Towards fast online intrafraction replanning for free-breathing stereotactic body radiation therapy with the MR-linac

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Abstract

The hybrid MRI-radiotherapy machines, like the MR-linac (Elekta AB, Stockholm, Sweden) installed at the UMC Utrecht (Utrecht, The Netherlands), will be able to provide real-time patient imaging during treatment. In order to take advantage of the system’s capabilities and enable online adaptive treatments, a new generation of software should be developed, ranging from motion estimation to treatment plan adaptation. In this work we present a proof of principle adaptive pipeline designed for high precision stereotactic body radiation therapy (SBRT) suitable for sites affected by respiratory motion, like renal cell carcinoma (RCC). We utilized our research MRL treatment planning system (MRLTP) to simulate a single fraction 25 Gy free-breathing SBRT treatment for RCC by performing inter-beam replanning for two patients and one volunteer. The simulated pipeline included a combination of (pre-beam) 4D-MRI and (online) 2D cine-MR acquisitions. The 4DMRI was used to generate the mid-position reference volume, while the cine-MRI, via an in-house motion model, provided three-dimensional (3D) deformable vector fields (DVFs) describing the anatomical changes during treatment. During the treatment fraction, at an inter-beam interval, the mid-position volume of the patient was updated and the delivered dose was accurately reconstructed on the underlying motion calculated by the model. Fast online replanning, targeting the latest anatomy and incorporating the previously delivered dose was then simulated with MRLTP. The adaptive treatment was compared to a conventional mid-position SBRT plan with a 3 mm planning target volume.
margin reconstructed on the same motion trace. We demonstrate that our system produced tighter dose distributions and thus spared the healthy tissue, while delivering more dose to the target. The pipeline was able to account for baseline variations/drifts that occurred during treatment ensuring target coverage at the end of the treatment fraction.

Keywords: fast online replanning, intrafraction plan adaptation, IMRT, MR-linac, stereotactic body radiation therapy (SBRT), stereotactic ablative radiotherapy (SABR), kidney renal cell carcinoma (RCC)

(Some figures may appear in colour only in the online journal)

1. Introduction

In the recent years stereotactic body radiation therapy (SBRT) has been applied in both primary cancer and oligometastatic disease in various treatment sites showcasing increased tumor local control and reduced toxicity (Alongi et al 2012, Rubio et al 2013). Compared to conventional external body radiation therapy (EBRT), SBRT consists of hypofractionated treatments with high dose per fraction along with steep gradients around the target and thus highly depends on the accurate geometrical delivery of the planned dose.

Four dimensional (4D) CT and MR imaging have been utilized to investigate the motion of organs affected by respiratory motion in the thoracic and abdominal regions which can experience large displacements reaching amplitudes of more than 2 cm (Brandner et al 2006) in the Superior-Inferior (SI) direction. Indicatively, during free breathing, the left and right kidneys can undergo displacements of up to 2.4 and 3.5 cm (Moerland et al 1994). Moreover, baseline variations/shifts compared to the pre-treatment reference position can occur during treatment reaching displacements of more than 1 cm (von Siebenthal et al 2007).

Several combinations of planning techniques and margin selection have been developed in an effort to account for the positioning uncertainty and motion enabling better target coverage and/or healthy tissue sparing. They span from internal tumor volume (ITV) where the volume covering the whole breathing cycle is targeted (Rietzel et al 2006), to gating where irradiation is only performed in a part of the respiratory cycle (Berson et al 2004) and the mid-position approach where the geometric time-weighted mean tumor position is used (Wolthaus et al 2008). Online compensation via MLC tracking has recently been clinically employed in lung SBRT based on implanted electromagnetic transponders (Booth et al 2016). Dose reconstruction techniques based on both CT and MR data have been used to assess the actual delivered dose (Velec et al 2012, Glitzner et al 2015).

The variation of the frequency and amplitude of the respiratory motion along with the potential baseline changes demand the presence of online 3D imaging during treatment. The new hybrid MRI-radiotherapy machines—like the MR-linac (Elekta AB, Stockholm, Sweden) which combines a 7 MV linear accelerator with a 1.5 T MRI scanner recently installed in University Medical Center Utrecht (Lagendijk et al 2014), the MRIdian (ViewRay Inc., Cleveland, OH, USA) which was the first commercially available clinical system combining a 0.35 T MRI with 3 60Co sources (Mutic and Dempsey 2014) and similar systems (Keall et al 2014, Fallone 2014)—will be able to visualize the patient’s anatomy in a real-time fashion during treatment.

The presence of intrafraction imaging also demands a new set of online tools ranging from motion estimation to treatment plan adaptation. In our institute we have previously developed a method which combines a statistical motion model, derived from a 4D-MRI, with fast 2D cine-MR images to generate deformable vector fields (DVFs) able to provide the 3D...
Given these high frequency online 3D motion data, a new generation of planning systems should be developed that is able to: (1) include anatomical changes into the plan optimization process in a fast online manner, (2) adapt the plan based on these anatomical changes, in both an offline and online fashion, (3) ensure convergence to the intended dose at the end of the adaptive treatment and (4) be fast enough to facilitate online applications. In our previous works (Kontaxis et al 2015a, 2015b), we have presented the adaptive sequencer (ASEQ), a new treatment planning methodology for intensity-modulated radiation therapy (IMRT) which enables replanning based on 3D anatomical changes. We have recently optimized and integrated ASEQ into our MRL treatment planning (MRLTP) specifically designed to support fast online pipelines for the new hybrid radiotherapy machines.

In this work we present the technical feasibility of a novel adaptive free-breathing SBRT treatment for renal cell carcinoma (RCC) based on 3D anatomical deformations precalculated from high frequency MRI motion data, for two patients and one volunteer. A single fraction high dose IMRT treatment was simulated by performing inter-beam replanning while: (1) incorporating the previously delivered dose—accurately accumulated on the underlying moving anatomy—into the optimization and (2) updating the patient anatomy according to the online 3D DVFs. The adaptive approach was compared to a conventional offline plan with predefined margins affected by the underlying motion. The ability of the system to account for baseline variations and lead to tighter dose distributions was evaluated in terms of target coverage and healthy tissue sparing.

2. Materials and methods

A single fraction SBRT adaptive treatment was simulated for two RCC patients and one healthy volunteer (figure 1). The simulated treatment consists of two parts, which under an MR-linac setting, would be the time period between patient positioning and treatment delivery (pre-beam) and the time period during the actual treatment (online). For each subject a 4D-MRI and multiple 2D cine-MR images were acquired corresponding to the pre-beam and online phases of this study. The reference volume was extracted from the 4D-MRI and an initial treatment plan was calculated based on a predefined set of beam angles. Consequently, each beam was delivered to a linac emulator. The calculated 3D motion states during the beam delivery, based on the 2D MR data, are used to update the anatomical volume and accurately reconstruct the beam dose which increments the total delivered treatment dose. The updated anatomy and the previously delivered dose are then fed into the planning system which performs a full replanning for the remaining beam angles.

2.1. Treatment planning software

MRLTP was initially developed in our clinic as an IMRT planning platform able to include the magnetic field into the fluence plan optimization (Bol et al 2012). We have recently upgraded MRLTP to a full planning system including the necessary modules to perform a two-phase IMRT optimization for several linear accelerator (linac) and multi-leaf collimator (MLC) combinations including the MR-linac. It utilizes the research version of the GPU-based Monte Carlo dose engine (GPUMCD, Elekta AB) (Hissoiny et al 2011a, 2011b) which supports calculations under the presence of the magnetic field, along with our custom implementation of the inverse dose optimization presented in Ziegenhein et al (2013), based on minimum and maximum dose prescription per voxel/structure.
MRLTP can be used in a variety of different treatment scenarios by implementing several planning pipelines whose core is ASEQ, a sequencing methodology that iteratively converges to an ideal dose distribution (Kontaxis et al. 2015b). Its pipeline enables the inclusion of anatomical changes described by 3D DVFs in a segment-by-segment basis during the plan calculation, by performing a fluence optimization targeting the latest anatomical state in each iteration (Kontaxis et al. 2015a). In this work we utilize MRLTP and ASEQ to simulate an inter-beam replanning application targeting the latest anatomical state of the patient, updated in these time intervals.

The experiments were performed on a system with a dual Intel® Xeon® E5-2670 v3, 64 GB RAM and two NVIDIA® GTX Titan X cards for the GPUMCD dose engine, similar in specs with the current industry standard for a treatment planning computer system.

2.2. Imaging and motion estimation

In this section, the different MRI acquisitions and their role in the simulated treatment are presented (figure 1, Imaging).

2.2.1 MRI. For every subject, an exhale-triggered T2-weighted turbo spin echo (TSE) was acquired (spatial resolution = 0.6 x 0.6 x 3.5 mm³) to be used for delineation of the volumes of interest (VOIs). Furthermore, a respiratory-correlated 4D-MRI (3D bSSFP, field-of-view (FOV) = 300 x 300 x 132 or 300 x 300 x 152 mm³, spatial resolution = 1.88 x 1.88 x 4.0 mm³, flip angle = 30°, TR/TE = 3.0/1.45 ms, readout bandwidth = 866.9 or 1868.8 Hz/px) was acquired (Stemkens et al. 2015). The FOV of every subject was adjusted so that both kidneys were fully included in the volume.

Finally, for the purpose of online motion estimation, two fast interleaved 2D cine-MRI slices (2D bSSFP, FOV = 450 x 347 mm², slice thickness = 8 mm, spatial resolution = 2.34 x 2.34 mm², flip angle = 30°, TR/TE = 3.0/1.45 ms, readout bandwidth = 2034.2 Hz/px) were acquired over a certain period of time. For all subjects sagittal and coronal orthogonal slices were positioned through the tumor and the ipsilateral kidney. Each set of slices were acquired with a temporal resolution of 360 ms. For this work, cine-MR imaging was performed over a period of 5 min for the two patients due to study restrictions and 7 min for the healthy volunteer.
2.2.2. Reference volume and motion estimation. Throughout this work motion estimation was performed by utilizing the 3D optical flow algorithm (Roujol et al 2010) previously validated by Østergaard Noe et al (2008) and Stemkens et al (2016).

Pre-beam. The 3D reference treatment volume followed the mid-position (Wolthaus et al 2008) concept, extracted from the 4D-MRI by applying the average motion DVF to the exhale volume. The mid-position volume contains all patient structures in their time-weighted mean respiratory 3D position.

The same average DVF was applied to the T2 scan used for delineation. For all subjects the same radiation oncologist delineated on this volume all VOIs, while in the volunteer the tumor volume was artificially positioned in the left kidney. In an MR-linac treatment analogy, the T2 scan and the delineation process would be either performed in the pre-beam phase or—due to time restrictions—during a pre-treatment simulation phase. In the latter case, during each daily fraction, the pre-treatment delineations would be propagated to the daily anatomy prior to the online plan calculation.

Online. The image-based motion model previously presented in Stemkens et al (2016), was used to generate the online 3D motion fields. More specifically, PCA was applied to the 4D-MRI to generate a parameterized motion model. Then, via an optimization procedure, each set of the acquired 2D cine-MR images produced one set of 3D DVFs (along with a dynamic 3D volume) by calculating the appropriate parameter weights that scale the model so that the corresponding warped reference volume matches the 2D slices. Under the MR-linac setting, the cine-MR imaging would be performed during the treatment and the motion model would be applied to calculate the anatomical changes in an online fashion.

2.3. Experiments

Treatment planning was performed using the latest specifications of the MR-linac system installed in UMC Utrecht. The installed MLC is fixed at 90 degrees rotation, has 80 leaf pairs with 7.15 mm leaf width and a maximum field size of 57.2 and 22 cm in the perpendicular and parallel to leaf travel direction respectively. A beamlet size of 7.15 × 2.5 mm² and a dose grid of 3 × 3 × 3 mm³ were used while all the dose calculations were performed under the presence of 1.5 T transverse field using 3% MonteCarlo statistical uncertainty. The latest 7 MV flattening filter free (FFF) beam model calibrated in our department as described in Wolthaus et al (2015) and a dose rate of 740 MU min⁻¹ were used. The planning volumes were generated by assigning the density of the body to 1.0 g cm⁻³ (Stam et al 2013).

A single fraction SBRT treatment was simulated where the gross tumor volume (GTV) was prescribed to 25 Gy (Siva et al 2016). For each subject six IMRT beam angles were used depending on the location of the tumor (table 1). The beam angles were selected from the experimental 15-beam configuration in Stam et al (2013), after establishing that they were adequate to provide the required coverage for each subject. Table 2 includes the clinical constraints used, from which the organ at risk (OAR) constraints were proposed in table 3 of Siva et al (2016). For all subjects the same operator performed the planning for both the conventional and adaptive treatments. The GTV volume for the two patients and the healthy volunteer was 1 cm³ (female, 43 years, solid tumor in the upper pole of the left kidney), 8.5 cm³ (male, 63 years, cystic tumor in the upper pole of the right kidney) and 4.4 cm³ (male, 31 years, artificial lesion interpolar of the left kidney) respectively.
For all simulations, the calculated plans were delivered to a linac emulator (computer software imitating the physical linac and its functions) (Elekta AB, Stockholm, Sweden) of the currently installed MR-linac in our department. For every delivered beam a log file including the complete machine state (leaf positions, dose rate, delivered MUs etc) every 40 ms, is generated. The log files are then used to match the machine parameters to the timepoints of the dynamic 3D volumes described in section 2.2.2 leading to several segment-to-dynamic volume combinations (Glitzner et al 2015). These segments were then delivered using the MRLTP dose engine and their dose was warped and summed to the reference grid leading to the respective reconstructed dose. Due to the limited amount of online data, in the cases where

**Table 1.** Beam angles used for the individual cases.

| Case           | Beam angles                  |
|----------------|------------------------------|
| Patient 1      | 72°, 96°, 120°, 144°, 168°, 192° |
| Patient 2      | 192°, 216°, 240°, 264°, 288°, 312° |
| Volunteer      | 48°, 72°, 96°, 120°, 144°, 168° |

**Table 2.** Planning constraints.

| VOI              | Constraints          |
|------------------|----------------------|
| GTV 99% vol      | >= 25 Gy             |
| Max              | <= 37.5 Gy           |
| PTV 99% vol      | >= 23.75 Gy          |
| Minimum          | 22.5 Gy              |
| 1% vol           | <= 27.5 Gy           |
| Spinal cord 1 cm³ | <= 8 Gy              |
| 0.03 cm³         | <= 12 Gy             |
| Small bowel 20 cm³ | <= 14 Gy            |
| Full circumference | <= 12.5 Gy         |
| Stomach 10 cm³  | <= 11 Gy             |
| 5 cm³            | <= 22.5 Gy           |
| Skin Max         | <= 24 Gy             |
| Heart 15 cm³    | <= 16 Gy             |
| Large bowel      | As low as reasonably achievable (ALARA) |
| Ipsilateral kidney | ALARA                |
| Contralateral kidney | ALARA            |

**Table 3.** Mean mid-position displacements (SD) relative to pre-treatment reference volume and differences to the true displacements as calculated by the adaptive replanning pipeline in mm. The two columns show the corresponding values by either including or excluding the first beam targeting the pre-treatment anatomy.

| Case           | ADAPT Overall | ADAPT (after beam 1) |
|----------------|---------------|----------------------|
| Pat. 1 Mid-pos | -0.2, -0.3, 2.8 (0.1, 0.2, 1.4) | -0.2, -0.4, 3.4 (0.02, 0.02, 0.03) |
| Diff           | -0.03, -0.07, 0.56 | 0.002, 0.001, -0.01 |
| Pat. 2 Mid-pos | -0.1, -0.3, -0.3 (0.1, 0.3, 0.4) | -0.1, -0.3, -0.4 (0.1, 0.2, 0.4) |
| Diff           | -0.01, -0.05, -0.06 | 0.001, 0.02, 0.04 |
| Volum. Mid-pos | 0.1, 0.1, -0.7 (0.1, 0.1, 0.4) | 0.201 - 0.8 (0.0, 0.1, 0.2) |
| Diff           | 0.03, 0.03, 0.15 | 0.004, -0.01, -0.04 |
treatment time exceeded the available imaging data, the timeline was extended by copying the motion trace (DVFs and dynamic volumes) in an unmirrored fashion.

2.3.1. Adaptive treatment. For the adaptive treatment (ADAPT) no PTV margin was used in an effort to generate the tightest possible dose distributions. Initially, given the reference mid-position volume, the delineated VOIs (section 2.2.2) and the beam configuration (table 1), a treatment plan was generated satisfying the clinical constraints (table 2). Then, an inter-beam adaptive treatment was simulated, given the precalculated dynamic DVFs and 3D volumes as the underlying online anatomical changes. As depicted in figure 1 (Inter-beam replanning), starting from the beam with the maximum prescribed MUs, each beam was delivered on an MR-linac emulator, where the resulting linac log files were used to correlate the beam delivery time ($T_{\text{beam}}$) to the appropriate dynamic motion data ($DYN_{\text{beam}}$). The beam dose was reconstructed using the $DYN_{\text{beam}}$ volumes and was added to the total treatment dose. Moreover the mean DVF during $T_{\text{beam}}$—which describes the average motion for all structures—was calculated and used to propagate the reference mid-position volume along with the pre-treatment VOI contours to the updated treatment position. Finally, the delivered beam is removed from the beam configuration and a new MRLTP plan is generated targeting the updated anatomy while taking into account the previously delivered treatment dose during the optimization. The following beam angle is then processed in the same fashion while continuing the motion timeline from the last timepoint of the previous beam.

2.3.2. Static treatment. The adaptive treatment presented above was compared to a conventional single plan treatment utilizing the mid-position volume with a 3 mm PTV margin (REF_PTV) following the kidney SBRT treatment guidelines in our clinic using the same beam angle configuration and constraints. The dose of the static plan was also reconstructed using the dynamic motion data to provide the ground truth motion-affected plan (RECON_PTV).

3. Results

The two treatment regimes, Static and Adaptive, were simulated by generating MRLTP plans that fulfilled all clinical constraints. The treatment parameters were similar between the two regimes where an average of 32 and 26 segments respectively were used between the three subjects for Static and Adaptive while the mean treatment delivery time was 16.7 min and 18.5 min. The average interval between the inter-beam replannings was 2.8 min among all cases. For both regimes, the available motion data were concatenated in order to accommodate for the extended treatment times.

3.1. Motion

Figures 2(a)–(c) show the mean GTV SI displacement in mm during the simulated treatments from the reference mid-position volume for all subjects. The mean displacement in mm and standard deviation of the motion in the left–right (LR), anterior-posterior (AP) and SI directions was $-0.2 (0.3), -0.4 (0.1), 3.3 (1.1)$ for Patient 1, $-0.1 (0.5), -0.4 (1.2), -0.5 (2.5)$ for Patient 2 and $0.2 (0.3), 0.1 (0.4), -0.8 (1.3)$ for the volunteer respectively. Patient 2 and the healthy subject showed high amplitude breathing cycles with small baseline displacements, with the target being on average at an inferior position compared to the pre-treatment volume. In contrast, patient 1 had a more stable breathing cycle but underwent a baseline shift of approximately 3 mm superiorly after the 4D-MRI and prior to the online imaging.
3.2. Motion-affected static plans (RECON_PTV)

Figure 3 shows the effect of motion on the conventional pre-treatment plans with the 3 mm PTV margin for all subjects. Underdosage can be observed (positive values in the color scales) in the cranial direction in Patient 1 and primarily in caudal direction in Patient 2 and the healthy volunteer. For Patient 1, as expected from the small GTV size and the initial baseline variation, target coverage was greatly reduced leading to a D99% of 23.1 Gy against 26.1 Gy in the REF_PTV plan and a GTV minimum dose of 21.4 Gy compared to 25.7 Gy. While the other two subjects were not greatly affected due to the relatively larger target size and more stable motion, in both cases the minimum GTV dose dropped below the 25 Gy threshold to 24.9 and 24.5 Gy respectively.

3.3. Inter-beam replanning

The intrafraction adapted plans were generated by producing the tightest possible dose distributions around the GTV during the plan adaptations in-between beam deliveries which
fulfilled all clinical constraints (table 2). Figure 4 shows the central coronal GTV slice from the ADAPT replanning regime for all subjects.

3.3.1. Mid-position update. Table 3 shows the average GTV displacement relative to the reference imaging, extracted from the updated anatomies used during the inter-beam plan adaptation. These displacements are visualized with horizontal dashed lines in figure 2 (vertical dashed lines indicate the different replanning segments). The mean mid-position GTV displacement was very close to the actual treatment GTV displacement (section 3.1). By comparing the mid-pos displacement of each replanning phase to the true displacement of that period, we establish the performance of the mid-position update regime (table 3, Diff). Small mean differences are overall observed, only hampered by the baseline variations occurring between the delivery of the first beam and the pre-treatment mid-position. As shown in the last column, the mid-position update employed after the initial beam, greatly decreases these differences, leading to a relative magnitude reduction by 72.2%, 68.9% and 68.3% for each motion component.

3.3.2. Target coverage. Figures 5(a), (c) and (e) show the DVH plots of the REF_PTV (solid lines), RECON_PTV (dashed lines) and ADAPT (dotted lines) for all subjects. In all cases the online replanning ensured higher GTV coverage than RECON_PTV (25.7 versus 23.1 Gy, 26.1 versus 25.8 Gy and 25.9 versus 25.2 Gy respectively). The minimum GTV dose was maintained above 25 Gy (25.3, 25.2 and 25.2 Gy) while the mean delivered GTV dose was higher (27.3 versus 26.9 Gy, 28.5 versus 27.8 and 28 versus 27.4 Gy).
Regarding baseline variations, the initial 3 mm target shift exhibited by Patient 1 was captured after the first delivered beam leading to full GTV coverage at the end of treatment. This is also visualized in figure 6 where the GTV curve of the motion reconstructed static plan with no PTV margin (RECON), along with the RECON_PTV and ADAPT plans are plotted. The V25Gy (minimum acceptable 99%) increased from 71.5% in RECON to 90.5% in RECON_PTV to 100% in the ADAPT regime.

3.3.3. Healthy tissue sparing. Besides the better overall target coverage, the adaptive regime generated tighter dose distributions, the effect of which can be observed in figures 5(b), (d) and (f) which show the difference between RECON_PTV and ADAPT for the central sagittal
GTV slice. ADAPT considerably reduced the dose to the GTV surroundings (positive color-map scale), also depicted by the shallower DVH lines of the 3 mm PTV expansion in all subjects. The higher dose at the cranial direction of the GTV in the ADAPT plan of Patient 1, is a combination of effects caused by the initial baseline shift. These consist of the severe underdosage that RECON_PTV underwent at that region (figure 3(a)) and the extra dose that the ADAPT regime deposited in order to compensate for the loss from the first non-adapted beam.

The sparing of the high dose region around the target can be quantified by the average delivered dose in a 2 cm radius area around the GTV which was reduced by 27.8% on average (10.5 versus 7.7 Gy, 12.8 versus 10.4 Gy and 12.4 versus 10 Gy). Similarly, the mean dose delivered to the ipsilateral kidney was reduced by 22.9% on average (3.5 versus 2.7 Gy, 6.2 versus 5.1 Gy and 6 versus 5.1 Gy).

3.4. Timings

Table 4 presents indicative replanning timings for the different subjects during the individual steps of the adaptive treatment, while using the same number of calculated segments. Each replanning includes the time required to process the input anatomy, delineations and DVFs, calculate the corresponding dose influence data, followed by an iterative ASEQ segment calculation and a final segment weight optimization (SWO). MRLTP replanning ranged from 43.3 s on average for the 6-beam pre-treatment plans to 10.9 s on average for the final single beam plans. For every subject the adaptive replanning took on average 25.6 s, enabling future online usage of MRLTP.

4. Discussion

We have presented a new intrafraction adaptation pipeline for online replanning on hybrid radiotherapy machines like the MR-linac. We utilized our fast research planning system to simulate inter-beam replanning while updating the 3D mid-position volume of the patient and including the previously delivered dose into the subsequent optimizations. The mid-position update enables the pipeline to capture and correct for baseline variations/drifts that might occur.
during treatment. By taking into account the delivered dose to the patient—reconstructed on the actual 3D anatomy—emerging hotspots or underdosed regions caused by more subtle 3D anatomical changes can be addressed. We demonstrate that by combining the two, we can generate free-breathing SBRT treatments with tighter dose distributions leading to increased tissue sparing in the high dose regions. At the same time the framework ensures equal or higher target coverage compared to precalculated static plans with predefined PTV margins.

4.1. MR-only treatment

The reference volume was generated by assigning the whole body to water-equivalent tissue (Stam et al 2013), which was then warped accordingly to generate the dynamic volumes. Several techniques (bulk assignment-based, voxel-based and atlas-based) have been developed for MR-only pseudo-CT generation in an effort to fully substitute the electron density information included in a CT scan (Maspero et al 2017). Generally, dose differences in a dynamic setting can be attributed to two factors, the change of the physical path length and the varying tissue density information. The former one forms the main contributing factor in treatment sites with kidney-like tissue properties (Kerkhof et al 2010). Since the path length changes are included in the dynamic volumes produced by the pipeline, we regard the bulk-assignment technique to be adequate for the purpose of this work.

4.2. Performance

The presented results show the technical feasibility of a replanning framework that utilizes multiple components previously developed in our department. MRLTP has been optimized for the performance requirements of online interventions and the average replanning time of 25.6 s is already promising for online usage in timeframes similar to the presented application. MRLTP was developed to take advantage of parallel CPU/GPU computing and its scalability to higher-end computer configurations should be further investigated.

The other components of the pipeline were originally developed for offline usage and thus should be optimized to qualify for online application. The dose reconstruction module (Glitzner et al 2015) currently performs a beam reconstruction in the order of minutes, while the motion model (Stemkens et al 2016) is able to calculate a new 3D dynamic volume in the order of seconds. We are now working towards the full integration of the individual modules and the optimization of the complete framework.

Table 4. MRLTP timings for the adaptive replanning (seconds). Each row covers one stage of the adaptive treatment progressively reducing the number of beams/segments ranging from 6 beams/35 segments for the pre-treatment plan to 1 beam/5 segments for replanning before the last beam.

| Replanning beams/segments | Patient 1 (s) | Patient 2 (s) | Volunteer (s) |
|--------------------------|--------------|--------------|--------------|
| 6/35                     | 32           | 53.2         | 44.6         |
| 5/29                     | 26.1         | 40.6         | 35.7         |
| 4/23                     | 21.3         | 31.8         | 29.4         |
| 3/17                     | 17.3         | 25.1         | 22.6         |
| 2/11                     | 12.7         | 19.4         | 16.6         |
| 1/5                      | 10.3         | 11.8         | 10.6         |
| Mean                     | 19.9         | 30.3         | 26.6         |
4.3. **Motion data**

Due to the high dose 25 Gy single fraction prescription, the simulated treatment resulted in long delivery times of around 18 min. Consequently, the available motion data of 5 and 7 min for the patients and the volunteer respectively had to be concatenated to facilitate the whole treatment time. The range of motion has been correlated to the imaging/treatment times (von Siebenthal et al. 2007), which would mean that the actual motion trace could exhibit further drifts and/or amplitude variations as the treatment progresses. Observed over the time scale of a single-beam replanning in this work, these changes could lead either to better agreement between the reference anatomy and the online target position or to larger deviations caused by new baseline variations/drifts. Consequently, these changes would have either neutral or further negative impact to the conventional static treatment. In contrast, our method would lead to tighter distributions in the case of small changes (figures 5(d) and (f)) and ensure target coverage in the case of larger variations (figures 5(b) and 6).

Due to the limited motion data available, the replanning time was not included in the treatment timeline. In this way, the results represent the technical feasibility of fast online adaptation and its possible clinical benefits as replanning times further decrease in the future.

4.4. **Quality assurance (QA)**

The introduction of intrafraction adaptive treatments will require thorough QA procedures. Both the motion estimation and the online-adapted dose distributions should be carefully evaluated. In Stemkens et al. (2016) an MR-compatible motion phantom was used to quantify the geometric accuracy of the model leading to an average difference of 1–1.5 mm. For a simultaneous end-to-end test of both motion estimation and plan adaptation, a motion phantom in combination with 3D dosimetric gel target could be used, ideally with the ability to introduce controlled 3D deformations (Mann et al. 2017). However, the relatively high systematic deviations of approximately 5% in gel dosimetry (Vandecasteele and De Deene 2013) should be carefully factored in when evaluating high precision SBRT treatments.

4.5. **Replanning frequency**

In the proposed framework large anatomical variations during the beam-on time intervals between the online adaptations can produce deviations from the planned dose. This is especially the case for the first beam targeting the reference anatomy and the last beam prior to the end of treatment. These effects can be reduced leading to even better conformity and overall plan quality, by utilizing more beam angles/replanning steps, which would reduce the contribution/dose of each beam and provide a more up-to-date mid-position volume.

The scale of the anatomical changes that could be accounted for by this regime depends on the replanning frequency which is mainly limited by the performance capabilities of the complete system. This includes the individual hardware latencies, imaging and motion estimation as well as the replanning speed. The mid-position update framework allows for a direct correlation between the replanning interval and the underlying anatomical changes. By increasing the replanning frequency, we can progressively account for more subtle changes with the mid-position converging to a single anatomical instance and the replanning to real-time inter-segment plan adaptation.

Under this context the same concept could be applied in dynamic IMRT treatments with volumetric arc therapy (VMAT) where individual beams can be substituted with separate arcs.
with in-between replanning sections. The replanning frequency will then be correlated with the number and radii of the utilized arcs depending on the application.

4.6. Method scope

Respiratory-gated treatments have been employed in an effort to reduce the free-breathing motion, by delivering radiation only to part of the treatment cycle with the smallest relative residual motion and healthy tissue exposure. The reduced duty cycle can lead to 4–15 times longer IMRT treatments (Keall et al 2006). This increase in treatment time would be restrictive for applications like the single fraction 25 Gy treatment used in this work.

Tracking techniques have also been used to follow the tumor by dynamically adjusting the MLC leaf positions based on several tumor-localization methods, leading to increased target conformality and high duty cycle (Giraud and Houle 2013). However, during tracking the dosimetric impact of the (smaller) out-of-plane motion and, more importantly, the 3D deformations of the target and OARs are not taken into account. Furthermore, during target tracking the spatial dependence of fluence in FFF beams is not addressed.

In our method, we utilize MR-imaging data to extract the 3D anatomical deformations of the target and OARs during treatment and perform inter-beam replanning based on an updated patient volume. The mid-position concept enables high duty cycle treatments suitable for ablative radiotherapy applications. Moreover, the inclusion of the previously delivered dose to the patient into the planning, accounts for the dosimetric effects of residual motion and/or 3D deformations occurring during the beam delivery. Future applications of our method can also be combined with tracking techniques during radiation delivery in-between replannings to compensate for baseline variations occurring during beam-on.

5. Conclusion

We have presented the proof of principle of an intrafraction adaptation framework for treatment sites affected by respiratory motion under the new hybrid MRI-radiotherapy regime. We simulated a single fraction free-breathing SBRT adaptive treatment for renal cell Carcinoma, by performing inter-beam replanning targeting a dynamically updated 3D mid-position volume and including the previously delivered dose into the plan adaptation. The underlying online high-frequency 3D motion data provided by a statistical motion model, were used to accurately reconstruct each beam dose and calculate the corresponding anatomical changes over the beam delivery time. We showed that the adaptive replanning framework is able to produce much more conformal dose distributions when compared to a static mid-position SBRT plan with a 3 mm PTV margin and thus reduces the dose in healthy tissue. In addition, by updating the mid-position volume baseline variations/drifts can be corrected in the replanning interval window, ensuring convergence to the prescribed target dose.

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