

ORIGINAL ARTICLE



Simulated dosimetric impact of online replanning for stereotactic body radiation therapy of lymph node oligometastases on the 1.5T MR-linac

Dennis Winkel, Petra S. Kroon, Anita M. Werensteijn-Honingh, Gijsbert H. Bol, Bas W. Raaymakers and Ina M. Jürgenliemk-Schulz

Department of Radiotherapy, University Medical Center, Utrecht, The Netherlands

ABSTRACT

Purpose: Online 1.5T MR imaging on the MR-linac gives better target visualization compared to CBCT and facilitates online adaptive treatment strategies including daily replanning. In this simulation study, the dosimetric impact of online replanning was investigated for SBRT of lymph node oligometastases as a method for correcting for inter-fraction anatomical changes.

Methods: Pre-treatment plans were created for 17 pelvic and para-aortic lymph nodes, with 3 and 8 mm PTV margins reflecting our clinical practice for lymph nodes with good and poor visibility on CBCT. The dose-volume parameters of the pre-treatment plans were evaluated on daily anatomy as visible on the repeated MRIs and compared to online replanning.

Results: With online MRI-based replanning significant dosimetric improvements are obtained for the rectum, bladder, bowel and sigmoid without compromising the target dose. The amount of unintended violations of the dose constraints for target and surrounding organs could be reduced by 75% for 8 mm and 66% for 3 mm PTV margins.

Conclusion: The use of online replanning based on the actual anatomy as seen on repeated MRI compared to online position correction for lymph node oligometastases SBRT gives beneficial dosimetric outcomes and reduces the amount of unplanned violations of dose constraints.

ARTICLE HISTORY

Received 18 December 2017

Accepted 4 August 2018

Introduction

Image-guided radiation therapy (IGRT) has become increasingly important in modern radiotherapy to reduce the effect of treatment variations, such as setup errors and geometric variations of the target volume and organs at risk (OAR). Currently, most modern radiotherapy treatment systems are equipped with cone-beam computed tomography (CBCT) to visualize the tumour [1]. CBCT has greatly contributed to precision radiotherapy for sites in which the tumour is clearly visible on CBCT, however it yields relatively poor soft tissue contrast. The lack of soft tissue contrast can make it difficult to accurately identify the target and surrounding OARs for soft tissue targets; therefore bony anatomy or artificial markers are frequently used as a surrogate for position verification [2–4]. These procedures still result in quite large planning target volume (PTV) margins [5] or are invasive with additional burden for the patient.

Magnetic resonance imaging (MRI) guided radiotherapy treatment systems are commercially available and used in clinical practice and allow improving plan quality through online adaptation [6–8]. With the 1.5T MR-linac [9], diagnostic quality images are available of the actual patient anatomy during treatment and MR-guided online adaptive workflows can be used [10].

Based on our institutional clinical experience, lymph node oligometastases are often small with mean gross tumour volumes (GTV) of <3 cc, (as defined by expert radiation oncologists) and are poorly visible on CBCT in about 30% of all cases. The superior soft tissue contrast of online MR-images gives a better visibility of the target and surrounding OAR when compared to CBCT [11] which will potentially help to reduce the PTV margins.

For treatment of lymph node oligometastases, stereotactic body radiation therapy (SBRT) [12–14] is an often applied technique in which a relatively high amount of dose is delivered in few fractions with a very steep dose gradient [15]. In current clinical practice of SBRT for these targets inter-fraction motion is accounted for by online couch translation and (sometimes) small table rotations. Online couch translations account for rigid motion of the target, but do not deal with non-rigid changes of the PTV such as changes in size or shape. Differences between the planned and delivered dose after position corrections can also occur because of changes in the physical path and changes in tissue attenuation relative to the original plan [16]. When treating these tumours on the MR-linac, one can account for geometric variations of the target and OARs, as well as changes in the physical path and tissue attenuation. To accomplish this for external beam

CONTACT Dennis Winkel ✉ d.winkel-2@umcutrecht.nl 📧 University Medical Center Utrecht, Department of Radiotherapy, Q.00.3.11, P.O. Box 85500, 3508 GA Utrecht, The Netherlands

© 2018 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.

radiotherapy, online replanning is the optimal approach to fully incorporate all available anatomical data provided on the MR-linac and to deliver a highly conformal dose to the tumour, while optimally sparing the OARs.

A recent study on SBRT for the treatment of oligometastatic disease of the abdomen and central thorax has shown that a combination of high dose, few fractions and a steep dose gradient improves with adaptive treatment on MR guided radiotherapy systems in terms of precise and conformal dose delivery and preventing potentially toxic violations of dose constraints [17]. Similar benefits could potentially be achieved with full online replanning of lymph node oligometastases for the pelvic and para-aortic region. By performing full online replanning a new plan is created on the daily anatomy while the patient is on the table, without making use of a pre-treatment plan. Further dosimetric benefits could potentially be gained by a reduction of the PTV, because of better target visualization when treating on an MR-linac for lymph node oligometastases with poor visibility on CBCT. MRI guidance is already commonly applied in brachytherapy to minimize dose differences, which can occur between planning and irradiations [18].

This study is a R-IDEAL [19] stage 0 study in preparation of a clinical workflow for the treatment of lymph node oligometastases on the 1.5T MR-linac. R-IDEAL is a framework for systematic clinical evaluation of technical innovations in radiation oncology such as the MR-linac. Stage 0 covers all preparatory work needed before the innovation is ready for clinical use. In this study, we investigate whether online replanning for SBRT of lymph node oligometastases on the 1.5T MR-linac yields beneficial dosimetric values compared to online position correction as performed on CBCT-linacs in current clinical practice.

Material and methods

Patient data characteristics

For this simulation study, 17 pelvic and para-aortic pathological lymph nodes were included from five female patients with locally advanced cervical cancer. The patients had 2, 2, 4, 8 and 1 pathologic lymph nodes, respectively. The lymph node locations are spread relative to each other and are representative for lymph node oligometastases as treated in our clinic. All patients gave written informed consent for the use of their scans for research purposes. All patients had undergone pre-treatment and repeated MR imaging, suitable for radiotherapy, on a 1.5T Philips Ingenia (Best, The Netherlands) before and during the first three weeks of curative chemo-radiotherapy treatment. During imaging acquisition the rectum was required to be as empty as possible. In case of a significant presence of gas and faeces with a rectum diameter >4 cm the patient was asked to empty the rectum, or the rectum was deflated using a rectal cannula. For each patient, pre-treatment data and one inter-fraction dataset obtained during the course of EBRT were used with MRI-based delineations of lymph node GTV(s) and surrounding OAR (bladder, rectum, bowel bag, sigmoid, cauda equina and femoral bones). The mean GTV (in this

Table 1. Clinically used dose criteria for SBRT lymph node oligometastases treatment plans used for plan evaluation.

Structure	Constraint
PTV	$V_{35\text{Gy}} > 95\%$ $D_{\text{max}} < 135\%$
Bladder ^{a,b}	$V_{38\text{Gy}} < 0.5 \text{ cc}$ $V_{18.3\text{Gy}} < 15 \text{ cc}$
Bowel ^a	$V_{35\text{Gy}} < 0.5 \text{ cc}$ $V_{25\text{Gy}} < 10 \text{ cc}$
Rectum ^c	$D_{\text{max}} < 40 \text{ Gy}$ $V_{35\text{Gy}} < 1 \text{ cc}$
Sigmoid ^c	$D_{\text{max}} < 40 \text{ Gy}$ $V_{35\text{Gy}} < 1 \text{ cc}$

^aUK SABR consortium guidelines 2016 [24].

^bGrim et al. 2011 [25].

^cIn-house clinical constraints.

case also demarcating the clinical target volume) of the lymph nodes was $2.5 \pm 2.8 \text{ cc}$ (range, 0.4–15.8 cc), based on expert delineations. There were no exclusion criteria.

Plan generation

For each lymph node five plans were generated to simulate the different treatment approaches: (1) pre-treatment plan with a 3 mm PTV margin and (2) calculated on daily anatomy after position correction, (3) pre-treatment plan with a 8 mm PTV margin and (4) calculated on daily anatomy after position correction, and (5) complete new plan generated on the daily anatomy (full online replanning). By means of these five plans the dosimetric situation of the current CBCT-linac treatment can be estimated (comparisons plan 1 and 2; or plan 3 and 4). In addition, the potential dosimetric benefit of a MR-linac treatment can be evaluated using plan 2 and 5, and using plan 4 and 5.

All plans were generated with a prescribed dose of $5 \times 7 \text{ Gy}$ to 95% of the PTV using the Monaco treatment planning software (TPS) research version 5.19.03d by Elekta AB (Stockholm, Sweden). To do a clean comparison of our technique we have eliminated differences in machine characteristics by creating all plans with the 7MV FFF beam model of the Elekta MR-linac and the 1.5 T magnetic field in superior–inferior patient direction which is present when treating patients on the MR-linac. The dose constraints (Table 1) used for the OAR are considered hard dose constraints. OAR dose was attempted to be as low as possible, while maintaining adequate target coverage. Plan quality was evaluated by a multi-disciplinary SBRT oligo lymph node clinical team consisting of a radiation therapist, physicist and physician. Seven non-uniform beam orientations were used for these plans and were selected individually for each PTV to optimally account for patient anatomy and the location of the PTV. Unfavourable beam angles due to couch characteristics or the location of the cryostat were avoided. The statistical uncertainty for the Monte Carlo dose calculations was 3% per control point and the calculation grid size was 3 mm. The maximum amount of segments per plan was 45 with a minimum area of 1.5 cm^2 and width of 0.5 cm.

Generation of pre-treatment plans on the planning CT

Two pre-treatment plans were created for each lymph node, with a 3 mm as well as with a 8 mm PTV margin and a

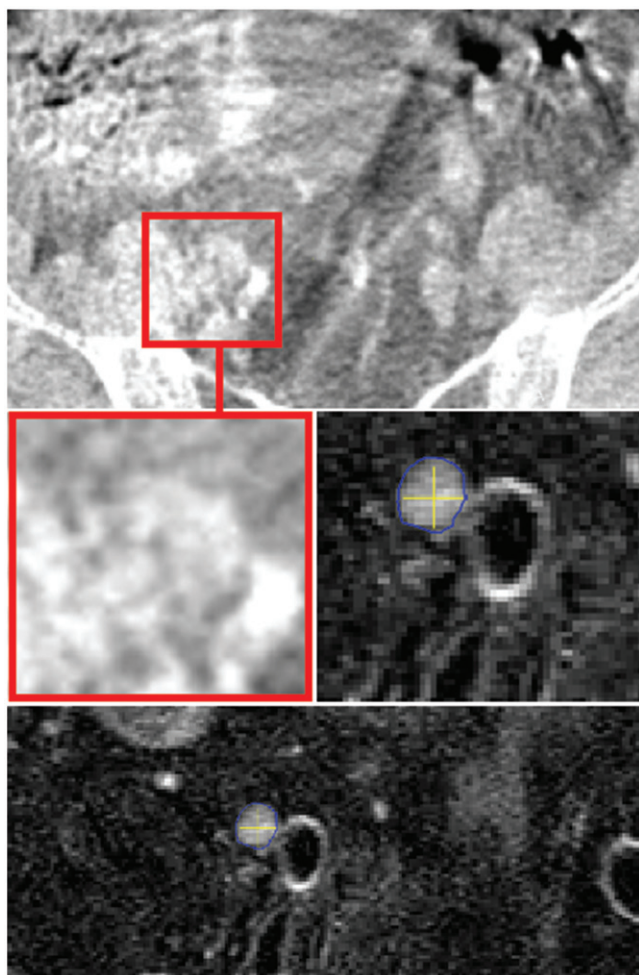


Figure 1. Transversal CBCT image (top and left) and a transversal T2-weighted mDIXON water image (bottom and right) of the same patient. The lymph node in the left iliac region is poorly visible on the CBCT and would therefore be treated with an 8 mm PTV margin to sufficiently incorporate uncertainties, especially position verification.

prescription dose of 5×7 Gy to 95% of the PTV. The center of the PTV was set as plan isocenter. Using these margins we simulate cases of both good and poor visibility. In our current clinical protocol, a CBCT simulation is performed in the pre-treatment preparation phase. A physician determines whether the lymph node oligometastases is well visible or not. A PTV margin of 8 mm is used for poorly visible lymph nodes (Figure 1) and 3 mm for visible lymph nodes. Using a vacuum cushion for immobilization, these PTV margins are considered to be sufficient to handle patient setup, intra-fraction motion and machine related uncertainties [20–23].

Generation of plans by recalculating on the daily anatomy

As a simulation of current clinical practice, we calculated daily dose-volume histogram (DVH) parameters twice for each lymph node by calculating the dose of the pre-treatment plans with 3 and 8 mm PTV margins on the daily anatomy. To simulate the daily anatomy, a MRI dataset (Philips Ingenia, 1.5T, mDIXON 3D FFE T1W, flip angle 10° , TE1/TE2 = 1.6/3.9 ms, TR = 5.7 ms, reconstructed voxel $1.05 \times 1.05 \times 2.5$ mm³, FOV $552 \times 552 \times 300$ mm³) obtained at least one week into

treatment was used. The target and the OARs were manually contoured. Electron density information was taken into account by matching and deforming the initial planning CT to the MRI data (Figure 2). In our clinic, CBCT-based online correction is performed by matching using a 0.5 cm mask around the GTV or a clipbox with nearby structures for lymph nodes with good or poor visibility, respectively. To simulate the online correction protocol we assumed that the reference point of this correction is equal to the center of the PTV and placed the plan isocenter at the center of the PTV according to the daily anatomy.

Generation of a new plan on the daily anatomy

To simulate replanning in a full-online workflow for the MR-linac, one new fully optimized treatment plans was created for each lymph node using daily target and OAR definitions based on the simulated daily patient anatomy. The used beam angles for online replanning were equal to those in the pre-treatment plan. For these plans, a PTV margin of 3 mm was applied, simulating the good visibility of lymph nodes on MRI. As the 1.5T MR-linac only allows for movement in superior–inferior direction, the isocenter is fixed in the center of the bore for the other directions. The isocenter position in the superior–inferior direction is set as close to center of the PTV as possible.

Evaluation

To estimate the dosimetric situation of the current CBCT-linac treatment and to evaluate the dosimetric impact of online replanning for the MR-linac all plans were evaluated using the target and OAR dose criteria. The plans with 8 and 3 mm PTV margins were both compared with online replanning using a 3 mm PTV margin, simulating treatment with good visibility of lymph nodes on the MR-linac. The DVH parameters for the PTV, rectum, bladder, bowel and sigmoid were compared between the initial plans simulated on the daily anatomy and the online plans. The PTV was evaluated using the PTV margin as was used during planning. The reference plans were evaluated using the original pre-treatment contours. The simulation plans using online translation or full-online replanning were evaluated using the contours from the simulated daily anatomy. Significance of these differences was determined using Wilcoxon matched-pairs signed rank tests. Results were considered significant with a p value $< .05$.

Results

When a 3 mm PTV margin was taken, it was possible to create pre-treatment plans that met clinical dose criteria for all 17 lymph nodes: all plans had adequate target coverage and did not violate OAR dose constraints. When the pre-treatment plans were evaluated after rigid table correction using daily anatomical contours from the repeated MRIs, six plans failed to meet all criteria. In two plans, the $V_{35\text{Gy}}$ of the bowel was violated with 2.1 and 9.1 cc. In one plan the $V_{25\text{Gy}}$ of the bowel was violated with 21.9 cc. In one plan, the $V_{35\text{Gy}}$

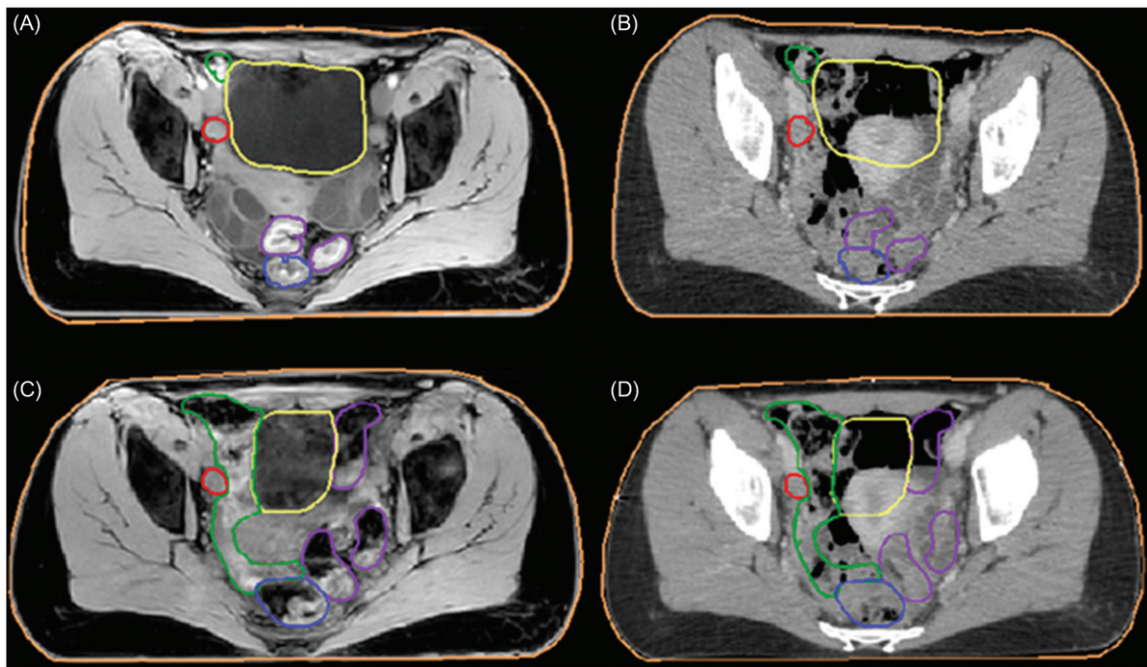


Figure 2. Pre-treatment T1-weighted mDIXON water MRI (A) and pre-treatment CT (B) data. MRI data obtained in-between fractions (C) and a deformed CT (D) based on the MRI data used to simulate daily patient anatomy. The target lymph node is visible in red. Large inter-fraction differences can be observed with regards to the location of large bowel (green contours), bladder (yellow contours), rectum (blue contours) and sigmoid (purple contours).

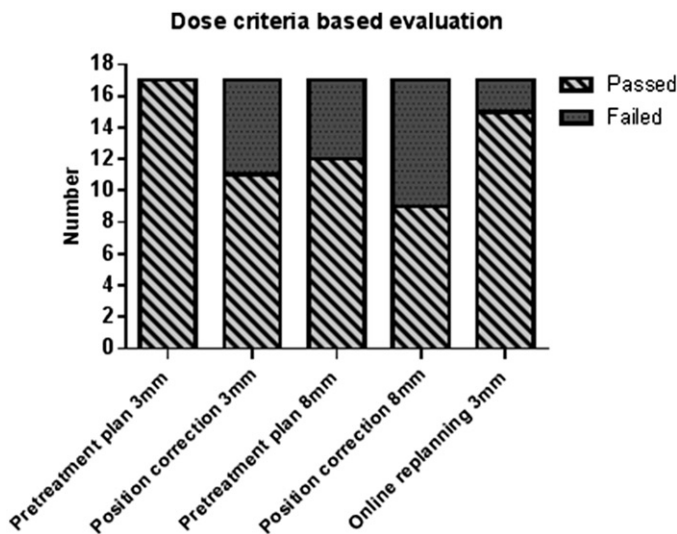


Figure 3. Number of plans ($N = 17$) that passed or failed based on dose criteria for the initial plan, the initial plan calculated on the daily anatomy and full online replanning (simulating MR-linac treatment).

and $D_{\max}$ (highest measured dose in a voxel) of the sigmoid were violated with 1.8 cc and 44.7 Gy, respectively. PTV coverage was insufficient in three plans with a $V_{100\%}$ in the range of 86.2–94.0% (should be $>95\%$). GTV coverage was sufficient for all plans.

When an 8 mm PTV margin was used, 12 of the 17 created pre-treatment plans met all dose criteria. When evaluating these plans on the anatomy as visible on the repeated MRIs this amount decreased to 8. Of these cases, two both violated dose constraints for the OARs and had insufficient PTV coverage with 89.7% and 94.8% of the prescribed dose instead of $>95\%$ as intended. Two plans violated both the $V_{35\text{Gy}}$ and

$V_{25\text{Gy}}$ of the bowel with 24.6 and 48.4 cc for one plan and 7.9 and 16.9 cc for the other plan. The $V_{35\text{Gy}}$ of the bowel was violated with 0.9 cc for one plan. For one plan, the $V_{18.3\text{Gy}}$ of the bladder was violated with 17.5 cc. Two plans violated both the $V_{35\text{Gy}}$ and $D_{\max}$ of the sigmoid with 1.1 cc and 43.0 Gy for one plan and with 2.5 cc and 43.8 Gy for the other plan. The $V_{35\text{Gy}}$ of the sigmoid was violated with 6.1 cc for one plan. One plan did not have adequate PTV coverage with 89.9%. GTV coverage was sufficient for all plans. The dosimetric violations occurred in four out of five patients.

Full online replanning, simulating MR-linac treatment, resulted in a reduction of violations to the OARs. The number of instances of violation was reduced from 6 to 2 (66%) and 8 to 2 (75%) for lymph node oligometastases with a 3 and 8 mm margin, respectively. The two plans that did not meet requirements during replanning violated the $V_{35\text{Gy}}$ of the bowel with 0.5 and 1 cc (Figure 3). In these cases the target position was closer to the bowel for the simulated daily anatomy compared to the situation at initial treatment planning, which caused large overlap between the rectum and PTV.

A comparison of DVH parameters between pre-treatment plans calculated on the simulated repeated MRI anatomy and online replanned plans shows that online replanning yields significant dosimetric benefits for OAR dose (Figure 4). For the pre-treatment plans made with a 3 mm PTV margin, the mean dose was significantly reduced for the bladder, bowel, rectum and sigmoid (Table 2). The maximum dose and $D_{2\text{cc}}$ of the bladder and the $D_{2\text{cc}}$ of the rectum were also significantly reduced. For pre-treatment plans made with an 8 mm PTV margin, online replanning shows additional dosimetric benefits apart from the significant reductions already present with the 3 mm PTV margin (Table 3). The $V_{25\text{Gy}}$ for the bowel was significantly reduced. The maximum dose and $D_{2\text{cc}}$ for the bowel and sigmoid was also significantly lower.

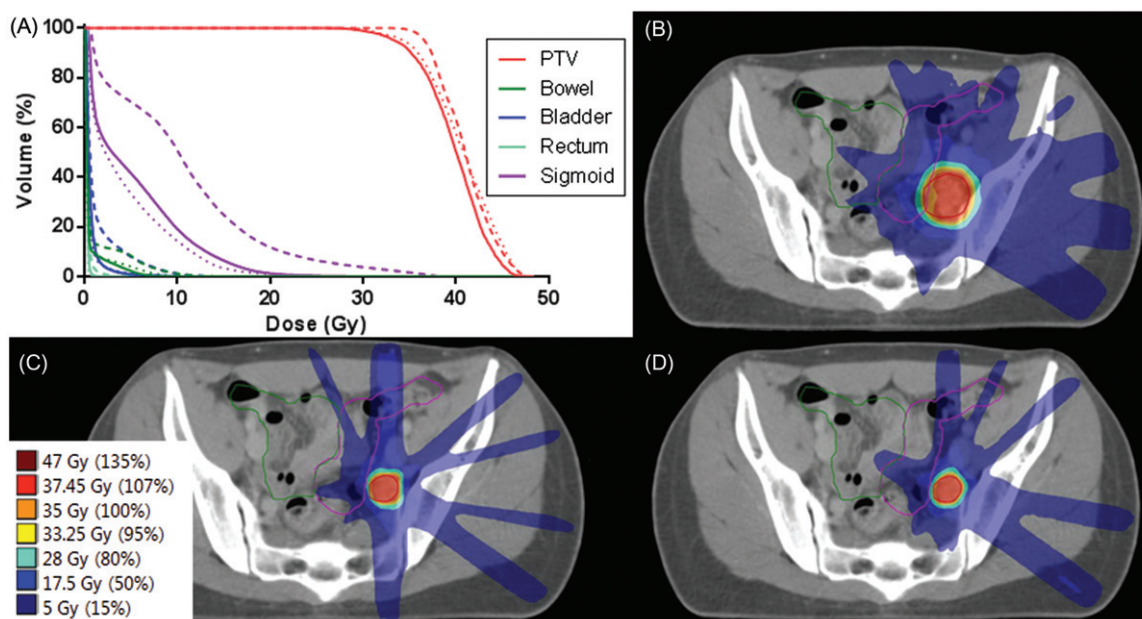


Figure 4. Sample DVH (A) and dose distributions of 8 mm PTV (B/dashed line) and 3 mm PTV (C/solid line) reference plans on the daily anatomy after position correction and full online replanning (D/dotted line). Anatomical contours are shown for PTV (red), large bowel (green) and sigmoid (purple).

Table 2. Dosimetric outcomes for lymph node oligometastases with a 3 mm CTV-PTV margin.

Structure	Parameter	Plan _{PT3mm}	Plan _{PC3mm}	Plan _{MRL}	<i>p</i> value
PTV	$V_{35\text{Gy}}$ (%)	98.0 [95.1–100]	96.6 [86.2–100]	97.8 [92.5–100]	.82
Bladder	$V_{38\text{Gy}}$ (cc)	0.0 [0–0.1]	0.0 [0–0.1]	0	>.99
	$V_{18.3\text{Gy}}$ (cc)	0.9 [0–5.8]	0.4 [0–5.1]	0.1 [0–0.9]	.50
	D_{mean} (Gy)	1.2 [0.2–3.4]	1.0 [0.2–3.6]	0.6 [0.1–2.7]	<.01*
	D_{max} (Gy)	13.1 [0.4–40.7]	10.5 [0.5–40.3]	9.0 [0.2–37.4]	<.01*
	$D_{2\text{cc}}$ (Gy)	7.2 [0.5–24.5]	5.9 [0.4–23.6]	4.9 [0.1–22.0]	.02*
Bowel	$V_{35\text{Gy}}$ (cc)	0.0 [0–0.1]	0.7 [0–9.1]	0.1 [0–1.0]	.50
	$V_{25\text{Gy}}$ (cc)	0.2 [0–1.9]	1.7 [0–22.0]	0.6 [0–6.4]	.13
	D_{mean} (Gy)	0.6 [0.2–19.3]	1.2 [0.1–5.0]	0.7 [0.1–1.6]	<.01*
	D_{max} (Gy)	22.9 [9.1–36.7]	19.3 [0.7–46.2]	18.0 [0.8–39.5]	.35
	$D_{2\text{cc}}$ (Gy)	14.9 [5.7–24.9]	13.2 [0.4–41.7]	11.8 [0.3–37.3]	.22
Rectum	$V_{35\text{Gy}}$ (cc)	0	0	0	–
	D_{mean} (Gy)	0.8 [0.2–2.2]	0.6 [0.1–1.6]	0.4 [0.1–2.0]	.01*
	D_{max} (Gy)	5.1 [0.4–14.4]	4.7 [0.2–16.8]	3.9 [0.3–10.3]	.74
	$D_{2\text{cc}}$ (Gy)	3.7 [0.4–12.2]	3.2 [0.2–11.9]	2.0 [0.2–9.6]	.02*
	$V_{35\text{Gy}}$ (cc)	0.0 [0–0.1]	0.1 [0–1.8]	0.0 [0–0.5]	.13
Sigmoid	D_{mean} (Gy)	3.0 [0.4–10.2]	2.8 [0.6–5.5]	2.1 [0.5–5.3]	<.01*
	D_{max} (Gy)	13.1 [1.0–36.7]	21.0 [6.7–44.7]	19.2 [6.7–38.4]	.05
	$D_{2\text{cc}}$ (Gy)	7.5 [0.7–16.6]	13.1 [4.8–34.4]	12.4 [3.7–32.2]	.15

Dosimetric outcomes (mean and range) for the pre-treatment plans (PT) for lymph node oligometastases with a 3 mm CTV-PTV margin, their respective simulations on daily anatomy after online position correction (PC) and replanning on the MR-linac (MRL).

p value obtained using Wilcoxon matched-pairs signed rank tests (*p* < .05 is significant and denoted with an asterix).

Discussion

Inter-fraction motion of pelvic lymph nodes can occur with translations ranging between 7 and 30 mm based on pre-treatment CT imaging and CT imaging during treatment [26]. The current clinical protocol in which online correction is performed based on CBCT images is sufficient to correct for translations. It does not however account for changes in size and shape of the target and OARs, which can vary significantly over the course of treatment [27]. A correlation is found between volume changes of organs at risk and target shifts [28]. This can result in rotations of the targets which, when ellipse-shaped, can largely differentiate from the pre-treatment situation. In current clinical practice, rotations are not often corrected for. In Figure 2(A) substantial discrepancy can be seen between the state of the internal organs on the

pre-treatment MRI and the pre-treatment CT. This example emphasizes the advantage of correcting for inter-fraction organ motion; also in other studies daily plan adaptation has been shown to improve dose volume parameters [29–33]. With the use of online replanning a completely new daily treatment plan can be created, which accounts for deformations of the PTV, as well as the actual OAR location.

Online replanning reduces the amount of unplanned violations to the OARs. When moving from online position correction to online replanning, the number of instances of violation to the OARs can be significantly reduced, both for lymph nodes with good and poor visibility on CBCT. It can therefore be advocated to use online replanning to take non-rigid anatomical changes into account. The largest benefit is reached for lymph nodes that are poorly visible on CBCT. The superior soft tissue contrast on the MR-linac will

Table 3. Dosimetric outcomes for lymph node oligometastases with an 8 mm CTV-PTV margin.

Structure	Parameter	Plan _{PT8mm}	Plan _{PC8mm}	Plan _{MRL}	<i>p</i> value
PTV	$V_{35\text{Gy}}$ (%)	98.2 [96.5–100]	97.4 [89.0–100]	97.8 [92.5–100]	.67
Bladder	$V_{38\text{Gy}}$ (cc)	0	0.0 [0–0.4]	0	.50
	$V_{18.3\text{Gy}}$ (cc)	3.69 [0–18.27]	2.2 [0–21.3]	0.1 [0–0.9]	.13
	D_{mean} (Gy)	1.8 [0.2–6.4]	1.6 [0.2–6.9]	0.6 [0.1–2.7]	<.01*
	D_{max} (Gy)	14.8 [0.4–38.0]	13.3 [0.5–39.1]	9.0 [0.2–37.4]	<.01*
	$D_{2\text{cc}}$ (Gy)	11.6 [0.3–35.5]	9.4 [0.4–36.0]	4.9 [0.1–22.0]	<.01*
Bowel	$V_{35\text{Gy}}$ (cc)	0.4 [0–4.0]	2.0 [0–24.7]	0.1 [0–1.0]	.13
	$V_{25\text{Gy}}$ (cc)	2.4 [0–19.4]	4.2 [0–48.4]	0.6 [0–6.4]	.03*
	D_{mean} (Gy)	0.8 [0.3–3.0]	1.7 [0.1–7.1]	0.7 [0.1–1.6]	<.01*
	D_{max} (Gy)	29.8 [16.0–40.1]	23.1 [1.2–45.5]	18.0 [0.8–39.5]	<.01*
	$D_{2\text{cc}}$ (Gy)	21.1 [11.8–36.8]	16.2 [0.6–41.5]	11.8 [0.3–37.3]	<.01*
Rectum	$V_{35\text{Gy}}$ (cc)	0	0	0	–
	D_{mean} (Gy)	1.3 [0.2–4.2]	1.1 [0.1–4.5]	0.4 [0.1–2.0]	<.01*
	D_{max} (Gy)	6.4 [0.5–17.4]	5.6 [0.3–16.8]	3.9 [0.3–10.3]	.03*
	$D_{2\text{cc}}$ (Gy)	4.5 [0.5–13.2]	3.7 [0.2–13.4]	2.0 [0.2–9.6]	<.01*
	$V_{35\text{Gy}}$ (cc)	0.1 [0–0.9]	0.6 [0–6.1]	0.0 [0–0.5]	.06
Sigmoid	D_{mean} (Gy)	4.7 [0.8–20.4]	4.4 [1.4–10.2]	2.1 [0.5–5.3]	<.01*
	D_{max} (Gy)	15.3 [3.7–40.3]	26.4 [12.2–43.8]	19.2 [6.7–38.4]	<.01*
	$D_{2\text{cc}}$ (Gy)	10.9 [2.1–31.5]	17.9 [3.9–36.8]	12.4 [3.7–32.2]	<.01*

Dosimetric outcomes (mean and range) for the pre-treatment plans (PT) for lymph node oligometastases with an 8 mm CTV-PTV margin, their respective simulations on daily anatomy after online position correction (PC) and replanning on the MR-linac (MRL).

p value obtained using Wilcoxon matched-pairs signed rank tests (*p* < .05 is significant and denoted with an asterix).

allow for a considerable reduction of the PTV margin (i.e. reduction from 8 to 3 mm in this particular situation), which importantly reduces the overlap between PTV and OARs.

A large variety of dose and fractionation schemes are currently being used for SBRT treatment of lymph node oligometastases varying between 5×5 and 1×24 Gy [22]. A smaller PTV margin, as well as full-online replanning may allow for dose escalation and hypofractionation. Dose escalation is regarded to be desirable, in order to achieve improved and durable local control [34,35]. On the interfraction CBCTs the visibility of the target and OARs are not sufficient to perform these analyses. The improved target structure visibility with the MR-linac, combined with online replanning could also provide opportunities for hypofractionation, without the need for invasive marker placement procedures, compared with hypofractionated SBRT using the CyberKnife [36,37]. Future, clinical trials must show whether dose escalation and hypofractionation are possible and whether this results in clinically relevant endpoints. SBRT treatment of lymph node oligometastases on the MR-linac using online replanning therefore opens up possibilities for dose escalation, without increasing the risk on OAR dose constraint violations.

For the purpose of this study, we have only simulated online replanning on daily anatomy for one fraction, for which it yields significantly better dosimetric values. This shows that online replanning for high dose single-fraction SBRT of oligo lymph nodes is required to achieve a lower dose to the OARs while maintaining adequate target coverage. The exact benefit for treatment with multiple fractions is yet to be investigated for lymph node oligometastases. Dosimetric benefits are however expected during the whole course of treatment as the daily anatomy is optimally taken into account with daily online replanning or similar daily plan adaptation approaches [38,39]. Based on these promising results, a clinical workflow for the 1.5T MR-linac is being developed for treatment of lymph node oligometastases in the near future.

For our simulations, we have considered each pathological lymph node as an individual target with an individual treatment plan. Based on clinical experience about 25% of all patients present with multiple lymph node oligometastases which are mostly treated simultaneously using one treatment plan [40]. Independent inter-fraction motion between multiple lymph node targets can occur [41]. When multiple lymph node oligometastases are treated simultaneously, the inter-fraction motion of the targets relative to each other cannot always be accurately corrected for by translations. The dosimetric benefit of online replanning for this group is therefore expected to be even larger than in the current study. Future studies are necessary to determine the exact dosimetric benefit.

The amount of patients included in this study is limited because of the field-of-view of the MRI-datasets. More data would be beneficial to obtain more robust results. However, we do believe that our study shows clear qualitative findings and gives us confidence to apply our proposed methodology in R-IDEAL stage 1/2a studies in which expected outcomes are proof of concept, technical improvements, feasibility and safety. After these studies we aim to work towards single-fraction radiotherapy treatment of these targets.

This study solely focuses on the application of online replanning for SBRT of lymph node oligometastases in the pelvic and para-aortic region. However, these results could also be indicative for other tumour sites, which present with inter-fraction variability of target size, shape and location of OARs in the proximity of the target. As PTVs were very small within this study, with an average PTV is 4.4 ± 2.7 cc (range, 1.6–10.3 cc), and a similar workflow was used as in the first-in-man study [11], online replanning based on the Monaco TPS could be performed in a timely manner suitable for online treatment. Full online replanning is the preferred method, as it optimally takes daily anatomy information into account. For larger PTVs it might not be possible to perform online replanning in a timeframe suitable for online adaptive treatment therefore other adaptation techniques will be

needed such as virtual couch shift (VCS) which corrects for translations and rotations [42]. Further research will be performed to investigate opportunities for dose escalation and hypofractionation, as well as online replanning for multiple targets.

Conclusions

The use of online replanning for SBRT of lymph node oligometastases on the MR-linac yields beneficial dosimetric values compared to CBCT-based online position correction using couch translations. Online replanning reduces the number of unplanned violations of dose constraints for surrounding OARs. The proposed method for online replanning is most beneficial for lymph nodes poorly visible on CBCT, as for these targets both margin reduction and online replanning are applied, however dosimetric improvements remain present for lymph nodes with good visibility on CBCT.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the Dutch Cancer Society [grant number 2015-0848].

References

- Jaffray DA, Siewerdsen JH, Wong JW, et al. Flat-panel cone-beam computed tomography for image-guided radiation therapy. *Int J Radiat Oncol Biol Phys.* 2002;53:1337–1349.
- Purdie TG, Bissonnette J, Franks K, et al. Cone-beam computed tomography for on-line image guidance of lung stereotactic radiotherapy: localization, verification, and intrafraction tumor position. *Int J Radiat Oncol Biol Phys.* 2007;68:243–252.
- Litzenberg D, Dawson LA, Sandler H, et al. Daily prostate targeting using implanted radiopaque markers. *Int J Radiat Oncol Biol Phys.* 2002;52:699–703.
- Dehnad H, Nederveen AJ, van der Heide UA, et al. Clinical feasibility study for the use of implanted gold seeds in the prostate as reliable positioning markers during megavoltage irradiation. *Radiation Oncol.* 2003;67:295–302.
- Yeung R, Hamm J, Liu M, et al. Institutional analysis of stereotactic body radiotherapy (SBRT) for oligometastatic lymph node metastases. *Radiat Oncol.* 2017;12:105.
- Mutic S, Dempsey JF. The ViewRay System: magnetic resonance-guided and controlled radiotherapy. *Semin Radiat Oncol.* 2014;24:196–199.
- Acharya S, Fischer-Valuck BW, Kashani R, et al. Online magnetic resonance image guided adaptive radiation therapy: first clinical applications. *Int J Radiat Oncol Biol Phys.* 2016;94:394–403.
- Bohoudi O, Bruynzeel AME, Senan S, et al. Fast and robust online adaptive planning in stereotactic MR-guided adaptive radiation therapy (SMART) for pancreatic cancer. *Radiation Oncol.* 2017;125:439–444.
- Lagendijk JJW, Raaymakers BW, Van Der Heide U. MRI guided radiotherapy: Mri as position verification system for IMRT. *Radiation Oncol.* 2002;64:S75–S76.
- Raaymakers BW, Jürgenliemk-Schulz IM, Bol GH, et al. First patients treated with a 1.5T MR-linac: clinical proof of concept of a high-precision, high-field MRI guided radiotherapy treatment. *Phys Med Biol.* 2017;62:L41–L50.
- Noel CE, Parikh PJ, Spencer CR, et al. Comparison of onboard low-field magnetic resonance imaging versus onboard computed tomography for anatomy visualization in radiotherapy. *Acta Oncol.* 2015;54:1474–1482.
- Timmerman RD, Kavanagh BD. Stereotactic body radiation therapy. *Curr Probl Cancer.* 2005;29:120–157.
- Timmerman RD, Kavanagh BD, Cho LC, et al. Stereotactic body radiation therapy in multiple organ sites. *J Clin Oncol.* 2007;25:947–952.
- Scorsetti M, Clerici E, Comito T. Stereotactic body radiation therapy for liver metastases. *J Gastrointest Oncol.* 2014;5:190–197.
- Park HJ, Chang AR, Seo Y, et al. Stereotactic body radiation therapy for recurrent or oligometastatic uterine cervix cancer: a cooperative study of the Korean radiation oncology group (KROG 14-11). *Anticancer Res.* 2015;35:5103–5110.
- Kerkhof EM, Balter JM, Vineberg K, et al. Treatment plan adaptation for MRI-guided radiotherapy using solely MRI data: a CT-based simulation study. *Phys Med Biol.* 2010;55:N433–N440.
- Henke L, Kashani R, Yang D, et al. Simulated online adaptive magnetic resonance-guided stereotactic body radiation therapy for the treatment of oligometastatic disease of the abdomen and central thorax: characterization of potential advantages. *Int J Radiat Oncol Biol Phys.* 2016;96:1078–1086.
- Nomden CN, AAC d. L, Roesink JM, et al. Intra-fraction uncertainties of MRI guided brachytherapy in patients with cervical cancer. *Radiation Oncol.* 2014;112:217–220.
- Verkooijen HM, Kerkmeijer LGW, Fuller CD, et al. R-IDEAL: a framework for systematic clinical evaluation of technical innovations in radiation oncology. *Front Oncol.* 2017;7:59.
- Wiersema L, Borst G, Nakhaee S, et al. First IGRT results for SBRT bone and lymph node oligometastases within the pelvic region. *Radiation Oncol.* 2017;123:S1006.
- Gerlich AS, Van der Velden JM, Fanetti G, et al. The immobilizing effect of the vacuum cushion in spinal SBRT and the impact of pain. *Radiation Oncol.* 2017;123:S876–S877.
- Ponti E, Lancia A, Ost P, et al. Exploring all avenues for radiotherapy in oligorecurrent prostate cancer disease limited to lymph nodes: A systematic review of the rule of stereotactic body radiotherapy. *Eur Urol Focus.* 2017;3:538–544.
- Seravalli E, van Haaren PMA, van der Toorn PP, et al. A comprehensive evaluation of treatment accuracy, including end-to-end tests and clinical data, applied to intracranial stereotactic radiotherapy. *Radiation Oncol.* 2015;116:131–138.
- UK SABR consortium guidelines [Internet]. 2016. [Cited 2016 Jul 5]. Available from: <http://www.actionradiotherapy.org/wp-content/uploads/2016/02/UKSABRConsortiumGuidelinesv51.pdf>
- Grimm J, LaCouture T, Croce R, et al. Dose tolerance limits and dose volume histogram evaluation for stereotactic body radiotherapy. *J Appl Clin Med Phys.* 2011;12:267–292.
- Velema LA, Bondar ML, Mens JW, et al. Nodal CTV deformations cannot be neglected in highly conformal radiotherapy of cervical cancer patients. *Radiation Oncol.* 2012;103:S185–S186.
- Schippers M, Bol GH, de Leeuw AAC. Position shifts and volume changes of pelvic and para-aortic nodes during IMRT of patients with cervical cancer. *Radiation Oncol.* 2014;111:442–445.
- Van de Bunt L, Jürgenliemk-Schulz IM, De Kort GAP, et al. Motion and deformation of the target volumes during IMRT for cervical cancer: what margins do we need? *Radiation Oncol.* 2008;88:233–240.
- Liu F, Erickson B, Peng C, et al. Characterization and management of interfractional anatomic changes for pancreatic cancer radiotherapy. *Int J Radiat Oncol Biol Phys.* 2011;83:e423–e429.
- Peng C, Ahunbay E, Chen G, et al. Characterizing interfraction variations and their dosimetric effects in prostate cancer radiotherapy. *Int J Radiat Oncol Biol Phys.* 2011;79:909–914.
- Thor M, Bentzen L, Hysing LB, et al. Prediction of rectum and bladder morbidity following radiotherapy of prostate cancer based on motion-inclusive dose distributions. *Radiation Oncol.* 2013;107:147–152.

- [32] Thörnqvist S, Hysing LB, Tuomikoski L, et al. Adaptive radiotherapy strategies for pelvic tumors – a systematic review of clinical implementations. *Acta Oncol.* 2016;55:943–958.
- [33] Wahl M, Descovich M, Shugard E, et al. Interfraction anatomical variability can lead to significantly increased rectal dose for patients undergoing stereotactic body radiotherapy for prostate cancer. *Technol Cancer Res Treat.* 2017;16:178–187.
- [34] Greco C, Zelefsky MJ, Loveblock M, et al. Predictors of local control after single-dose stereotactic image-guided intensity-modulated radiotherapy for extracranial metastases. *Int J Radiat Oncol Biol Phys.* 2011;79:1151–1157.
- [35] Salama JK, Hasselle MD, Chmura SJ, et al. Stereotactic body radiotherapy for multisite extracranial oligometastases: final report of a dose escalation trial in patients with 1 to 5 sites of metastatic disease. *Cancer.* 2012;118:2962–2970.
- [36] Jereczek-Fossa BA, Beltramo G, Fariselli L, et al. Robotic image-guided stereotactic radiotherapy, for isolated recurrent primary, lymph node or metastatic prostate cancer. *Int J Radiat Oncol Biol Phys.* 2012;82:889–897.
- [37] Detti B, Bonomo P, Masi L, et al. Stereotactic radiotherapy for isolated nodal recurrence of prostate cancer. *World J Urol.* 2015;33:1197–1203.
- [38] Li YBS, Hoisak JDP, Li NBS, et al. Dosimetric benefit of adaptive re-planning in pancreatic cancer stereotactic body radiotherapy. *Med Dosim.* 2015;40:318–324.
- [39] Van de Schoot AJAJ, De Boer P, Visser J, et al. Dosimetric advantages of a clinical daily adaptive plan selection strategy compared with a non-adaptive strategy in cervical cancer radiation therapy. *Acta Oncol.* 2017;56:667–674.
- [40] Clark GM, Popple RA, Prendergast BM, et al. Plan quality and treatment planning technique for single isocenter cranial radiosurgery with volumetric modulated arc therapy. *Pract Radiat Oncol.* 2012;2:306–313.
- [41] Chen G, Wang K, Li X. Independent interfraction motion of regional lymph nodes and breast targets in image-guided radiotherapy of breast cancer. *Int J Radiat Oncol Biol Phys.* 2009;75:S208.
- [42] Bol GH, Lagendijk JJ, Raaymakers BW. Virtual couch shift (VCS): accounting for patient translation and rotation by online IMRT re-optimization. *Phys Med Biol.* 2013;58:2989–3000.