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Original Article

Planning target volume margin assessment for online adaptive MR-guided dose-escalation in rectal cancer on a 1.5 T MR-Linac

Hidde Eijkelenkamp [a,*], Mick R. Boekhoff [a], Maaike E. Verweij [a], Femke P. Peters [b,c], Gert J. Meijer [a], Martijn P.W. Intven [a]

[a] Department of Radiation Oncology, University Medical Center Utrecht; [b] Department of Radiation Oncology, Leiden University Medical Center; and [c] Department of Radiation Oncology, Netherlands Cancer Institute/Antoni van Leeuwenhoek, The Netherlands

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ABSTRACT

Purpose: This study assessed the margins needed to cover tumor intrafraction motion during an MR-guided radiotherapy (MRgRT) dose-escalation strategy in intermediate risk rectal cancer.
Methods: Fifteen patients with rectal cancer were treated with neoadjuvant short-course radiotherapy, 5x5 Gy, according to an online adaptive workflow on a 1.5 T MR-linac. Per patient, 26 3D T2 weighted MRIs were made; one reference scan preceding treatment and five scans per treatment fraction. The primary tumor was delineated on each scan as gross tumor volume (GTV). Target coverage margins were assessed by isotropically expanding the reference GTV until more than 95% of the voxels of the sequential GTVs were covered. A margin with a coverage probability threshold of 90% was defined as adequate. Intra- and interfraction margins to cope with the movement of the GTV in the period between scans were calculated to indicate the target volume margins. Furthermore, the margin needed to cover GTV movement was calculated for different time intervals.
Results: The required margins to cover inter- and intrafraction GTV motion were 17 mm and 6 mm, respectively. Analysis based on time intervals between scans showed smaller margins were needed for adequate GTV coverage as time intervals became shorter, with a 4 mm margin required for a procedure of 15 min or less.
Conclusion: The shorter the treatment time, the smaller the margins needed to cover for the GTV movement during an online adaptive MRgRT dose-escalation strategy for intermediate risk rectal cancer. When time intervals between replanning and the end of dose delivery could be reduced to 15 min, a 4 mm margin would allow adequate target coverage.

North European guidelines recommend short-course radiotherapy (SCRT), 25 Gy in 5 fractions, followed by total mesorectal excision (TME) surgery for intermediate risk rectal cancer [1–3]. The addition of SCRT to TME surgery in this patient group reduces the risk of local recurrences compared to TME surgery alone [3,4]. In addition, the Stockholm III trial showed fewer postoperative complications after a prolonged interval between SCRT and TME compared to direct surgery after SCRT [5]. Therefore, many institutes changed the interval between radiotherapy and surgery to 6–8 weeks. The introduction of a prolonged interval also allows for organ-sparing treatment strategies in patients with a good response after SCRT. This treatment strategy without the need for TME surgery was introduced by Habr-Gama for patients with clinical complete response after neoadjuvant therapy and is now increasingly being used more in clinical practice after publications on clinical safety and functional outcomes [6–8].

However, the proportion of patients suitable for this kind of approach after SCRT is currently around 10% [9,10]. This rate is lower than reported after chemoradiotherapy, probably because of the lower biological effective dose of SCRT and the shorter interval between neoadjuvant treatment and surgery [11,12]. Since the response to radiotherapy is dose-dependent, an approach to increase the probability of obtaining a complete response after SCRT and move towards organ preservation, could be to escalate the irradiation dose to the rectal tumor [13–15]. This approach in rectal cancer was already explored in clinical trials in patients receiving dose-escalated neoadjuvant chemoradiation, showing an increased tumor response with a higher irradiation dose [16–18].

However, dose-escalation with conventional radiotherapy techniques in rectal cancer is challenging. Cone-beam CT has suboptimal soft-tissue contrast to visualize the tumor. Besides, large

* Corresponding author at: Department of Radiation Oncology, University Medical Center Utrecht, Heidelberglaan 100, 3584CX Utrecht, The Netherlands.
E-mail address: H.Eijkelenkamp-2@umcutrecht.nl (H. Eijkelenkamp).

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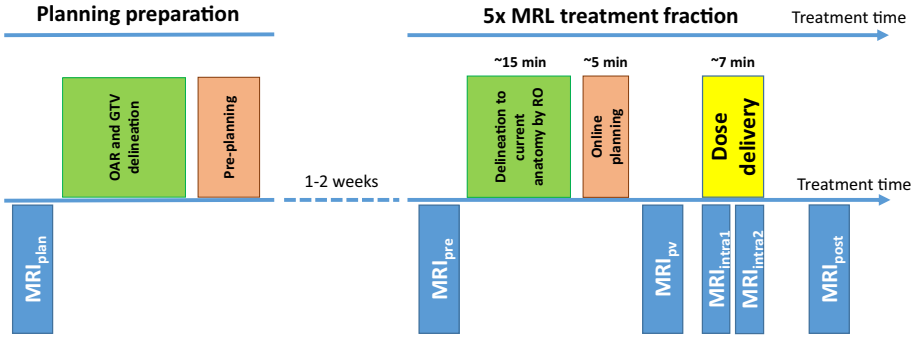

Fig. 1. Acquisition of MRIs and treatment timing during the online adaptive workflow for short-course radiotherapy designed by the Department of Radiation Oncology of the University Medical Centre Utrecht (UMCU), the Netherlands. Abbreviations: MRL, MR-Linac; OAR, organs-at-risk; GTV, gross tumor volume; RO, radiation oncologist.

treatment volumes are needed due to daily differences in rectal and bladder filling, causing variations in tumor location. These large treatment fields induce toxicity and limit the total dose delivered on the rectal tumor, decreasing the chance of a complete response.

The introduction of online adaptive MR-guided radiotherapy (MRgRT) provides the opportunity to cope with these treatment challenges in rectal cancer [13,19]. MRI and its superior soft-tissue contrast makes it possible to see the rectal tumor while you treat it. MR-guided radiotherapy platforms facilitate daily adaptations of the treatment plan based on the actual anatomy [20]. Despite these advantages, residual uncertainties in target coverage remain [19]. These uncertainties are mainly caused by the intrafraction motion as interfractional changes are inherently accounted for by the online plan adaptation procedures. The purpose of this study was to assess the intrafraction movement of rectal tumors during MRgRT to specify target volume margins needed for an MR-guided boost strategy in intermediate risk rectal cancer.

Materials and methods

Patients

Fifteen consecutive patients with rectal cancer, treated with MR-guided online adaptive neoadjuvant SCRT between March 2019 and July 2019 were part of this study. Fourteen patients had intermediate risk rectal cancer. One patient had a cT4aN2 tumor with invasion of the visceral peritoneum, but was also treated with SCRT in a neoadjuvant setting. All patients consented for the use of their data either in the Dutch Prospective Data Collection Initiative on Colorectal Cancer (PLCRC) or the MOMENTUM study (NCT04075305). Both studies have been approved by the Medical Research Ethics Committee of the University Medical Centre Utrecht in the Netherlands [21–23].

MR-Linac treatment protocol and imaging

All patients were treated on a 1.5 T MR-Linac (MRL) (Unity, Elekta AB, Stockholm Sweden) using an online adaptive workflow. Details of this workflow have been published in previous work [20]. In short, patients received a planning CT and MRI scan for treatment planning (Philips 1.5 T Ingenia MR-RT). The MRI scan protocol of all sessions contained, among other sequences, a 3D T2 weighted (T2w) MRI sequence (FOV: 400 × 400 × 300 mm, voxel size: 0.62 × 0.62 × 2.00 mm, TE/TR: 124/1500 ms, FA: 90°). The planning CT and 3D T2w MRI scans were registered, target volumes and organs-at-risk (OAR) were delineated based on both imaging modalities, and a treatment plan was generated. On average, one week after the planning imaging, the treatment was delivered in five consecutive daily fractions of 5 Gy. The elective clinical target volumes were recontoured on the pre-treatment MRI (MRI_{pre}) acquired at the beginning of each fraction. Based on these new contours, a full replanning was performed, the position was rechecked on a position verification MRI (MRI_{pv}), and the dose was delivered. Due to the online adaptive procedure, no specific bladder or bowel preparation was advised besides not entering the treatment room with a full bladder because of urgency issues during the procedure. Per treatment fraction, five online 3D T2w MRI scans were made: MRI_{pre}, MRI_{pv}, intrafraction 1 (MRI_{intra1}), intrafraction 2 (MRI_{intra2}), and post-treatment scan (MRI_{post}) (Fig. 1). Including the MRI_{plan}, 26 MRI scans could be obtained per patient. 327 MRI scans were made in total and used in the analysis. The MRI_{intra2} was not acquired when dose delivery was already completed or close to completion at the end of MRI_{intra1}, which was the case in 37 of the 73 fraction deliveries. Two patients received a fifth treatment fraction on a conventional accelerator due to treatment on holidays and therefore had five scans less.

Delineations

The primary rectal tumor was delineated on each 3D T2w scan as Gross Tumor Volume (GTV). Delineations were made by a single observer and independently verified/adjusted by another observer. Delineations were performed using an in house developed delineation tool, Volumetool [24,25].

Tumor coverage assessment

To provide more insight into the movement of rectal cancer tumors, tumor displacement and subsequent target coverage were analyzed for multiple scenarios (Fig. 2).

(A) Interfraction: The MRI scans were rigidly aligned based on the bony anatomy to the planning MRI scan. Next, the margin around the reference GTV_{plan}, required to geometrically cover interfraction changes, was assessed for each treatment fraction. These motion patterns reflect the uncertainties associated with a conventional treatment strategy.

(B) Intrafraction: Tumor geometries of GTV_{pv}, GTV_{intra} and GTV_{post} compared to reference GTV_{pre} were analyzed. Here, margins required to cover intrafraction motion between MRI_{pv}, MRI_{intra}, and MRI_{post} compared to MRI_{pre} were assessed for each scan. This method resembled an adapt-to-shape (ATS) workflow where at each fraction a new treatment plan is created based on the daily anatomy [26,27]. Furthermore, the margins per treatment fraction based on the intrafraction GTV motion were calculated to provide an overview of interpatient variations.

(C) Time intervals: Target coverage was assessed between all the time intervals. All MRI scans within a single fraction were paired, making every possible combination (MRI_{pre}/MRI_{pv}, MRI_{pre}/MRI_{in-}

$_{tra1}$,... MRI_{intra2}/MRI_{post}), as shown in Fig. 2C. For every pair, the first scan was used as reference scan and subsequently the margin required to cover the GTV in the follow-up scan was assessed. The time interval between the two scans was determined and the pairs were distributed into time bins of 5 min based on the duration of the interval. Finally, the required margins for geometric target coverage for every time interval was analyzed. Margins more than 10 mm were considered as outliers and inspected a second time. Furthermore, to determine if intrafraction GTV motion magnitude changed in during treatment, the difference in tumor displacement was assessed for approximately the first and second half of the procedure. Knowing the MRI_{pv} was taken almost halfway through the treatment, the margins needed to cover GTV motion from the MRI_{pre} to the MRI_{pv}, and from the MRI_{pv} to the last MRI were calculated.

Margin assessment

The geometric coverage probability of the follow-up scans was assessed with expanded margins varying from 0 mm to 30 mm around the reference GTV. For every previously described scenario the reference GTV was isotropically expanded to a new structure with increments of 1 mm for the interfraction analysis and increments of 0.5 mm for both the intrafraction and time analyses. Then, coverage was analyzed with in-house developed software Volumetool [24]. A follow-up GTV was marked as covered if more than 95% of the voxels were covered by the expanded reference GTV. This approach is conform earlier studies in rectal cancer [28,29]. Subsequently, a margin was defined suitable if it geometrically covered 90% of all registered GTVs within the corresponding inter- or intrafraction group or 5 min time bin [29,30].

Statistics

Baseline patient and tumor characteristics were presented as median with range or interquartile range (IQR), as average with standard deviation (SD) or as frequencies with percentages depending on their distribution. Data were visualized using Statistical Package for Social Sciences (SPSS) version 25 (Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Results

Patient and tumor characteristics are summarized in Table 1. The group consisted of 6 females and 9 males, of whom 9 patients had a proximal located tumor (≥11 cm from the anal verge). The median GTV was 12.1 cm^3 with an IQR of 7.8–19.3 cm^3. No tumor regression or progression trend was observed throughout the treatment based on the tumor volumes (GTV), as illustrated in Suppl. Fig. 1.

(A) Interfraction: This analysis included 15 planning MRIs and 312 MRL treatment MRIs. The average time interval between the MRI_{plan} and the start of the MRL treatment was ten days. Substantial anatomical changes between the pre-treatment reference scan (MRI_{plan}) and online MRI scans (MRI_{pre}, MRI_{pv}, MRI_{intra} and MRI_{post}) were observed (Suppl. Fig. 2). A margin of 17 mm covered the GTV in 90% of the fractions (Fig. 3).

(B) Intrafraction: This analysis included scans from 73 MRL treatment fractions, consisting of 73 MRI_{pre} and 239 follow-up scans. Fig. 4 illustrates an example of the observed intrafraction tumor motion on the 3D T2w MRI scans. Based on the scan times, the average procedure time was 35 min (range 24–54 min). The

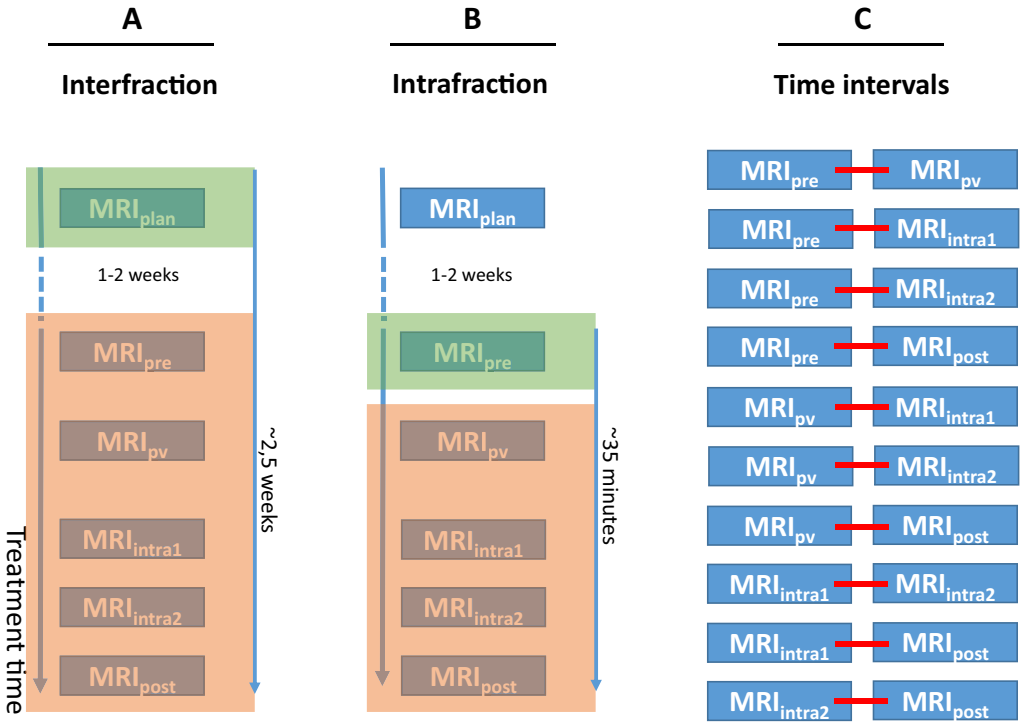

Fig. 2. Schematic overview of the different motion analyses. (A) Interfraction: representing the conventional treatment strategy where motion is observed over 2-3 weeks. The MRI_{plan} (green) was used as reference on which the online MRIs (orange) were registered. (B) Intrafraction: the online adaptive workflow on the MR-Linac, where intrafraction motion should be covered during 35 minutes on average. The MRI_{pre} (green), the first online MRI, was used as reference on which the sequential online MRIs (orange) were registered. (C) Time intervals: all the possible online MRI scan pairs created for the time interval analysis.

Table 1
Baseline patient and tumor characteristics of 15 consecutive rectal cancer patients treated with short-course radiotherapy on the MR-Linac. Data are displayed as numbers (%) unless indicated otherwise. Clinical TNM stage is based on UICC TNM 7th edition. MRF- = no involvement of the mesorectal fascia.

Baseline characteristics	*N* = 15 (%)
Age (median, range)	60; 47–76
Sex	
Male	9 (60)
Female	6 (40)
Tumor location	
Distal (≤5 cm)	2 (13)
Mid (6–10 cm)	4 (27)
Proximal (≥11 cm)	9 (60)
Tumor stage	
cT2	7 (47)
cT3, MRF-	7 (47)
cT4a	1 (7)
Nodal stage	
cN0	1 (7)
cN1	13 (87)
cN2	1 (7)
Metastatic stage	
cM0	15 (100)

isotropic margin needed to cover intrafraction GTV motion geometrically was 6 mm (Fig. 4). Interpatient variation is visualized in Suppl. Fig. 3 showing the margins per fraction per patient needed to cover the GTV intrafraction motion. The patients with the largest margins per fraction (patient 8, 10, 11 and 14) had proximal located tumors and needed a median margin of 10 mm (range 9–21 mm).

(C) Time intervals: A total of 519 pairs were registered from the MRL treatment scans and distributed in 5 min accumulating time bins based on the time interval between the scans in each pair (Suppl. Fig. 4). The median time interval was 15 min (range 4–54 min). A 4 mm margin was sufficient for more than 90% GTV coverage within a 15 min time frame (Fig. 5). 15 of the 519 time pairs required more than a 10 mm margin and they were inspected a second time. These 15 outliers were found in the same 4 patients with a proximal located tumor as in the intrafraction analysis, of which 12 pairs originated from 2 patients. Visual inspection estimated rectal and bladder filling contributed the most in these extensive GTV shifts.

The needed margins per treatment procedure half was assessed. The average time between the MRI_{pre} and MRI_{pv} was 20 min (range 12–37 min) and needed a 6.5 mm margin to fully cover for intrafraction GTV motion in this first half of the workflow. The average time between the MRI_{pv} and the last MRI was 14 min (range 10–30 min) and required a 4 mm margin for the second half of the workflow.

Discussion

This study assessed the inter- and intrafraction tumor movement and motion over time in a cohort of patients with rectal cancer to assess margins needed for an MR-guided dose-escalation strategy. Our findings showed that substantial margin reduction can be realized with an online adaptive workflow. The isotropic margin needed with conventional non-adaptive radiotherapy to cover 90% of interfraction GTV motion was 17 mm. With online adaptive MRgRT, the margin needed to cover intrafraction GTV motion was 6 mm. The required margin could be even reduced to 4 mm when the duration of the procedure becomes 15 min or less.

Our data indicate the need for fast online adaptive MRgRT procedures to accomplish a 4 mm margin for local GTV boosting strategies. The potential clinical benefits by switching from 6 mm to 4 mm margins need to be considered to reduce the chance of rectal and urogenital toxicity, especially with dose-escalation strategies. Larger margins are still needed because some steps of these online adaptive workflows take considerable time before dose delivery can start [20]. For instance, the manual adaption of the propagated contours to the daily anatomy can last up to 15 min. An example of overcoming this problem, leading to a shorter duration between planning and dose delivery, is an ATS strategy on the MRI_{pre} followed by an adapt-to-position (ATP) strategy on the MRI_{pv} just before dose delivery. An ATP strategy can translate the whole delineation to the current position of the GTV on the MRI_{pv} [26,31]. After this translation, planning and dose delivery can be completed within 15 min [20]. The downside of

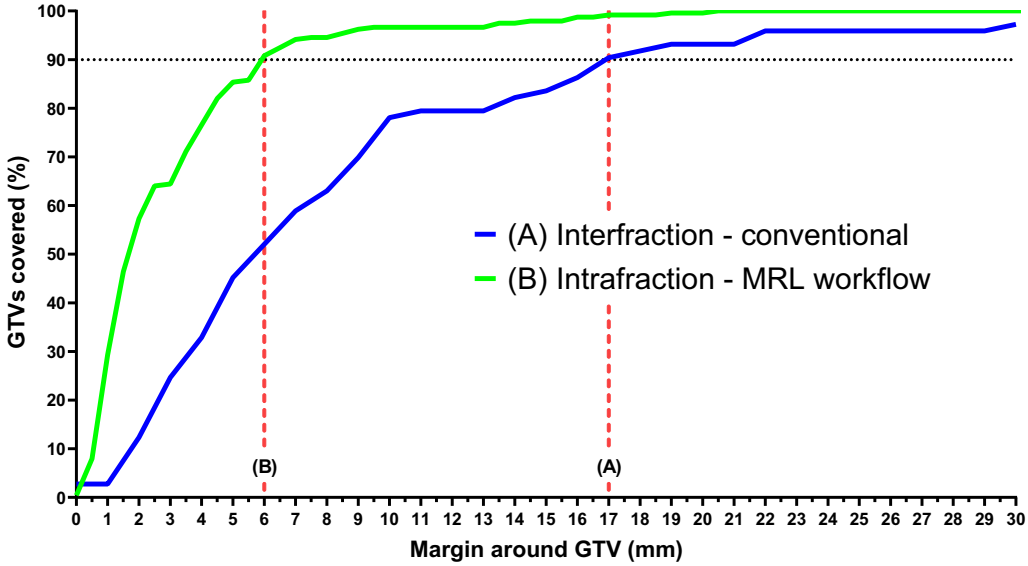

Fig. 3. Margins needed around the reference GTV to cover 95% of their registered GTVs in (A) the interfraction analysis, with MRI_{plan} as reference on which all online MRIs were registered, and (B) the intrafraction analysis, with the first online MRI (MRI_{pre}) as reference on which all sequential online MRIs (MRI_{pv}, MRI_{intra1}, MRI_{intra2}, MRI_{post}) were registered. The margins with a coverage probability threshold of 90% in A and B were 17 mm and 6 mm.

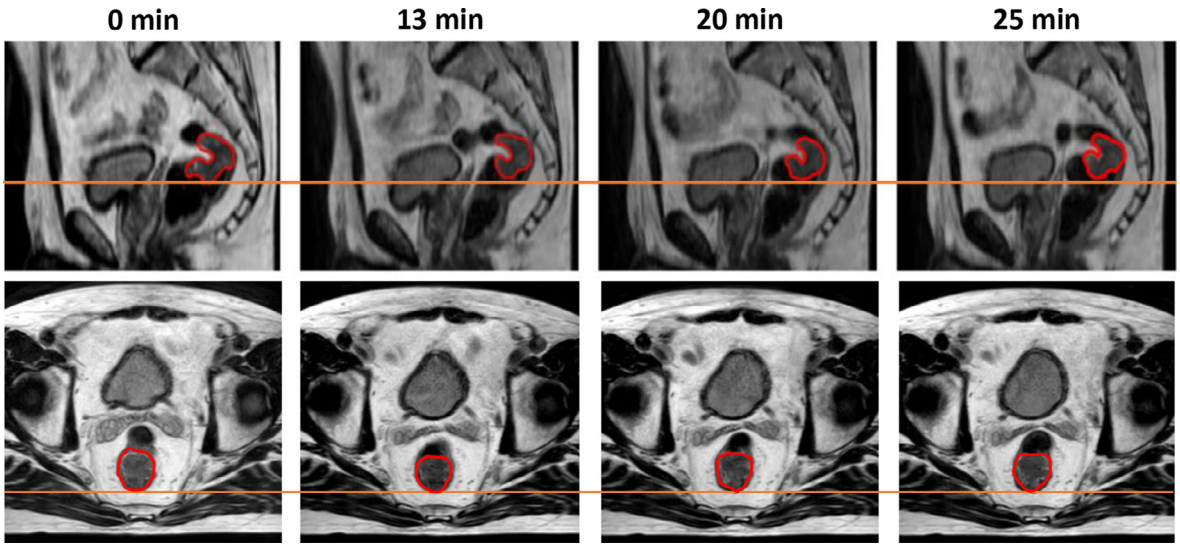

Fig. 4. Example of GTV displacement within a fraction. The GTV (red) is delineated in the sagittal and axial plane on four sequential 3D T2w MRIs during the first treatment fraction. The orange line indicates the GTVs most caudal and dorsal point on the first MRI.

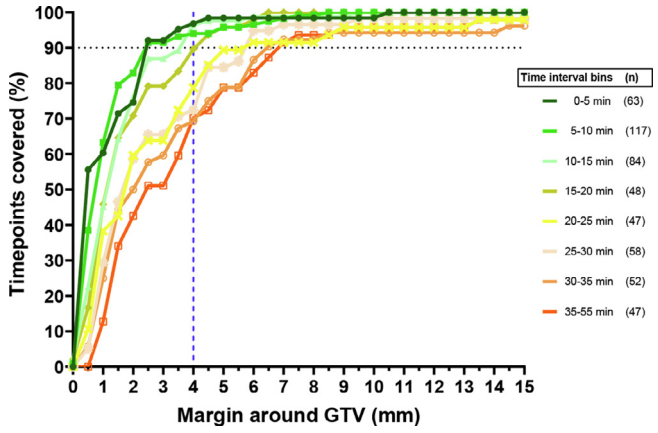

Fig. 5. Required margins based on time between scans. Percentage of time pairs (all the possible combinations of the online MRIs) fully covered in cumulative time interval bins with varying margins (n=519). Longer time interval between scans required a larger margin to cover 90% of timepoints (red line) than a short time period between scans (green line). A margin of 4 mm was sufficient to cover GTV motion within 15 minutes (blue line).

ATP is that it does not take deformations and rotations into account. However, the prior ATS strategy adjusted the GTV to the anatomical situation of the day, and visual inspection on the pre-dose delivery MRI scan can be used to verify if there are no substantial intrafractional rotations and deformations. In case there are, margins could be adjusted. To explore motion patterns, we determined if GTV motion was dependent on how long the patient had been in supine position on the treatment table. We hypothesized that this motion could probably be larger directly after positioning the patient due to organs drifting away from their original position. However, the margin needed for the first half of the online adaptive procedure was almost equal to the margin needed during the second half, indicating that the magnitude of GTV motion is not dependent on the time that the patient is lying in the same position.

To our knowledge, this is the first study that explores the margins to compensate for intrafraction GTV motion during online adaptive procedures. The benefit of online adaptive MRgRT is that it accounts for all interfraction variation, leaving only the intrafraction variation. Therefore, it allows smaller margins compared to non-adaptive strategies. Furthermore, we expect that the use of smaller margins in an online adaptive MRgRT setting allows for treatment intensification by increasing boost dosage on the tumor without additional OAR toxicity [32]. A change in margin size from 17 mm to 4 mm results in a substantial decrease in radiotherapy field size and irradiated healthy tissue.

A few previous studies have reported on the margins within the context of dose escalation of the primary tumor in locally advanced rectal cancer for a bone registration workflow [33–39]. Burbach et al. proposed an anisotropic margin with 7, 11, and 13 mm in the lateral, anteroposterior, and cranial/caudal (CC) directions. A more recent study of our group recently came to the same margins needed as Burbach et al. except for a 1 mm larger margin in CC direction, 14 mm [28]. These margins published for locally advanced rectal cancer were slightly smaller than our 17 mm margin for intermediate risk rectal cancer. The tumor stage could be an explanation for this discrepancy. Locally advanced rectal cancers might be more fixated than intermediate risk rectal cancers due to their greater average volume and infiltration of the surrounding mesorectal fat tissue. Another possible explanation for this difference can be found in the different approaches to assess the margins. Whereas the earlier listed margins are based on statistical distributions combined with margin recipes, in the current work margins are derived from the geometric coverage on a fraction-by-fraction basis.

A limitation of our presented workflow was that active gating or tracking techniques were unavailable at our system at the time of this study. However, Chiloiro *et al.* demonstrated the clinical use of the gating window at a preset threshold is feasible for treatment of rectal cancers [19]. These techniques could very likely also be implemented in a local boost which also allows further margin reduction. Ultimately, future online tracking and trailing techniques could enable precise online targeting where the beam apertures continuously move along with the tumor displacements. Another limitation of this study is the limited number of patients, which hampers proper stratification to tumor location of the GTV within the rectum. However, it should be noted that patients with the largest margins per fraction had proximal located tumors. This observation may be a consequence of the proximal rectum being more affected by bowel and bladder filling. In the temporal dimension however, we analyzed 327 3D T2w MRIs over multiple treat-

ment timepoints, and we believe that this is an adequate number of samples to assess the intrafractional changes properly.

In conclusion, online adaptive MRgRT can correct the interfraction changes, but intrafraction tumor motion remains of concern. The margin to dose-escalate the GTV with adequate target coverage was 6 mm for an online adaptive MR-guided procedure. Shortening the time between imaging and end of irradiation to 15 min or less can reduce the required margin to 4 mm.

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 data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.07.011.

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