE protocol, were previous pelvic surgery, poor urinary function (international prostate symptom score; IPSS $\geq$ 20), prostate volume $\geq$ 90 mL, or bilateral hip replacements (impairing CT visibility). For these patients, according to the institutional protocol, the prostate and the entire or the base of the SVs were included in the clinical target volume at the discretion of the treating physician, depending on the local tumor stage, as defined in the TNM classification version 8[25] and (extent of) growth into the SVs. Treatment preparation consisted of the implantation of 3 to 4 gold fiducial markers. Patients received instructions to drink 300 to 400 mL water half an hour prior to the planning CT scan and every treatment fraction. Treatment consisted of 6 weekly fractions of 600 cGy[23] with online adaptation on the CyberKnife, using a PTV margin of 3 mm around the prostate[26] and a reduced PTV margin of 5 mm around the SVs. The dose was prescribed to the 95% isodose line, aiming for dose to 95% of the PTV $\geq$ 99%. All treatment plans were multileave collimator-based and generated using the VOLO optimizer in Precision (version 3.1.0.0), which is the treatment planning system of Accuray.[27]

Online adaptive workflow description

The entire online adaptive workflow is shown in Fig. 1 and consisted of the following steps: (1) patient alignment and acquisition of a prefraction CT scan, (2) contour adaptation, (3) online plan generation and evaluation, (4) plan quality assurance and digital reconstructed radiograph generation, and finally, (5) treatment delivery.

Contour adaptation

All contour editing was done in MIM software (version 7.1.6) by an experienced radiation oncologist. See Appendix E1 for a full list of contour definitions.

Treatment plan generation and evaluation

A fast optimization template was created on the planning CT, which was subsequently used to generate new plans on the fraction CTs according to the composed and validated UPRATE constraints.

Quality assurance

Plan quality assurance was performed by an independent 3-dimensional (3D) dose calculation using the SciMoCa algorithm (Scientific RT).[28] Further details are given below.

Adaptive workflow development and preclinical validation

To determine the fastest method for contour adaptation, the editing times of rigid registration, deformable image registration (from planning CT to fraction CT), and a deep-learning auto-contouring solution (MIM Protégé, version 2.0, MIM Software) were compared for all targets and OARs in 3 previously treated patients. After deformable image registration or deep-learning auto-contouring, the contours were visually inspected by an experienced radiation oncologist. Contour adaptation was then done under the supervision of the radiation oncologist, and adaptation time per organ or target was recorded.

To further aid fast contour editing during online plan adaptation, only editing the OAR contour limited to within 3.5 cm from the target instead of editing all contours on the entire CT scan was investigated.[24,29] In practice, this approach would mean that only absolute instead of relative OAR constraints could be used.[16] The composed absolute UPRATE constraints are shown in Table 1. To ensure compliance with all known absolute and relative constraints from large randomized controlled trials for PCa, ie, the PACE, HYPO-RT-PC, and STAMPEDE trials,[4,23,30] the composed absolute UPRATE constraints were tested on 10 previously treated PCa patients, of which 1 planning CT and 3 repeat CT scans were available prior to the start of the trial. To this end, the dose parameters of the PACE and HYPO-RT-PC trials[4,30] were converted in equivalent dose at 2 Gy per fraction (EQD2) using α/β values of 300 cGy for the rectum and bladder, 200 cGy for the bowel/sigmoid, 150 cGy for the prostate, and 80 cGy for femoral heads (Table 1).[4] Regarding the HYPO-RT-PC trial constraints, longstanding local clinical experience showed the feasibility of implementing stricter anus and rectum constraints at our institute. These stricter constraints were chosen instead of the HYPO-RT-PC constraints in order to make no concessions on OAR doses regarding current clinical practice.

Subsequently, all 10 previously treated PCa patients were delineated by XX (anonymized) under the supervision of a radiation oncologist (XX anonymized). Together with a radiation technician, treatment plans were generated for both the planning and repeat CT scans, which were approved by a radiation oncologist (XX anonymized). These plans were optimized using the set of absolute planning constraints, and after adhering to these constraints, the constraints were then tested by checking the plans for the constraints used in the STAMPEDE,[23] PACE,[30] and HYPO-RT-PC[4] trials (see Results).

The workflow's fast optimization template, "quickplan template," which was designed to generate treatment planning parameters leading to short optimization times,

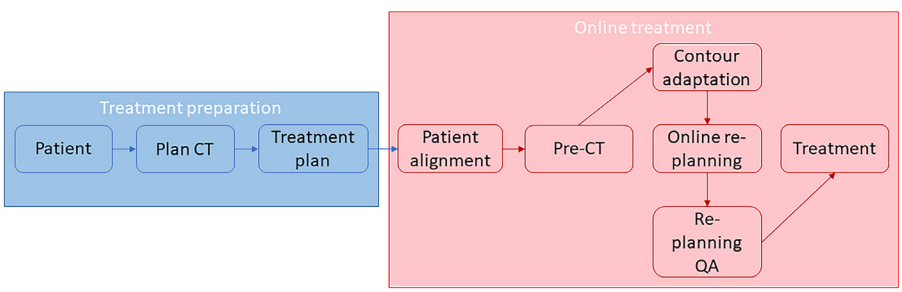

Figure 1 Flowchart representing the online adaptive workflow for patients treated in the UPRATE trial. Blue steps are done offline during treatment preparation. Red steps are performed online and repeated every fraction. The purple step is done only for research purposes.

Abbreviations: CT = computed tomography; Plan CT = planning CT scan; Post-CT = postfraction CT scan; Pre-CT = prefraction CT scan; QA = quality assurance; SV = seminal vesicle.

Table 1 The newly derived absolute UPRATE constraints compared with the constraints used in the STAMPEDE, PACE, and HYPO-RT-PC trials[4,22,29]

	UPRATE 36 Gy (6 × 6 Gy)		STAMPEDE 36 Gy (6 × 6 Gy)		PACE 36.25 Gy (5 × 7.25 Gy)		Erasmus MC, derived from HYPO-RT-PC 42.7 Gy (7 × 6.1 Gy)	
Volume	**Constraints**	**EQD2**	**Constraints**	**EQD2**	**Constraints**	**EQD2**	**Constraints**	**EQD2**
PTV	V34.2 Gy (V95%) > 99%	65.8	V34.2 (V95%) > 99%	65.8	V36.25 (V100%) > 95%	83.8	V40.6 (V95%) > 98%	79.2
	-	-	-	-	V34.4 (V95%) > 98%	76.4	-	-
	Dmax < 38.5 Gy (107%)	81.0	-	-	Dmax < 48 (133%)	139.2	Dmax 45.7 (V105%)	97.4
Rectum	V36 (V100%) < 5 cm^3	64.8	V33.3 (V93%) < 50%	56.9	V36 (V99%) < 1 cm^3*	73.4	-	-
	V34.2 (V95%) < 10 cm^3	59.5	V27.8 (V77%) < 60%	42.4	V29 (V80%) < 20%	51.0	V38.4 (V90%) < 15%	65.2
	V26.5 (V74%) < 25%	39.3	V16.7 (V46%) < 80%	19.3	V18.1 (V50%) < 50%	24.0	V28 (V66%) < 25%	39.2
Bladder	V37.8 (V105%) < 5 cm^3	70.3	V33.3 (V93%) < 25%	56.9	V37 (V102%) < 5 cm^3†	77.0	-	-
	-	-	V27.8 (V77%) < 50%	42.4	V18.1 (V50%) < 40%	24.0	-	-
Sigmoid/ bowel	V32.4 (V90%) < 1 cm^3	60	-	-	V30 (V83%) < 1 cm^3	60	V35 (V82%) < 2 cm^3	61.3
	V19.4 (V54%) < 5 cm^3	25.4	-	-	V18.1 (V50%) < 5 cm^3	25.4	-	-
Anus	Dmean < 17 Gy	19.8	-	-	-	-	Dmean < 20 Gy	23.4
Femur heads	V25 (V70%) < 0.1 cm^3	44.3	-	-	V14.5 (V40%) < 5%‡	19.2	Dmax < 29 Gy	51.2
Urethra	-	-	-	-	V42 (V116%) < 50%	109	-	-

EQD2 values are calculated using α/β values of 3 for the rectum and bladder, 2 for the bowel/sigmoid, 1.5 for the prostate, and 0.8 for femoral heads.
Abbreviations: Dmax = maximum dose; Dmean = mean dose; EQD2 = equivalent dose 2; PTV = planning target volume.
*Optimal constraint, mandatory is <2 cm^3.
†Optimal constraint, mandatory is <10 cm^3.
‡Optimal constraint, no mandatory constraint available.

was previously published for pancreatic cancer and oligometastatic lymph nodes.[24,29] First, a treatment plan without optimization time restriction (unrestricted) was generated based on the planning CT. The sample points of all structures were then drastically reduced (total ≤ 50,000 from approximately 500,000) without changing any optimization goals or weights. The optimization was then run again, resulting in a new "quickplan" with reduced optimization times. If the quickplan was clinically acceptable, the quickplan's template was saved and used for all upcoming fractions. To ensure the validity of this approach for the current patient group, it had to be validated prior to clinical use. Using the planning CTs of the 10 previously treated patients, unrestricted plans and subsequent quickplans were generated. Both the unrestricted plans and quickplans were compared based on the set of absolute constraints, the treatment time, and the optimization time. Statistical significance was determined using a Wilcoxon signed rank test (IBM SPSS statistics, version 28.0.1.0), with $P < .05$ being defined as statistically significant.

First-in-men clinical testing and experience

Clinical testing of the quickplan method was carried out in the first 10 UPRATE trial patients. Adherence to the UPRATE constraints were monitored, as well as any need for additional optimizations after the initial running of the quickplan template to adjust for possible constraint breaches. Additionally, the total fraction duration distributed over all individual workflow steps (Fig. 1) was also recorded for all eligible fractions. An eligible fraction was defined as complete timing data without any unforeseen breaks. In addition, a patient experience questionnaire was developed based on similar questionnaires used in magnetic resonance (MR) guided radiation therapy[31] and brachytherapy studies conducted at our institute (not yet published). This questionnaire was given to the first 10 patients of the UPRATE trial to obtain feedback on their experience with this online adaptive treatment and the clearness of the radiation therapy technologist (RTT) instructions (see Appendix E2).

Results

Adaptive workflow development and preclinical validation

Contour adaptation

Rigid fiducial-based registration was chosen for the prostate, given the anticipated small deformations and the need to ensure consistency in contouring between the planning CT and fraction CT scans. However, due to the large deformation observed in the OARs and SVs, rigid registration was found to be unsuitable for these structures. Comparing contour editing times, it was observed that deep learning–based auto-contouring outperformed contour propagation based on deformable image registration for the rectum and bladder (2.6 vs 3.6 minutes and 3.8 vs 4.3 minutes, respectively). In contrast, for the SVs, deformable image registration resulted in shorter editing times than deep learning–based auto-contouring (3.5 vs 4.5 minutes, respectively). Overall, deep learning–based auto-contouring was chosen for both OARs and SVs, as this method demonstrated fast overall adaptation times and was shown to be less prone to large errors caused by big anatomic changes.

Validation of absolute dose-volume constraints

Table 1 shows the definitive set of constraints compared with those used in the STAMPEDE,[23] PACE,[30] and HYPO-RT-PC trials, including the stricter Erasmus MC rectum and anus constraints.[4] For the validation process, 2 repeat CT scans for 1 out of the 10 patients were found to be unsuitable for dose calculation as the patient was partially outside the field of view. During the development phase, the composed absolute rectum constraints showed to be inadequate for generating plans that would adhere to the Erasmus MC's V2800 cGy < 25% rectum constraint. Therefore, the decision was made to add this relative rectum constraint to the absolute constraints, meaning that the entire volume of the rectum needed to be contoured. By combining the set of absolute constraints with the relative rectum constraint, 21 out of 28 evaluated treatment plans immediately met the composed UPRATE constraints and the constraints of the STAMPEDE, PACE, and Erasmus MC/HYPO-RT-PC trials.[4,23,30] Of the 7 plans that initially failed to meet all constraints, 2 plans complied after adjusting the prescription isodose line (to 94% or 96%) or lowering the weight of an optimization goal followed by an additional optimization. Increasing the prescription isodose line generally results in a lower OAR dose at the expense of a lower maximum dose (Dmax) and lower PTV coverage. Conversely, lowering the prescription isodose line increases Dmax and PTV coverage but increases OAR dose. These adjustments provide a quick solution to minor target coverage or OAR constraint violations and can be executed swiftly during online adaptation (0.5 minutes for adjusting the isodose line or 3.5 minutes for 1 additional optimization). Two plans showed underdosage of the PTV (98.9% and 97.6%), attributed to an overlap of a bowel loop with the PTV. Two other plans failed the PACE bladder constraint (V1810 cGy < 40%) due to small bladder volumes (<100 cm^3). Lastly, 1 plan showed a combination of PTV underdosage caused by an adjacent bowel loop and a bladder constraint violation resulting from a small bladder volume.

Quickplan validation

Of the 10 previously treated patients, 3 exhibited constraint violations in the quickplans, whereas the unrestricted plans did not. For 2 of these patients, the minor coverage violations in the quickplan were resolved by lowering the prescription isodose line to 94%. In 1 patient, slight adjustments to the weights and goals of the optimization objectives were made to achieve an acceptable plan. Table 2 presents the comparison of optimization and treatment times, as well as relevant dose-volume parameters. The use of the quickplan template resulted in a factor 2.7 reduction in optimization time, from an average of 10.0 minutes to 3.5 minutes (P = .005). Besides optimization times, no significant differences between unrestricted plans and quickplans were observed.

First-in-men clinical testing

Quickplan

Of the 60 delivered fractions, 49 immediately adhered to all constraints. Of the 11 fractions that did not meet all constraints, 4 fractions met all constraints after an additional optimization, where the optimization parameters were adjusted to address the violations (2 times increasing the weight of PTV coverage, once adding a bowel goal, and once adding an anus goal). The remaining 7 fractions did not meet all constraints after additional optimizations (details in Fig. E1, Appendix E3). For 2 fractions of 1 patient, this was caused by a large rectal gas pocket inside the PTV (Fig. 2).

Fraction duration analysis

Of the 60 fractions, 10 fractions in 5 patients were excluded due to urination during treatment; 1 fraction had missing timing data. Furthermore, 2 outliers due to technical delays of 30 minutes or more were excluded. For the remaining 47 fractions, the average fraction duration time was 67.7 minutes (ranging from 52.7 to 89.8 minutes). Average treatment times per patient were within the range of 61 to 74 minutes. Figure 3 illustrates the breakdown of the time per adaptive step, while Fig. 4 indicates a trend toward decreasing treatment time (P = .166).

Patient experience

The first 10 patients filled out the questionnaire on their experience during the treatment. Eight out of 10 patients described the relatively long treatment time as acceptable or good. Nine of the 10 patients described being at ease during the entire treatment. Furthermore, 8 of the 10 patients described being comfortable or better during treatment. Five of the 10 patients described controlling the bladder during treatment as being difficult, with the remaining 5 patients describing it as easy or very easy. Lastly, 9 of the 10 patients described all instructions given as being clear or very clear.

Discussion

In this study, the development, preclinical validation, and first-in-men clinical experience of online ART for PCa on the CyberKnife system with an in-room CT scanner using an in-house developed workflow is described. Furthermore, fraction duration and patient experience of the first 10 patients are reported. To our knowledge, this is currently the only study reporting clinical use of online adaptive SBRT on the CyberKnife.

In theory, quickplans could lead to poorer plan quality as a reduction in sample points could result in plans of lower quality than those optimized with the full amount of sample points (in this case, ≤50,000 compared with

Table 2 Comparison of unrestricted plan and quickplan templates on average optimization time, treatment time, and relevant dose-volume parameters (per fraction, in cGy)

	Unrestricted plan	Quickplan	Statistical significance, P
Mean optimization time in minutes (range)	10.0 (6.4-15.6)	3.5 (2.2-6.4)	<.001*
Mean treatment time in minutes (range)	18.1 (11-23)	18.3 (11-23)	.443
PTV coverage (≥99%)	99.49	99.41	.196
Rectum V600 cGy (<5 cm^3)	1.46	1.43	.833
Rectum V570 cGy (<10 cm^3)	5.98	5.96	.902
Rectum V442 cGy (<25%)	21.17	21.20	.889
Bowel V542 cGy (<1 cm^3)	0.10	0.10	.343
Bowel V323 cGy (<5 cm^3)	0.61	0.58	.213
Bladder V630 cGy (<5 cm^3)	0.0	0.0	.343

Abbreviations: PTV = planning target volume.
*P < .05 is considered statistically significant.

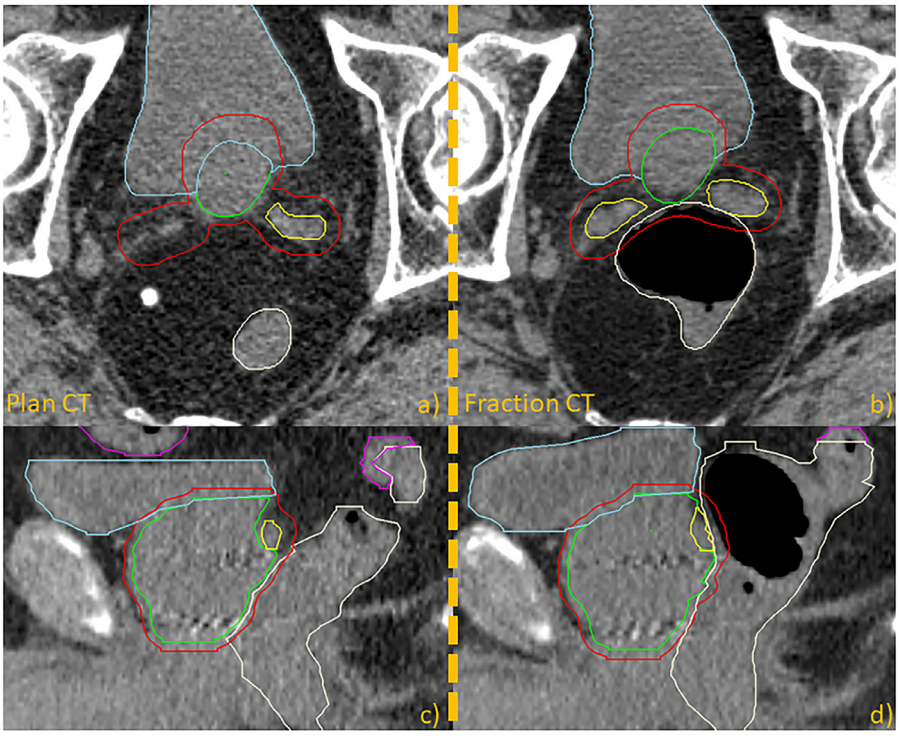

Figure 2 Axial and sagittal views of a patient with a large rectal bubble changing anatomy. (A) Plan computed tomography (CT) − axial; (B) fraction CT − axial; (C) plan CT − sagittal; and (D) fraction CT − sagittal. Contours: red = planning target volume; green = prostate; yellow = seminal vesicles; white = rectum; purple = bowel.

500,000). However, this work builds on earlier work in which the concept of quickplans has been extensively investigated. It was shown that quickplans result in comparable and clinically acceptable treatment plans, as judged by experienced radiation oncologists, compared with unrestricted plans.[24,29] Furthermore, the time gained using these quickplans can contribute to a more accurate dose delivery as intrafraction anatomic changes may increase with increasing treatment time.[32] Additionally, this study shows that the differences between unrestricted plans and quickplans are statistically insignificant, and only 7 (11%) quickplan treatment plans showed persistent constraint violations after additional optimization. After inspection and evaluation by a radiation oncologist, all 7 were deemed clinically acceptable in light of previous treatment fractions and were subsequently delivered. Hence, the quickplan optimization template can be employed to create treatment plans in an online adaptive setting without a clinically significant compromise in plan quality. This is in line with the literature on CBCT-based ART for PCa, where all 220 adaptive treatments were also chosen, even though 49 of 220 (22%) adaptive treatment plans violated bladder and/or rectum constraints.[33]

Using the CyberKnife system for online adaptive SBRT comes with multiple potential advantages. First, the CyberKnife uses intrafraction tracking of the intraprostatic

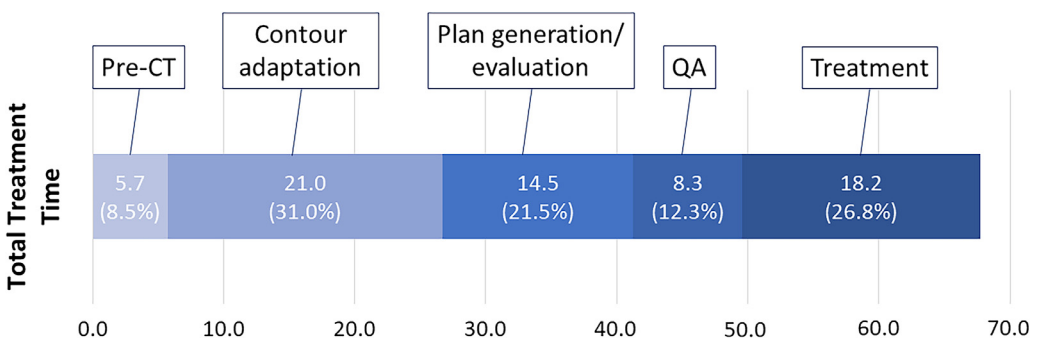

Figure 3 Average total treatment time, in minutes broken down in average time (minutes), per adaptive step (with percentages).
Abbreviations: Pre-CT = computed tomography scan prior to treatment; QA = treatment quality assurance.

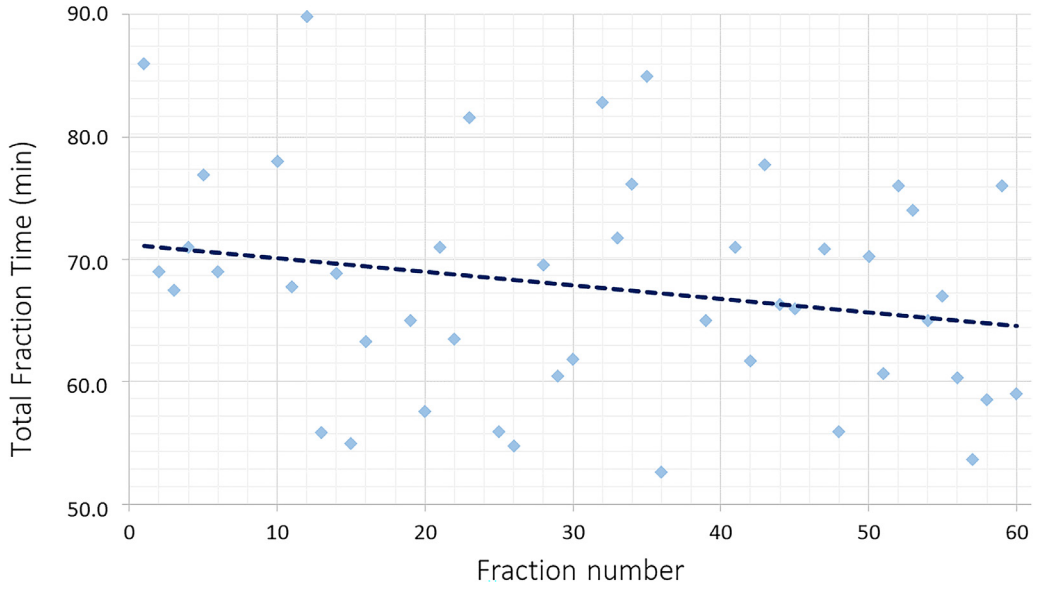

Figure 4 Total fraction duration in minutes plotted against the fraction number since starting the trial.

fiducials capable of correcting for both translations and rotations, hence ensuring good prostate coverage.[34] Important to note, however, is that the results of the UPRATE study have to be awaited with regard to safely reducing the PTV margin around the SVs in this setting, as the SVs move partially uncorrelated to the prostate.[12] Second, another advantage can be the use of noncoplanar beam angles by the CyberKnife in an online ART setting. A previous study has shown that prostate treatment with 3800 cGy in 4 fractions using noncoplanar compared with coplanar beam angles resulted in advantageous dose distributions.[35] The biggest differences were seen in rectum dose-volume parameters with noncoplanar beam angles that showed reductions of 5% in the dose to 0.1cm^3 (P = .002), 32% in V6000 cGy EQD2 (P = .001), and 4% for mean dose (P = .05) compared with coplanar beam angles.

A drawback of online adaptive treatments compared with nonadaptive treatments can be the increased time between daily image acquisition on behalf of ART and plan delivery, as it is well known that the target and OAR can show large intrafraction motion during plan adaptation.[36,37] Besides the advantages of relying on fast treatment times for CBCT-based adaptive treatments[19] or gating for MR-based adaptive treatments,[16] both MR and CBCT solutions also offer 3D imaging directly prior to treatment delivery to facilitate a (virtual) couch shift compensating for intrafraction prostate motion during online adaptive replanning.[33,38] In the CyberKnife workflow, acquiring an additional CT scan after plan optimization and moving the couch back to the treatment position would take approximately 8 additional minutes and is, therefore, less attractive. However, both translations and rotations are corrected just prior to beam delivery by using CyberKnife's tracking system based on implanted fiducial markers and KV imaging, hence ensuring good prostate coverage without the need for new 3D imaging.[34]

A possible limitation of the current approach is the relatively long total treatment time. Currently, the average treatment time is 67.7 minutes, which is longer than reported in the literature for MR- and CBCT-based systems, with averages of 42.7 to 61 minutes and 33.56 minutes, respectively.[16-19,39] This difference in average treatment time has 3 causes: first, the current online adaptive SBRT workflow is not integrated within the treatment system, leading to extra steps and time (an additional 6.8 minutes on average) spent on communication between different systems. However, a nonintegrated solution also provides more flexibility, for instance, with the option to make adjustments to the optimization parameters if an online plan showed constraint violations, which was used for 4 of the 60 clinically delivered fractions for which integrated solutions could have limited options.[33,40,41] Second, the noncoplanar CyberKnife system has an inherently long dose delivery time, which is approximately 18.2 minutes compared with averages of 11 to 5.6 minutes and 5.6 minutes of coplanar MR- or CBCT-based treatments, respectively.[18,33,37] This can, in part, be explained by the intrafraction motion tracking, which does take additional time.[34] Third, the UPRATE trial includes the SVs in the treatment, creating a larger target volume to be edited compared with what is reported for MR guided or CBCT-based online ART treatments.[16-19,33,39] Important to note here is that this online adaptive workflow is new at our institute, as it is worth mentioning that studies have shown a decrease in overall treatment times of ART with ongoing experience.[42] Therefore, it is likely that the abovementioned

average overall treatment times will probably decrease over time, as is already suggested in Fig. 4.

Improvements to the current online workflow could further decrease treatment times. Similar to previously published studies,[24] contour adaptation remains the most time-consuming step in the workflow. Although deep-learning auto-contouring of the OARs and SVs resulted in the fastest adaptation times (21 minutes), editing all contours still takes, on average, 31% of the total treatment time, which is longer than the reported MR-based (12.6 ± 3.8 minutes)[42] or CBCT-based ART editing times (6.5 ± 2.5 minutes).[33] Also, some MR-based and CBCT-based online ART solutions have reported that no editing of contours was needed during their ART workflow.[19,42] However, in the current online adaptive SBRT workflow, all contours so far have been edited. A technical solution for this could be the use of improved auto-contouring models, which would reduce the amount of required editing. A study using a different 3D convolutional neural network on PCa data reported a success rate (no contour editing needed to adhere to all dosimetric constraints) of 80%.[43] Other technical solutions to speed up adaptation times could include clinical integration of MIM Protégé version 4.0, which does autocontour the sigmoid and bowel, or the use of institute-specific artificial intelligence models. Physician-specific artificial intelligence models have been studied for postprostatectomy patients, and it was found that the resulting contours scored, on average, 3.4% higher on the Dice similarity coefficient compared with the general model.[44] More practically, parallel delineation, during which the RTT edits the auto-contours of OARs while the radiation oncologist edits the targets, could save approximately 6 minutes (8.0% of total treatment time), which is currently being developed for the UPRATE trial. It has been shown in the literature that similar approaches in which RTTs are responsible for delineation can be successful.[42,45,46] Similarly, further research could be done into the exact cutoff limit for the editing region of OARs, which is already suggested to be 1.5[47] to 2[42] cm instead of 3.5 cm.

The fact that 2-dimensional KV imaging is available, as opposed to online imaging during treatment, implies that intraprostatic fiducial markers have to be used to facilitate intrafraction target tracking. This does justify the use of a small 3 mm PTV margin around the prostate but could be a drawback for this treatment since markerless treatment options are becoming increasingly available with inherent benefits regarding cost and patient comfort.[16-18] In addition, the soft tissue contrast on CT is limited compared with MRI, which leads to a possible overestimation of the prostate volume[48,49] and an increase in interobserver variation in prostate contours.[48,50] Studies comparing CT-based and MRI-based SV delineation are scarce and inconclusive. Doemer et al[49] reported a nonsignificant ($P = .454$) overestimation of the SV volume (1.7%) with CT delineation compared with MRI delineation.

Conclusions

In conclusion, this is the first study describing the development, preclinical validation, and clinical testing of an online adaptive SBRT workflow using the CyberKnife with an in-room CT scanner. The online adaptive workflow for PCa with the entire SVs in the target volume seems to be clinically feasible and is currently used for the patients in the UPRATE trial. Although the average overall treatment time is substantial, it is expected to decrease with growing experience and workflow-related and technical improvements.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2024.101701.

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