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Original Research Article

1.5 T MR-linac planning study to compare two different strategies of rectal boost irradiation

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ABSTRACT

Purpose: To compare treatment plans of two different rectal boost strategies: up-front versus adaptive boost at the 1.5 T MR-Linac.
Methods: Patients with locally advanced rectal cancer (LARC) underwent standard neoadjuvant radiochemotherapy with 50.4 Gy in 28 fractions. T2-weighted MRI prior and after the treatment session were acquired to contour gross tumor volumes (GTVs) and organs at risk (OARs). The datasets were used to simulate four different boost strategies (all with 15 Gy/5 fractions in addition to 50.4 Gy): up-front boost (5 daily fractions in the first week of treatment) and an adaptive boost (one boost fraction per week). Both strategies were planned using standard and reduced PTV margins. Intra-fraction motion was assessed by pre- and post-treatment MRI-based contours.
Results: Five patients were included and a total of 44 MRI sets were evaluated. The median PTV volumes of the adaptive boost were significantly smaller than for the up-front boost (81.4 cm^3 vs 44.4 cm^3 for PTV with standard margins; 31.2 cm^3 vs 15 cm^3 for PTV with reduced margins; $p = 0.031$). With reduced margins the rectum was significantly better spared with an adaptive boost rather than with an up-front boost: V60Gy and V65Gy were 41.2% and 24.8% compared with 59% and 29.9%, respectively ($p = 0.031$). Median GTV intra-fractional motion was 2 mm (range 0–8 mm).
Conclusions: The data suggest that the adaptive boost strategy exploiting tumor-shrinkage and reduced margin might result in better sparing of rectum and anal canal. Individual margin assessment, motion management and real-time adaptive radiotherapy appear attractive applications of the 1.5 T MR-Linac for further testing of individualized and safe dose escalation in patients with rectal cancer.
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1. Introduction

Current standard-of-care for locally advanced rectal cancer (LARC) includes neoadjuvant chemo-radiotherapy (CRT) followed by total mesorectal excision (TME) [1]. Pathological complete response (pCR) after neoadjuvant CRT represents a favorable prognostic factor for loco-regional control, distant metastasis-free survival and overall survival [2–6]. Furthermore, a growing body of evidence suggests that patients without residual tumor (cCR, clinical complete response) after CRT might be safely managed with watch-and-wait and, in case of local regrowth, with salvage surgery [7]. This organ-preservation approach may allow sparing perioperative and long-term morbidity as well as improve quality of life (QoL) [8–11]. However, with standard CRT protocols only about 15% of the patients achieve a pCR at the time of surgery, i.e. approximately eight weeks after completion of CRT.

Various strategies to increase cCR and pCR have been studied such as the prolongation of the interval between CRT and surgery, intensification of concomitant systemic treatment, the application of deep regional hyperthermia and the use of consolidative chemotherapy [12]. In addition, a *meta*-analysis demonstrated that radiotherapy (RT) dose escalation may also be a viable strategy to increase the pCR rate [13]. Relatively high radiation doses, e.g.

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above 60 Gy normalized to 2 Gy per fraction seem to be necessary to achieve a clinically relevant gain in pCR [14,15]. However, this leads to several challenges for precise dose escalation to the primary tumor as increased toxicity is of particular concern: firstly, the anatomy of the rectum, the tumor and surrounding normal tissues might show relevant day-to-day variation in position. Secondly, tumors might shrink considerably during treatment [16,17]. Thirdly, the optimal timing for a primary tumor boost has not been established yet. In addition, intra-fractional motion of the tumor needs to be accounted for by adding a safety margin to ensure adequate target coverage but on the other hand this increases the irradiated volume and thereby the risk of toxicity. Hybrid devices combining a linear accelerator with magnetic resonance imaging (MR-Linac) have been recently introduced in clinical practice, providing a promising solution for these challenges [18,19]. Of particular interest is the capacity of the MR-linac to generate images with high soft-tissue contrast in the treatment workflow for real-time adaptive boost simulation and delivery, also taking anatomical and functional treatment response into account [20]. In the present planning study, we hypothesized that an adaptive MR-guided boost to the primary rectal tumor with reduced margins results in better sparing of organs at risk (OARs) than an up-front boost due to shrinkage of the gross tumor volume (GTV) throughout the course of treatment.

2. Methods

2.1. Patient and treatment characteristics

Inclusion criteria include histologically confirmed, locally advanced adenocarcinoma of the middle- or lower rectum (stage II-III according to AJCC/TNM 8th ed. [21]) with an indication for preoperative CRT. Exclusion criteria were any contraindications for MRI (such as claustrophobia or electronic devices including defibrillators, cochlear implants, pacemakers, etc.) and clinical conditions precluding the administration of standard treatment. Prior to treatment, all patients underwent a diagnostic pelvic MRI with gadolinium enhancement, contrast-enhanced thorax and abdomen computed tomography CT, endoscopy (with biopsy) and clinical examination. CT simulation (Brilliance Big Bore, Philips, Eindhoven, The Netherlands) and MR simulation (1.5 T Unity MR-Linac, Elekta, AB, Stockholm, Sweden) were performed on the same day in supine position. Patients were instructed to drink approximately 400 cc of water 30 min prior to the simulation and to empty the bowels before the simulation. According to our institutional standard, RT was given to a total dose of 50.4 Gy in 28 fractions. Simultaneous chemotherapy consisted of continuous intravenous infusion of 5-fluorouracil 1000 mg/m^2 per day over 120 h during weeks one and five. TME as deep anterior resection or abdominoperineal resection was scheduled approximately 8 weeks after the end of RT. All patients were treated within a phase 2 MR-Linac feasibility trial (NCT04172753) which has been approved by the IRB of the Medical Faculty Tübingen (659/2017BO1).

2.2. Imaging, boost strategies, OAR and target volume definition, planning

The Elekta Unity® (Elekta AB, Stockholm, Sweden) hybrid system combines a 1.5 Tesla (T) MR with a 7 MV flattening filter free accelerator mounted on a rotating gantry system that provides real-time, "on-board" MRI in the treatment room to guide IMRT planning and delivery based on daily anatomy changes [22–24]. For each treatment fraction, T2-weighted scans were performed before and after radiation delivery (pre-treatment and post-treatment T2w-2 min). Based on the daily pre-treatment T2w-2 min images, the daily plan was adapted using a virtual couch shift by the so called "adapt to position" (ATP) workflow with segment weight optimization [23]. The daily post-treatment T2w-2 min images were acquired for quality assurance and research purposes. At the end of the first 5 fractions and then once a week, all patients underwent the following additional MRI sequences (cf. supplement for sequence details): T2-weighted 3D pseudo steady-state (pss) (T2w-6 min) and T2-weighted 3D fat suppression SPAIR (T2w-SPAIR).

To address to hypothesis of our planning study, four different boost strategies were compared (Fig. 1):

1) up-front boost with standard margin: A boost of 15 Gy to the GTV in 5 fractions during the first week of treatment with an anisotropic 7–10 mm PTV margin (7 mm laterally and 10 mm in all other directions) followed by the standard treatment (50.4 Gy in 28 fractions)
2) up-front boost with reduced margin: A boost of 15 Gy to the GTV in 5 fractions during the first week of treatment with an isotropic 3 mm PTV margin followed by the standard treatment
3) Adaptive boost with standard margin: A boost of 15 Gy to the GTV in 5 fractions with one boost fraction per week and with an anisotropic 7–10 mm PTV margin (7 mm laterally and 10 mm in all other directions), the boost is integrated in the standard treatment (50.4 Gy in 28 fractions)
4) Adaptive boost with reduced margin: A boost of 15 Gy to the GTV in 5 fractions with one boost fraction per week and with an isotropic 3 mm PTV margin, the boost is integrated in the standard treatment.

The linear-quadratic *iso*-effect model with α/β value of 10 Gy for tumor was applied to calculate biologically equivalent total doses (TD) normalized to 2 Gy/fraction (EQD2). For all boost strategies, the total EQD2 to the GTV was 66.25 Gy. For OARs an α/β value of 3 Gy was applied.

OARs were contoured (according to the Radiation Therapy Oncology Group contouring guidelines [25]) in T2w-6 min images. For GTV definition T2w-SPAIR images were registered to the respective T2w-6 min images and used to additionally inform GTV definition. The anal-sphincter was defined as the muscle layer around the anal canal [26,27]. Other OARs and respective dose parameters include: rectum (Dmean, V60, V65), bladder (Dmean, V40), anal canal (Dmean), penile bulb (Dmean).

A CT-based treatment plan with 50.4 Gy prescribed to the PTV and the MR-based plans (MR of the day) with adapted target volumes were retrospectively simulated for each patient. A total of 20 MR-based plans with adapted target volumes were calculated for each patient, i.e. five plans for each of the four boost strategies described above. All treatment plans consisted of step-and-shoot IMRT created in the treatment planning system (TPS) Monaco® 5.4 (Elekta AB, Stockholm, Sweden). Simulated dose distributions on the MRI of the day were planned based on the MR-Linac adapt-to-shape workflow [23] using a synthetic CT with mean densities of the primary CT assigned to femur, pelvis, sacrum, rectum, bladder and not further defined soft tissue. All treatment plans were optimized based on the same planning template with nine beam angles, 3 mm dose grid, 1% calculation uncertainty and clinically used sequencing parameters. During the optimization for all treatment plans, the *iso*-effects on the OARs were tightened with the following priority: rectum, sigmoid, bladder and conformality until the PTV coverage was D98 = 14.25 Gy (95% of the prescribed Dose) ± 0.1 Gy. To enable direct comparison, we normalized the plans for all boost strategies to the same PTV coverage level D (98%) of 14.25 Gy, i.e. 98% target covered by 95% of the prescribed dose.

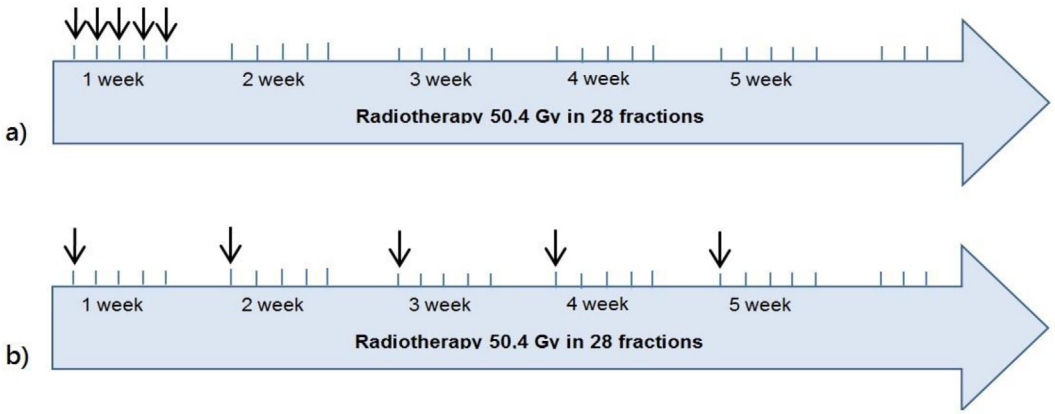

Fig. 1. Study design with time points for imaging and boost planning (arrows for additional T2w-6 min and T2w-SPAIR) for a) UpFront and b) Adaptive boost.

2.3. Assessment of intrafraction motion

GTVs were contoured on the T2w-6 min images acquired after the radiation delivery and were propagated on the pre-treatment T2w-2 min scan where the GTV contours were adapted to the pre-treatment anatomy (e.g. editing the target because of changes in rectum air filling). The time elapsed between pre and post imaging was recorded. The open-source DICOM toolkit (DCMTK) was used to create masks of the GTV contours identifying voxels occupied by GTV in the pre and post treatment scan on a MRI voxel grid of $0.83 \times 0.83 \times 1$ mm^3. For every voxel of the post-treatment GTV, a minimal Euclidean distance to a voxel occupied by the GTV in the pre-treatment scan was calculated in Matlab (Version 2020). For this voxel-based minimal distance, the percentage GTV coverage for isotropic margins from zero to 20 mm was calculated.

2.4. Statistical analysis

Statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS, version 26, Inc., Chicago, IL). The non-parametric Wilcoxon signed-rank test was used to evaluate the differences between pairwise comparisons. A one-tailed p-value was calculated and $p \leq 0.05$ was considered statistically significant.

3. Results

Table 1 shows the patient and tumor characteristics of the five patients enrolled in the present planning study. All patients completed neoadjuvant CRT with 50.4 Gy and 5-fluorouracil as prescribed. A total of 44 MRI datasets obtained at the 1.5 T MR-Linac were available. For logistic reasons during the COVID-19 pandemic, one patient received the first week of treatment at the 1.5 T MR-Linac and continued then at a conventional linac (6 MV VMAT, IGRT with cone-beam CT). For the purpose of this study, he was scanned weekly at the 1.5 T Unity MR-Linac and MR-images were acquired for the calculation of boost plans. For another patient it was not possible to image after completion of a treatment session in week three at the MR-Linac. Thus, for this patient only four boost plans were available. For the analysis, the missing dataset was replaced by the mean of the four adaptive boost plans. During the first week of treatment and over the entire RT course the median primary GTV shrinkage was 10.1 cm^3 (1.7–11.5 cm^3) and 15.7 cm^3 (6.2–35.5 cm^3), respectively (Fig. 2). The difference between shrinkage during week one and the entire treatment course was statistically significant (Z = -2.023; p = 0.043). The data for the respective PTVs are summarized in Table 2 showing that adaptive boost with reduced margins revealed the smallest PTV (Z = -2.023, p = 0.031). Fig. 3 shows an example of the imaging and dose distribution. In all plans acceptable PTV coverage with D98 of 95% of the prescribed dose was achieved. Dosimetric parameters for OARs are shown in Table 3. For the two male patients the dose to the penile bulb was kept below the constraint of Dmean < 50 Gy. Applying the QUANTEC recommendations for rectal bleeding (rectum V65 $\leq$ 25% for grade $\geq$ 2 risk < 15% and grade $\geq$ 3 risk < 10% [28,29]) three out of five patients would have been eligible for a boost irradiation if the adaptive planning strategy with reduced margin was used. In contrast, none of patients would have been eligible with the up-front boost strategy irrespective of the margin and only one patient receiving the adaptive boost with standard margin. Similar results were found for rectum V60. The dosimetric differences for urinary bladder and anal canal between the different boost strategies were small.

For assessment of intra-fractional tumor motion, a total of 41 fractions with pre- and post-treatment images were analyzed with a median time of 13 min (range 9–32 min) between the start of the pre-treatment and the end of the post-treatment imaging. Fig. 4 shows that an isotropic expansion of 3 mm would lead to a 95% coverage of the GTV during the treatment session.

4. Discussion

In the present planning study we hypothesized that tumor shrinkage and margin reduction based on the assessment of intra-fraction motion results in better sparing of OAR allowing

Table 1
Patient and tumour characteristics.

Patient	Age(years)	Gender	Stage	Primary tumour size*		Distance from anal verge (cm)*
				Length (cm)	Volume (cm^3)	
1	54	female	T3N1M0	4	7.5	9
2	52	female	T2N1M0	2.8	22.6	7
3	65	male	T3N1M0	6	52.5	2
4	55	male	T3N1M0	3	10.4	6
5	73	female	T3N1M0	6.2	19.4	9

*Measured on baseline diagnostic MRI (the distance from sphincter was measured on sagittal plane. TNM AJCC 8th ed.

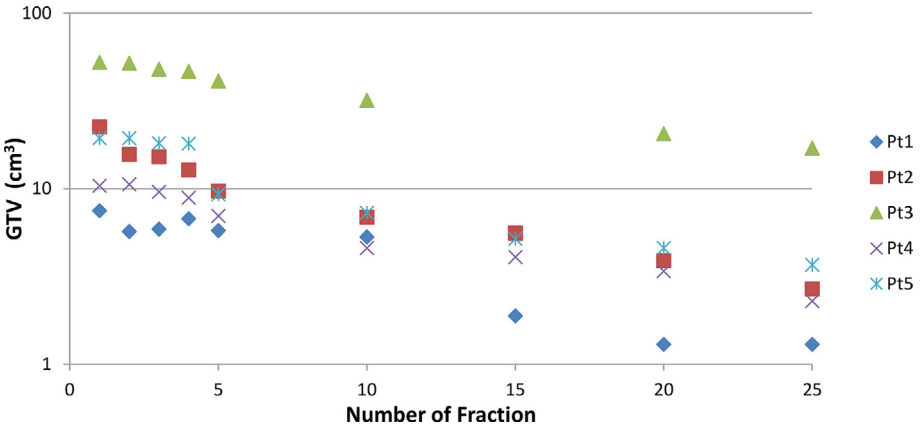

Fig. 2. Primary tumour volume (GTV) during the course of fractionated radiotherapy.

Table 2
Median PTV boost volumes with interquartile range for all five patients with standard and reduced margins for upfront versus adaptive boost.

PTV	UpFront Boost (cm^3)*	Adaptive Boost (cm^3)*	*p* value**
Standard margins	81.4 (43.2–181.3)	44.4 (15–173.5)	0.031
Reduced margins	31.2 (14.6–93.1)	15 (3–89.2)	0.031

*UpFront Boost: median of the PTV boost volumes of the first five days of treatment; Adaptive Boost: median of the weekly PTV boost volumes. **Wilcoxon signed-rank test between median values of UpFront and Adaptive boost for all five patients.

dose escalation to primary rectal cancer using real-time MR-guided radiotherapy. To the best of our knowledge of the authors this kind of such an analysis has not been published before. Although limited by the small number of patients, our findings suggest that both elements, i.e. adaptive boost spread out over five weeks to exploit tumor shrinkage and margin reduction, resulted in the most effective sparing of the rectum. In our dataset, only this planning strategy would allow that the majority of patients would qualify based on rectal sparing for a real-time MR-guided adaptive boost trial using 15 Gy in five fractions to the primary tumor. Despite of considerably tumor shrinkage, the GTV was visible in all patients including week four and five (no complete remission) in the present study. It appears possible that in patients with very sensitive tumors a complete or near-complete remission already occurs during long-course CRT. However, these patients would not be candidates for further dose-escalation and potential toxicity could be spared. This individualization, i.e. boost only if the tumor is sufficiently visible, appears to be another potential benefit of the adaptive versus up-front boost. As dosimetric results from planning studies might not necessarily translate in actual clinical effects, these findings are hypothesis-generating and need to be validated in clinical trials using escalated radiation doses. The present planning study used a long-course CRT as a backbone for dose escalation. Thus, our results do not apply to the emerging new standard of care of short-course radiotherapy and total neoadjuvant therapy as tested in the RAPIDO trial [30,31]. Integration of real-time MR-guided dose escalation in the short-course backbone will be challenged by the fact that shrinkage might not occur similar to the up-front scenario described in the present study and other approaches such as functional imaging and dose-painting may have to be explored. Our data suggest that just margin reduction may be not sufficient to allow safe dose escalation to the primary rectal tumor.

In the framework of a clinical trial various strategies for RT dose escalation for rectal cancer have been studied or have been adopted in on-going clinical trials [32–35]. The WW3 trial of the Danish group [34] and the APHRODITE trial of the Leeds group [35] investigate a dose-escalation up to 62 Gy in rectal cancer patients using a simultaneous integrated boost (SIB) technique.

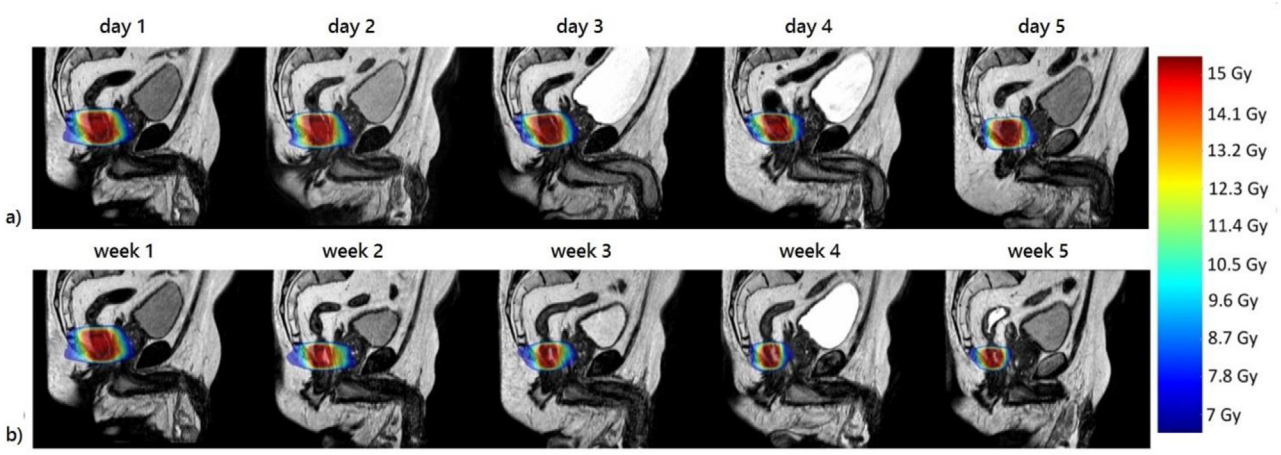

Fig. 3. Sagittal views (T2w-6 min images) of target volume (*red lines*) and dose distribution in the boost plans of patient 4. a) UpFront boost with reduced margins on day 1 to 5 during week 1; b) Adaptive boost with reduced margins once per week during week 1 to 5. Only the dose distribution of the boost is shown. All patients received 50.4 Gy in 28 fractions to the pelvis.

Table 3
Dosimetric parameters to the rectum, bladder and anal canal.

Parameter	Reduced Margins UpFront Boost Median	IQR	Adaptive Boost Median	IQR	*p* value*	Standard Margins UpFront Boost Median	IQR	Adaptive Boost Median	IQR	*p* value*
Rectum										
Dmean§	59.5	58.6–61	56.8	56.1–58.8	0.031	60.8	60.3–63.3	58.6	58.5–61.1	0.031
V60†	59	49.5–66.7	41.2	32–55.2	0.031	69.1	66.9–83.2	55.5	49.8–68.1	0.031
V65†	29.9	27.5–37.4	24.8	17.1–29.4	0.031	32.8	25.7–43.4	29	23.8–36	0.031
Urinary bladder										
Dmean§	34.3	31.7–36	34.3	31.6–35.7	0.125	34.7	32.4–36.9	34.4	32.1–36.1	0.063
V40†	25.9	20.7–39.1	26	20.7–38.8	0.063	26.5	22.1–39.8	26.1	22.4–39.2	0.063
Anal Canal										
Dmean§	45.2	41.1–65.1	45	40.7–63.4	0.031	45.3	42.1–65.8	45.2	41.2–64.5	0.031

IQR, interquartile range, *Wilcoxon signed-rank test, § Values are reported in Gy, † Values are reported in % (percentage of volume of the OAR considered).

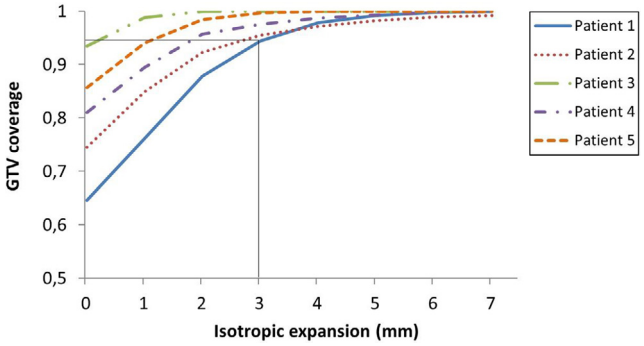

Fig. 4. Isotropic expansion of the GTV and relative GTV coverage during the treatment session.

In the RECTAL-BOOST phase II randomized trial, patients with LARC were treated with an external-beam up-front boost of 15 Gy in five fractions to the primary rectal tumor followed by standard neoadjuvant CRT. No statistical significant improvement in pCR-rate or 2-year clinical complete response was observed in the boost arm compared with the standard arm. The latter showed an unexpected high rate of pCR beyond 30%. However, in comparison to the standard arm, a higher rate of TRG 1–2 and of sphincter preservation were observed in the dose escalation group without excess in grade $\geq$ 3 toxicity one year after treatment. In addition, due to preset planning constraints compromises in target coverage in the boost arm were necessary. Thus, not all patients received dose escalation as defined per protocol. The high pCR rate in the control group underlines the need of precise identification of patients who might benefit from further dose escalation. Adequate patient selection is also key for the design of future trials. An interesting approach for patient stratification might include imaging biomarkers for early response assessment such as DWI [16]. A major challenge with cone-beam CT workflows results from the poor visualization of primary target in the based workflow and the subsequent safety margins to assure appropriate volume coverage. As a consequence rather large volumes had to be treated with an increased risk of toxicity. Conceptually, the 1.5 T MR-Linac hybrid device offers superior soft tissue contrast for image guidance, functional imaging including DWI, real-time adaptive dose planning and motion monitoring during delivery. The latter is of particular importance as anatomical shifts might occur during the session and might jeopardize margin reduction. Here we show that an average margin of three millimeters would ensure 95% coverage of the tumor in all five patients. More data is needed to validate this margin concept for future trials taking also into account that for an adaptive MR-guided boost an adapt-to-shape (ATS) workflow might be necessary which might take longer time and therefore more probability of intrafraction motion. Potential interventions and optimizations for further margin reduction in this scenario of low and middle rectum tumors include rectal filling, parasymphaticolytic drugs, patient instruction and more personalized margin recipes.

As a criterion for eligibility, in the present planning study we used dose-volume constraints to the rectum with the endpoint of bleeding which were obtained in patients treated for prostate cancer [28,29]. Whether this represents a relevant parameter in the context of organ preservation in rectal cancer needs to be addressed in future investigations. Interestingly, rectal bleeding was one of the dominant late toxicities in a prospective study on dose escalated radiotherapy using a brachytherapy boost to a total dose of 65 Gy [36]. Regarding anal sphincter function, in a retrospective study of patients with LARC [37] a series of dosimetric parameters was correlated with loss of sphincter function. In our study the reduction of the anal sphincter dose was small which was also due to the tumor location in the lower rectum in two patients. Thus, the expected benefit of the proposed adaptive boost strategy on sphincter function will also depend on the tumor localisation.

In conclusion, the data suggest that the adaptive boost strategy exploiting tumor-shrinkage and reduced margin during long-course CRT might result in better sparing of the rectum. Individual margin assessment, motion management and real-time adaptive radiotherapy appear attractive applications of the 1.5 T MR-Linac for further testing of individualized and safe dose escalation in patients with rectal cancer.

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.

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Declaration of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2020.11.016.

References

[1] National Comprehensive Cancer Network. Rectal Cancer (Version 4.2020). May 25, 2020]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf.
[2] Maas M, Nelemans PJ, Valentini V, Das P, Rödel C, Kuo LJ, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 2010;11(9):835–44.
[3] Valentini V, Coco C, Picciocchi A, Morganti AG, Trodella L, Ciabattoni A, et al. Does downstaging predict improved outcome after preoperative chemoradiation for extraperitoneal locally advanced rectal cancer? A long-term analysis of 165 patients. Int J Radiat Oncol Biol Phys 2002;53(3):664–74.
[4] Vecchio FM, Valentini V, Minsky BD, Padula GD, Venkatraman ES, Balducci M, et al. The relationship of pathologic tumor regression grade (TRG) and outcomes after preoperative therapy in rectal cancer. Int J Radiat Oncol Biol Phys 2005;62(3):752–60.
[5] Capirci C, Valentini V, Cionini L, De Paoli A, Rodel C, Glynne-Jones R, et al. Prognostic value of pathologic complete response after neoadjuvant therapy in locally advanced rectal cancer: long-term analysis of 566 ypCR patients. Int J Radiat Oncol Biol Phys 2008;72(1):99–107.
[6] Díaz-González JA, Calvo FA, Cortés J, García-Sabrido JL, Gómez-Espí M, Del Valle E, et al. Prognostic factors for disease-free survival in patients with T3–4 or N+ rectal cancer treated with preoperative chemoradiation therapy, surgery, and intraoperative irradiation. Int J Radiat Oncol Biol Phys 2006;64(4):1122–8.
[7] van der Valk MJM, Hilling DE, Bastiaannet E, Meershoek-Klein Kranenbarg E, Beets GL, Figueiredo NL, et al. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. Lancet 2018;391(10139):2537–45.
[8] Guren MG, Eriksen MT, Wiig JN, Carlsen E, Nesbakken A, Sigurdsson HK, et al. Quality of life and functional outcome following anterior or abdominoperineal resection for rectal cancer. Eur J Surg Oncol 2005;31(7):735–42.
[9] Fazio VW, Zutshi M, Remzi FH, Parc Y, Ruppert R, Furst A, et al. A randomized multicenter trial to compare long-term functional outcome, quality of life, and complications of surgical procedures for low rectal cancers. Ann Surg 2007;246(3).
[10] Gani C, Gani N, Zschaeck S, Eberle F, Schaeffeler N, Hehr T, et al. Organ Preservation in Rectal Cancer: The Patients' Perspective. Front Oncol 2019;9:318.
[11] Gani C, Bonomo P, Zwirner K, Schroeder C, Menegakis A, Rödel C, et al. Organ preservation in rectal cancer - Challenges and future strategies. Clin Transl Radiat Oncol 2017;3:9–15.
[12] Gani C, Schroeder C, Heinrich V, Spillner P, Lamprecht U, Berger B, et al. Long-term local control and survival after preoperative radiochemotherapy in combination with deep regional hyperthermia in locally advanced rectal cancer. Int J Hyperthermia 2016;32(2):187–92.
[13] Burbach JP, den Harder AM, Intven M, van Vulpen M, Verkooijen HM, Reerink O. Impact of radiotherapy boost on pathological complete response in patients with locally advanced rectal cancer: a systematic review and meta-analysis. Radiother Oncol 2014;113(1):1–9.
[14] Wiltshire KL, Ward IG, Swallow C, Oza AM, Cummings B, Pond GR, et al. Preoperative radiation with concurrent chemotherapy for resectable rectal cancer: effect of dose escalation on pathologic complete response, local recurrence-free survival, disease-free survival, and overall survival. Int J Radiat Oncol Biol Phys 2006;64(3):709–16.
[15] Appelt AL, Pløen J, Vogelius IR, Bentzen SM, Jakobsen A. Radiation dose-response model for locally advanced rectal cancer after preoperative chemoradiation therapy. Int J Radiat Oncol Biol Phys 2013;85(1):74–80.
[16] Lambrecht M, Vandecaveye V, De Keyzer F, Roels S, Penninckx F, Van Cutsem E, et al. Value of diffusion-weighted magnetic resonance imaging for prediction and early assessment of response to neoadjuvant radiochemotherapy in rectal cancer: preliminary results. Int J Radiat Oncol Biol Phys 2012;82(2):863–70.
[17] Van den Begin R, Kleijnen JP, Engels B, Philippens M, van Asselen B, Raaymakers B, et al. Tumor volume regression during preoperative chemoradiotherapy for rectal cancer: a prospective observational study with weekly MRI. Acta Oncol 2018;57(6):723–7.
[18] Raaymakers BW, Jürgenliemk-Schulz IM, Bol GH, Glitzner M, Kotte A, van Asselen B, et al. First patients treated with a 1.5 T MRI-Linac: clinical proof of concept of a high-precision, high-field MRI guided radiotherapy treatment. Phys Med Biol 2017;62(23):L41–50.
[19] Grégoire V, Guckenberger M, Haustermans K, Lagendijk JJW, Ménard C, Pötter R, et al. Image guidance in radiation therapy for better cure of cancer. Mol Oncol 2020;14(7):1470–91.
[20] Thorwarth D, Ege M, Nachbar M, Mönnich D, Gani C, Zips D, et al. Quantitative magnetic resonance imaging on hybrid magnetic resonance linear accelerators: Perspective on technical and clinical validation. Physics and Imaging in Radiation Oncology 2020;16:69–73.
[21] Edge SB, Byrd DR, Carducci MA, Compton CC, Fritz A, Greene F. AJCC cancer staging manual, Vol. 649. New York: Springer; 2010.
[22] Gani C, Boldrini L, Valentini V. Online MR guided radiotherapy for rectal cancer. *New opportunities.* Clin Transl Radiat Oncol 2019;18:66–7.
[23] Winkel D, Bol GH, Kroon PS, van Asselen B, Hackett SS, Werensteijn-Honingh AM, et al. Adaptive radiotherapy: The Elekta Unity MR-linac concept. Clin Transl Radiat Oncol 2019;18:54–9.
[24] Chiloiro G, Boldrini L, Meldolesi E, Re A, Cellini F, Cusumano D, et al. MR-guided radiotherapy in rectal cancer: First clinical experience of an innovative technology. Clin Transl Radiat Oncol 2019;18:80–6.
[25] Gay HA, Barthold HJ, O'Meara E, Bosch WR, El Naqa I, Al-Lozi R, et al. Pelvic normal tissue contouring guidelines for radiation therapy: a Radiation Therapy Oncology Group consensus panel atlas. Int J Radiat Oncol Biol Phys 2012;83(3):e353–62.
[26] Peeters ST, Lebesque JV, Heemsbergen WD, van Putten WL, Slot A, Dielwart MF, et al. Localized volume effects for late rectal and anal toxicity after radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2006;64(4):1151–61.
[27] Wilkins A, Naismith O, Brand D, Fernandez K, Hall E, Dearnaley D, et al. Derivation of Dose/Volume Constraints for the Anorectum from Clinician- and Patient-Reported Outcomes in the CHHiP Trial of Radiation Therapy Fractionation. Int J Radiat Oncol Biol Phys 2020;106(5):928–38.
[28] Fiorino C, Valdagni R, Rancati T, Sanguineti G. Dose-volume effects for normal tissues in external radiotherapy: pelvis. Radiother Oncol 2009;93(2):153–67.
[29] Michalski JM, Gay H, Jackson A, Tucker SL, Deasy JO. Radiation dose-volume effects in radiation-induced rectal injury. Int J Radiat Oncol Biol Phys 2010;76(3 Suppl):S123–9.
[30] Hospers, G., R.R. Bahadoer, E.A. Dijkstra, B.v. Etten, C. Marijnen, H. Putter, et al., Short-course radiotherapy followed by chemotherapy before TME in locally advanced rectal cancer: The randomized RAPIDO trial. Journal of Clinical Oncology, 2020. 38(15_suppl): p. 4006-4006.
[31] van der Valk MJM, Marijnen CAM, van Etten B, Dijkstra EA, Hilling DE, Kranenbarg EM, et al. Compliance and tolerability of short-course radiotherapy followed by preoperative chemotherapy and surgery for high-risk rectal cancer - Results of the international randomized RAPIDO-trial. Radiother Oncol 2020;147:75–83.
[32] Owens R, Mukherjee S, Padmanaban S, Hawes E, Jacobs C, Weaver A, et al. Intensity-Modulated Radiotherapy With a Simultaneous Integrated Boost in Rectal Cancer. Clin Oncol (R Coll Radiol) 2020;32(1):35–42.
[33] Couwenberg AM, Burbach JPM, Berbee M, Lacle MM, Arensman R, Raicu MG, et al. Efficacy of dose-escalated chemoradiation on complete tumour response in patients with locally advanced rectal cancer (RECTAL-BOOST); a phase 2 randomised controlled trial. Int J Radiat Oncol Biol Phys 2020.
[34] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29-. Identifier NCT04095299. Standard Dose Versus High Dose of Radiotherapy in Rectal Preservation With Chemo-radiotherapy in Rectal Cancer Patients (WW3); 2019 Sep 17 [cited 2020 Nov 26]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04095299#contacts
[35] ISRCTN registry [Internet]. London: BMC. ISRCTN16158514. APHRODITE - A phase II trial of higher radiotherapy dose in the eradication of early rectal cancer; 2019 Oct 17 [cited 2020 Nov 26]. Available from: http://www.isrctn.com/ISRCTN16158514
[36] Dizdarevic E, Frøstrup Hansen T, Pløen J, Henrik Jensen L, Lindebjerg J, Rafaelsen S, et al. Long-Term Patient-Reported Outcomes After High-Dose Chemoradiation Therapy for Nonsurgical Management of Distal Rectal Cancer. Int J Radiat Oncol Biol Phys 2020;106(3):556–63.
[37] Arias F, Eito C, Asín G, Mora I, Cambra K, Mañeru F, et al. Fecal incontinence and radiation dose on anal sphincter in patients with locally advanced rectal cancer (LARC) treated with preoperative chemoradiotherapy: a retrospective, single-institutional study. Clin Transl Oncol 2017;19(8):969–75.