



Original Research Article

Clinical implementation and feasibility of long-course fractionated MR-guided chemoradiotherapy for patients with esophageal cancer: An R-IDEAL stage 1b/2a evaluation of technical innovation

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ABSTRACT

Purpose: This R-Ideal stage 1b/2a study describes the workflow and feasibility of long-course fractionated online adaptive MR-guided chemoradiotherapy with reduced CTV-to-PTV margins on the 1.5T MR-Linac for patients with esophageal cancer.

Methods: Patients with esophageal cancer scheduled to undergo chemoradiation were treated on a 1.5T MR-Linac. Daily MR-images were acquired for online contour adaptation and replanning. Contours were manually adapted to match the daily anatomy and an isotropic CTV-to-PTV margin of 6 mm was applied. Time was recorded for all individual steps in the workflow. Feasibility and patient tolerability were defined as on-table time of ≤ 60 min and completion of $>95\%$ of the fractions on the MR-Linac, respectively. Positioning verification and post-treatment MRIs were retrospectively analyzed and dosimetric parameters were compared to standard non-adaptive conventional treatment plans.

Results: Nine patients with esophageal cancer were treated with chemoradiation; eight patients received 41.4 Gy in 23 fractions and one received 50.4 Gy in 28 fractions. Four patients received all planned fractions on the MR-Linac, whereas for two patients $>5\%$ of fractions were rescheduled to a conventional linac for reasons of discomfort. A total of 183 (86%) of 212 scheduled fractions were successfully delivered on the MR-Linac. Three fractions ended prematurely due to technical issues and 26 fractions were rescheduled on a conventional linac due to MR-Linac downtime ($n = 10$), logistical reasons ($n = 3$) or discomfort ($n = 13$).

The median time per fraction was 53 min (IQR = 3 min). Daily adapted MR-Linac plans had similar target coverage, whereas dose to the organs-at-risk was significantly reduced compared to conventional treatment (26% and 12% reduction in mean lung and heart dose, respectively).

Conclusion: Daily online adaptive fractionated chemoradiotherapy with reduced PTV margins is moderately feasible for esophageal cancer and results in better sparing of heart and lungs. Future studies should focus on further optimization and acceleration of the current workflow.

1. Introduction

Magnetic Resonance Imaging (MRI) is an imaging modality which provides excellent soft tissue contrast allowing clear visualization of both the esophageal tumor and surrounding organs at risk. Integrated MR-guided radiotherapy (MRgRT) systems such as the Elekta Unity 1.5T MR-Linac (Elekta AB, Stockholm, Sweden) allow for an adaptive

workflow with online contour adaptation and replanning [1–3]. Moreover, MRgRT provides real-time imaging to characterize and eventually track intrafraction motion to ensure even more precise and accurate dose delivery. On the downside, online MRgRT will substantially increase the treatment time per fraction. Therefore, most clinical experience with MRgRT with online plan adaptation has been achieved for confined target volumes that are treated with hypofractionated

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regimens such as lymph nodes, prostate, pancreas and lung lesions [4–8]. For patients with esophageal cancer the role of MRgRT is relatively unexplored, although MRgRT has some potential benefits over contemporary cone-beam CT (CBCT) guided radiotherapy [9].

Firstly, the clinical target volume (CTV), which contains the esophageal tract and sometimes the proximal stomach, is subject to large interfraction variations [10]. Due to the limited soft-tissue contrast of CBCT imaging, these variations are often unnoted. Moreover, because of limited soft tissue contrast patients are typically aligned on the bony anatomy (e.g. vertebrae) during treatment. To account for these patient positioning and other inaccuracies the CTV is expanded to a relatively large planning target volume (PTV). Recent studies have suggested margins varying between 7 mm and 12 mm for different directions, resulting in PTVs that are about three times the volume of the CTV [11–14]. Online MRI provides excellent soft tissue contrast, thereby enabling accurate target definition for each fraction and with online plan adaptation, interfractional variations (including potential tumor shrinkage) can be corrected for [15].

Secondly, respiratory motion and changes in respiratory patterns together with patient movements and relaxation could lead to intrafractional tumor changes [16–18]. Online cine-MR can capture these intrafraction changes and thereby potentially allows for gating and tracking strategies. In addition, during free breathing treatment dose delivery treatment can be interrupted in case intrafraction motion exceeds a preset threshold [19]. These motion management strategies will increase treatment accuracy.

Thirdly, the onboard MRI also allows for online functional diffusion-weighted imaging (DWI). Multiple studies have shown that the change in DWI signal is a biomarker for treatment response [20–22]. It could be hypothesized that functional imaging potentially allows for dose painting and smart dose escalation strategies based on the residual disease demarcated by the DWI signal, which might increase treatment efficacy.

However, MRgRT presents some disadvantages as well. Online imaging, replanning and verification procedures generally take more time and might be more demanding from a patient perspective. In addition, at this moment treatment costs of MRgRT will be higher compared to conventional CBCT guided radiotherapy. Therefore, systematic evaluation of MRgRT in esophageal cancer according to the R-Ideal framework is of utmost importance for evidence-based implementation [23].

As a first step to gain experience in the treatment of esophageal cancer on an MR-Linac and to explore the feasibility of MRgRT, we started an R-Ideal stage 1b/2a study, treating patients with esophageal cancer with fractionated chemoradiotherapy on the 1.5T MR-Linac (Unity) with reduced PTV margins, at our institute, from July 2019 onwards. In this study we describe the workflow of MRgRT on a 1.5T MR-Linac and report on our first clinical experiences in terms of treatment times, patient compliance and dose reduction to normal tissue.

2. Materials and methods

2.1. Patients

Patients referred for chemoradiotherapy in accordance with the Dutch guidelines, with a good performance status and limited nodal disease, were eligible for treatment on a 1.5T MR-Linac (Elekta Unity, Elekta AB, Stockholm, Sweden). The chemoradiotherapy regimen consisted of 5 weeks or 6 weeks radiotherapy of 41.4 Gy in 23 fractions or 50.4 Gy in 28 fractions, with concurrent weekly intravenous administration of carboplatin and paclitaxel. Exclusion criteria were general contraindications for 1.5T MRI, an inability to tolerate a one-hour treatment as judged by the radiation oncologist, and an expected cranio-caudal length of the clinical target volume (CTV) of >18 cm because of limitations in maximum field size on the MR-Linac. All patients consented to the MOMENTUM study (NCT04075305), which has been approved by the Medical Research Ethics Committee of the

University Medical Centre Utrecht in the Netherlands [24].

2.2. Clinical workflow

All steps of the workflow are depicted in Fig. 1 and described in detail below.

2.2.1. Pre-treatment imaging

Pre-treatment imaging consisted of an MRI scan and a planning (^{18}F -FDG PET)-4DCT. MR imaging was acquired on a 1.5T Philips Ingenia MRI scanner (Philips Medical Systems, Best, NL). Patients were scanned in free breathing conditions in head-first, supine treatment position with arms down for patient comfort, on a flat table top. The patient set-up was indexed to a special table overlay as described by Werensteijn-Honing et al. (2019) [4] and an anatomical 3D-T2-weighted scan ($0.59 \times 0.59 \times 0.2 \text{ mm}^3$, TE = 87.5, TR = 1300 ms, scan time = 6 min) was acquired.

2.2.2. Delineations

Target volumes were delineated on the anatomy of the pre-treatment MR images. As this 3D-scan was acquired under free breathing conditions over 5–6 min, the time averaged anatomy was reconstructed over multiple breathing cycles with Cartesian k -space sampling [25]. First, the GTV was delineated on the 3D T2 weighted MR scan by a radiation oncologist subspecialized in esophageal cancer, where fused PET and CT images were used as extra guidance. Subsequently, the CTV was defined as the gross tumor volume (GTV) of the primary tumor with a 3-cm cranio-caudal extension along the gastroesophageal tract (2 cm in caudal direction in cases where the CTV extended in the stomach) and radially with a 5-mm margin excluding anatomical structures such as heart, lungs, large vessels, trachea and main bronchi and vertebrae. Pathologic lymph nodes were also included in the CTV with a 5-mm margin where the previously listed anatomical structures were excluded. As the CTV was confined by both geometrical and anatomical borders that varied on a day-to-day basis, a multi-step delineation procedure was initiated involving three aiding structures (Fig. 2). The first aiding structure (AID₁) was defined as the GTV with a 0-cm cranial margin and a 3-cm margin (or 2 cm in case of tumor extension in the stomach) in all other directions. This structure was used to indicate the ultimate geometric limits of the caudal part of the CTV in the stomach region. The second aiding structure (AID₂) was constructed by adding a 3-cm cranial margin to AID₁. This structure was used to mark the upper transversal slice to be included in CTV definition. A third aiding structure (AID₃) was defined as the GTV with an isotropic margin of 5 mm to mark the radial extensions of the CTV around the GTV. In an earlier in-silico study we demonstrated that a CTV-to-PTV margin of 2 mm in axial and 5 mm in cranial-caudal direction was large enough to absorb the residual intrafraction motion in the vast majority of patients [9]. However, in this clinical pilot study the PTV was conservatively created by an isotropic expansion of the CTV with 6 mm. OARs were delineated by a specialized radiation therapy technologist and checked and - if necessary - adapted by a radiation oncologist.

2.2.3. Pre-treatment planning

A pre-treatment step-and-shoot intensity-modulated radiotherapy (IMRT) plan was created in Monaco, to serve as a patient-specific template for online treatment planning. Here a dose of 41.4 Gy in 23 fractions (or 50.4 Gy in 28 fractions) was prescribed to 95% of the PTV, while minimizing the dose to the lungs, heart and spinal cord (Table 1). The calculation grid size for the Monte-Carlo dose engine was 4 mm and the relative electron densities for lungs, trachea, main bronchi and bony tissue were adapted from the planning CT, while the density of the remaining body tissue was set to 1.01 g/cm³. The 1.5T magnetic field along the direction of the scanner bore was taken into account for all dose calculations. Seven non-uniformly spaced beam angles were used, avoiding the couch at beam angles of 115°–135° and 225°–245° the

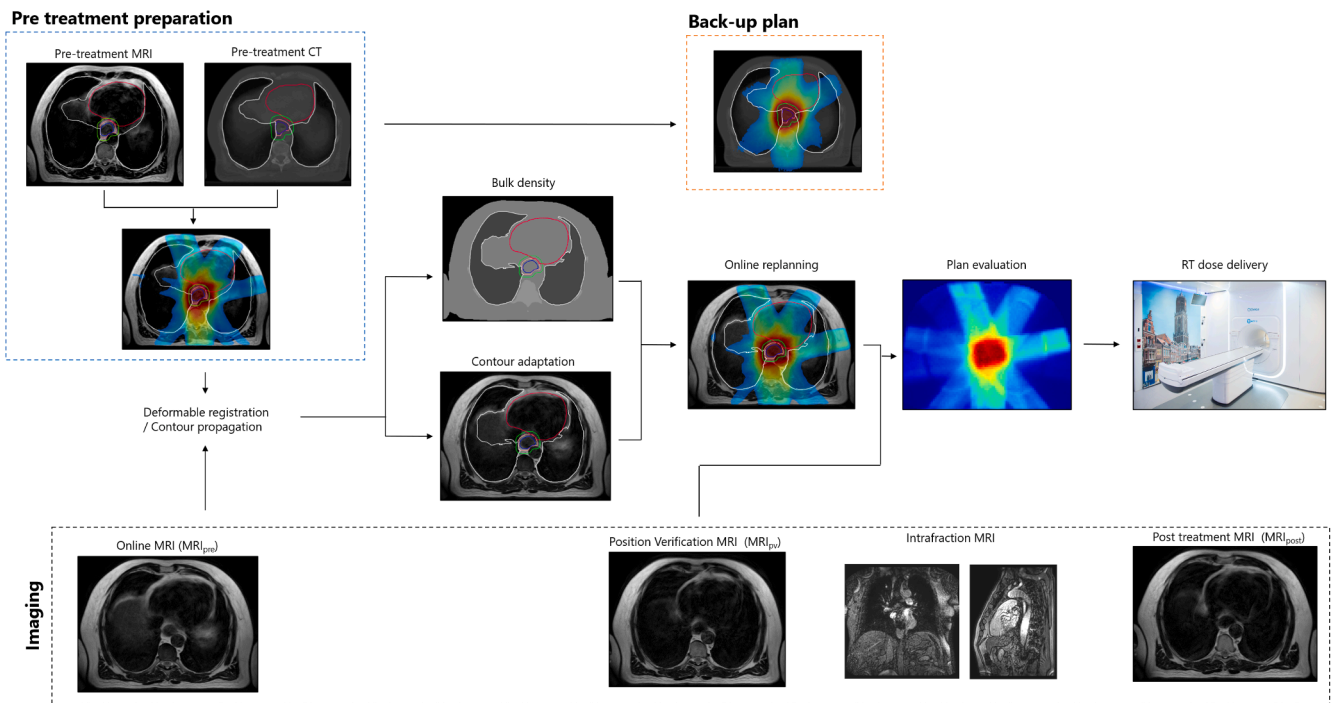


Fig. 1. Clinical workflow for online adaptive radiotherapy on the MR-Linac for patients with esophageal cancer.

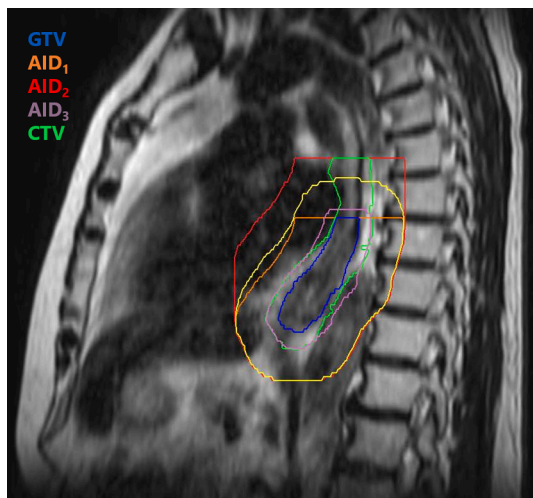


Fig. 2. Aiding structures for fast reproducible online CTV definition. The first aiding structure (AID₁) was defined as the online manually adapted GTV with a 0-cm cranial margin and a 3-cm margin (or 2 cm in case of tumor extension in the stomach) in all other directions. The second aiding structure (AID₂) was constructed by adding a 3 cm cranial margin to AID₁. A third aiding structure (AID₃) was defined as the online manually adapted GTV with an isotropic margin of 5 mm. The propagated CTV was automatically confined by AID₂ and subsequently adapted manually according to anatomy visible on the MRI. AID₃ was used to facilitate manual adaptation of the CTV.

cryostat connection pipe at 8°-18° and avoiding patients' arms at beam incidence. Furthermore, a back-up plan was generated in case the patient needed to be rescheduled to a conventional linear accelerator. Therefore, a VMAT plan was generated with a 10-mm isotropic CTV-to-PTV margin based on the anatomy of the phase-averaged 4D planning CT.

Table 1

Dosimetric parameters and objectives for online replanning. V107%, V95% and V90% represent the volume which receive at least 107, 95 and 90 of the prescribed dose, respectively. V5Gy, V20Gy and V40Gy represent the volume which receives 5, 20 and 40 Gy, respectively. Dmean represents the mean dose to the corresponding organ.

Organ	Dosimetric parameter	Objective
PTV	V107%	< 2 cm ³
	V95%	> 98 %
	V90%	> 99 %
Lungs	V20Gy	< 30 %
	V5Gy	< 75 %
Heart	V40Gy	< 30 %
Spleen	Dmean	< 20 Gy
CTV	V95%	> 99 %

2.3. Online workflow

2.3.1. Online patient setup

Patients were in supine position with arms down on the MR-Linac couch using specific couch index points, which were intended to ensure that the position of the patient along the length of the couch was known and reproducible between the pre-treatment planning scans and each treatment session. In addition, an institutionally added in-room laser system was used for patient positioning on the MR-Linac.

2.3.2. Online contour adaptation and replanning

After patient alignment, a 3D T2 MRI scan (MRI_{pre}) was acquired

using the same parameters as for the pre-treatment scan. Contours were propagated from the pre-treatment MRI using first a rigid and then a deformable registration in Monaco, version 5.40.01 (Elekta AB, Stockholm, Sweden). Next, the propagated GTVs were adapted by a specialized radiation oncologist. Then, the aiding structures AID₁, AID₂ and AID₃ were regenerated and the propagated CTV was automatically confined by AID₂ and subsequently adapted manually according to anatomy visible on the MRI. AID₃ was used to facilitate manual adaptation of the CTV. Finally, a PTV of 6 mm in all directions was generated for the adapted CTV and, if deemed necessary, the contours of the propagated OARs were partially adapted. Once all contours were adapted to the anatomy of the day, online replanning was started using the objectives of the pretreatment IMRT plan, which is also referred to as the ‘adapt to shape’ workflow [4,26].

2.3.3. Plan evaluation, motion management and dose delivery

The new treatment plan was evaluated by the radiation oncologist. During plan optimization, a position verification (PV) MRI scan (MRI_{pv}) was acquired, with the same parameters as the online planning MRI scan. Visual inspection of an overlay of adapted contours from MRI_{pre}, especially the CTV, on the PV scan was used to observe the presence of significant target motion that possibly occurred during the recontouring and recalculation phase. If target shifts were judged to be inappropriate the plan could be readjusted in two manners. If the difference in the CTV anatomy was characterized by a shift, then the MRI_{pre} was rigidly registered to the MRI_{pv}. The corresponding translations were used to virtually shift the isocenter and the leaf positions of the multi-leaf-collimator, effectuating a virtual couch correction. Furthermore, the beam weights of the adapted segments were optimized to mimic the dose distribution of the earlier generated IMRT dose distribution. This procedure is also referred to as the adapt-to-position (ATP) procedure and is fast (typically 1 min) [27]. However, if the anatomical changes between MRI_{pre} and MRI_{pv} could not be captured by a rigid translation, the contours were adapted to the new anatomy and the entire replanning procedure was restarted, including a new position verification scan and plan evaluation.

Meanwhile, an in-house made dose-check assessed the complexity of the treatment plan by comparing the total number of monitor units, number of segments, beam irregularity, and beam modulation to the pre-treatment plan. Furthermore, an independent 3D dose check was performed (Oncentra, Elekta AB, Stockholm, Sweden) [28]. This independent dose calculation was based on a collapsed cone dose algorithm, therefore no magnetic field effect was taken into account.

2.3.4. Treatment delivery

After approval of the plan and independent dose check, radiotherapy delivery was initiated using 7 MV FFF IMRT. Over the entire delivery time, interleaved sagittal and coronal cine-MRIs were acquired at 1.6 Hz to visually inspect unexpected patient motion during treatment. Immediately after treatment, a 3D T2 MRI scan (MRI_{post}) was acquired for offline assessment of intrafraction shifts. No gating strategies were used as this was not supported by the system.

2.3.5. Outcomes

In order to assess the feasibility and the patient tolerability of the treatment, the percentage of treatment fractions delivered on the MR-Linac and the percentage of patients who received all treatment fractions on the MR-Linac were determined. In addition, total on-table time per fraction, as well as the duration of all steps of the workflow were recorded and for each step the median duration was calculated over all delivered MR-Linac treatment fractions. The treatment was arbitrarily scored as feasible when the on-table time interval was ≤60 min for >75% of the treatment fractions and completion of >95% of fractions on the MR-Linac, reflecting patient tolerability. Wilcoxon signed rank testing was performed to compare the target coverage, heart dose and lung dose between adaptive MRgRT plans and the back-up plan. Data

were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY).

2.4. Intrafraction drifts

Intrafraction target drifts during treatment were assessed by registering the MRI_{post} to the MRI_{pv}. Here a rigid registration was performed with the Elastix toolbox using only the grey values within the CTV mask [29].

3. Results

Nine patients with esophageal cancer were scheduled to undergo chemoradiation on the MR-Linac between July 2019 and January 2021. Patient and tumor characteristics are summarized in Table 2. Most patients had a good WHO score and limited nodal disease. Eight patients were scheduled for 23 treatment fractions and one patient for 28 treatment fractions. Out of 212 scheduled treatment fractions, a total of 186 fractions were initiated on the MR-Linac, of which 183 were completed successfully. Two of the three unsuccessfully delivered treatment fractions were prematurely ended due to technical issues (at 89% and 63% of the delivered dose, respectively) and for one fraction it was decided to switch to the conventional back-up plan because of a cranial-caudal misalignment of the patient, which was only detected in the planning phase and inhibited the PTV expansion (Fig. 3). Twenty-six fractions were rescheduled on a conventional linac prior to start of the treatment fraction due to MR-Linac downtime (n = 10), logistical reasons (n = 3) or reasons of discomfort associated with the long on-table times (n = 13). For two patients (patient 5 and 6) >5% of fractions were rescheduled to a conventional system for reasons of discomfort (after fraction 16 and 18 respectively), to reduce the burden of the long on-table times. For one patient (patient 8) this was only for a single fraction when the patient was suffering from a tickling cough. Lastly, in four patients all treatment fractions were delivered on the MR-Linac as planned.

The median total time per fraction was 53 min (IQR 3 min), of which 19 min (36%) consisted of GTV, CTV and OAR delineation adjustments (Fig. 4, Suppl. Table 1). The median time between the start of the first MRI and the end of treatment was 49 min (IQR 10 min). The median

Table 2
Patient and tumor characteristics.

	Median (range)	N (%)
Age (yrs)	59 (51–73)	
WHO performance status		
	0	1 (11 %)
	1	7 (78 %)
	2	1 (11 %)
Histology		
	Adenocarcinoma	5 (56 %)
	Squamous cell carcinoma	4 (44 %)
Tumor location		
	Mid	2 (22 %)
	Distal	5 (56 %)
	Gastroesophageal junction	2 (22 %)
Clinical T stage		
	2	1 (11 %)
	3	7 (78 %)
	4b	1 (11 %)
Clinical N stage		
	0	6 (67 %)
	1	3 (33 %)

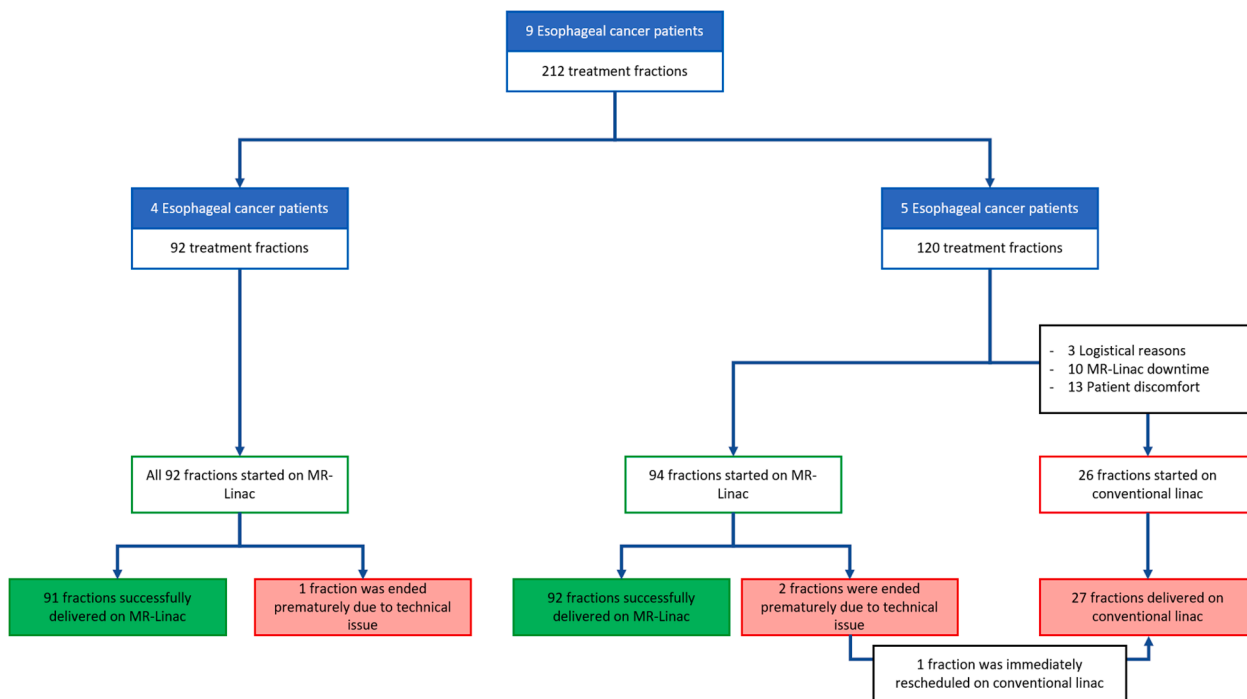


Fig. 3. Flowchart of planned and delivered fractions on MR-Linac for nine patients with esophageal cancer.

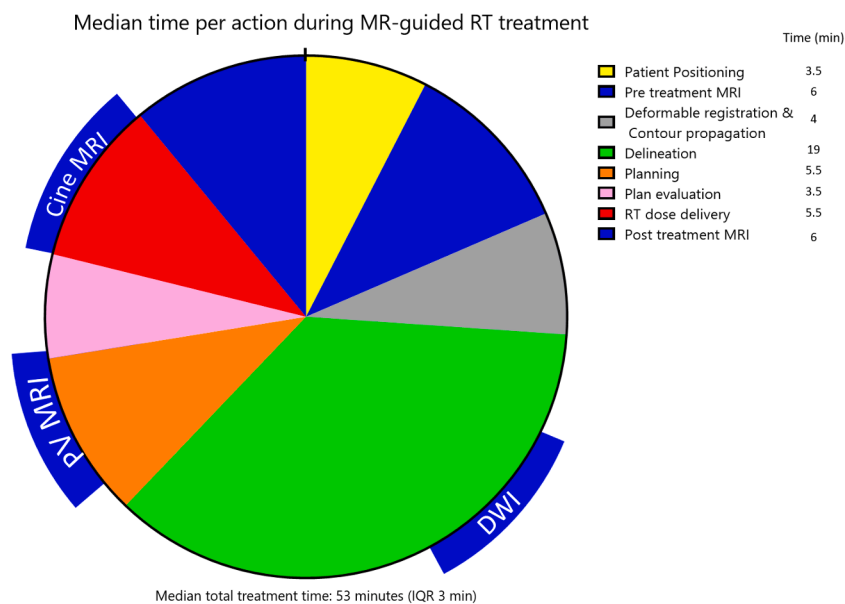


Fig. 4. Overview of timings per action of the online workflow of MR-guided radiotherapy for patients with esophageal cancer.

planning time was 5 min and could take up to 12 min when ATP (3×) or full replanning (5×) procedures were performed after the initial online planning.

Comparison between the daily adapted MR-Linac plans and the back-up plan showed similar PTV coverages ($p = 0.91$) (Fig. 5). In an incidental case (10 out of 186 fractions) PTV coverage was below <97%, however CTV coverage was >99% in all treatment fractions and therefore this was deemed acceptable. However, the dose to the OARs was significantly reduced with daily adaptive MRgRT. The average mean lung dose reduced by 26 % ($p < 0.001$) and the average mean heart dose by 12% ($p < 0.001$) compared to the VMAT back-up plan. Furthermore, a reduction in high dose to the heart (V40Gy), and dose to the lungs (V5Gy and V20Gy) was observed for most adapted plans in comparison

to the back-up plans ($p < 0.001$).

The median intrafraction motion during beam on time (between MRI_{pv} and MRI_{post}) was 0.9 mm (IQR 1.0 mm) (Fig. 6). Subanalysis revealed that the intrafraction motion was smallest in the left–right (average -0.2 mm, SD 1.0 mm) and anterior-posterior (average 0 mm, SD 0.6 mm) directions. Some fractions displayed larger motion in cranio-caudal direction (average -0.4 mm, SD 1.7 mm).

Furthermore, it was observed that tumor volumes were smaller in the second half of the treatment course, compared to first half, which also was reflected in the volume of the CTVs and PTVs (Fig. 7).

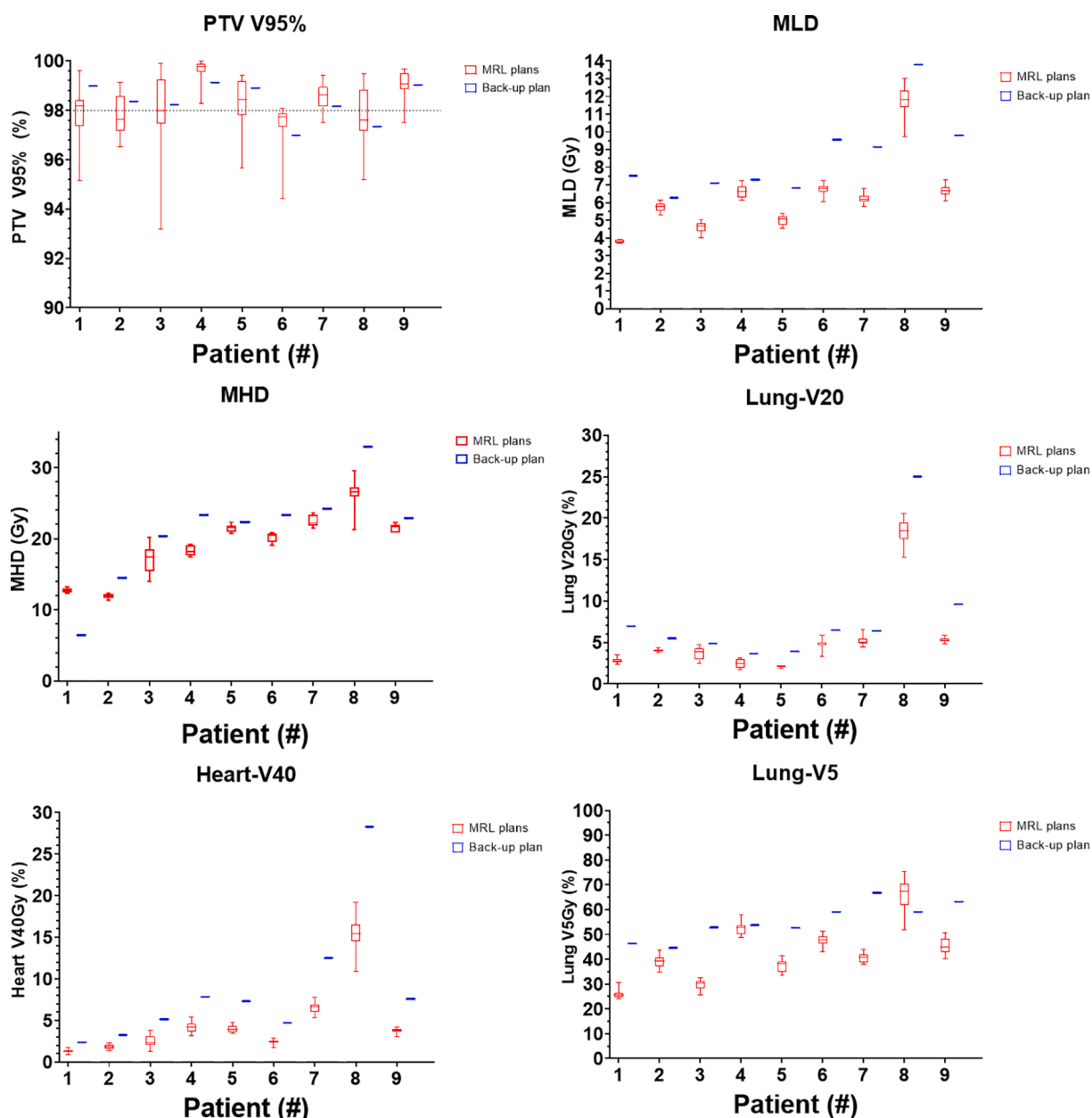


Fig. 5. Comparison of target coverage and dose to the organs at risk between daily adapted MR-Linac plans (red) and the back-up plan (blue). The boxes show the 25th to 75th percentiles, where the median is displayed by a line inside the box. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

To our knowledge, this is the first report on the clinical implementation of online MRgRT for patients with esophageal cancer, with an on-table re-imaging and replanning workflow. The presented workflow was feasible with a median time per fraction of 53 min (IQR 3 min). In addition, 2 out of 9 patients required treatment on a conventional linac for reasons of discomfort for more than 5% of fractions, therefore long-course fractionated chemoradiation on the 1.5T MR-Linac with the current workflow is moderately tolerable in selected patients with esophageal cancer. The use of daily plan adaptation allowed for an initial experience with smaller treatment margins, resulting in reduced dose to heart and lungs in comparison to the back-up treatment plan, while similar target coverage was achieved.

The presented workflow for the on-table adaptive MRgRT for esophageal cancer was associated with some complexities, which are

often unfamiliar to other treatment sites treated with online adaptive MRgRT. First, the size of the target volume for chemoradiation of esophageal cancers is large, which requires more extensive delineation of both target volume and adjacent organs at risk. Second, the online definition of the target volume involves recontouring of the GTV as well as a regeneration and adaptation of the CTV, instead of the generally applied GTV-to-PTV concept in stereotactic adaptive MRgRT. Therefore, the workflow for online adaptive MRgRT for esophageal cancer is more labor intensive and did require the onsite presence of a radiation oncologist. Third, the total treatment consisted of 23 or 28 fractions, which is at least uncommon, if not unprecedented, within the general framework of online adaptive MRgRT. These elements made the online adaptive MR-guided radiotherapy workflow for chemoradiation in esophageal cancer not only more demanding for patients and staff, but also required extensive logistic planning.

These tumor specific complexities and challenges require a well-

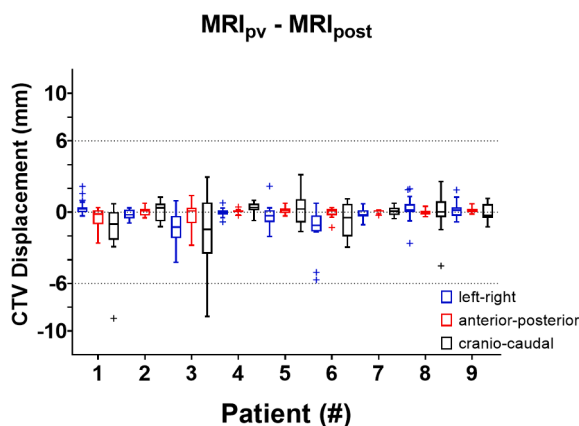


Fig. 6. Box plot of the intrafraction drift of the CTV during beam-on time, for left–right (blue), anterior–posterior (red) and cranio–caudal (black) directions for all patients. Negative values represent a shift in right, anterior and caudal direction. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

structured optimization and evaluation of the workflow, to facilitate timely and evidence-based implementation of MRgRT in esophageal cancer. According to the R-Ideal framework, we therefore conducted this phase 1b/2a study to provide the first experience of fractionated long-course chemoradiotherapy on the MR-Linac [23]. For this feasibility study we aimed to enroll 10 patients, however, due to the COVID pandemic only 9 patients could be enrolled within a reasonable time-frame. Nevertheless, still 186 treatment fractions on the MR-Linac were available for analyses.

For most patients the long on-table procedure was tolerated well. However, the long overall treatment time (23 or 28 fractions) in combination with concurrent chemotherapy induced toxicity during the course of treatment negatively influenced the patients' compliance. For 2 out of 9 patients the physical condition gradually worsened over time making the long on-table workflows difficult to tolerate. It was therefore decided to divert to a regular CBCT-guided workflow at the cost of an approximate 40% increase in mean lung dose for the remaining fractions (Fig. 5). The moderate tolerability emphasizes the need for shorter on-table times. In the current procedures a large proportion of the preparation time (19 min) was spent on contour adaptation and regeneration of the CTV. Daily redefinition was necessary as the anatomy of the GTV and CTV changed from fraction to fraction for example due to changes in stomach filling and also due to tumor shrinkage (Fig. 7) [10,30]. Enhanced deformable registration procedures together with improved contour propagation techniques could potentially fully automate the online target and OAR definition process and thereby drastically reducing the pre-beam process. This would then allow on-table workflows of 20 min–25 min which we believe would substantially increase patient compliance.

In this feasibility study an isotropic CTV-to-PTV margin of 6 mm was pragmatically and conservatively chosen, which already yielded a considerable dose reduction to the lungs and heart compared to our regular CBCT-guided RT plans while maintaining target coverage in line with findings of Nachbar et al. [31]. In only 3 out of 186 fractions an interfractional drift was observed that exceeded the 6-mm margin, most likely as result of a change in breathing pattern (Suppl. Fig. 1).

Further dose reduction could be obtained by prospectively adapting patients' individual margins based on the measured intrafraction motion. In a previous in-silico study we have demonstrated that an axial margin of 2 mm in combination with a 5-mm cranial caudal margin could well absorb the intrafraction motion in almost all patients [9]. This work substantiates the earlier findings, as we showed that the lateral and anterior-posterior components of the intrafraction motion were small and random of nature, allowing smaller margins to be

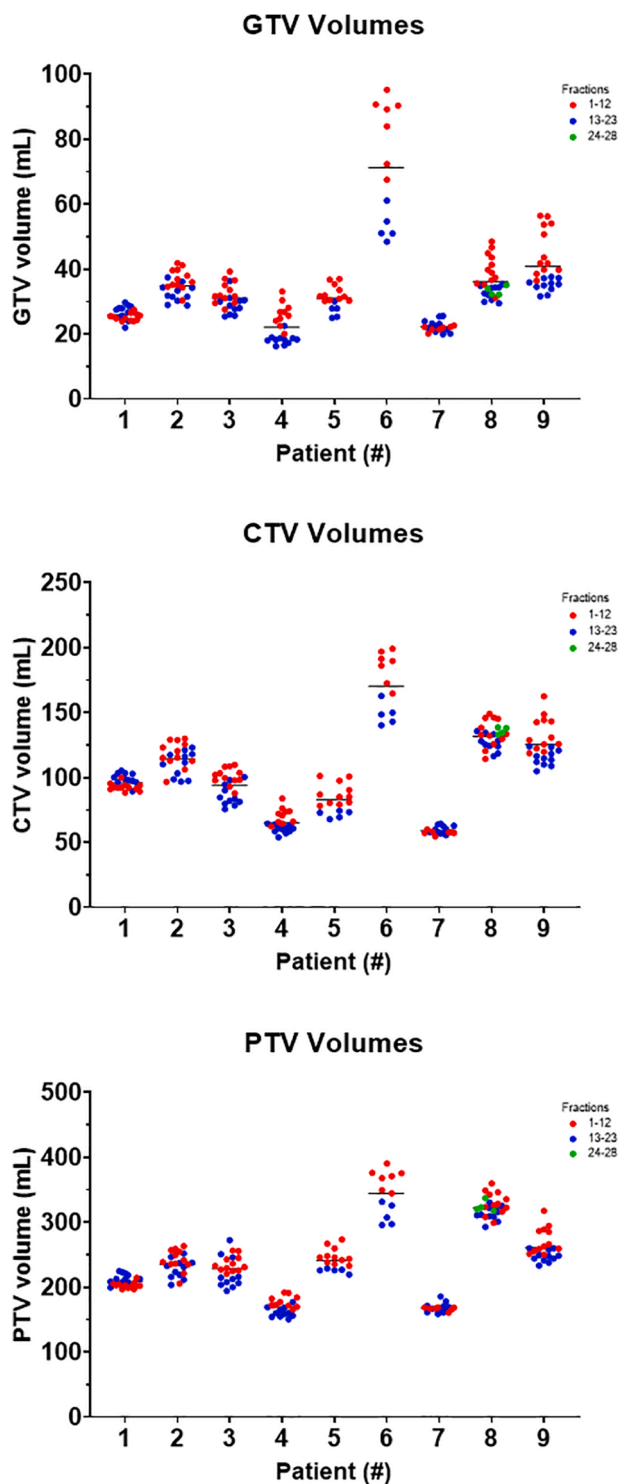


Fig. 7. Change in GTV, CTV and PTV volume over the course of treatment. Difference between first half of the fractions and final half of the fractions is visible for most patients.

applied in these directions, thereby further reducing the dose to lungs and heart.

On a different note, treatment on an MR-Linac opens up the possibility of functional MR imaging. In particular, for patients with esophageal cancer changes in the diffusion-weighted imaging (DWI) signal have been shown to correlate to treatment response [20–22,32]. MR-Linac treatments potentially allow for daily quantification of these signal changes over the entire treatment without an increase in

treatment time, as these 2-minute DWI scans can be acquired during the recontouring phase (Fig. 4). Although beyond the scope of this work, an example of the changes of the b500 signal over the course of treatment are depicted in Suppl. Fig. 2.

In conclusion, an online adaptive workflow with full replanning to the daily anatomy for esophageal cancer radiotherapy on a 1.5T MR-Linac results in a reduced dose to the organs-at-risk without compromising target coverage compared to our conventional CBCT treatment. However, due to the long treatment times MRgRT was only moderately feasible in a selected patient group. Future studies should be focused on further optimization and acceleration of the current workflow and on employing the full potential of daily MR-guided radiotherapy for the development of new treatment strategies, such as biology-driven dose escalation.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The Radiation Oncology Department of the University Medical Center Utrecht receives financial and technical support under research agreements as well sponsoring for travels and scientific symposia from: Elekta AB (Stockholm, Sweden), Philips NV (Best, The Netherlands).

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctro.2022.03.008>.

References

- Legendijk JJW, Raaymakers BW, Van den Berg CAT, Moerland MA, Philippens ME, van Vulpen M. MR guidance in radiotherapy. *Phys Med Biol* 2014;59(21):R349. <https://doi.org/10.1088/0031-9155/59/21/R349>.
- Mutic S, Dempsey JF. The ViewRay system: magnetic resonance-guided and controlled radiotherapy. *Semin Radiat Oncol* 2014;24(3):196–9. <https://doi.org/10.1016/j.semradonc.2014.02.008>.
- Keall PJ, Barton M, Crozier S. The Australian Magnetic Resonance Imaging-Linac Program. *Semin Radiat Oncol* 2014;24(3):203–6. <https://doi.org/10.1016/j.semradonc.2014.02.015>.
- Werensteijn-Honingh AM, Kroon PS, Winkel D, Aalbers EM, van Asselen B, Bol GH, et al. Feasibility of stereotactic radiotherapy using a 1.5 T MR-linac: Multi-fraction treatment of pelvic lymph node oligometastases. *Radiother Oncol* 2019;134:50–4. <https://doi.org/10.1016/j.radonc.2019.01.024>.
- Kontaxis C, Bol GH, Kerkmeijer LGW, Legendijk JJW, Raaymakers BW. Fast online replanning for interfraction rotation correction in prostate radiotherapy. *Med Phys* 2017;44(10):5034–42. <https://doi.org/10.1002/mp.12467>.
- Bohoudi O, Bruynzeel AME, Senan S, Cuijpers JP, Slotman BJ, Lagerwaard FJ, et al. Fast and robust online adaptive planning in stereotactic MR-guided adaptive radiation therapy (SMART) for pancreatic cancer. *Radiother Oncol* 2017;125(3):439–44. <https://doi.org/10.1016/j.radonc.2017.07.028>.
- Henke LE, Olsen JR, Contreras JA, Curcuro A, DeWees TA, Green OL, et al. Stereotactic MR-Guided Online Adaptive Radiation Therapy (SMART) for ultracentral thorax malignancies: results of a phase 1 trial. *Adv Radiat Oncol* 2019;4(1):201–9. <https://doi.org/10.1016/j.adro.2018.10.003>.
- Finazzi T, Palacios MA, Haasbeek CJA, Admiraal MA, Spoelstra FOB, Bruynzeel AME, et al. Stereotactic MR-guided adaptive radiation therapy for peripheral lung tumors. *Radiother Oncol* 2020;144:46–52. <https://doi.org/10.1016/j.radonc.2019.10.013>.
- Boekhoff M, Defize I, Borggreve A, van Hillegersberg R, Kotte A, Legendijk J, et al. An in-silico assessment of the dosimetric benefits of MR-guided radiotherapy for esophageal cancer patients. *Radiother Oncol* 2021;162:76–84. <https://doi.org/10.1016/j.radonc.2021.06.038>.
- Boekhoff MR, Defize IL, Borggreve AS, Takahashi N, van Lier ALHMW, Ruurda JP, et al. 3-Dimensional target coverage assessment for MRI guided esophageal cancer radiotherapy. *Radiother Oncol* 2020;147:1–7. <https://doi.org/10.1016/j.radonc.2020.03.007>.
- Jin P, Hulshof MCCM, van Wieringen N, Bel A, Alderliesten T. Interfractional variability of respiration-induced esophageal tumor motion quantified using fiducial markers and four-dimensional cone-beam computed tomography. *Radiother Oncol* 2017;124(1):147–54. <https://doi.org/10.1016/j.radonc.2017.05.015>.
- Hoffmann L, Poulsen PR, Ravkilde T, Bertholet J, Krulikava I, Helbo BL, et al. Setup strategies and uncertainties in esophageal radiotherapy based on detailed intra- and interfractional tumor motion mapping. *Radiother Oncol* 2019;136:161–8. <https://doi.org/10.1016/j.radonc.2019.04.014>.
- Voncken FEM, Nakhaee S, Stam B, Wiersema L, Vollenbrock SE, van Dieren JM, et al. Quantification of esophageal tumor motion and investigation of different image-guided correction strategies. *Pract Radiat Oncol* 2020;10(2):84–92. <https://doi.org/10.1016/j.prro.2019.11.012>.
- Boekhoff MR, Defize IL, Borggreve AS, van Hillegersberg R, Kotte ANTJ, Legendijk JJW, et al. CTV-to-PTV margin assessment for esophageal cancer radiotherapy based on an accumulated dose analysis. *Radiother Oncol* 2021;161:16–22. <https://doi.org/10.1016/j.radonc.2021.05.005>.
- Winkel D, Bol GH, Werensteijn-Honingh AM, Intven MPW, Eppinga WSC, Hes J, et al. Target coverage and dose criteria based evaluation of the first clinical 1.5T MR-linac SBRT treatments of lymph node oligometastases compared with conventional CBCT-linac treatment. *Radiother Oncol* 2020;146:118–25. <https://doi.org/10.1016/j.radonc.2020.02.011>.
- Jin P, Hulshof MCCM, de Jong R, van Hoof JE, Bel A, Alderliesten T. Quantification of respiration-induced esophageal tumor motion using fiducial markers and four-dimensional computed tomography. *Radiother Oncol* 2016;118(3):492–7. <https://doi.org/10.1016/j.radonc.2016.01.005>.
- Lever FM, Lips IM, Crijns SPM, et al. Quantification of esophageal tumor motion on cine-magnetic resonance imaging. *Int J Radiat Oncol Biol Phys*. 2013. 10.1016/j.ijrobp.2013.10.036.
- Heethuis SE, Borggreve AS, Goense L, van Rossum PSN, Mook S, van Hillegersberg R, et al. Quantification of variations in intra-fraction motion of esophageal tumors over the course of neoadjuvant chemoradiotherapy based on cine-MRI. *Phys Med Biol* 2018;63(14):145019.
- Hunt A, Hansen VN, Oelfke U, Nil S, Hafeez S. Adaptive radiotherapy enabled by MRI guidance. *Clin Oncol* 2018;30(11):711–9. <https://doi.org/10.1016/j.clon.2018.08.001>.
- van Rossum PSN, van Lier ALHMW, van Vulpen M, Reerink O, Legendijk JJW, Lin SH, et al. Diffusion-weighted magnetic resonance imaging for the prediction of pathologic response to neoadjuvant chemoradiotherapy in esophageal cancer. *Radiother Oncol* 2015;115(2):163–70. <https://doi.org/10.1016/j.radonc.2015.04.027>.
- Fang P, Musall BC, Son JB, Moreno AC, Hobbs BP, Carter BW, et al. Multimodal Imaging of Pathologic Response to Chemoradiation in Esophageal Cancer. *Int J Radiat Oncol* 2018;102(4):996–1001. <https://doi.org/10.1016/j.ijrobp.2018.02.029>.
- Borggreve AS, Heethuis SE, Boekhoff MR, Goense L, van Rossum PSN, Brosens LAA, et al. Optimal timing for prediction of pathologic complete response to neoadjuvant chemoradiotherapy with diffusion-weighted MRI in patients with esophageal cancer. *Eur Radiol* 2020;30(4):1896–907. <https://doi.org/10.1007/s00330-019-06513-0>.
- Verkooijen HM, Kerkmeijer LGW, Fuller CD, Huddart R, Favre-Finn C, Verheij M, et al. R-IDEAL: A framework for systematic clinical evaluation of technical innovations in radiation oncology. *Front Oncol* 2017;7. <https://doi.org/10.3389/fonc.2017.00059>.
- de Mol van Otterloo SR, Christodouleas JP, Blezer ELA, Akhlat H, Brown K, Choudhury A, et al. The MOMENTUM study: an international registry for the evidence-based introduction of MR-guided adaptive therapy. *Front Oncol* 2020;10. <https://doi.org/10.3389/fonc.2020.01328>.
- Stemkens B, Paulson ES, Tijssen RHN. Nuts and bolts of 4D-MRI for radiotherapy. *Phys Med Biol* 2018;63(21):21TR01. <https://doi.org/10.1088/1361-6560/aae56d>.
- 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. <https://doi.org/10.1016/j.ctro.2019.04.001>.
- Winkel D, Bol GH, Werensteijn-Honingh AM, Kiekebosch IH, van Asselen B, Intven MPW, et al. Evaluation of plan adaptation strategies for stereotactic radiotherapy of lymph node oligometastases using online magnetic resonance image guidance. *Phys Imaging Radiat Oncol* 2019;9:58–64.
- Hackett S, van Asselen B, Feist G, et al. SU-F-J-148: A Collapsed Cone Algorithm Can Be Used for Quality Assurance for Monaco Treatment Plans for the MR-Linac. *Med Phys*. 2016;43(6Part11):3441–3441. 10.1118/1.4956056.
- Klein S, Staring M, Murphy K, Viergever MA, Pluim J. elastix: A toolbox for intensity-based medical image registration. *IEEE Trans Med Imaging* 2010;29(1):196–205. <https://doi.org/10.1109/TMI.2009.2035616>.
- Defize IL, Boekhoff MR, Borggreve AS, van Lier ALHMW, Takahashi N, Haj Mohammad N, et al. Tumor volume regression during neoadjuvant chemoradiotherapy for esophageal cancer: a prospective study with weekly MRI. *Acta Oncol (Madr)* 2020;59(7):753–9. <https://doi.org/10.1080/0284186X.2020.1759819>.
- Nachbar M, Mönnich D, Kalwa P, Zips D, Thorwarth D, Gani C. Comparison of treatment plans for a high-field MRI-linac and a conventional linac for esophageal cancer. *Strahlentherapie und Onkol* 2019;195(4):327–34. <https://doi.org/10.1007/s00066-018-1386-z>.
- Heethuis SE, Goense L, van Rossum PSN, et al. DW-MRI and DCE-MRI are of complementary value in predicting pathologic response to neoadjuvant chemoradiotherapy for esophageal cancer. *Acta Oncol (Madr)* 2018:1–8. <https://doi.org/10.1080/0284186X.2018.1473637>.