Radiotherapy and Oncology 161 (2021) 16–22

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

CTV-to-PTV margin assessment for esophageal cancer radiotherapy based on an accumulated dose analysis

M.R. Boekhoff [a,*], I.L. Defize [a,b], A.S. Borggreve [a,b], R. van Hillegersberg [b], A.N.T.J. Kotte [a], J.J.W. Lagendijk [a], A.L.H.M.W. van Lier [a], J.P. Ruurda [b], N. Takahashi [a,c], S. Mook [a,1], G.J. Meijer [a,1,*]

[a] Department of Radiation Oncology; [b] Department of Surgery, University Medical Center Utrecht, Utrecht University, the Netherlands; [c] Department of Radiation Oncology, Tohoku University Graduate School of Medicine, Sendai, Japan

ARTICLE INFO

Article history:
Received 27 November 2020
Received in revised form 5 May 2021
Accepted 6 May 2021
Available online 14 May 2021

Keywords:
Esophageal cancer
Adaptive radiotherapy
Interfractional motion
Treatment margin
Deformable image registration
MRI guided radiation therapy

ABSTRACT

Purpose: This study aimed to assess the smallest clinical target volume (CTV) to planned target volume (PTV) margins for esophageal cancer radiotherapy using daily online registration to the bony anatomy that yield full dosimetric coverage over the course of treatment.

Methods: 29 esophageal cancer patients underwent six T2-weighted MRI scans at weekly intervals. An online bone-match image-guided radiotherapy treatment of five fractions was simulated for each patient. Multiple conformal treatment plans with increasing margins around the CTV were created for each patient. Then, the dose was warped to obtain an accumulated dose per simulated fraction. Full target coverage by 95% of the prescribed dose was assessed as a function of margin expansion in six directions. If target coverage in a single direction was accomplished, then the respective margin remained fixed for the subsequent dose plans. Margins in uncovered directions were increased in a new dose plan until full target coverage was achieved.

Results: The smallest set of CTV-to-PTV margins that yielded full dosimetric CTV coverage was 8 mm in posterior and right direction, 9 mm in anterior and cranial direction and 10 mm in left and caudal direction for 27 out of 29 patients. In two patients the curvature of the esophagus considerably changed between fractions, which required a 17 and 23 mm margin in right direction.

Conclusion: Accumulated dose analysis revealed that CTV-to-PTV treatment margins of 8, 9 and 10 mm in posterior & right, anterior & cranial and left & caudal direction, respectively, are sufficient to account for interfraction tumor variations over the course of treatment when applying a daily online bone match. However, two patients with extreme esophageal interfraction motion were insufficiently covered with these margins and were identified as patients requiring replanning to achieve full target coverage.

© 2021 The Author(s). Published by Elsevier B.V. Radiotherapy and Oncology 161 (2021) 16–22 This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Esophageal cancer is the eight most prevalent cancer worldwide. Multimodal treatment strategies comprising neoadjuvant chemoradiotherapy plus surgery or definitive chemoradiotherapy have improved survival of patients with locally advanced esophageal cancer [1–3]. Irradiation of esophageal cancer often comes with large clinical target volumes (CTVs) with complex shapes to secure optimal dose delivery to all tumor cells. Image-guided radiation therapy (IGRT) allows rigid alignment of the bony anatomy on kilo-/megavoltage cone-beam CT (CBCT) or 2D fluoroscopy images with the 3-dimensional (3D) planning computed tomography before radiation dose delivery [4–8]. However, considerable residual geometrical uncertainties due to interfraction tumor position variation and shape changes require the use of treatment margins to establish sufficient coverage of the CTV over the course of treatment.

Many studies have investigated these geometrical uncertainties in order to quantify the associated CTV-to-Planning Target Volume (PTV) margins with the use of repetitive CT, CBCT or Magnetic Resonance Imaging (MRI) over the course of treatment [6,7,9–16]. Of particular interest are the recent studies that reported on the inter- and intrafraction displacement on CBCTs of fiducial markers that were endoscopically placed at some anchor points in the tumor [13–15]. Here, the marker movements were used as a surrogate for the gross tumor volume (GTV) and CTV displacements as generally the 3D anatomy of the CTV cannot be adequately segmented on the CBCT. Based on these displacements, the well-known margin recipe of van Herk et al. was used to derive margins for various set-up strategies [17]. For the most commonly

* Corresponding authors at: Department of Radiation Oncology, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands.
E-mail addresses: M.R.Boekhoff@umcutrecht.nl (M.R. Boekhoff), G.J.Meijer@umcutrecht.nl (G.J. Meijer).
[1] Both authors contributed equally to the manuscript.

https://doi.org/10.1016/j.radonc.2021.05.005
0167-8140/© 2021 The Author(s). Published by Elsevier B.V.
This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

employed set-up strategy, i.e. daily alignment to the bony anatomy (predominantly vertebrae), these studies concluded that large margins are required.

Although these studies reported sound and reproducible data on the interfraction motion of the markers, the ensuing CTV-to-PTV margins using the 'van Herk'-recipe could be biased for a number of reasons. First, the margin recipe assumes rigid movements of the entire CTV, whereas the CTV interfraction variation is often characterized by shape changes. Second, the markers were sampled over the tumor (GTV) and not over the CTV which may lead to different motion characteristics. Thirdly, the margin recipe assumes perfect conformity at every surface element of the PTV surface often in conjunction with steep dose gradients outside the PTV.

Aim of the current report was to overcome these aforementioned limitations by doing a full dosimetric assessment in a cohort of esophageal cancer patients and to assess the smallest CTV-to-PTV margins that yield full target coverage in a virtual daily online bone match image-guided treatment series using five weekly acquired MRI scans as treatment samples. By doing so, not only the dosimetric impact of day-to-day translations of the tumor itself is accounted for, but also the dosimetric effects of all morphologic changes (e.g tumor regression) over the course of treatment are incorporated.

Materials & methods

Patient inclusion

A total of thirty-two patients with histopathologically confirmed esophageal cancer who were scheduled to undergo neoadjuvant chemoradiotherapy according to the CROSS regimen (23 fractions of 1.8 Gy with concurrent carboplatin/paclitaxel [3]) were included in this single-center prospective cohort study between December 2015 and April 2018. Exclusion criteria for enrollment in the study were age < 18 years, previous thoracic surgery or thoracic radiotherapy, and contraindications for MRI. The study was approved by the institutional review board of the University Medical Center Utrecht (protocol ID 15–340). All participants provided written informed consent. In our previous paper, we reported on the isotropic margins required for geometric target coverage for a bone match setup and a rigid tumor registration setup for individual fractions for these patients [16]. In the current work, we assessed the treatment margins in all directions which yielded sufficient target coverage for a whole treatment, based on a full accumulated dosimetric analysis.

Image acquisition

Each patient underwent six times T2-weighted MRI scans, one prior to treatment and five times during neoadjuvant chemoradiotherapy at weekly intervals. Images were acquired on a 1.5 T Philips Ingenia (Best, the Netherlands), using anterior/posterior (28 channel) receive coils. Patients were positioned in supine position with both arms next to the body for increased patient comfort during MRI scanning, in contrary to positioning during a conventional treatment session, when arms are positioned above the head.

Respiratory-triggered transversal and sagittal anatomical T2-weighted scans (T2W) were acquired with a multi-slice turbo spin echo sequence in the first 19 patients (TR/TE = 1604/100 ms and 1431/100 ms, resolution = 0.67 × 0.67 × 6.48 mm^3 and 4.4 × 0.7 × 0.7 mm^3, for transversal and sagittal scans, respectively). From the 20th patient onwards, respiratory-triggered sagittal and transversal T2W MultiVane XD (MVXD) scans were acquired instead of the previously mentioned scans, as these scans demonstrated improved image quality (TR/TE = 2039/100 ms and 2243/100 ms, resolution = 0.62 × 0.62 × 3.0 mm^3 and 3.0 × 0.63 × 0.63 mm^3, for transversal and sagittal scans, respectively).

Delineations

A certified radiation oncologist (N.T.) delineated the GTV on each MRI which was subsequently reviewed by a radiation oncologist specialized in upper gastrointestinal malignancies (S.M.). Any disagreements were solved through a consensus discussion. Next, the CTV was created using a margin of 0.5 cm around the GTV in the left, right, anterior and posterior directions (excluding the heart, large vessels, trachea, bronchial tree and lungs), 3 cm in cranial direction and 2 or 3 cm caudally (2 cm in case of tumor extension in the stomach).

Treatment simulation

An online bone-match IGRT treatment of five fractions was simulated for each patient. The first MRI scan was used as a reference scan and the five follow-up scans were used as individual samples of the patient's anatomy over the course of treatment. The reference MRI was rigidly aligned, based on a bone match, to the clinical planning CT, which was acquired on the same day as the reference MRI scan. Then, the CTV of the reference MRI was projected on the structure set of the planning CT, which consisted of organs at risk. These steps were necessary so that density information of the CT could be used in subsequent treatment planning. For every patient, single full arc Volumetric-Modulated Arc (VMAT) plans with varying CTV-to-PTV margins were generated using the autoplanning module of the Pinnacle 16.2 treatment planning system, (Koninklijke Philips NV, Eindhoven, The Netherlands). The reason for using the Pinnacle system instead of the Monaco 5.40.01 treatment planning system (Elekta AB, Stockholm, Sweden) that we clinically use, was that the advanced scripting and autoplanning capabilities required for this study, were not yet available in the Monaco system at the time of this research. The target dose to the PTV was set to 41.4 Gy at 23 fractions (1.8 Gy/fraction), whereas the optimization goals in the autoplanning toolkit were set to a mean lung dose < 4.2 Gy (high priority) and a mean heart dose < 10 Gy (medium priority). Additional auxiliary structures were automatically generated to achieve a high 3D-conformity of the 95% isodose surface with respect to the PTV, as loose 95% isodose surfaces could yield an underestimation of the final margins in this study.

For each plan, an online IGRT treatment was simulated by rigidly projecting the planned dose distributions on the follow-up scans by a bone-match registration (Fig. 1). As patient positioning and alignment on the MRI scanner was less thoroughly performed (without laser guidance) than typically at the treatment unit, translational registrations based on the bony anatomy between the follow-up MRI and reference MRI could not directly be used for the treatment simulation, since this would result in an overestimated residual rotation. Therefore a multi-step registration was performed to simulate patient positioning on a conventional treatment system. First, to adjust for the overestimated residual rotation, follow-up MRI scans were rigidly aligned (translations and rotations allowed) to the reference MRI scan based on grey values in a box around the vertebrae, located over the length of the tumor (typically four or five vertebrae), using the Elastix toolbox [18]. Then, a rotation correction was added to mimic a realistic rotational misalignment. The rotation correction was obtained from the rotational error of the clinical treatment fraction of the corresponding day of MRI acquisition measured with X-ray volume imaging software (Elekta AB, Stockholm, Sweden).

After the rigid alignment and rotation correction we assumed that the patient's anatomy was representative of positioning on a conventional treatment system. Next, each projected dose distri-

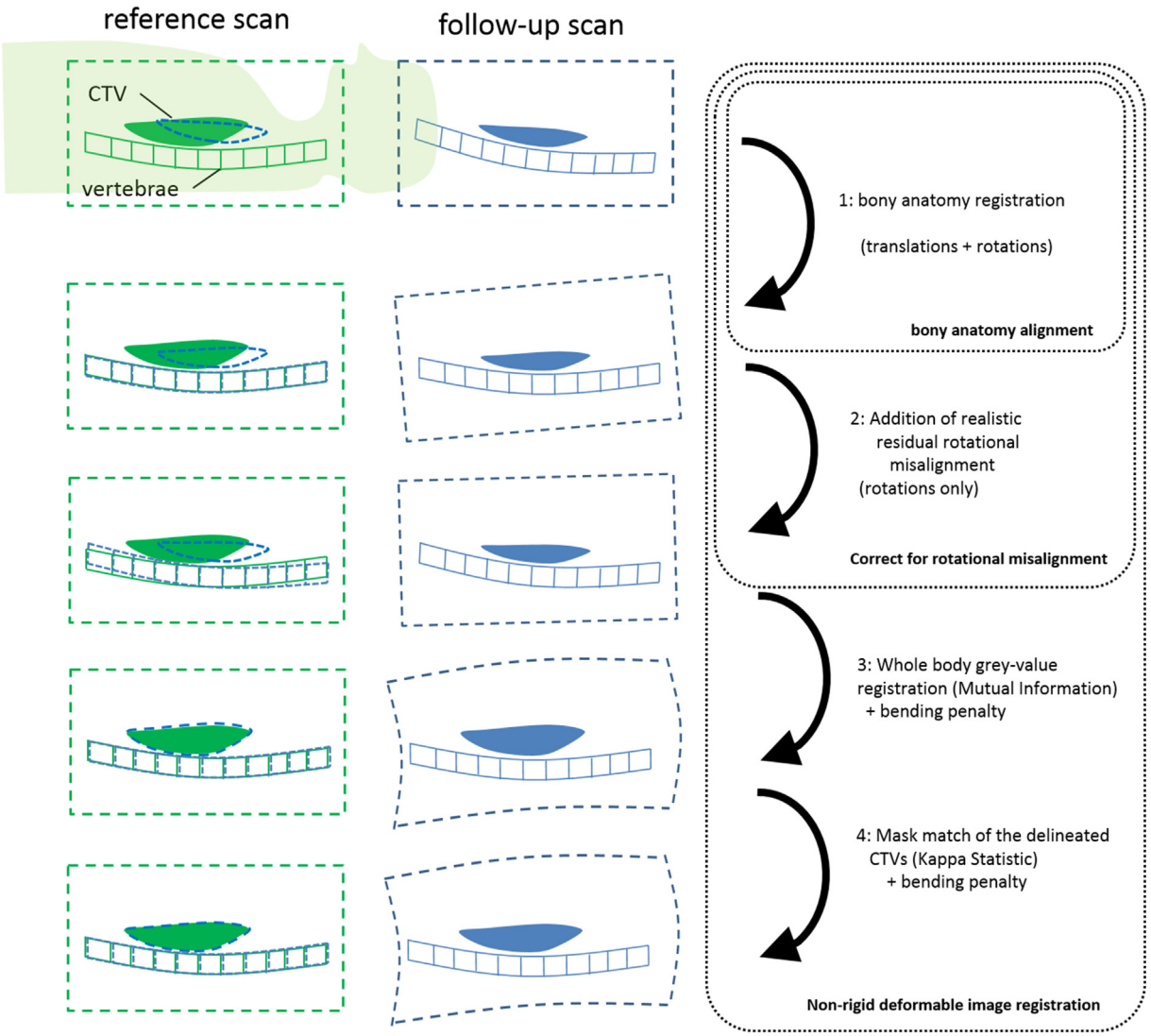

Fig. 1. Schematic illustration of the registration steps applied to simulate an online IGRT set-up procedure based on bony anatomy alignment (Step 1 and 2) followed by a two-step non-rigid deformable image registration used to accurately register the voxels from the follow-up scan to the reference scan in order to obtain an accumulated dose. First, a whole body grey-value registration (mutual information metric) was applied in combination with a bending penalty metric (Step 3). The second step consisted of a mask match of the delineated CTVs were the previous step was used as initial transform (Step 4). The deformation vector field is the combination of both non-rigid deformable image registration steps (Steps 3 + 4). The blue panels depict the follow-up scan after each registration step. In the green panels a sagittal view of the CTV and vertebrae of the reference scan is depicted. The dashed blue structure in the reference scan refers to the propagated CTV from the follow-up scan.

bution on the follow-up scans was non-rigidly warped to the reference scan. For this, a two-step non-rigid B-spline image registration from the Elastix toolbox was used to accurately register the voxels from the follow-up scan to the reference scan for both the transversal and sagittal scans. First, a whole body grey-value registration (mutual information metric) was applied in combination with a bending penalty metric. To ensure correct mapping of the CTV a second registration step was performed. The second registration step consisted of a mask match of the delineated CTVs (kappa statistic metric), which again was also combined with a bending penalty metric.[i]

Subsequently, the deformation vector field (DVF) was applied to the projected dose to obtain the 'delivered' dose per fraction (Fig. 2). All warped dose distributions of the follow-up scans were summed and projected on the reference scan to obtain a surrogate of the total accumulated/delivered dose distribution for each patient.

The accuracy of the deformable registration was determined by calculating the dice coefficient between a warped mask of the follow-up CTV and the mask of the reference CTV.

Target coverage assessment

For every voxel of the reference CTV that was not covered by the total accumulated dose with 95% of the prescription dose, the shortest vector to the 95% prescription dose surface was calculated (Fig. 2E). Vector analysis was performed to assess the coverage in all 6 cardinal directions. A direction was marked as covered if no voxels in this direction were outside the 95% accumulated dose. Coverage of the anterior-posterior (AP) and left–right (LR) direction was assessed with deformation vector fields following registration on the transversal scan, as resolution in these directions is the highest in the transversal plane. Similarly, coverage of the cranial

[i] The parameter file can be found on the Elastix website: https://elastix.lumc.nl/modelzoo/par0062/

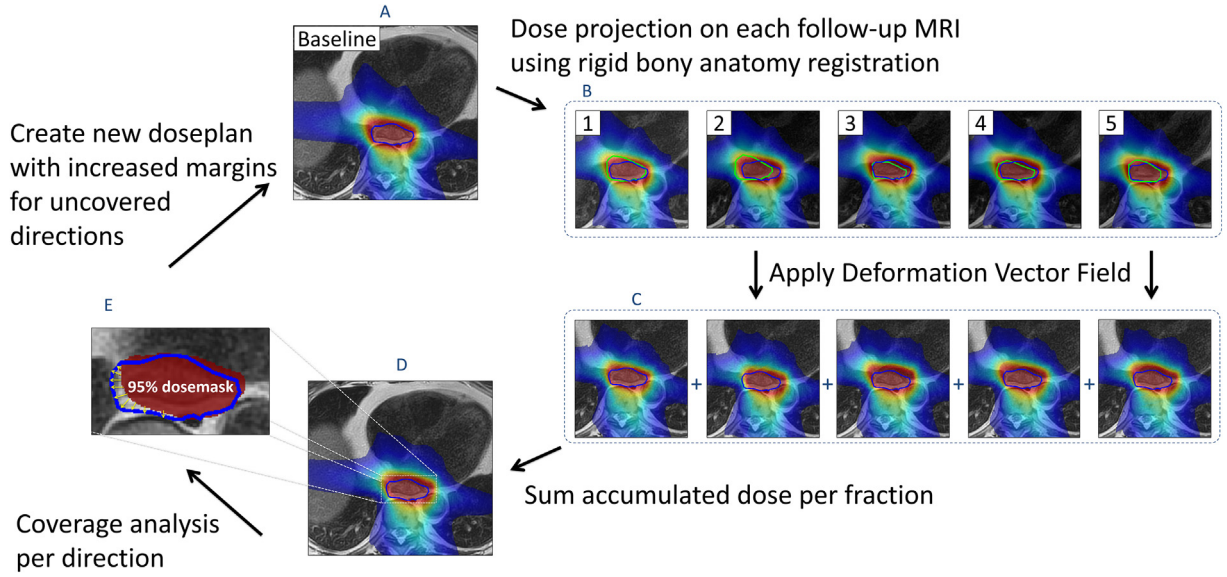

Fig. 2. Schematic overview of dose warp and coverage analysis of a simulated treatment. First, a dose plan with 0 mm CTV-to-PTV margins in all directions was created (A) based on the delineated CTV (blue delineations) in the baseline scan. Then, the dose was rigidly projected on the follow-up fractions (B). Here, the daily CTVs are shown by the green delineations. The deformation vector field, obtained from deformable image registration, was applied on the projected doses and resulted in a warped dose per fraction (C). These warped doses were summed to obtain the total accumulated dose over the course of treatment for a treatment plan with 0 mm margins (D). Coverage analysis of the CTV by 95% of the prescribed dose indicated whether a direction was required an additional margin or not (E). Given an uncovered direction, the CTV-to-PTV margin in that direction was increased with + 1 mm and steps A-E are repeated with a new dose plan.

caudal (CC) direction was assessed with the DVF following from sagittal registration.

PTV margin determination

In the search for the smallest set of anisotropic CTV-to-PTV margins that yield full target coverage for all patients an iterative loop was initiated. Starting point was the dosimetric assessment of the accumulated dose of 0-mm plans where the PTV coincides with the CTV for all patients. For each direction the fraction of patients who obtained full coverage in this direction was assessed. In the next iteration the margin for each of the six main directions was increased with 1 millimeter if target coverage was not achieved in the direction in question for at least one patient. If target coverage in a single direction was accomplished for all patients, then the respective margin remained fixed for the subsequent dose plans.

Results

A total of 32 patients with newly diagnosed esophageal cancer were enrolled in this prospective study. Two patients were excluded based on a limited field of view in the cranial caudal direction on the reference scan and one because of withdrawal from study participation. Of the remaining 29 patients, three patients requested cancellation of a follow-up scan and 5 transversal follow-up scans were excluded based on a limited field of view in the cranial-caudal direction and 11 sagittal follow-up scans were excluded based on a limited field of view in the left–right direction. The final study population consisted of 29 patients who underwent a total of 140 transversal and 134 sagittal follow-up scans. Baseline patient and tumor characteristics are presented in Table 1.

For all treatment plans the autoplanning module yielded very conformal dose distributions. The volume of the 95% isodose surfaces was on average only 14% larger than the PTV volume, which corresponded to an average distance of 1.5 mm between the PTV surface and the 95% isodose surface. This high conformity could generally be achieved without sacrificing any PTV coverage. The median V95 was 99.2% and the 25% and 75% interquartile ranges were 98.5 and 99.8, respectively.

Table 1
Clinical characteristics of the study population.

Characteristics		Full cohort (n = 32) *n*	(%)
Age at diagnosis (years), mean (range)		65 (46–77)	
Sex			
	Male	28	87.5
	Female	4	12.5
Tumor Location			
	Proximal esophagus	0	0
	Middle esophagus	2	6
	Distal esophagus	27	84
	Gastroesophageal junction (GEJ)	3	10
Clinical T stage*			
	cT2	2	6
	cT3	30	94
Clinical N stage*			
	cN0	9	28
	cN1	17	53
	cN2	5	16
	cN3	1	3
Histology			
	Squamous cell carcinoma	9	28
	Adenocarcinoma	22	69
	Other	1	3

*Clinical and histopathologic T- and N- stage are based on UICC TNM 7th edition.

The average dice coefficient of the warped CTVs was 0.91 ± 0.02 and 0.92 ± 0.02 for transversal and sagittal registrations, respectively. Further visual inspection of all registered images revealed no abnormalities in surrounding tissue (i.e. deformed vertebrae or aorta).

As anticipated, at a 0-mm CTV-to-PTV margin underdosing of the CTV occurred in all directions for all patients. The only exception here was patient 2 where the minimum dose of all caudal CTV voxels remained above the 95% prescription dose threshold after the dose warping procedure.

Increase of the CTV-to-PTV margin resulted in an increase of target coverage and an isotropic margin of 5 mm yielded full dosimetric CTV coverage for 31% of the patients, whereas an isotropic 8-mm margin resulted in full coverage for 83% of the patients (Fig. 3). In Supplementary Table 1 the anisotropic margins that would yield full dosimetric CTV coverage are listed for each individual patient.

The smallest set of CTV-to-PTV margins that yielded full dosimetric CTV coverage in 27 out of 29 patients was 8 mm in the posterior and right direction, 9 mm in the anterior and cranial direction and 10 mm in the left and caudal direction (Fig. 4 & Suppl. Fig. 1).

In two patients (patients 12 and 15) the curvature of the esophagus considerably changed over the course of treatment. In both patients the esophageal tract at the level of the heart was located left from the midline at the reference scan, however after two weeks of treatment this tract moved entirely over the midline in the right direction. In patient 15 this change was permanent, whereas in patient 12 the tract moved back to its original position in week 4 (Suppl. Fig. 2). Subanalysis revealed that for patient 12 a margin of 17 mm in the right direction was required to assure adequate CTV coverage whereas for patient 15 an even larger margin of 23 mm was needed.

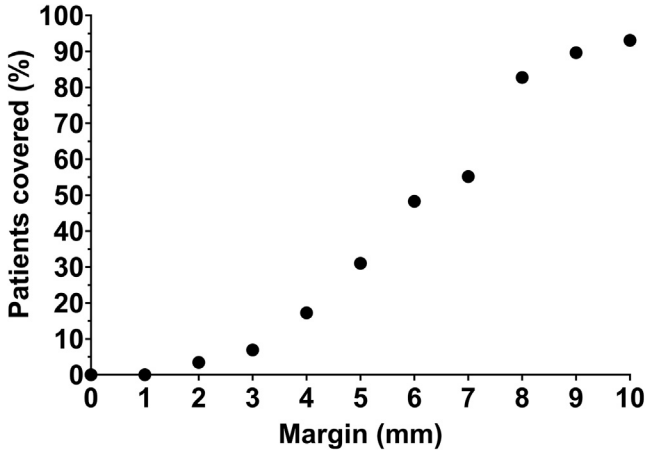

Fig. 3. Percentage of patients where the CTV is fully covered in all directions on all fractions when an isotropic margin around the CTV is used.

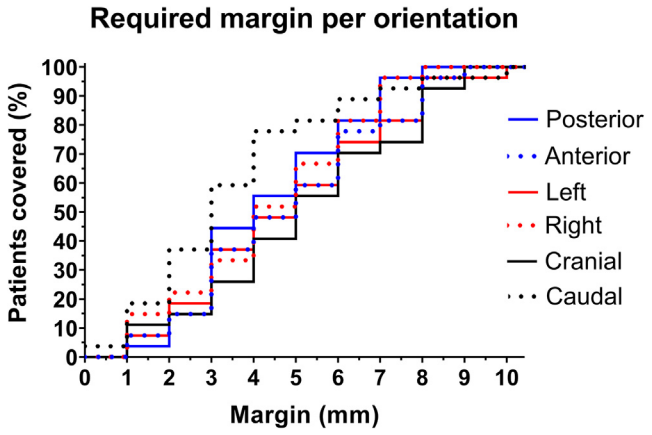

Fig. 4. CTV covered per CTV-to-PTV margin for each direction. Posterior and right direction require a margin of 8 mm, cranial and anterior direction need a 9 mm margin and left and caudal direction requires a margin of 10 mm for full CTV coverage in 27 out of 29 patients.

Discussion

In this study the dosimetric target coverage was assessed in a cohort of esophageal cancer patients where each patient was virtually treated with a 5-fraction radiotherapy regimen using an online bone match. Accumulated dose analysis via dose warping after MR image registration was used to establish adequate CTV-to-PTV margins.

Two patients revealed a very mobile esophagus where part of the esophageal tract crossed the midline of the patient during treatment at the level of the heart, whereas the cardia remained in place. This was quite remarkable as the left–right movement was generally modest in the remaining patients. The movements in these patients were quite substantial and only a local PTV margin in the right direction of 23 mm could dosimetrically absorb this deformation when aligning these patients to the bony anatomy. This was clinically of concern as these shape changes, although very evident on MRI, remained unnoticed during our clinical CBCT procedures (see Suppl. Fig. 2) and only fiducial markers might have helped us identifying these patients.

If we consider the two patients with the extreme mobile esophagus as outliers then our analysis revealed that CTV-to-PTV margins of 8 mm in posterior and right, 9 mm in anterior and cranial and 10 mm in left and caudal direction are required to ensure adequate target coverage in 27 out of 29 patients. Smallest margins were observed in the posterior and right direction. This could partly be explained by the shape of the CTV and its anatomical orientation with respect to the vertebrae. In most patients, large parts of the CTV posteriorly lie adjacent to the vertebrae and therefore motion in this direction is physically hampered. Largest margins were needed in the left and caudal direction, which was related to typical caudal curvature of the esophagus towards the stomach and variations in stomach filling in this patient cohort.

Previously published studies on CTV-to-PTV margins for esophageal cancer - based on the relative motion statistics of implanted gold markers in combination with the 'van Herk'-recipe - reported comparable anistropic margins for the three main directions. Substantial marker position variability with respect to the bony anatomy has been reported by Voncken et al. yielding PTV margins of 10, 13 and 7 mm in LR, CC and AP direction, respectively [15]. Similarly, Jin et al. reported that a margin of 9 mm in LR direction, 12 mm in CC direction and 7 mm in AP direction should provide sufficient target coverage [13]. Hoffmann et al. reported similar anisotropic margins of 9, 11 and 7 mm in LR, CC and AP directions, respectively [14]. Our findings are to a large extent in agreement with these previously reported margins (Table 2). However, we found smaller CC margins and slightly larger AP margins. A possible explanation for the smaller CC margins could be that the CC motion of the markers (placed in or close to the tumor) could largely be compensated for by AP and LR margins of surrounding CTV tissue, which typically extends in the CC direction due to the shape of the esophagus.

In contrast to the marker studies, we were able to independently quantify CTV-to-PTV margins required to compensate for interfraction motion in all 6 main directions by sampling the full CTV surface. As a result, we found larger margins in left, caudal and anterior direction, which are mainly associated with the changes in stomach volume. These variations would remain unseen in marker studies which only give point-based motion measurements. It should be noted that in our patient cohort 30 of 32 patients had a distal esophageal tumor or a tumor at the gastroesophageal junction and as a consequence the CTV includes the proximal stomach in most patients. This means that potentially smaller margins could be applied for patients with proximal

Table 2
Comparison of CTV-to-PTV margins as assessed in our study with other publications.

	Patients	Left (mm)	Right (mm)	Cranial (mm)	Caudal (mm)	Posterior (mm)	Anterior (mm)
This work	27 out of 29	10	8	9	10	8	9
Jin et al. [13]	24	9	9	12	12	7	7
Hoffmann et al. [14]	21	9	9	11	11	7	7
Voncken et al. [15]	56	10	10	13	13	7	7

tumors where the caudal part of the CTV does not extend beyond the gastro-esophageal junction.

Our study has a few weaknesses. First, due to the use of respiratory triggering, imaging is frozen at a near expiration state, while cardiac motion was not or partly (MVXD images) corrected for which leads to slight image blurring. However, this cyclic intrafraction motion leads only to a slight dose blurring and therefore we believe has a minimal effect on the total required margin [14]. Second, because of respiratory-triggered scans, intrafraction motion during dose delivery has not been taken into account. However, we believe that the impact of the intrafraction motion on the CTV-to-PTV margin will be modest. The respiratory motion will generally cause a blurring of the dose in predominantly the CC direction which could only yield a modest increase of the margin of 1.6 mm or less [14]. In addition, we also believe that the impact of tumor/CTV drifts during treatment will only slightly impact the reported margins. This has been shown in a previous study of our group where we reported that not only the mean tumor drift over a 10 minute interval was just 1.5 mm but also that these drifts were generally random, meaning that drifts were different from day to day causing no systematic error, and thus do not substantially add to the required margin [19]. As such, we believe that the impact of respiratory motion and drifts on the total accumulated dose are only marginal and the CTV-to-PTV margins of tumor drifts of individual fractions are of less concern than large day-to-day interfraction motion.

The third weakness of our study is the relatively small sample size of our study population and MRI study simulation. Although we were able to perform a thorough dosimetric analysis on 140 'fractions', the total number of patients eligible for analysis was 29 which is about the lower border for properly assessing a CTV-to-PTV margin. Similarly, the total number of simulated treatment fractions was 5 whereas our clinical regimen consist of 23 fractions. Although we believe that the systematic interfraction changes (Σ) can be properly captured in 5 samples, the tails of these distributions will inherently be undersampled. This means that the impact of an outlier could be overly expressed in the resulting margin, but also reversely, outliers in the real distribution that would have contributed to an increment in the margin could have been missed due to the coarse sampling rate.

Fourthly, in our study we assumed the dose distribution to be invariant to density changes between treatment fractions. This means that density changes due to interfractional shifts of the diaphragm are not accounted in the dose analysis, although occasionally these changes could influence the CTV coverage at the level of the diaphragm when lateral fluences are involved, which is the case for our VMAT plans [20]. Therefore, the margins listed in this work do not warrant sufficient dose coverage in case of large base line shifts of the diaphragm.

Fifthly, although the deformable image registration yielded high dice coefficients (0.91 ± 0.02 and 0.92 ± 0.02 for transversal and sagittal registrations, respectively), small registration errors did still exist which could have had an impact on the accumulated dose distributions and therefore our listed margins. However, we believe that the impact of these inaccuracies on the final margins are modest, as each accumulated dose distribution comes from the deformation vector fields of five registrations with each a separate error. An increase in registration accuracy could potentially be achieved with improved out of plane image resolutions.

Finally, in this simulation study the MRI-scans were acquired in supine position with both arms next to the body whereas in daily clinic patients are typically treated with arms upwards. We believe that this difference in patient positioning did not impact the overall results as the arms-down anatomy was maintained in both the planning and simulation phase. Furthermore an in-house study with volunteers demonstrated that the anatomy of the esophageal tract in relation to the vertebrae was not sensitive to the position of the arms (no data shown).

This work again demonstrates that in the absence of proper online target visualization (and adaptation) large margins are required to ensure proper adequate CTV coverage when applying daily online set-up based on bony anatomy. With the advent of MR Linacs, daily MR imaging could be used to correct online for the interfraction variability leaving only a CTV-to-PTV margin for the residual intrafraction motion and delineation uncertainty [16,21–24]. Online segmentation and replanning would not only reduce the dose to the organs at risk (e.g. heart and lungs) but would also be of particular benefit for the few patients who exhibit extreme deformations that are not absorbed by the current suggested margins and are unlikely to be recognized on CBCT images.

In conclusion, in this study we have analyzed and assessed the direction-specific CTV-to-PTV margins based on an extensive dose warping analysis in 29 patients. These margins vary between 8 mm for posterior and right direction up to 10 mm for the left and caudal direction. Adequate target coverage in the vast majority (27 out of 29) of patients was demonstrated when patients are daily aligned to the bony anatomy. However, we have to acknowledge that even at these rather generous margins outlying patients still do exist who may be underdosed and need special attention.

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.2021.05.005.

References

[1] Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. Eur J Cancer 2013;49(6):1374–403. https://doi.org/10.1016/j.ejca.2012.12.027.
[2] Gwynne S, Hurt C, Evans M, Holden C, Vout L, Crosby T. Definitive chemoradiation for oesophageal cancer – a standard of care in patients with non-metastatic oesophageal cancer. Clin Oncol 2011;23(3):182–8. https://doi.org/10.1016/j.clon.2010.12.001.
[3] Shapiro J, van Lanschot JJB, Hulshof MCCM, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): Long-term results of a randomised controlled trial. Lancet Oncol 2015;16(9):1090–8. https://doi.org/10.1016/S1470-2045(15)00040-6.
[4] Chen YJ, Han C, Liu A, et al. Setup variations in radiotherapy of esophageal cancer: evaluation by daily megavoltage computed tomographic localization.

Int J Radiat Oncol Biol Phys 2007;68(5):1537–45. https://doi.org/10.1016/j.ijrobp.2007.04.023.
[5] Hawkins MA, Brooks C, Hansen VN, Aitken A, Tait DM. Cone beam computed tomography-derived adaptive radiotherapy for radical treatment of esophageal cancer. Int J Radiat Oncol Biol Phys 2010;77(2):378–83. https://doi.org/10.1016/j.ijrobp.2009.05.045.
[6] Yamashita H, Haga A, Hayakawa Y, et al. Patient setup error and day-to-day esophageal motion error analyzed by cone-beam computed tomography in radiation therapy. Acta Oncol (Madr) 2010;49(4):485–90. https://doi.org/10.3109/02841861003652574.
[7] Fukada J, Hanada T, Kawaguchi O, et al. Detection of esophageal fiducial marker displacement during radiation therapy with a 2-dimensional on-board imager: Analysis of internal margin for esophageal cancer. Int J Radiat Oncol Biol Phys 2013;85(4):991–8. https://doi.org/10.1016/j.ijrobp.2012.07.2358.
[8] Machiels M, Van Hooft J, Jin P, et al. Endoscopy/EUS-guided fiducial marker placement in patients with esophageal cancer: A comparative analysis of 3 types of markers. Gastrointest Endosc 2015;82(4):641–9. https://doi.org/10.1016/j.gie.2015.03.1972.
[9] Cohen RJ, Paskalev K, Litwin S, Price Jr RA, Feigenberg SJ, Konski AA. Original article: Esophageal motion during radiotherapy: quantification and margin implications. Dis Esophagus 2010;23(6):473–9. https://doi.org/10.1111/j.1442-2050.2009.01037.x.
[10] Wang J-Z, Li J-B, Wang W, et al. Detection of interfraction displacement and volume variance during radiotherapy of primary thoracic esophageal cancer based on repeated four-dimensional CT scans. Radiat Oncol 2013;8(1):1. https://doi.org/10.1186/1748-717X-8-224.
[11] Cardenas ML, Mazur TR, Tsien CI, Green OL. A rapid, computational approach for assessing interfraction esophageal motion for use in stereotactic body radiation therapy planning. Adv Radiat Oncol 2018;3(2):209–15. https://doi.org/10.1016/j.adro.2017.10.003.
[12] Machiels M, Jin P, van Gurp CH, van Hooft JE, Alderliesten T, Hulshof MCCM. Comparison of carina-based versus bony anatomy-based registration for setup verification in esophageal cancer radiotherapy. Radiat Oncol 2018;13(1):1–9. https://doi.org/10.1186/s13014-018-0986-1.
[13] Jin P, van der Horst A, de Jong R, et al. Marker-based quantification of interfractional tumor position variation and the use of markers for setup verification in radiation therapy for esophageal cancer. Radiother Oncol 2015;117(3):412–8. https://doi.org/10.1016/j.radonc.2015.10.005.
[14] Hoffmann L, Poulsen PR, Ravkilde T, 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.
[15] Voncken FEM, Nakhaee S, Stam B, 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.
[16] Boekhoff MR, Defize IL, Borggreve AS, 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.
[17] Van Herk M, Remeijer P, Rasch C, Lebesque JV. The probability of correct target dosage: Dose-population histograms for deriving treatment margins in radiotherapy. Int J Radiat Oncol Biol Phys 2000;47(4):1121–35. https://doi.org/10.1016/S0360-3016(00)00518-6.
[18] 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.
[19] Heethuis SE, Borggreve AS, Goense L, 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). https://doi.org/10.1088/1361-6560/aacfb5.
[20] Nyeng TB, Nordsmark M, Hoffmann L. Dosimetric evaluation of anatomical changes during treatment to identify criteria for adaptive radiotherapy in oesophageal cancer patients. Acta Oncol (Madr) 2015;54(9):1467–73. https://doi.org/10.3109/0284186X.2015.1068449.
[21] 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.
[22] Lagendijk 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.
[23] Kontaxis C, Bol GH, Kerkmeijer LGW, Lagendijk 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.
[24] Corradini S, Alongi F, Andratschke N, et al. MR-guidance in clinical reality: Current treatment challenges and future perspectives. Radiat Oncol 2019;14(1):1–12. https://doi.org/10.1186/s13014-019-1308-y.