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Physics Contribution

Diaphragm-Based Position Verification to Improve Daily Target Dose Coverage in Proton and Photon Radiation Therapy Treatment of Distal Esophageal Cancer

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Purpose: In modern conformal radiation therapy of distal esophageal cancer, target coverage can be affected by variations in the diaphragm position. We investigated if daily position verification (PV) extended by a diaphragm position correction would optimize target dose coverage for esophageal cancer treatment.

Methods and Materials: For 15 esophageal cancer patients, intensity modulated proton therapy (IMPT) and volumetric modulated arc therapy (VMAT) plans were computed. Displacements of the target volume were correlated with diaphragm displacements using repeated 4-dimensional computed tomography images to determine the correction needed to account for diaphragm variations. Afterwards, target coverage was evaluated for 3 PV approaches based on: (1) bony anatomy (PV_B), (2) bony anatomy corrected for the diaphragm position (PV_BD) and (3) target volume (PV_T).

Results: The cranial-caudal mean target displacement was congruent with almost half of the diaphragm displacement ($y = 0.459x$), which was used for the diaphragm correction in PV_BD. Target dose coverage using PV_B was adequate for most patients with diaphragm displacements up till 10 mm (≥94% of the dose in 98% of the volume [$D_{98\%}$]). For larger displacements, the target coverage was better maintained by PV_T and PV_BD. Overall, PV_BD accounted best for target displacements, especially in combination with tissue density variations ($D_{98\%}$: IMPT 94% ± 5%, VMAT 96% ± 5%). Diaphragm displacements of more than 10 mm were observed in 22% of the cases.

Conclusions: PV_B was sufficient to achieve adequate target dose coverage in case of small deviations in diaphragm position. However, large deviations of the diaphragm were best mitigated by PV_BD. To detect the cases where target dose coverage could be compromised due to diaphragm position variations, we recommend monitoring of the diaphragm position before treatment through online imaging.

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Introduction

For the treatment of esophageal cancer, chemoradiotherapy plays an important role in the definitive as well as in the preoperative setting.[1] In radiation therapy, the aim is to achieve adequate target dose coverage while reducing dose to nearby organs at risk (OARs). Radiation therapy can be delivered using state-of-the-art photon therapy (eg, volumetric modulated arc therapy [VMAT] or intensity modulated radiation therapy [IMRT]) or proton therapy (eg, intensity modulated proton therapy [IMPT]).[2,3] These more conformal radiation therapy modalities are particularly relevant in the treatment of esophageal cancer, because the esophagus is surrounded by several critical OARs such as the lungs and the heart.[4-6] Reducing the dose to the OARs is associated with improved overall survival as the risk of treatment related pulmonary and cardiac complications reduces.[7]

Radiation therapy in the thorax is challenged by motion and deformation of the anatomy, for example caused by respiration.[8,9] For the treatment of distally located esophageal cancer, the diaphragm is a moving anatomic structure located in the beam path. A recent study by our group concluded that the variations of the diaphragm position can lead to deformations of the target volume and disturbances in the dose distribution, which consequently have a great effect on the target dose coverage in IMPT for distal esophageal cancer.[10] Similar outcomes were reported for IMRT and single field uniform dose (proton) plans.[11,12] To some degree, diaphragm variations can be accounted for during treatment planning by applying robust optimization and choosing beam angles that are more robust to diaphragm variations.[13,14] Additionally, comprehensive optimization strategies have been investigated to address the problem, including robust 4-dimensional (4D) optimization and the application of diaphragm density overrides, but these have also been found insufficient to cope with large diaphragm position variations.[10,15] These approaches account for the diaphragm motion amplitude, but are not able to fully account for diaphragm position offsets.

It is essential to monitor the position of the diaphragm before treatment. Daily online imaging can be deployed to detect diaphragm variations using cone beam computed tomography (CBCT). This is particularly relevant for proton therapy, because protons are more sensitive to range and setup errors resulting in larger dose deviations.[16] In case of large diaphragm variations, plan evaluation that takes the actual anatomy into account is necessary to decide whether plan adaptation is required.[17] Replanning is time and resource intensive and therefore, a method to improve target coverage on a daily basis is desired.

Image registration based on bony anatomy is common clinical practice for position verification (PV) for esophageal cancer.[11,18-21] With upcoming 3-dimensional (3D) and 4D imaging techniques, several studies investigated motion and displacements of the target volume relative to bony anatomy and argued the added value of soft tissue matching.[18,22,23] However, the low contrast of the CBCT in the mediastinum and abdominal region compromises accurate patient setup.[18] Improving the image quality of the CBCT will be often at the expense of additional daily imaging dose.[24] Fiducial markers could facilitate PV, but have been found insufficient to rely on completely due to tissue deformation, visibility and marker migration, and have the disadvantage of adding an invasive procedure.[20,23] Additionally, the markers could create artifacts, compromising diagnostic and dosimetric accuracy.[14,25] However, for the purpose of motion evaluation, fiducial markers facilitated detailed inter- and intrafractional analysis of the gross tumor volume (GTV). Multiple studies showed that the largest motion occurs in the lower part of the esophagus and proximal stomach and predominantly in the cranial-caudal direction.[14,20-23,26] Furthermore, studies have shown that the target volume moves congruently with the diaphragm.[27,28] Therefore, we hypothesized that the position of the diaphragm can be used to improve alignment of the target volume. The first objective of this study was to investigate to what extent target volume displacements correlate with diaphragm variations. The daily diaphragm position served as input to improve alignment of the target volume during PV (based on bony anatomy). In addition, the incidence and magnitude of diaphragm variations during the whole treatment course was assessed by daily CBCT imaging. The intrafractional reproducibility of the diaphragm position was specifically assessed to evaluate the persistence of diaphragm variations throughout a treatment fraction and to validate the applicability of a diaphragm-based correction. Finally, a dosimetric analysis was employed to evaluate if the proposed PV method would result in target dose coverage improvement compared to a bony anatomy or target volume match.

Methods and Materials

Patient data

A prospective cohort pilot study (REACT, ClinicalTrials.gov Identifier NCT03024138) of 20 consecutive patients provided a unique data set consisting of weekly repeated 4D computed tomography (CT) and daily (4D)CBCT data for esophageal cancer patients. A second (4D)CBCT was acquired at the end of each treatment fraction twice a week. The 4DCTs and (4D) CBCTs were reconstructed into ten breathing phases following phase-based binning and for each set an average (CB)CT was created. The patients were treated with VMAT at our clinic, and treatment duration was either 5 or 6 weeks, depending on the dose prescription (4140 cGy or 5040 cGy, respectively). Ten distal esophageal cancer patients were selected from the cohort, based on the image quality of the available 4DCTs. For 2 patients 7 weekly 4DCTs were available; for 7 patients six 4DCTs were available and for 1 patient five 4DCTs were available. For 1 patient, the repeated 4DCT of the first week of

treatment was selected as the planning CT because the original planning 4DCT contained major artifacts.

A second group of patients was available, who were treated with 23 fractions (4140 $cGy_{(RBE)}$) IMPT in our proton clinic. Patients were monitored with weekly repeated 4DCTs, with a total acquisition of 5 to 6 4DCTs throughout their treatment. Five patients were selected from this data set based on large deviations of the diaphragm position. This second cohort was added to the first patient group to support the most important evaluations.

Data preparation

For all available average CT scans, a clinical target volume (CTV) was available, created by a 30 mm extension in cranial-caudal direction of the GTV of the primary tumor plus a 7 mm isotropic expansion of the GTV of the lymph nodes. The fatty mediastinal tissue was included in the CTV along the target length. Additionally, the CTV contour was created on the end-of-expiration phase and manually expanded for all breathing phases of the corresponding 4DCT to create the internal target volume (ITV). Finally, a planning target volume (PTV) was created by an isotropic 8 mm expansion of the ITV.

Correlations between CTV and diaphragm displacements

The correlation between interfractional displacements of the target volume and the left diaphragm was assessed by linear regression. Because esophageal tumors are usually more oriented to the left side, we chose to focus on the left diaphragm, and from here on, diaphragm can be interpreted as left diaphragm throughout the paper. To obtain both the CTV and the diaphragm displacement, the bony anatomy was used as reference. PV was rigidly performed based on the bony anatomy (PV_B), where a box region was created around the vertebrae at the cranial-caudal level of the target to serve as the region of interest (ROI) during image registration (Fig. 1). The registration was performed between each average weekly repeated 4DCT and the average planning 4DCT. Afterwards, a deformable image registration (DIR) was created between the end-of-expiration phase of each weekly repeated 4DCT and the end-of-expiration phase of the planning 4DCT using the Anaconda DIR available in RayStation (RaySearch Laboratories, Stockholm, Sweden), with the corresponding CTV as controlling ROI.[29,30] The resulting deformation vectors within the entire CTV were evaluated in all cardinal directions using an in-house developed script. Four parameters were defined and calculated: (1) the mean CTV displacement, (2) the 95-percentile (near-maximum) CTV displacement, (3) the cranial CTV border displacement and (4) the caudal CTV border displacement. The most important displacement evaluation of the CTV (the mean cranial-caudal CTV displacement) and the displacement evaluation of the diaphragm were performed for all 15 patients. The displacement of the diaphragm resulted from an adjusted rigid registration. The PV_B match was used as starting point, and only the cranial-caudal direction was adjusted to find the best possible registration of the diaphragm domes on the 2 images.

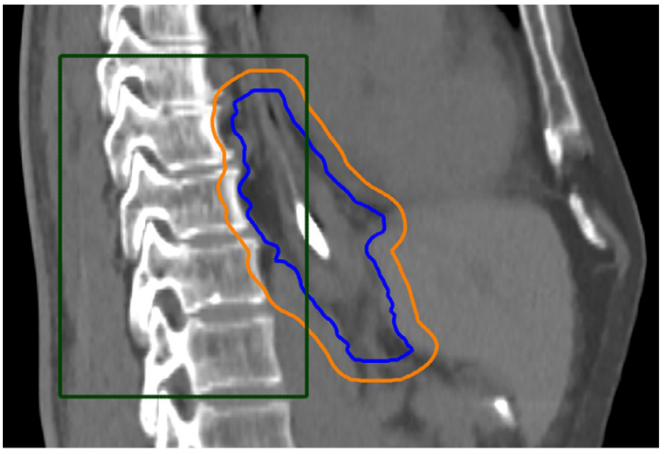

Fig. 1. Sagittal view of a representative patient presenting the different ROIs for image registration. The PTV (orange) and ITV (blue) are shown, as well as the box used as ROI during position verification based on bony anatomy (green).

Position verification method comparison

Three different PV methods were evaluated that were all based on image registration. The image registrations were performed in RayStation with 6° of freedom. All 3 methods simulated PV at the treatment machine by registering the averages of the repeated 4DCTs to the average planning CT. The first method was based on bony anatomy (PV_B), as previously described. The second method was based on PV_B, but corrected by an additional cranial-caudal shift to account for the change in position of the left diaphragm relative to the bony anatomy (PV_BD). Only the cranial-caudal displacement was taken into account because previous studies showed that displacements particularly occur in this direction.[20-23,26] The additional cranial-caudal shift to account for the diaphragm displacement resulted from the previously described section that investigates the correlation between the left diaphragm displacement and the CTV displacement. The third method (PV_T) consisted of registering the target, by appointing the PTV as ROI during image registration (Fig. 1).

Inter- and intrafractional diaphragm reproducibility

Additionally, inter- and intrafractional baseline shifts of the left diaphragm relative to the bony anatomy were

investigated to a greater extent by performing PV for the averages of the 4DCBCTs or the available 3DCBCTs. This was done for both pre- and post-treatment CBCTs to investigate the inter- and intrafractional reproducibility of the diaphragm position. CBCTs were only available for the first group of patients.

Treatment planning

Clinically approved VMAT and IMPT plans were created on the average planning CT in RayStation for the 10 patients in the first group. For the second group, clinical VMAT and IMPT plans were available. Dose distributions were calculated with Collapsed Cone and Monte Carlo, respectively. All plans were optimized according to clinical criteria to achieve acceptable target dose coverage ($D_{98\%}$ ≥95%) and as low as possible OAR doses. The VMAT plans consisted of 2 full arcs with a beam energy of 6 MV. The plans were nonrobustly optimized using the PTV and evaluated for its robustness by simulating 8 mm shifts after the nominal plan met all clinical criteria. IMPT treatment plans were created with typically 2 fields; one posterior (180^0) and one right-posterior-oblique beam (210^0-220^0). The posterior beams were used to limit the influence of the diaphragm motion.[13] The IMPT treatment plans were robustly optimized using the ITV. The nominal plan was optimized to meet the same criteria concerning OARs doses as the corresponding VMAT plan. Next, robustness evaluation for the IMPT plans was performed by simulating setup uncertainties of 8.0 mm and range errors of ±3%. The same criteria were used for both VMAT and IMPT for the resulting voxel-wise minimum (Vw_{min}) and maximum (Vw_{max}) dose distributions from the robustness evaluation.[31] The first criterion was that the dose to 98% of the ITV volume ($D_{98\%}$) had to be at least 95% of the prescription dose in the Vw_{min} dose distribution. For the Vw_{max} dose distribution, hotspots below 110% and 115% of the prescribed dose were allowed to 2 cc and 0 cc within the body volume, respectively.

Dosimetric assessment of position verification methods

Interfractional robustness of all treatment plans for every PV method was evaluated by simulating errors in position (2 mm) (for both VMAT and IMPT) and range (±3%) (for IMPT only) on the average image of each weekly repeated 4DCT. The 2 mm error shift accounts for the residual errors that still exist during treatment after online position correction based on CBCT, such as intrafractional motion and uncertainties in isocenter position and other mechanical uncertainties of the imaging and treatment systems.[15,17,32,33] Target coverage was evaluated by the $D_{98\%}$ of the ITV on the resulting Vw_{min} dose distribution.[31] A minimum ITV dose coverage ($D_{98\%}$) of 94% of the prescribed dose was considered clinically acceptable for the repeated CTs.[17]

Results

Correlations between CTV and diaphragm displacements

For the 10 patients, the mean interfractional CTV displacements for the weekly 4DCTs ranged between −1.2 and 3.3 mm (median: 0.0 mm) for the left-right direction, −6.6 mm and 2.6 mm (median: −0.7 mm) for the anterior-posterior direction and between −6.5 and 13.5 mm (median: −0.2 mm) for the cranial-caudal direction. Four parameters were specifically investigated for these translational directions; the mean, the near-maximum (95-percentile), the cranial border and the caudal border displacement of the CTV. Figure E1 shows significant and strong correlations for the cranial-caudal CTV displacement and the diaphragm displacement for all parameters, meaning that the CTV volume is moving congruently with the diaphragm in cranial-caudal direction. A negative and moderate correlation was found for the anterior-posterior CTV displacement, meaning that the CTV volume is often moving posteriorly where the diaphragm is moving cranially. Weak and non-significant correlations were found for the left-right CTV displacement, except for the near-maximum left-right displacement (r = .408, P = .003) (Fig. E1). Overall, the strongest correlations were found for the mean CTV displacement, followed by the near-maximum and the caudal border displacement. Displacements of the cranial border remained small in all cardinal directions. Figure 2 visualizes 2 examples of CTV displacements together with 2 large oppositely displaced diaphragms. This figure shows that the largest CTV displacements are found just below the diaphragm in the region of the gastro esophageal junction (GEJ). The interfractional CTV displacement analysis was performed to establish an additional shift to PV_B to perform PV_BD. We found that almost half of the cranial-caudal diaphragm displacement was congruent to the cranial-caudal mean CTV displacement (y = 0.439x) (See Fig. E1). For feasability in the clinic, we decided to multiply the cranial-caudal diaphragm displacement by 0.5 to perform the shift for PV_BD. Because the correlation between the cranial-caudal diaphragm displacement and the mean CTV displacement forms the basis of PV_BD, this result was validated by including the 5 clinical proton patients showing deviating diaphragm positions. Figure 3 shows this correlation based on all 15 patients. Inclusion of the 5 clinical patients made the correlation stronger.

Position verification method comparison

The resulting couch correction for each of the PV methods are presented in the Supplementary Materials (Suppl. Fig. B). The translations were the largest for the cranial-caudal (up to 20 mm) and left-right (up to 16 mm) directions, compared to the anterior-posterior (up to 8 mm) direction. Differences between the registration methods were usually

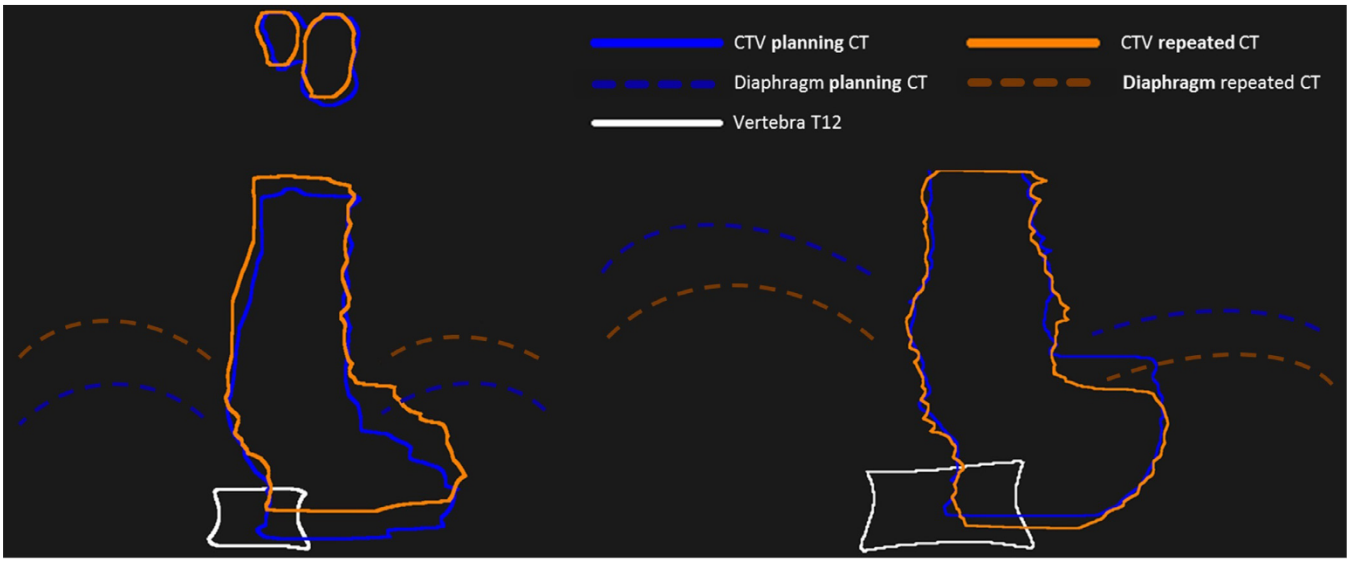

Fig. 2. Coronal views of the CTV and diaphragm contours for 2 sample cases (left: patient 9 − week 0 vs. week 1, right: patient 4 − week 0 vs. week 3). Large interfractional diaphragm displacements are observed in opposite directions, which caused congruent CTV displacements, most apparent in the gastro esophageal junction region and the caudal border of the CTV.

small for the anterior-posterior and the left-right direction, but substantial for the cranial-caudal direction (up to 6 mm differences). In several cases, the cranial-caudal translation for PV_B and PV_BD, and PV_T were even in opposite direction. In general, the applied rotations were larger for the PV_T method compared to the PV_B and PV_BD methods, with differences in couch corrections up to 1.9°, 0.9°, and 1.0° for pitch, roll, and yaw, respectively.

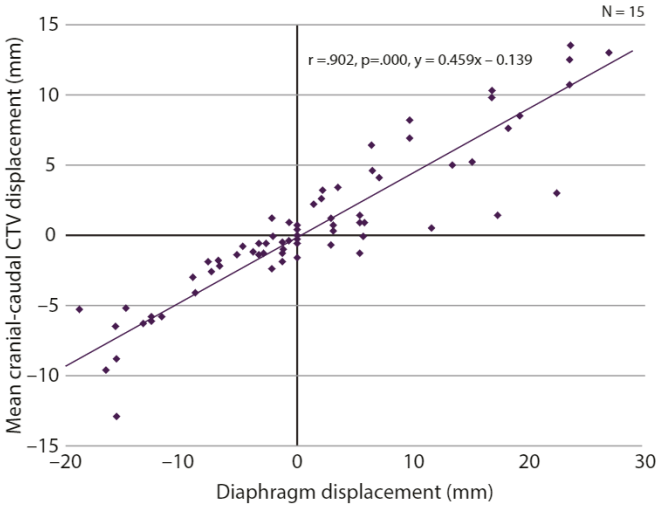

Fig. 3. Analysis of the mean cranial-caudal CTV displacement and correlations with the left diaphragm displacement. Fifteen patients were evaluated with each showing 4 to 6 datapoints, resulting from the evaluation of the registration of the weekly repeated 4DCTs to the planning 4DCT. Negative shifts of the diaphragm and the CTV represent a caudal displacement.

Inter- and intrafractional diaphragm reproducibility

The inter- and intrafractional reproducibility of the diaphragm was analyzed using repeated (4D)CBCT and 4DCT data. For each patient, displacements of the diaphragm relative to bony anatomy during the whole treatment course are presented in Figure 4. For some patients, a trend of increasing or decreasing diaphragm displacements is clearly visible (patients 1-4), whereas others remain fairly constant (patients 6-8 and 10) during treatment. Patients 1, 5, and 9 showed a larger and varying range of displacements throughout the treatment course. The displacements of all 10 patients are additionally summarized in the 2 histograms, showing a greater extent of diaphragm displacements interfractionally than intrafractionally. Results of the interfractional displacement range using the 4DCT or (4D)CBCT for all measurements were similar (57% and 55% ≤4 mm, respectively). Intrafractional displacements, as observed in the CBCT images, remained usually small (76% of all treatments fractions ≤4 mm), where both small and large deviations persisted through a treatment fraction for most cases. There was no trend seen in deviations getting smaller or larger intrafractionally for initially small and large deviations independently. Patient 3 showed for 2 fractions a pre-treatment shift of less than 10 mm, that increased beyond 10 mm post-treatment. Patient 9 showed for 3 treatment fractions an initial displacement up to 30 mm, which was decreased to less than 10 mm after the treatment fraction. Five patients showed consistent intrafractional drifts of the diaphragm, whereas for 2 patients almost all deviations increased during the fraction. Furthermore, cranial displacements of the diaphragm occurred

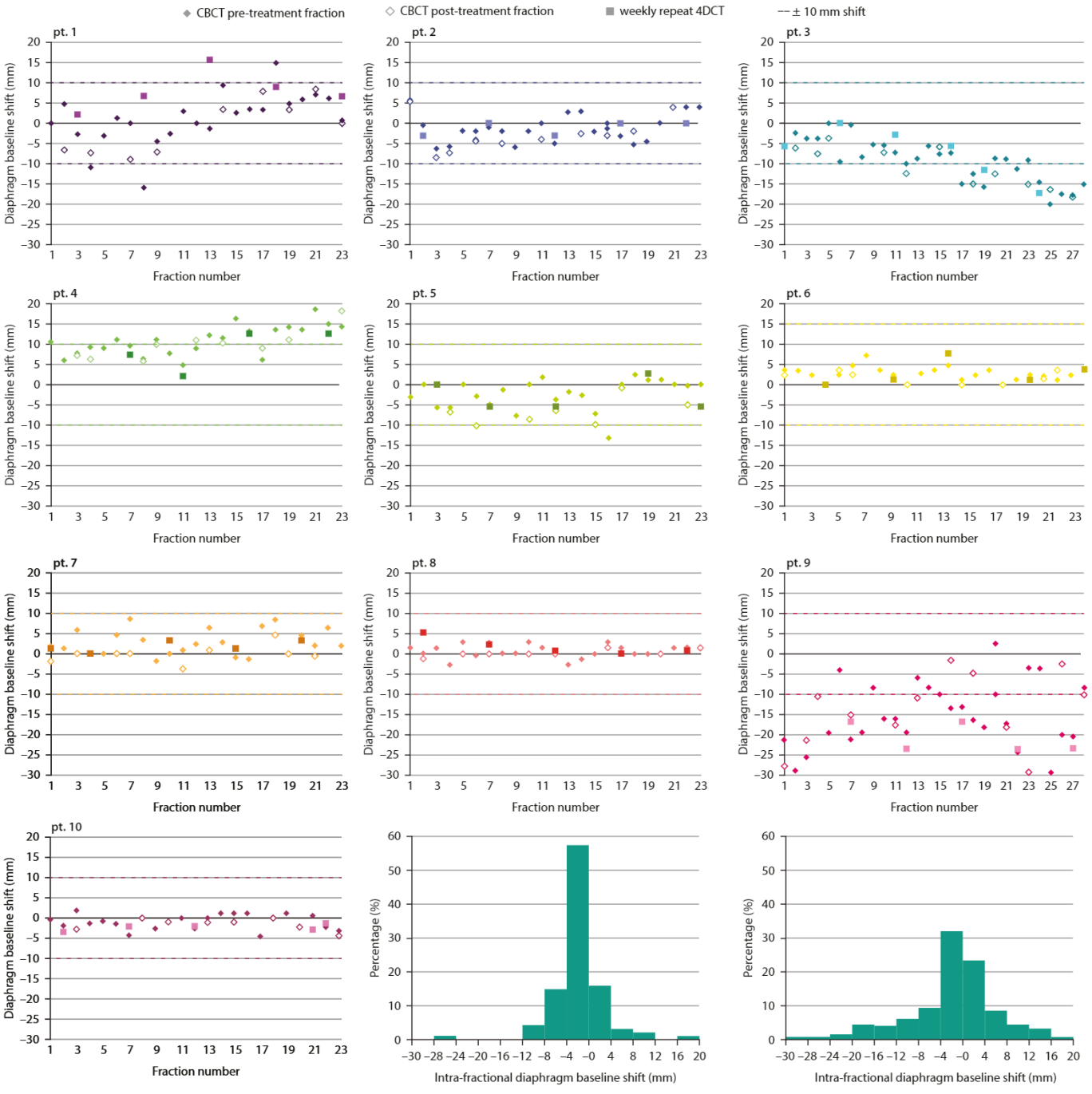

Fig. 4. Inter- and intrafractional displacements of the left diaphragm relative to bony anatomy using 4DCT and (4D)CBCT data for each patient throughout the treatment course. The dotted line represents the threshold (10 mm) when diaphragm variations could lead to underdosage of the target volume. Combined intra- and interfractional displacements for the CBCT data are additionally shown in 2 histograms. Negative shifts of the diaphragm represent a caudal displacement.

more often than caudal displacements (47% and 68% cranial inter- and intrafractional displacements, respectively), which means that the initial cranial offset of the diaphragm tends to get worse intrafractionally, whereas negative offsets tend to reduce during a fraction. Diaphragm displacements beyond 10 mm occurred in 20% of the (4D)CBCTs before a treatment fraction compared to 22% in the 4DCTs.

Dosimetric assessment of position verification methods

The ITV dose coverage for the 3 different PV approaches was analyzed by means of the $D_{98\%}$ in the Vw_{min}. The weekly robustness evaluations together with the left diaphragm baseline displacements are shown in Figure 5. For the first patient

group, PV_B was sufficient in most cases (42/51 IMPT; 44/51 VMAT) to achieve adequate ITV coverage ($D_{98\%}$ ≥94% of the prescribed dose). For 1 patient (patient 9), all weekly evaluations resulted in unacceptable target dose coverage for both IMPT and VMAT. The remaining failing cases (3 in IMPT, 1 in VMAT) were a single failing evaluation of patients 1, 2, and 4. In the clinical proton group, target dose coverage for PV_B was unacceptable in most cases. Only 6 of 26 cases and 8 of 26 cases had sufficient target coverage for IMPT and VMAT, respectively. In 1 patient, and only for VMAT, target coverage with PV_B was sufficient in all weekly evaluations. For IMPT, unacceptable target coverage was found in all weekly evaluations in 3 of 5 patients. As shown in Figure 5 for evaluations of PV_B, target dose coverage starts to become unacceptable for IMPT and VMAT for diaphragm variations larger than 10 mm. Within this threshold, some failing cases are still present.

Overall, target dose coverage improved with PV_BD and PV_T, compared to PV_B. For PV_B, 29 cases (of the 77 cases in total) failed, which could be reduced to 24 and 21 by PV_BD and PV_T, respectively. For VMAT, a reduction from 25 to 16 and 12 failing cases could be achieved by PV_BD and PV_T, respectively. Figure 5 shows that, on average, the dose coverage for both the IMPT and VMAT plans was best for the PV_BD method. Especially for the cases showing diaphragm variations of more than 10 mm, PV_BD and PV_T were able to improve target dose coverage substantially. However, for some cases, target coverage remained unacceptable. For the IMPT plans of patients 9, 11 and 13, sufficient target dose coverage could not be reached in any of the evaluations, but target dose coverage improved up to 43% using PV_BD.

A visualization of the target coverage for the 3 PV methods is included in Figure 6, which shows that a caudal diaphragm offset resulted in target coverage loss at the caudal border of the CTV, as well as a dose increase in the diaphragm region next to the heart. Cranial diaphragm offsets resulted in even more target dose coverage loss, appearing in the diaphragm region. Both the underdosage and overdosage regions were reduced when using PV_BD or PV_T, compared to PV_B.

Discussion

This study shows the effect of diaphragm variations on proton and photon target dose coverage and the influence of different PV methods. Generally, both IMPT and VMAT proved to be sufficiently robust modalities for radiation therapy treatment of esophageal cancer. For most cases, the conventional PV_B is sufficient to achieve good target dose coverage. Diaphragm deviations up to 10 mm usually ensured a target dose coverage of at least 94% by the PV_B method. For these cases, PV_BD and PV_T performed equally well. Differences between the 3 investigated PV methods were only observed for diaphragm displacements of more than 10 mm when the PV_B method was not found sufficient anymore. The PV_BD and PV_T method showed an improvement of the target dose coverage for these cases compared to PV_B. Patient 9 is an example where replanning was necessary regardless of the chosen PV method. For this patient, the PV_BD restored the target dose coverage best and would be appropriate as a temporary solution until the adapted plan is available. Generally, the PV_BD method was found suitable in almost all cases. PV_T is the preferred method when the diaphragm is not clearly visible, which occurred in the last treatment weeks of patient 3 due to pleural effusion.

The effect of diaphragm offsets on the target dose coverage was larger for the cranial offset of the diaphragm compared to caudal offsets. For both directions, target deformation occurred, where the cranial shift of the diaphragm additionally resulted in increase of tissue densities in the beam path. As expected, VMAT was on average less sensitive to these density changes than IMPT. However, for specific patients (patient 15), the VMAT plan was more affected by the diaphragm displacement than the IMPT plan, congruent with the results of Møller et al[12] for IMRT. This can be explained by the greater lateral dose contribution in the photon plans, depending on how the optimization was steered to reduce heart dose. The increased density changes caused underdosage in the GEJ region, where the dose coverage of the GTV could also be affected. The caudal diaphragm offset caused underdosage at the caudal CTV border and beam overshoots. This mainly resulted in increased heart dose, due to the use of posterior beams in IMPT and hotspots that arose near the heart in VMAT. Similar target coverage loss and increased heart dose due to diaphragm variations has been reported by Nyeng et al,[11] which could clinically result in lower tumor control and increased risk of cardiac complications.

The CBCT-based intrafractional displacement analysis showed that diaphragm displacements pretreatment were usually still present posttreatment. This confirms that the pretreatment diaphragm position remains relatively constant during a fraction, that the potential target dose coverage loss (caused by the diaphragm deviation) persists, and that an additional correction indeed is beneficial. Nevertheless, smaller displacements tend to occur both intra- and interfractionally, and therefore we advise applying a threshold with regard to the diaphragm position correction rather than applying a correction as a default.

The CBCT-based motion analysis showed that interfractional cranial displacements of the diaphragm occurred more often than caudal displacements and were more likely to deviate further during a fraction. Cranial offsets especially have the risk to result in dose deviations. Generally, displacements seen in the 4DCTs followed the same trend as displacements seen in the (4D)CBCTs. Monitoring diaphragm positions is essential to evaluate trends and the need for replanning. Incidental deviations occurred, emphasizing the added value of the PV_BD method, to be able to handle deviations online in an efficient way. Additionally,

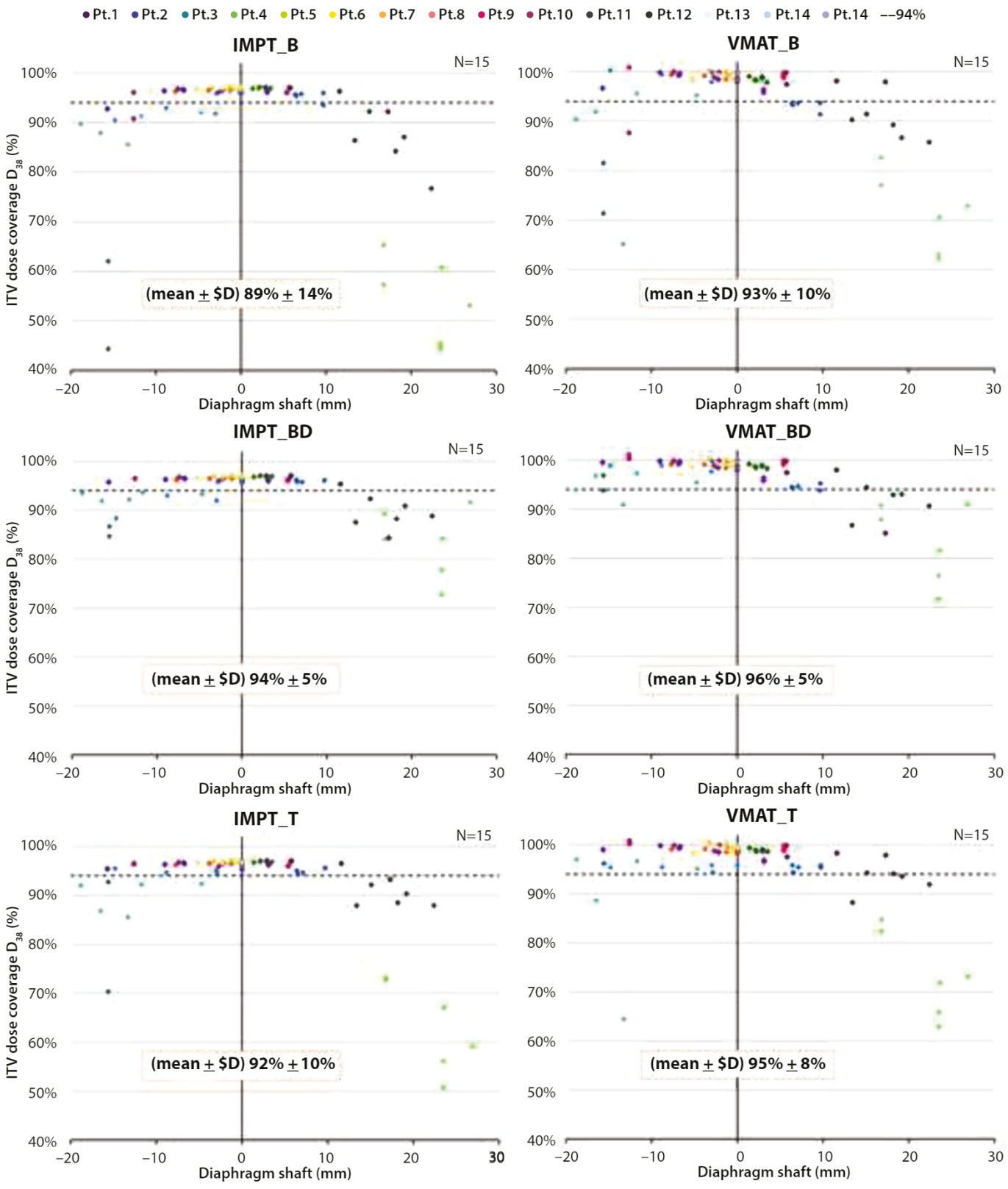

Fig. 5. Robustness evaluation outcomes of the target (ITV) coverage ($D_{98\%}$ [%]) against left diaphragm baseline shifts for both IMPT and VMAT treatments and for the 3 position verification methods. Fifteen patients were evaluated with each showing 4 to 6 datapoints, determined by evaluation on weekly repeated 4DCTs. The dotted line represents the acceptance level of 94% dose coverage. Negative shifts of the diaphragm represent a caudal displacement. *Abbreviations*: PV_B = position verification based on bony anatomy; PV_BD = position verification based on bony anatomy corrected for the diaphragm position; PV_T = position verification based on the target volume.

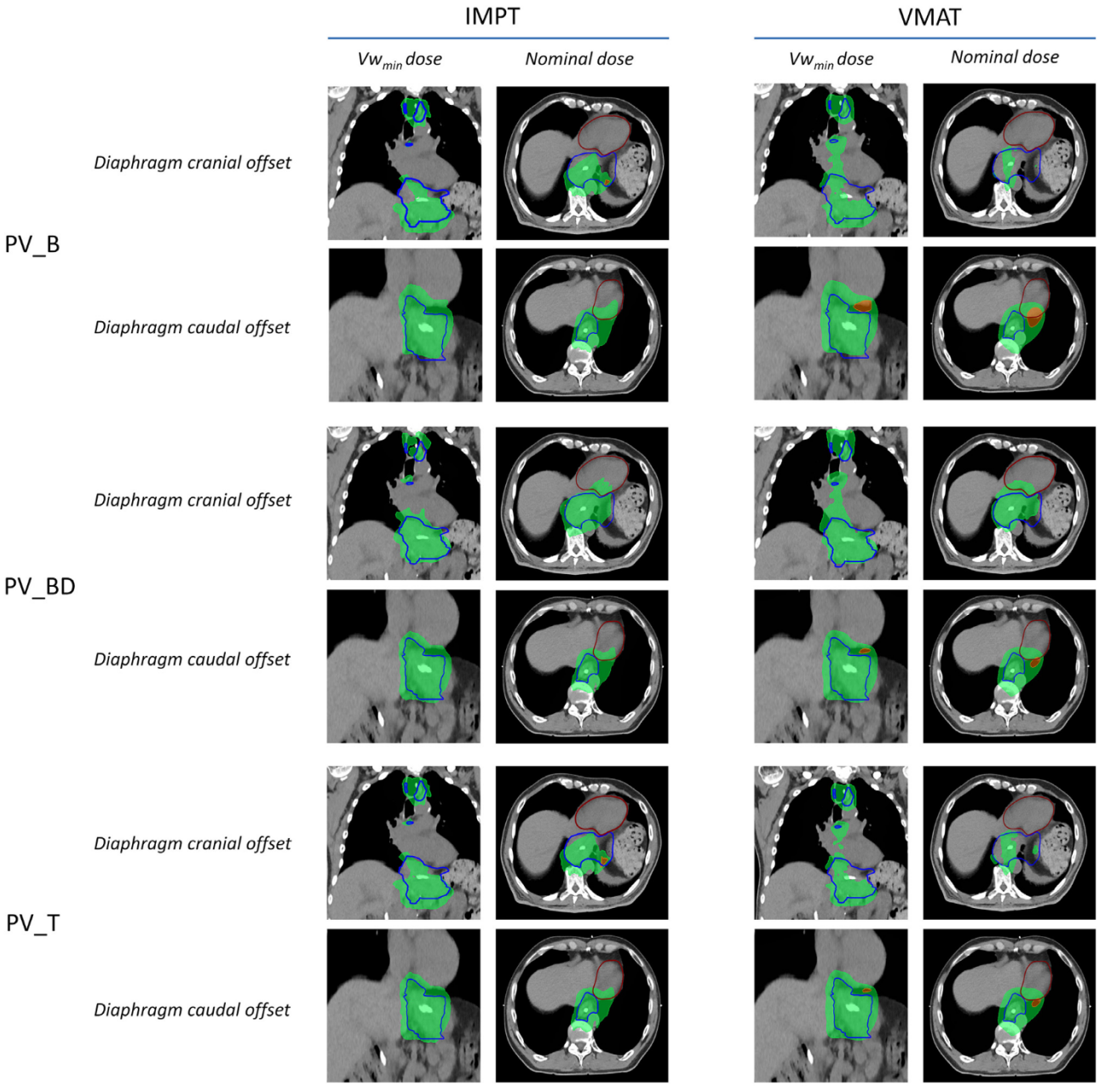

Fig. 6. Dosimetric results for patient 9 and patient 4, showing a cranial and caudal diaphragm offset, respectively. The voxel-wise minimum dose (Vw_{min}), which is evaluated for the target (ITV, blue) dose coverage, is shown in the coronal plane and the nominal dose, which is evaluated for the OARs (heart, red), is shown in the axial plane. The 94% and 107% dose is shown in green and orange, respectively. The cranial offset resulted in target dose coverage loss in the gastro esophageal junction region for both IMPT and VMAT for position verification based on bony anatomy. The caudal offset of the diaphragm resulted in target coverage loss at the caudal border of the target volume and overdosage in the heart region for both modalities. For both patients and both modalities, position verification based on bony anatomy corrected for the diaphragm position and based on the target volume were able to restore most of the target coverage loss and reduce undesired high dose regions outside the target. *Abbreviations*: PV_B = position verification based on bony anatomy; PV_BD = position verification based on bony anatomy corrected for the diaphragm position; PV_T = position verification based on the target volume.

in case of persistent small deviations, applying PV_BD could avoid the need for replanning. Applying efficient daily diaphragm corrections during PV becomes increasingly relevant to improve daily dose delivery in the context of more conformal treatments, margin reductions and hypofractionation.

Many inter- and intrafractional motion analyses in esophageal cancer have been described in literature.[20-23,26]

However, only a few studies describe the actual dosimetric effect of motion and displacements for this indication. This study shows the dosimetric effect of displacements of the target and the clearly relevant influence of changing anatomy outside the target. Markers and 4D imaging have facilitated accurate motion monitoring, mainly focusing on the GTV. However, the targeted volume is the CTV, which is usually extended outside the GTV by 30 mm in cranial-caudal direction and therefore might show different motion characteristics. Especially the caudal abdominal part is subject to anatomic changes. For the CTV, we found, congruent with previous studies, that the largest interfractional displacements occur in cranial-caudal direction, followed by the anterior-posterior direction.[20-23] These displacements were usually found in the GEJ region. Like Wang et al,[27] we concluded that the diaphragm could be a good surrogate for displacements in the GEJ region. However, other parts of the CTV shift in less extent and, as Voncken et al[23] showed, the diaphragm cannot be used as a full displacement surrogate for the entire target in esophageal cancer patients.

The line fitted through the mean CTV displacement as a function of the diaphragm displacement in the cranial-caudal direction had a slope of 0.439. Therefore, the CTV displacement was on average equal to 0.44 times the diaphragm displacement. We decided to round this up to half of the diaphragm displacement as the correction measure in PV_BD, because this approach is more practical to implement in clinical practice and more in line with the inclusion of the second patient group (where a slope of .459 was found). Our detailed motion analysis revealed that the cranial border is less subject to diaphragm displacements. Therefore, caution has to be taken to not shift the isocenter too far to prevent cranial miss. However, other parts of the CTV might profit from an extended correction. In our patient group, the isocenter was shifted more than 8 mm (which complies with the ITV-PTV margin, eg, robustness settings) in caudal direction in 3 patients. For these patients (where shifts around 10 to 15 mm were applied in PV_BD), one can observe cranial underdosage. Further analysis is necessary to determine whether thresholds need to be defined. Also, the target coverage is not only influenced by the diaphragm position. Other factors (eg, gastric filling, mediastinal changes and pleural effusion) can also influence the target coverage.[11,12] For patients 11, 12, and 13, lateral displacements of the target volume were observed next to diaphragm displacements. With PV_BD, we can correct for the diaphragm displacement and target coverage improved substantially. However, these other factors are not accounted for when employing the diaphragm-based position verification, and target coverage was still insufficient, but still, PV_BD gave better outcomes than PV_B and similar outcomes as PV_T. These disturbing factors highlight the importance of repeated imaging and should be monitored alongside the position of the diaphragm. In case of persisting deviations, replanning is unavoidable and PV_BD reduces the underdosage in the period the adjusted treatment plan is not available yet.

Not only the target should be aligned during PV, but also density changes in the beam path have to be accounted for, especially in proton therapy. In the current beam setup for IMPT, potential misalignment of the bony anatomy in the beam can lead to disturbances in the dose distribution. Additionally, diaphragm variations cause density changes in the beam paths for both IMPT and VMAT. Because this was better accounted for using the PV_BD method, this could explain the superiority of the PV_BD method compared to the PV_T method. Furthermore, other than PV_T, the PV_BD method could be compatible with both CBCT and two-dimensional kV verification. In both, the bony anatomy and the diaphragm can be visualized simultaneously. However, to mimic the current method, either the kV-acquisition in expiration has to be guaranteed, or fluoroscopy capturing the whole breathing cycle needs to be applied.

For our study, repeated 4DCTs were used for image registration and to assess the dosimetric effect of diaphragm displacements and different PV methods. However, the actual PV takes place between the average planning CT and the CBCT acquired before treatment, with different image registration algorithms and less soft tissue contrast compared to repeat CTs.[18] Especially the described PV_T method could become unsuitable because the registration is susceptible to inaccurate soft tissue matching. However, in the study of Hoffmann et al[22] all automatic soft tissue matches based on the CTV were manually checked and no corrections were indicated. The soft tissue match itself can also be conducted in different ways defined by the user, which can, in turn, lead to different results for the automatic soft tissue registration. Moreover, the PV_T resulted in increased rotational shifts of the treatment couch to account for larger target deformations, similar to the results of Hawkins et al.[18] Besides impractical reasons of larger rotations in terms of collisions and limitations of application on the treatment machine, larger residual errors were found for patients without fixation to the treatment couch, if larger pitch and roll rotations are applied.[34] Still, it is important to note that we found a benefit of PV_T compared to PV_B, which is in accordance with previous studies.[18,22]

In contrast to the registration focusing on bony anatomy or the target, in the registration focusing on the diaphragm, automatic registration is not always possible and must be performed manually. This could have caused interobserver variations in the performed analysis and may cause variations in the registrations performed clinically. From our experience, it is advisable to create auxiliary diaphragm structures to support diaphragm-based monitoring and registration. This makes the process more efficient and less error-prone.

We chose to focus on the diaphragm position in the expiration phase, because the highest border of the diaphragm is the easiest region to interpret on the CBCTs, whether 3D or 4D. More important, the most cranial position of the diaphragm proved to be the most important to detect increased tissue densities in the beam path. Moreover, we chose to

focus on the left diaphragm, because esophageal tumors are usually more oriented to the left side. However, in the context of increased densities in the beam path, the position of the right diaphragm might be equally important, especially for the used beam setup of IMPT. However, a previous study confirmed similar displacement patterns of the right and left diaphragm, and thus we assume that this would have little effect on the outcomes presented here.[10]

In the current study, ITV dose coverage was evaluated on the average CT. Although motion during the whole breathing cycle is partially captured by the ITV and the average CT, the average CT remains a static image and, therefore, questions arise whether this dose is representative, especially in proton therapy. Motion itself tends to have a blurring effect on the dose distribution. Accumulated dose evaluations based on calculation on all phases of the 4DCT resulted in similar target dose coverage compared to the average image.[10,35-37] However, the entire dose is not delivered to each single phase, and interplay has to be accounted for to simulate a more realistic dose evaluation.[14] Although the effect of interplay is usually considerable when only one fraction is considered, Yu et al[13] showed that, for most patients, the motion- and interplay-induced errors in one fraction were limited using robust optimization and posterior beams for esophageal cancer.[35,38,39] Other studies show how the effect of interplay- and motion-induced errors vanishes when including multiple fractions.[37,40,41] Active and/or passive motion management techniques, such as rescanning, limit the dose deviations even further.[42,43] These effects were not taken into account in this study, because we do not believe this is necessary in the current context. However, to support our decision and conclusion, we selected the most problematic patients from each of the 2 patient groups (in terms of diaphragm deviations, target underdosage and target motion) to validate our results in a comprehensive setting. This evaluation simulates the actual given fraction as realistically as possible, by including motion and interplay effects, next to setup and range errors.[15,32] Using this evaluation, we found the same conclusions (more details and results are included in the Supplementary Materials [Suppl. C]).

Our work resulted in a successful introduction of PV_BD as a new position verification protocol for esophageal cancer in both the proton and photon clinical workflows when diaphragm deviations larger than 8 mm occur. We chose to decrease the threshold from 10 to 8 mm, because the positioning on the treatment machine is usually better than on the CT, due to additional kV-imaging and optical surface monitoring assistance. Furthermore, we apply a maximal cranial-caudal shift of 8 mm to avoid overcompensating, which is in line with the used (robustness) margins.

Based on our findings and planning techniques, we recommend using online imaging and PV based on bony anatomy initially for both IMPT and VMAT in the treatment of distal esophageal cancer. The position of the diaphragm can be subsequently visualized and checked. As the target dose coverage was affected for diaphragm variations above 10 mm, an additional shift to correct for the diaphragm position (PV_BD) could be applied to achieve the most optimal target dose coverage. In this way, unexpected displacements can be handled efficiently to restore most of the target coverage loss and eliminate the need for replaning. Especially cases showing a cranial displacement of the diaphragm could benefit from this method. If the target dose coverage is still inadequate, PV_BD showed to improve the target coverage best and could serve as temporarily solution until replanning has been performed.

Conclusions

Position verification in VMAT and IMPT for esophageal cancer based on bony anatomy can be improved with an additional diaphragm position correction in case of large diaphragm displacements. Better target dose coverage can be achieved compared with image registration based on bony anatomy alone or based on the target.

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