

RESEARCH ARTICLE

Assessment of a diaphragm override strategy for robustly optimized proton therapy planning for esophageal cancer patients

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Abstract

Purpose: To ensure target coverage in the treatment of esophageal cancer, a density override to the region of diaphragm motion can be applied in the optimization process. Here, we evaluate the benefit of this approach during robust optimization for intensity modulated proton therapy (IMPT) planning.

Materials and methods: For 10 esophageal cancer patients, two robustly optimized IMPT plans were created either using (WDO) or not using (NDO) a diaphragm density override of 1.05 g/cm³ during plan optimization. The override was applied to the excursion of the diaphragm between exhale and inhale. Initial robustness evaluation was performed for plan acceptance (setup errors of 8 mm, range errors of ±3%), and subsequently, on all weekly repeated 4DCTs (setup errors of 2 mm, range errors of ±3%). Target coverage and hotspots were analyzed on the resulting voxel-wise minimum ($V_{w_{min}}$) and voxel-wise maximum ($V_{w_{max}}$) dose distributions.

Results: The nominal dose distributions were similar for both WDO and NDO plans. However, visual inspection of the $V_{w_{max}}$ of the WDO plans showed hotspots behind the right diaphragm override region. For one patient, target coverage and hotspots improved by applying the diaphragm override. We found no differences in target coverage in the weekly evaluations between the two approaches.

Conclusion: The diaphragm override approach did not result in a clinical benefit in terms of planning and interfractional robustness. Therefore, we do not see added value in employing this approach as a default option during robust optimization for IMPT planning in esophageal cancer.

KEYWORDS

3D robust optimization, density override, diaphragm, esophageal cancer, intensity modulated proton therapy

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1 | INTRODUCTION

Radiotherapy plays an essential role in the treatment of esophageal cancer. The esophagus is surrounded by several critical structures, such as the lung, heart, kidneys, spleen, liver, and spine. As various dose parameters of these structures have been correlated to treatment related toxicities, treatment planning focuses on delivering the desired dose to the target, while avoiding these critical structures as much as possible.^{1,2} Still, there is a substantial risk of treatment related toxicities. The risk of postoperative pulmonary complications seems to be related to lung dose.^{3–6} As a consequence of pulmonary and cardiac treatment related complications, overall survival seems affected by dose to both heart and lungs, independently.⁷ Recently, Lin et al.⁸ reported reduction in total toxicity burden after proton radiotherapy compared to photon radiotherapy in chemoradiotherapy treatment of esophageal cancer. Protons are, due to its favorable beam properties, capable of reducing the dose to all critical structures without doing concessions to the dose coverage of the target volume.⁹ The highest degree of target dose conformity, in combination with organ at risk (OAR) sparing, can be reached with intensity modulated proton therapy (IMPT).^{10,11}

Although preferable dose distributions can be achieved with IMPT, caution needs to be taken as proton dose distributions are more sensitive to range and setup errors.¹² Therefore, to assure the quality of the IMPT plan, it is essential to evaluate robustness. Treating thoracic indications, as esophageal cancer, brings even more challenges, as the tumor itself and all surrounding tissues are subject to respiratory motion. Several measures can be taken to mitigate motion effects. Breath-hold or gating techniques can be applied to minimize motion during treatment, but require patient compliance and prolong in-room treatment times.¹³ Rescanning or the use of increased spot sizes are also commonly used motion mitigation techniques, and these do not require patient compliance.¹⁴ Concerning the beam setup, considerations can be made to choose the most robust beam angles.

Yu et al.¹⁵ have shown the superiority of posterior beams in IMPT of esophageal cancer. Due to the diaphragm movement, the most significant density changes can be seen in the path of lateral beams. These density changes can have a major impact on the robustness of IMPT plans. A way to improve robustness is to override regions with highly variable densities during optimization. The use of target density overrides is widely applied in plan optimization for moving targets surrounded by air, for protons, as well as photons.^{16–18} As a measure against diaphragm motion, density overrides can be applied to the region where the diaphragm is moving. Cummings et al.¹⁹ described a diaphragm override method for treating lung tumors

close to the diaphragm with robustly optimized proton therapy. There, the lower boundary of the lung contour in maximum inspiration and expiration was used to define the region where the diaphragm is moving; the subtracted region was copied to the average CT and overridden to the density of muscle for robust optimization. Lee et al.²⁰ described a similar method in the scope of passively scattered proton therapy for distal esophageal cancer. Here, the average Hounsfield Unit in the override region of the maximum intensity projection image, generated from the 4DCT, was used as the override density.

No comparative studies can be found in literature, assessing the benefit of diaphragm overrides. The diaphragm override strategy for esophageal treatment originates from planning in photons, where non-robust optimization is the standard. The method was translated to non-robustly optimized proton therapy, as shown by Lee et al.,²⁰ to ensure adequate coverage at the distal end of the target. In both non-robust optimization techniques, the advantage of the density override is clearly seen when recalculating the plan on the maximum inspiration and expiration phases. However, in the scope of robust optimization, taking this extra step might not be necessary. The aim of this study was to evaluate the need of the diaphragm override approach in IMPT treatments of esophageal cancer patients, in terms of plan robustness.

2 | MATERIALS AND METHODS

2.1 | Patient data

In the Repeat CT Thoracic (REACT)-study (clinical-trial.gov NCT03024138), weekly repeated 4DCT and daily CBCT data were collected from 80 patients with thoracic tumors, to evaluate inter- and intrafractional changes during curative radiotherapy. Patients were imaged in head-first supine position with arms positioned above their head at a large bore 64-slice CT scanner Somatom AS Open 64-RT Pro (Siemens Medical Systems). No active motion management was applied, patients were treated in free breathing. Images were reconstructed with a 2 mm slice thickness and a 1 mm in-plane resolution. 4DCTs were reconstructed into 10 breathing phases and an average CT.

Twenty out of the 80 included patients had esophageal cancer. One of them withdrew consent for study participation after two weeks of treatment. From the remaining 19 patients, 10 patients were included in the current study. These patients were selected based on the image quality of the available 4DCTs. Weekly 4DCTs with major artifacts in the diaphragm region were omitted. Patients with more than one unacceptable 4DCT were completely excluded. Nine patients had a distal esophageal tumor, of which one also

presented pathological lymph nodes in the upper thorax. For one patient the location of the primary tumor was in the middle esophagus.

2.2 | Imaging and delineation

For all patients, an internal target volume (ITV) was created on all available average CTs, according to the following procedure. A radiation oncologist first delineated the gross tumor volume (GTV) based on the average CT, which includes the primary tumor and pathological lymph nodes. A clinical target volume (CTV) was created by expanding the GTV of the primary tumor by 3 cm cranio-caudally, and the GTV of the lymph nodes by 7 mm in all directions. Over the whole length of the target, the fatty mediastinal tissue was included in the CTV. Finally, an ITV was created by manually expanding the CTV to fit all breathing phases of the 4DCT. The ITV was used as planning and evaluation volume. All OARs were delineated by experienced radiation therapy technologists.

2.3 | Motion analysis and delineations of the diaphragm

Diaphragm positions and amplitudes were monitored during all weeks of treatment. The outcomes of the diaphragm motion analysis can be found in Table 1 and are visualized in the Supplementary Materials (Suppl. A). The 4DCT phases containing the extreme diaphragm positions (in cranial-caudal direction) were determined visually. To measure the diaphragm motion amplitude, the position of the domes of the diaphragm in both extreme phases was used. The position of the diaphragm dome, relative to the upper edge of the 12th vertebra, was assessed in cranio-caudal direction of the expiration phase of all weekly 4DCTs to determine baseline shifts. Diaphragm motion amplitudes and shifts were determined for the right and left dome of the diaphragm separately. Additionally, to define the diaphragm override region, the right and left domes of the diaphragm were delineated in the most extreme breathing phases. Next, all contours were copied to the average CT. The inspiration domes were then subtracted from the expiration domes, resulting in a structure framing the region where the diaphragm is moving during the breathing cycle (Figure 1).

2.4 | Treatment planning and robustness evaluation

For all 10 patients, two robustly optimized IMPT plans were created in a research version of RayStation 7 (RaySearch Laboratories) treatment planning system

with the RayStation Monte Carlo dose engine; one with (WDO) and one without (NDO) a diaphragm density override. Robust optimization was applied to the ITV expanded isotropically by 0.35 mm with a prescription dose of 4140 cGy in 23 fractions, for a constant RBE of 1.1. In the robust planning optimization (worst-case method), setup and range errors (5 mm and $\pm 3\%$, respectively) are considered.^{21,22} The average CT was used for both optimization and evaluation. Two beams were used for all patients; one posterior and one right posterior oblique field. In patient 9, an additional third beam was added at 0 degrees due to the cranial extension of the target volume. During the optimization process, the ITV (excluding bony anatomy) was overridden to the density of muscle (1.05 g/cm^3). Additionally, in the WDO plan, a density of 1.05 g/cm^3 was assigned to the delineated diaphragm region. Both the ITV and the diaphragm override were removed before final dose calculation. To ensure fair plan comparison within each patient, the same OAR objectives for the NDO and the WDO plans were used, aiming to spare critical structures as much as possible.

When all clinical criteria concerning target coverage and OARs dose were met, robustness evaluation was performed on the planning image (the average CT). The robustness evaluation implemented in our clinical workflow simulates errors in patient setup (8 mm) and CT densities ($\pm 3\%$). Fourteen setup error scenarios are created by shifting the patient 8 mm in all cardinal directions (6) and to the corresponding vertices of a cube (8). Subsequently, the plan is computed for these setup error scenarios, where the CT densities are scaled by -3% and $+3\%$, creating 28 scenarios ($[6 + 8] \cdot 2$). Evaluation takes place on the constructed voxel-wise minimum (Vw_{\min}) and voxel-wise maximum (Vw_{\max}) dose distributions.²³ Plans were only accepted when clinical predefined thresholds regarding target coverage, OARs dose and hotspots were met. The dose that 98% of the ITV receives ($D_{98\%}$) needed to be at least 95% of the prescribed dose in the Vw_{\min} . Hotspots with dose values above 110%, evaluated in the Vw_{\max} , were limited to 2 cm^3 , and a maximal point dose below 115% of the prescribed dose had to be achieved.

Other than robustness evaluation at planning stage, interfractional robustness was evaluated using weekly 4DCTs. First, robustness evaluation was performed on the reconstructed average CTs of each weekly 4DCT, considering setup and range errors (2 mm and $\pm 3\%$, respectively). The setup error was reduced to 2 mm for the weekly evaluations as the interfractional uncertainty is already accounted for when using repeat 4DCTs.²⁴ To verify the interfractional robustness outcomes in a more comprehensive 4D context (using all the phases rather than only the average CT), an additional robustness evaluation was performed using all the phases of each 4DCT. Scenario doses were created for each phase of each 4DCT by applying the same errors as

TABLE 1 Analyzed amplitudes and baseline shifts of the left and right diaphragm during all weeks of treatment. A positive shift reflects a more cranial position of the diaphragm

Patient	Week 0	Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	A (cm)	A (cm)	S (cm)	A (cm)	S (cm)	A (cm)	S (cm)	A (cm)	S (cm)	A (cm)	S (cm)	A (cm)	S (cm)
Amplitude and baseline shift left diaphragm													
1	1.4	1.4	-0.9			1.8	-1.7	1.8	-0.9	2.0	-1.1		
2	1.2	0.8	+0.2	1.4	+0.2	1.4	+0.5	1.6	+0.2	1.4	+0.0		
3	1.0	1.4	+0.6	1.2	-0.1	0.8	-0.2	1.0	+0.3	1.0	+0.5	1.0	+1.3
4	0.8	1.6	-0.7	0.8	+0.0	1.2	-1.1	0.8	-1.3				
5	1.2	1.4	+0.2	1.6	+0.4	1.2	+0.8	1.2	-0.3	1.2	+0.2		
6	1.2	0.6	+0.6	1.2	+0.3	0.4	-0.6	1.2	+0.5	0.8	+0.2		
7	1.0	0.6	-0.2	0.8	-0.1	0.8	-0.5	1.0	+0.1	1.2	-0.3		
8	1.2	0.8	-0.5	1.0	-0.3	1.0	-0.1	1.0	-0.7	1.2	-0.5		
9	0.8	1.0	+3.2	0.8	+2.2	1.6	+2.8	1.0	+2.4	1.8	+2.6	1.6	+2.9
10	1.0	1.0	+0.7	1.4	+0.3	1.2	+0.5	1.0	+0.5	1.0	+0.2		
Amplitude and baseline shift right diaphragm													
1	2.0	0.8	-1.3			0.8	-1.7	0.6	-1.3	1.2	-0.3		
2	1.2	1.2	+0.6	1.6	+0.2	1.4	+0.5	1.6	+0.0	2.2	+0.0		
3	2.2	1.6	+0.8	1.2	-1.5	1.8	-0.6	1.6	-0.1	1.2	+0.5	1.4	+0.9
4	1.2	1.8	-0.9	1.4	-0.6	0.8	-2.1	0.8	-2.1				
5	1.0	0.8	+0.2	1.2	0.4	0.4	+0.6	0.6	0.3	1.0	+0.4		
6	1.0	1.0	0.0	1.0	+0.1	0.6	-0.8	1.2	-0.5	1.2	-0.4		
7	1.4	1.6	0.0	1.0	-0.1	1.0	-0.5	1.6	-0.5	0.8	-0.5		
8	1.4	1.2	-0.5	1.2	-0.1	1.8	+0.3	1.4	-0.1	1.6	-0.1		
9	1.2	1.6	+3.2	1.6	+2.6	1.8	+2.6	1.4	+2.2	2.2	+2.6	2.0	+2.7
10	0.4	0.8	+0.9	0.8	+0.5	0.8	+0.9	1.0	+0.5	0.6	+0.8		

Abbreviations: A, amplitude; S, baseline shift.

**FIGURE 1** In red, the diaphragm override structure is shown on the maximal inspiration phase (left), the maximal expiration phase (middle), and on the average CT (right) [Color figure can be viewed at wileyonlinelibrary.com]

mentioned earlier (2 mm setup error and $\pm 3\%$ range uncertainty). Then, all scenario doses were warped to the expiration phase of the corresponding 4DCT using the ANACONDA deformable image registration method available in RayStation.²⁵ Here, a $V_{w_{\min}}$ dose distribution was reconstructed, using all scenario doses. The results of the $D_{98\%}$ (%) of the CTV on the expiration phase were then compared to the results of the $D_{98\%}$ (%) of the ITV on the average CT of the same 4DCT.

3 | RESULTS

For all patients, clinically acceptable WDO and NDO plans were obtained, where the nominal dose distributions only differed marginally. Small differences were seen in mean heart dose (MHD) and mean lung dose (MLD), as summarized in Figure 2. In seven patients, the lung dose decreased slightly in the WDO plans. In all 10 patients, the heart dose increased using the diaphragm override.

FIGURE 2 Mean heart dose (MHD) and mean lung dose (MLD) obtained with the WDO and the NDO plans [Color figure can be viewed at wileyonlinelibrary.com]

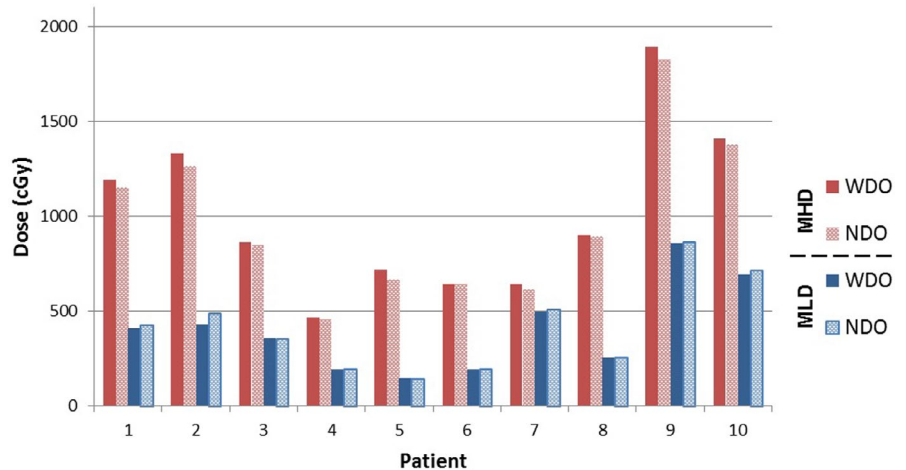
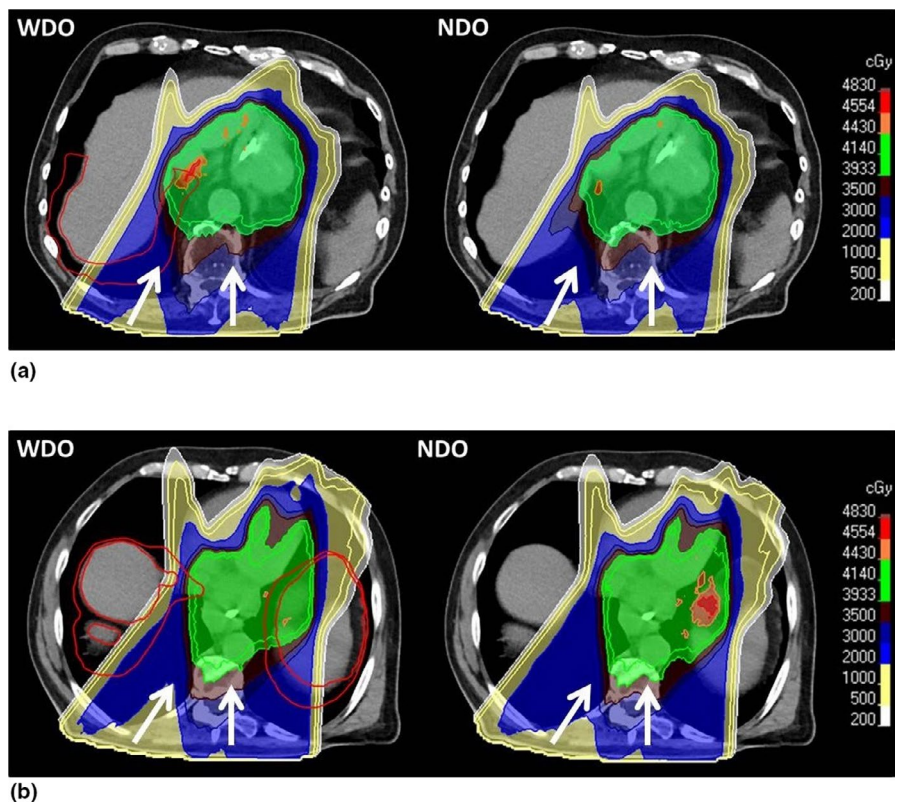


FIGURE 3 $V_{w_{max}}$ dose distributions on the average CT at planning stage with (WDO) and without (NDO) the diaphragm density override of patient 1 (a) and patient 2 (b). The diaphragm override region is delineated in red. The beam setup is shown in white [Color figure can be viewed at wileyonlinelibrary.com]



Target coverage in the $V_{w_{min}}$ was similar for the WDO and the NDO plans in all patients. Differences between the plans were more pronounced in the $V_{w_{max}}$. Visual inspection of the $V_{w_{max}}$, comparing the NDO to the WDO plan, showed a consistent lateral dose shift. In the WDO plans of six patients, this meant hotspots arose directly behind the right diaphragm override region, as shown in Figure 3a for patient 1. In patient 2, the dose shift made the WDO plan superior, as hotspots in the left diaphragm region disappeared, without compromising the target dose (Figure 3b). For this patient, the addition of the diaphragm override considerably simplified and speeded up the planning process, as the planning objectives were more easily reached.

For patient 2, hotspots were also reduced in most weekly robustness evaluations. Hotspots were analyzed in all patients by looking at the dose (relative to the prescription dose of 4140 cGy) that 2 cm³ of the body volume receives (D_{2cm^3}) on the $V_{w_{max}}$ (Table 2, top). In two other patients (#1 and #9), a benefit in terms of higher hotspots reduction (>110%) was seen for the WDO plan. However, no tendencies are seen in the general high dose regions (>107%), favoring the NDO or the WDO plan.

Results of the target dose coverage in the $V_{w_{min}}$ dose after robustness evaluation on the average CT for all patients throughout all weeks can be seen in Table 2 (bottom). For patient 9, target coverage was

TABLE 2 (Top) Hotspots in the weekly robustness evaluations of both WDO and NDO plans. The numbers highlighted in red (bold) resemble higher hotspots (>110%). (Bottom) Target coverage in the weekly robustness evaluations of both WDO and NDO plans. The numbers highlighted in red (bold) indicate where the target coverage criteria ($D_{98\%} > 94\%$) was not met

Patient	Week 0		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	WDO	NDO	WDO	NDO	WDO	NDO	WDO	NDO	WDO	NDO	WDO	NDO	WDO	NDO
Body D_{2cm3}														
1	108%	108%	109%	111%	109%	111%	109%	111%	109%	111%	108%	109%	108%	109%
2	108%	109%	108%	110%	108%	108%	109%	111%	108%	108%	110%	108%	110%	108%
3	108%	108%	108%	108%	108%	108%	108%	108%	108%	108%	108%	108%	108%	108%
4	108%	108%	109%	109%	109%	109%	109%	109%	108%	108%	108%	108%	108%	108%
5	107%	107%	107%	107%	107%	107%	107%	107%	107%	107%	107%	107%	107%	107%
6	106%	107%	106%	106%	106%	106%	107%	107%	106%	107%	107%	107%	107%	107%
7	108%	107%	108%	108%	107%	107%	108%	107%	109%	108%	108%	107%	108%	107%
8	107%	107%	108%	107%	108%	108%	108%	108%	108%	108%	108%	108%	108%	108%
9	108%	108%	110%	111%	110%	110%	110%	111%	110%	111%	110%	111%	110%	111%
10	108%	109%	109%	109%	109%	109%	109%	109%	109%	109%	109%	109%	109%	109%
ITV $D_{98\%}$														
1	97%	97%	96%	96%	96%	97%	91%	93%	95%	96%	96%	96%	96%	96%
2	96%	97%	95%	96%	96%	96%	96%	96%	96%	96%	96%	96%	96%	96%
3	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	96%	96%	92%
4	97%	97%	97%	97%	96%	97%	90%	91%	96%	96%	96%	96%	96%	96%
5	96%	96%	96%	96%	95%	96%	96%	96%	96%	96%	96%	96%	96%	96%
6	96%	96%	96%	96%	96%	96%	96%	96%	96%	96%	96%	96%	96%	96%
7	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%
8	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%
9	97%	97%	66%	53%	67%	57%	57%	44%	78%	66%	71%	61%	57%	45%
10	97%	97%	97%	97%	97%	97%	97%	97%	96%	97%	97%	97%	97%	97%

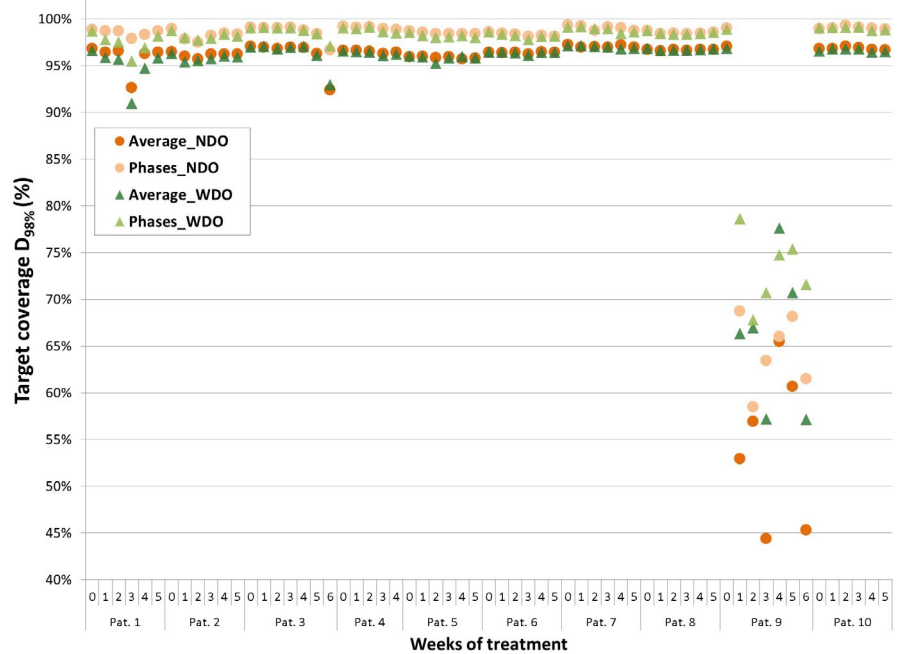
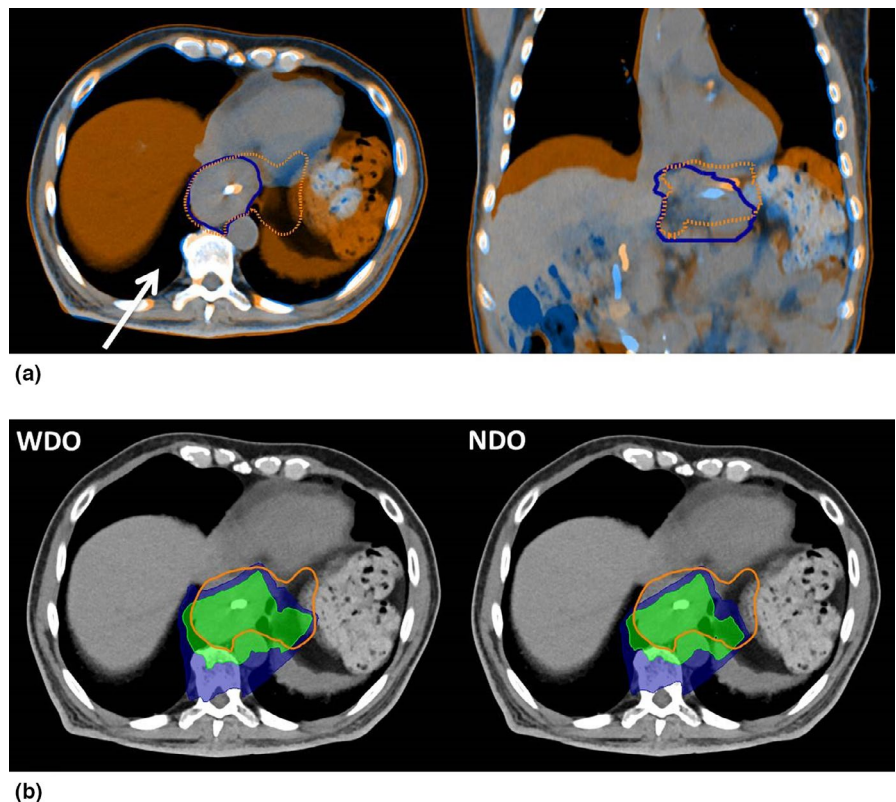


FIGURE 4 Visualization of the target dose coverage in the weekly robustness evaluations of both WDO and NDO plans based on the evaluation on the average CT (ITV) and on all the phases (CTV). Phases-based evaluation gave typically higher target dose coverage than average CT-based evaluation [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 5 (a) Axial and coronal view of the image registration between the average CT of week 0 (blue) and the average CT of week 1 (orange) of patient 9. The ITV is shown for week 0 and week 1 in blue and orange, respectively. The position of the diaphragm was found higher in the repeated CT compared to the planning CT. The diaphragm variation caused a displacement of the ITV and higher densities in the beam path of the right posterior oblique field (white arrow). (b) Presentation of the 95% dose coverage (green) and the 80% dose (blue) in the $V_{w_{min}}$ dose in week 1 of patient 9. The ITV is shown in orange [Color figure can be viewed at wileyonlinelibrary.com]



compromised in all weeks of treatment for the NDO and the WDO plan. The WDO plan however, performed better, with coverage improvement of up to 14%, compared to the NDO plan. Clinically, we accept a target coverage of 94% for the $D_{98\%}$ in the $V_{w_{min}}$ of the weekly evaluations. Of the remaining cases, six patients, both NDO and WDO plans, had an acceptable target coverage in all weeks of treatment. In three patients, the

$D_{98\%}$ was below 94% in one week, which would still result in an acceptable coverage over the whole treatment course. The interfractional robustness evaluation was further extended by encompassing all the phases of the 4DCT. From Figure 4, it can be observed that all but one value of the $D_{98\%}$ (%) improved by comparing the target dose coverage of the ITV on the average CT to the target dose coverage of the CTV based on all the

phases. In this evaluation, patient 9 is the only patient for whom target dose coverage is still compromised, although improved.

4 | DISCUSSION

Generally, the diaphragm override approach did not prove to be beneficial for robustly optimized IMPT planning. On the contrary, hotspots appeared behind the right diaphragm override region in the evaluation dose for most patients. Mostly, the right override region is located parallel to the right posterior oblique beam direction, which makes its proton path through the override region very long (Figure 3). That might be prevented when using other beam angles or arc therapy. However, the beam angles used were chosen because of the reduced density changes in the beam path during the respiratory cycle.¹⁵ Despite the arising hotspots on the right side using the override, a benefit was seen behind the left override region for one patient (#2) during the planning procedure. In this critical region, the gastroesophageal junction (GEJ) bridges the ITV to the stomach. Depending on the phase of the respiratory cycle, this part of the ITV could be either air or tissue. The window of an acceptable trade-off between hotspots and target coverage in this area is very small and was better manageable by the WDO plan. Target coverage improved, while hotspots were reduced. A topic of further investigation could be the assessment of the benefit of a left-sided diaphragm override approach to improve individual planning.

For most patients, our planning protocol showed to be robust during all weeks of treatment, regardless if the diaphragm density override was applied. Patient 9 fell out of the general trend and showed compromised target coverage in all weeks for the NDO, as well as the WDO plan. Looking at this patient in more detail, it was observed that the position of the diaphragm was significantly higher in all weekly repeated CTs compared to the planning CT (Figure 5). In a recent study, diaphragm variations were also the cause of target coverage loss for proton as well as photon therapy.²⁶ The changed position of the diaphragm seems to influence the target coverage in two ways. First, the anatomy of the ITV changes with the position of the diaphragm, as the stomach moves more cranial and pulls the GEJ along with it, which is part of the ITV. Secondly, the proton beam encounters more tissue in its beam path than planned due to the higher diaphragm position. That makes the better target coverage of the WDO plan plausible, as it accounts for higher densities due to the override.

Furthermore, target dose coverage of the ITV on the average CT proved to give a more pessimistic presentation of the target coverage compared to the target coverage using all the phases of the 4DCT. For all patients except patient 9, for whom a dose compromise

was observed in the initial dose evaluation using the average CT, adequate target dose coverage was reached based on the evaluation using all the phases. For patient 9, in most cases, a dose improvement was observed as well. Therefore, we conclude that a dose evaluation on the average CT can be used as a conservative estimate of the given dose and it is time-wise a more effective evaluation to implement in clinical practice. However, relative to the 4D evaluation presented here, a more comprehensive dose evaluation should also include fractionation and uncertainties, such as machine errors and interplay effects.^{24,27}

Recent literature on treating thoracic indications is tending toward 4D optimization, where all phases of the 4DCT can be included during treatment plan optimization.^{15,28,29} This could be an interesting approach for the treatment of esophageal cancer to handle motion and displacements more efficiently. In photon therapy, its value has been proven in terms of target dose coverage and OARs sparing.³⁰ In proton therapy, the value might be even greater due to its increased sensitivity to uncertainties. However, in proton therapy the planning process is usually different, by using robust optimization. Direct comparison of 3D robust optimization to 4D robust optimization was reported only in one study for IMPT in esophageal cancer, which showed no advantage of 4D over 3D optimization in terms of target coverage robustness.³¹ This conclusion contradicted published results of Liu et al.³² and Ge et al.³³ for IMPT in lung cancer. In the present study, we found adequate target dose coverage using 3D optimized treatment plans. For the patient with dose compromise in all weeks (patient 9), we compared the 3D optimization results (NDO and WDO) to results of a 4D optimized plan and did not find a benefit in terms of target coverage (results are included in the Supplementary Materials [Suppl. B]). Further investigation is needed to identify when 4D optimization is beneficial over 3D optimization, to further justify the increased workload of using 4D optimization in clinical practice.

Ten out of 20 esophageal cancer patients included in the REACT study were selected for this study, based on their image quality. Artifacts were primarily seen in the diaphragm region. In CTs with these artifacts, accurate delineation of the diaphragm is compromised and patients that exhibited these artifacts were consequently excluded from this study. Patient 3 had almost no overlap of the diaphragm with the ITV. All other patients had more distally located tumors, for which the treatment beams passed proportionally long distances through the diaphragm region. There is no basis for the use of diaphragm overrides for target volumes cranial to the most cranial position of the moving diaphragm.

The detailed analysis of the diaphragm position and amplitude gave insights into the motion variations of the diaphragm throughout the weeks of treatment. Position shifts showed a similar pattern for the left and right

diaphragm position, while the left and right diaphragm amplitude seem to be independent of each other. Also, it was observed that the planning CT is not always a good indicator for the diaphragm motion characteristics in the subsequent weeks of treatment. Results of this study indicate that the displacements of the diaphragm position are relevant rather than variations in the motion amplitude for the desired target coverage and should be monitored throughout the treatment course. Baseline shifts of the diaphragm can be detected using CBCT prior to treatment.

Using a density override approach requires some extra manual work before optimization can be initialized. The extreme positions of the diaphragm dome must be delineated and subsequently subtracted to obtain the override region. Furthermore, an override density must be chosen and applied during optimization. For the final dose calculation, the override must be removed again. Using the contouring method described by Cummings et al.¹⁹ and Lee et al.²⁰ parts of the delineation might be automated in the future. These papers do describe the diaphragm override approach in their methodology, but the approach itself was never topic of discussion.

Although override methods might lead to more robust plans, caution needs to be taken when employing them within robust proton optimization. The whole planning process might become more difficult to interpret, because proton dose distributions might look quite different with and without density overrides. When removing the override for the final dose calculation, proton overshoots can occur. Additionally, for the beam setup employed for esophagus patients, the heart is located at the distal end of the target, which results in a slightly higher mean dose to the heart for the WDO plans.

For non-robustly optimized therapy plans, the override approach was employed to “manually” steer the optimization process to create robust plans. In the more advanced robust optimization nowadays, this “manual” tweaking has become redundant. Plans are already made more robust to density changes using robust optimization. In this context, also the use of other override approaches, as for example, target override strategies, should be reviewed to assess their clinical benefit in robust optimization and their potential impact on the realization of automated treatment planning.

5 | CONCLUSION

The practice of using diaphragm density overrides was historically passed on from photon to proton treatment planning, and then further from non-robust to robust proton plan optimization. It requires the definition of the override region as well as the choice for an override density in the planning process.

This study does not show general benefits when using diaphragm overrides in robustly optimized

esophageal IMPT planning to justify its default clinical implementation. However, the approach might ease the planning process for individual esophageal cancer patients. To make the treatment planning approach generally more efficient, we recommend its use only if robustness evaluation criteria otherwise cannot be reached.

CONFLICT OF INTEREST

We have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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