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Original Article

Clinical application of a sub-fractionation workflow for intrafraction re-planning during prostate radiotherapy treatment on a 1.5 Tesla MR-Linac: A practical method to mitigate intrafraction motion

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ABSTRACT

Background: Intrafraction motion during radiotherapy limits margin reduction and dose escalation. Magnetic resonance (MR)-guided linear accelerators (MR-Linac) have emphasised this issue by enabling intrafraction imaging. We present and clinically apply a new workflow to counteract systematic intrafraction motion during MR-guided stereotactic body radiotherapy (SBRT).

Materials and methods: With the sub-fractionation workflow, the daily dose is delivered in multiple sequential parts (sub-fractions), each adapted to the latest anatomy. As each sub-fractionation treatment plan complies with the dose constraints, no online dose accumulation is required. Imaging and treatment planning are executed in parallel with dose delivery to minimise dead time, enabling an efficient workflow. The workflow was implemented on a 1.5 T MR-Linac and applied in 15 prostate cancer (PCa) patients treated with 5 × 7.25 Gy in two sub-fractions of 3.625 Gy (10 × 3.625 Gy in total). Intrafraction clinical target volume (CTV) motion was determined and compared to a workflow with single-plan delivery. Furthermore, required planning target volume (PTV) margins were determined.

Results: Average on-table time was 42.7 min. Except for two fractions, all fractions were delivered within 60 min. Average intrafraction 3D CTV displacement (±standard deviation) was 1.1 mm (± 0.7) with the sub-fractionation workflow, whereas this was up to 3.5 mm (± 2.4) without sub-fractionation. Calculated PTV margins required with sub-fractionation were 1.0 mm (left–right), 2.4 mm (cranial-caudal), and 2.6 mm (anterior-posterior).

Conclusion: Feasibility of the sub-fractionation workflow was demonstrated in 15 PCa patients treated with two sub-fractions on a 1.5 T MR-Linac. The workflow allows for significant PTV margin reduction in these patients by reducing systematic intrafraction motion during SBRT.

The clinical introduction of magnetic resonance (MR)-guided linear accelerators (MR-Linac) has majorly impacted radiotherapy workflows by enabling MR-imaging prior to and during beam-on [1–3]. Currently, these systems can counteract anatomical changes, including rotation and deformations of the target(s) and organs-at-risk (OARs), between treatment fractions by performing interfraction plan adaptation [4–7]. However, plan adaptation to counteract intrafraction changes has not yet been explored. Especially in case of ultra-hypofractionation or extreme hypofractionation (i.e. 1–5 fractions), the problem of intrafraction motion becomes more apparent due to long delivery times. Hypofractionated radiotherapy is of great interest for various tumour sites due to the potentially improved oncological outcomes in cancers with a higher intrinsic sensitivity to fractionation, such as prostate cancer (PCa) [8–10]. Besides oncological aspects, extremely hypofractionated radiotherapy also brings advantages in terms of patient comfort and departmental logistics (i.e. fewer visits and shorter overall treatment time). While oncological outcomes might be improved, a higher fractional dose also could increase the risk of toxicity due to a potentially higher dose received by the OARs when not properly considering intrafraction organ motion [11]. The impact of this intrafraction motion problem has become even more evident as a result of MR imaging during beam-on time and dose reconstructions, as previously shown in PCa treatment [4,11–13]. To counteract the effect of organ motion prior to and during beam-on time, and to maximally protect the OARs, intrafraction adaptation methods – such as tracking, gating, and online dose

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accumulation – are warranted [12,14]. However, these methods still face many technical hurdles, for example with respect to accuracy of online dose accumulation [15]. The current lack of clinically implemented intrafraction adaptation methods on MR-Linac systems hinders the progression towards extremely hypofractionated MR-guided radiotherapy in e.g. two fractions.

By delivering the treatment fraction in multiple parts (i.e. *sub-fractions*) during one treatment session using repetitive imaging and updated treatment plans, theoretically the effect of systematic intrafraction drift motion (drift) on a larger timescale (minutes) could be (partially) counteracted. As each sub-fraction complies with the dose-volume histogram (DVH) constraints, online dose accumulation is not required. Although the idea of sub-fractionation is not novel and prior studies have shown the possibility of treatment delivery in multiple parts [16], the clinically available software currently requires two separate, subsequent treatment sessions to do so. This inherently makes the idea of sub-fractionation less attractive or even unfeasible, as treatment times can become extensive. Here, we propose a new and improved '*sub-fractionation*' workflow that allows efficient treatment delivery in multiple sub-fractions within a single treatment session on a 1.5 Tesla (T) MR-Linac by performing imaging, treatment planning, and treatment delivery processes in parallel. In addition, the first clinical application of the workflow in prostate cancer patients is described and the effect on intrafraction target motion is assessed.

Materials and methods

Steps of the sub-fractionation workflow

The presented sub-fractionation workflow is an adaptation of the commercially-available clinical software for a 1.5 T MR-Linac system (Unity, Elekta AB, Stockholm, Sweden) [2]. The workflow consists of several steps and the exemplary workflow applied in prostate cancer patients is displayed in Fig. 1. The first part of the sub-fractionation workflow (**steps 1**–**5**) is similar to the current commercially-available interfraction-adaption ('Adapt-to-Shape' [ATS]) method [2]. Before treatment, a pre-treatment (offline) MRI is acquired, which is used for offline delineation of the target(s) and OARs and pre-treatment planning. During actual treatment, a daily MRI scan (PRE MRI) is acquired on the MR-Linac (**step 1**). Next, the ATS procedure is initiated (**step 2**). During this procedure, the PRE and offline MRI are registered using deformable image registration (DIR) software that is part of the commercially-available Monaco® (Elekta Inc., Sunnyvale, California, USA) treatment planning software, after which the contours from the offline scan are non-rigidly propagated to the PRE scan. The contours are visually checked and – if necessary – manually edited by the operator. After approval of the contours, treatment plan re-optimization is initiated. When the DVH constraints are met, the treatment plan is approved. Just prior to finishing treatment planning (after the first fluence optimization step), a position verification (PV) MRI scan (PV1) is acquired (**step 3**). In case shifts of > 1 mm occurred, an 'Adapt-to-Position' (ATP) procedure or 'virtual couch shift' is applied, in which the dose is shifted to correct for translations (**step 4**) [2]. Next, treatment delivery is started (**step 5**). These steps combined constitute one cycle of the sub-fractionation workflow, in which a predefined dose of *X* Gy is delivered without interruption. This first initiation cycle comprises interfraction adaptation.

The next cycle is initiated during beam-on time of the previous cycle and thus **steps 6** and **7** are executed in parallel with treatment delivery (**step 5**). First, right after start of beam-on, a new PV MRI scan (PV2) is obtained (**step 6**), which is rigidly registered to the initial daily MRI using the ATP procedure (**step 7**). Contours are now rigidly propagated, followed by treatment plan optimization. In case the treatment plan complies with the DVH constraints, treatment delivery is initiated (**step 8**). Simultaneously, new imaging can be acquired (**step 9**). **Steps 6**–**8** can be repeated a predefined number of times, based on e.g. the expected organ motion and/or deformations within a predefined time frame.

Software components

To enable this sub-fractionation workflow, several features of to the commercially available software for the Elekta Unity MR-Linac were used and extended. After approval and import of the initial daily treatment plan into the patient data management system MOSAIQ® (Elekta Inc., Sunnyvale, California, USA), the online treatment planning software Monaco does allow the optimization of a new treatment plan in the same session. However, the treatment session manager (TSM) does *not* allow a second treatment plan to be imported into the patient data management system MOSAIQ. The so-called '*JamTool*' was developed in-house to enable the import of a second treatment plan from Monaco into MOSAIQ. In short, JamTool moves the dicom file generated by the Monaco treatment planning system to the import directory of MOSAIQ and ensures that the identifiers (IDs) inspected by MOSAIQ are consistent with the current TSM session. The 'jam' procedure is triggered by an operator via a graphical user interface and is executed within 2 seconds. The JamTool software runs on a Windows-based PC within the MR-Linac treatment environment. JamTool was developed in accordance with the European Medical Device Regulation (MDR) within a dedicated software quality management system.

Clinical application, feasibility and intrafraction motion assessment

The workflow was clinically applied in 15 patients with low- or intermediate-risk PCa who were treated on an MR-Linac with 5 × 7.25 Gy over the course of 2.5 weeks. Patients were registered

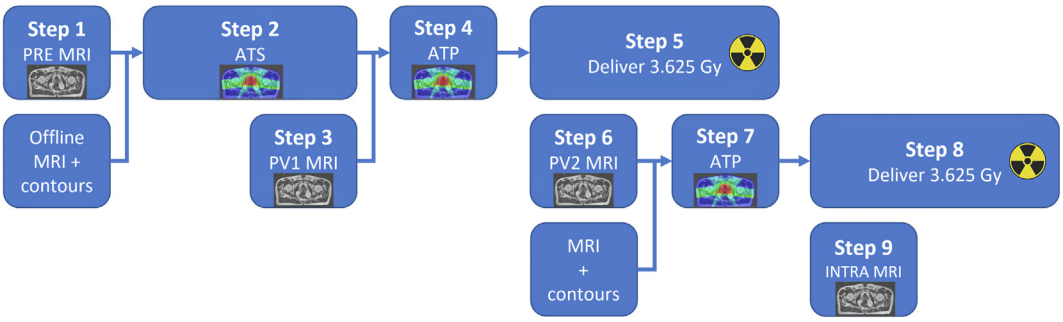

Fig. 1. Schematic overview of the sub-fractionation workflow. ATS = Adapt-to-Shape. ATP = Adapt-to-Position. PV = position verification.

as part of an institutional review board approved registration and imaging study. Each fraction was divided into two sub-fractions (Fig. 1), thus delivering 2 × 3.625 Gy each treatment session. Each first half was delivered using the previously described clinical workflow at the UMC Utrecht during which an interfraction correction is applied to correct translations, rotations, and deformations of the target and OARs (i.e. ATS procedure followed by an ATP procedure prior to beam-on) (Fig. 1, **steps 1–5**) [17]. The second half was delivered following an ATP procedure using the PV2 scan (acquired simultaneously with delivery of the first plan), correcting for translations only (**steps 6–8**). For each sub-fraction, a new treatment plan is created that complies with the DVH constraints, thereby discarding the need for dose accumulation. The constraints used for treatment planning and MRI parameters are displayed in Table S1 and S2 (Supplementary Data A). No standardised bladder filling protocol was applied in these patients.

All treatment sessions, including individual workflow steps, were timed. Feasibility was arbitrarily defined as being able to deliver two sequential sub-fractions in ≤ 60 min on-table time in ≥ 95% of the fractions. The 60 min cut-off was arbitrarily chosen: this is approximately 15 min longer than the average time needed with the current workflow, but still results in a feasible one-hour timeslot that is often used for MR-Linac treatments at our department [17].

Residual intrafraction clinical target volume (CTV) displacement in three translation directions were estimated from the four intrafraction MRI scans obtained during a single fraction (PRE, PV1, PV2, and INTRA). Rigid registration of the CTV among these scans was performed using in-house software (Volumetool [18]) with visual inspection and manual fine-tuning. Additionally, the residual 3D intrafraction displacements during each fraction were calculated using these translational shifts. For the sub-fractionation workflow, the average 3D displacement was calculated as the average of the intrafraction 3D displacement that occurred between PV2-PV1 (delivery of sub-fraction 1) and INTRA-PV2 (delivery of sub-fraction 2). Furthermore, intrafraction 3D displacements were estimated for two hypothetical clinical scenarios: (1) applying the previous clinical UMC Utrecht workflow (1xATS followed by 1xATP just before beam-on and delivery of 7.25 Gy in one go [17]) and (2) applying a single ATS procedure without additional ATP step(s). For scenario 1, residual intrafraction displacements were estimated from PV2-PV1 ('lower' limit, as PV2 captures the anatomy during the first 3 min of a 10 minute 7.25 Gy delivery) and INTRA-PV1 ('upper' limit, as the average time between PV1-INTRA is 17.3 min, which is slightly longer than the average 15 min actually involved [17]). For scenario 2, intrafraction motion was estimated from PV1-PRE. The estimated 3D displacements from these scenarios were compared to those from the applied sub-fractionation workflow. Finally, both the population systematic (Σ) and population random (σ) residue intrafraction motion components were calculated for the sub-fractionation scheme and PTV margins were determined for the anterior-posterior (AP), cranial-caudal (CC), and left–right (LR) direction using the van Herk formula (see Supplementary for full details) [19].

Results

Between December 2021 and May 2022, 15 PCa patients completed their treatment using the sub-fractionation workflow. Of the 75 fractions, 73 (97%) were executed according to plan following the sub-fractionation workflow. Two fractions (two patients) were excluded due to (human) errors leading to delays in treatment. In both cases, the 'jam' procedure was executed prematurely and therefore new treatment plans had to be created. In these patients, a second ATS procedure was employed to deliver the second sub-plan and the treatment was completed, delivering the prescribed dose per fraction.

The average time from start of PRE imaging to end of beam-on of the second sub-fraction (on-table time) was 42.7 min (Table 1). Except for the two excluded cases (on-table times of 76 and 80 min), on-table time was ≤ 60 min for all fractions (range: 35–58 min).

The intrafraction motion over the course of a fraction (between PRE and INTRA, see Fig. 1) was smallest in the left–right direction (0.3 mm, standard deviation [SD] 1.2 mm) and comparable in the cranial-caudal (−1.8 mm, SD 2.7 mm) and anterior-posterior direction (1.7 mm, SD 2.8). Average 1D intrafraction CTV displacement with the sub-fractionation workflow ranged between −2.5 mm and 2.0 mm in all directions (Fig. 2). The average 3D intrafraction CTV displacement was 1.1 mm (SD 0.7 mm) for the sub-fractionation workflow, 1.6 mm (SD 1.1 mm) and 2.3 mm (SD 1.4 mm) for the previous clinical workflow (lower and upper limit, respectively), and 3.5 mm (SD 2.4 mm) for the ATS-only workflow (Fig. 3). For the sub-fractionation workflow, the 3D intrafraction CTV displacement was ≤ 2.7 mm in all fractions, whereas this ranged up to 14.9 mm with the ATS-only workflow (Figs. 3 and 4).

Based on the population systematic (Σ) and population random (σ) errors of the (measured) intrafraction motion and accounting for remaining intrafraction rotation motion [20], PTV margins of 1.0 mm (LR), 2.4 mm (CC), and 2.6 mm (AP) would be required according the van Herk formula (Supplementary Data B).

Discussion

In this work, we have proposed and clinically applied a sub-fractionation workflow for MR-guided radiotherapy treatment on a 1.5 T MR-Linac system. The workflow is an adaptation of the previously routine clinical Unity system workflow. A treatment fraction is delivered in two sub-fractions within a single treatment session by performing several processes in parallel. The overall workflow is technically and clinically feasible within a timeframe very similar to the routine workflow. Furthermore, for prostate cancer SBRT, the workflow allows for PTV margin reduction based on the reduced intrafraction translational motion.

To be able to progress to extremely hypofractionated radiotherapy with high fractional doses, one preferably can counteract all intrafraction motion occurring during beam-on. However, intrafraction adaptation methods are currently not clinically implemented on Unity MR-Linac systems, partly due to challenges with real-time dose accumulation. Fully, online adaptive workflows with real-time plan adaptation are the ultimate goal, but are considered by some to currently still be a far stretch [14]. To start on this route, we aimed to provide a less challenging workflow for tackling intrafraction motion during SBRT, thereby bridging the gap between current interfraction-only and future fully intrafraction adaptive workflows for MR-guided radiotherapy [21]. By keeping the dose for one sub-fractionation cycle low, beam-on times are kept reasonably short. In our cohort of 15 patients, the total beam-on time was 11 min on average, so

Table 1
Average timings of the variable components of the sub-fractionation workflow.

Step	Average (min)	SD (min)
Adapt-to-Shape procedure (step 2)	19.2	4.7
First Adapt-to-Position procedure (step 4)	4.8	1.3
Second Adapt-to-Position procedure (step 7)*	6.7	1.6
Total beam-on time (step 5 and 8)	11.0	1.6
On-table time (step 1–8)	42.7	5.5

* Included (manual) workflow steps specific to JamTool procedure. SD = standard deviation.

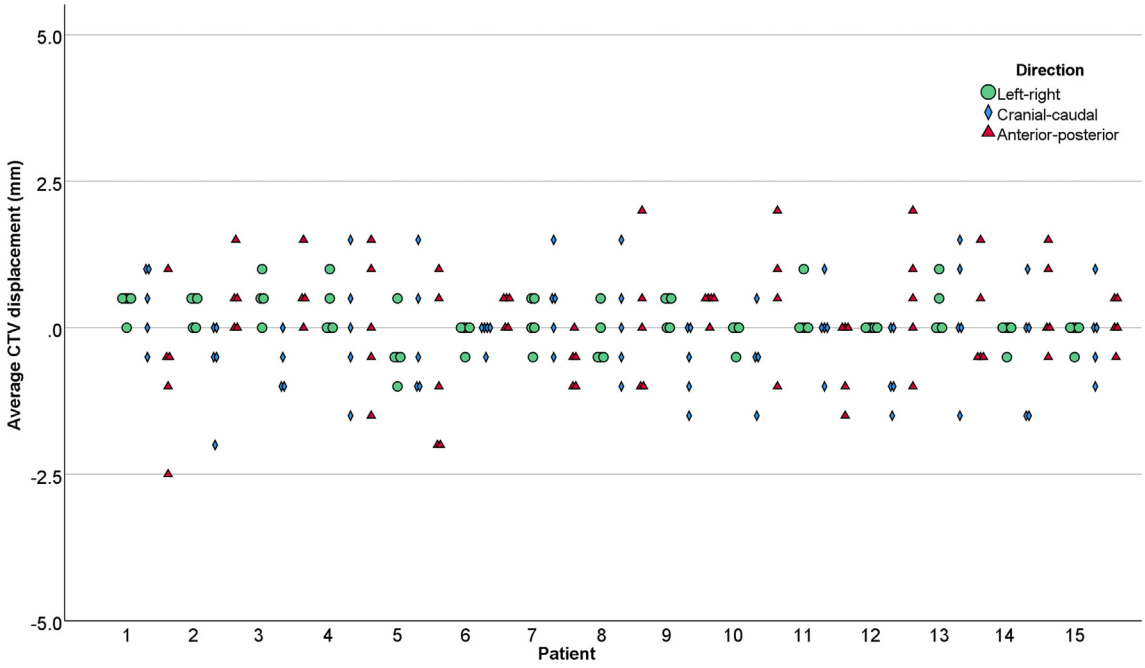

Fig. 2. Average residual intrafraction CTV displacement with the sub-fractionation workflow (1xATS + 2xATP) in the left–right, cranial-caudal, and anterior-posterior direction (as indicated by the dots, squares, and diamonds, respectively) for all fractions (n = 5) separately per patient. For clarity, for each patient the measurements are stratified horizontally by 'direction'. In case there are two or more measurements (for a single patient and in the same direction) with an equal value, these are displayed slightly shifted next to each other. Negative values are in the right, caudal, and anterior direction.

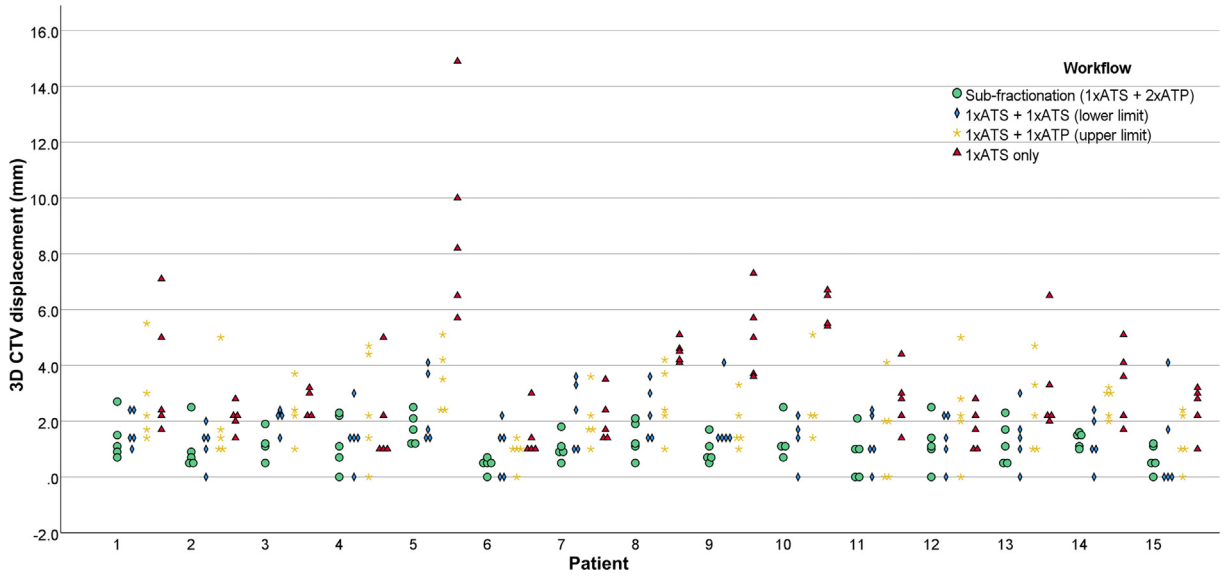

Fig. 3. Residual 3D intrafraction CTV displacement with the sub-fractionation workflow (1xATS + 2xATP), previously applied workflow (1xATS + 1xATP, both lower and upper limit), and ATS-only workflow (as indicated by the dots, squares, diamonds, and triangles, respectively) for all fractions (n = 5) separately per patient. For clarity, for each patient the measurements are stratified horizontally by 'workflow'. In case there are two or more measurements (for a single patient and for the same workflow) with an equal value, these are displayed slightly shifted next to each other.

approximately 5.5 min per 3.625 Gy. This is comparable to a single 7.25 Gy plan delivery time of around 10 min on the Unity MR-Linac [17]. Also, on-table time with the sub-fractionation workflow was on average 42.7 min (range 35–58 min), which is approximately 4 minutes longer than with the previously applied 1xATS followed by 1xATP workflow [17]. This makes the workflow feasible within a one-hour timeslot.

Because the same DVH criteria are met in each sub-fractionation cycle, any discrepancies between the prescribed and actual delivered cumulative dose will be kept to a minimum by spreading out effects of intrafraction motion over multiple sub-fractions. This is identical to the approach in conventional fractionation and prevents the need for online dose accumulation. Theoretically, the sub-fractionation workflow can more accurately deliver the dose to the target while sparing OARs when compared to the clinical ATS workflow in which the daily dose is delivered without interruption in a single cycle. This is supported by our findings with respect to the average 3D intrafraction CTV displacement,

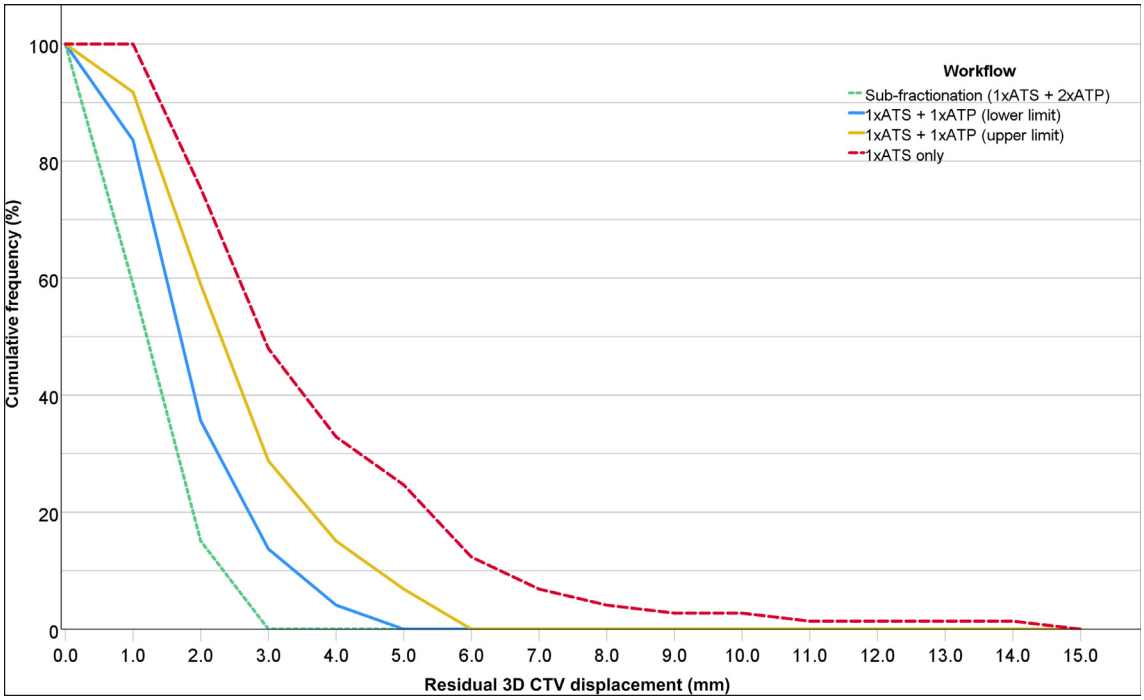

Fig. 4. Cumulative frequency (%) of residual 3D intrafraction CTV displacement in bins of 1 mm (i.e. 1.0 indicates that the 3D displacement was between 1.0–1.9 mm) with the sub-fractionation workflow (1xATS + 2xATP), previously applied workflow (1xATS + 1xATP, both lower and upper limit), and ATS-only workflow.

which was below 2.7 mm for all fractions with the sub-fractionation workflow. By increasing treatment accuracy, progression to extremely hypofractionated radiotherapy can be achieved. Furthermore, increased treatment accuracy could enable significant reduction in uncertainty margins. We calculated the required CTV-to-PTV margins needed using the sub-fractionation workflow and we therefore have now implemented anisotropic margins of 2 mm (LR and CC) and 3 mm (AP) for our prostate SBRT treatments on the MR-Linac. These margin reductions will potentially lower (acute) toxicity rates in these patients, as the dose to OAR can be significantly reduced [22]. Still, the effects on clinical outcomes have to be assessed prospectively. Our future work will also focus new applications of the sub-fractionation workflow, such as two-fraction SBRT for recurrent PCa.

The clinical application of a similar approach on an MRidian system was described in a case report by Lagerwaard et al. using conventional software and plan re-optimization after half the dose was delivered [16]. Contrary to Lagerwaard et al., our workflow is capable of simultaneous MRI acquisition and treatment planning during delivery of the previous sub-fractionation cycle within a single treatment session. This vastly reduces the overall treatment time compared to fully sequential imaging, treatment planning, and treatment delivery. Currently, the HERMES trial is investigating the safety and efficacy of two-fraction SBRT (2 $\times$ 12/13.5 Gy) for the treatment of primary PCa [23]. Because of the long beam-on times, treatment delivery in this trial is split in two parts. These are delivered in two separate, sequential treatment sessions and patients can leave the treatment table mid-treatment to empty their bladder. This leads to long treatment times (> 90 minutes). Especially for this kind of treatment, our sub-fractionation workflow could significantly improve efficiency and reduce overall fraction times, which will benefit departmental logistics.

The sub-fractionation workflow has some limitations. The workflow mainly counteracts drift motion and cannot act upon sudden large anatomical changes. Ultimately real-time adaptation methods will become clinically available that counteract intrafraction motion on the fly. The proposed sub-fractionation workflow only guarantees fulfilment of DVH criteria for each sub-fractionation cycle and is aimed at bridging the gap between the interfraction adaptive ATS workflow and future fully online adaptive workflows. Furthermore, the workflow still needs an operator who remains in control and who needs to perform quality checks, which creates lag time due to manual intervention. Currently, the software is not fully optimised for speed and together with the manual operator intervention, this leads to idle time. This is reflected in the timings we have reported. This idle time in turn can lead to (significant) intrafraction motion occurring during the various steps of the workflow, such as the time between MRI acquisition and actual start of treatment delivery. These effects have yet to be determined in clinical practice and are depending on the tumour site, although for prostate cancer the effects will be relatively small. Nevertheless, the ultimate goal will always be to have cycle times that are as short as (technically) possible. With respect to MRI acquisition timings, compressed sensing could lead to significant a reduction while maintaining image quality [24]. In addition, by applying an ATP step, we do not counteract intrafraction rotational motion. However, compared to interfraction rotations, which can be quite large, intrafraction rotations are relatively small [4,20]. With the current clinical software, adopting an ATS workflow for the second sub-fraction is not effective due to long workflow times (including manual editing of the contours, see also Table 1), as this would diminish the benefit of sub-fractionation.

While clinical feasibility of the workflow has been shown in PCa patients and has led to significant PTV margin reduction in our clinic, this does not guarantee improved clinical outcomes. Future research should assess the clinical benefits, such as the effect on (accumulated) dose distribution and toxicity. Furthermore, future work should focus optimization of individual workflow steps, such as deformable contour propagation and imaging, as this will increase efficiency and limit idle time. Different and/or improved DIR algorithms, such as anatomically-adaptive registration, deep

learning-based auto-contouring, or hybrid solutions could improve contour accuracy and reduce the need for manual operator intervention even further [25,26]. This would allow repetitive application of the ATS workflow within acceptable time frames.

Concluding, we have presented and clinically applied a sub-fractionation workflow for MR-guided SBRT. Clinical feasibility was demonstrated with a focus on the timing of the workflow in 15 PCa patients treated with SBRT. This workflow enables PTV margin reduction and can potentially bridge the gap between current clinical interfraction adaptive workflows and future fully, intrafraction adaptive workflows. Thereby the sub-fractionation workflow allows the pursuit of extremely hypofractionated radiotherapy and/or margin reduction for various tumour sites on short term.

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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.radonc.2022.09.004.

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