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Basic Original Report

Quantification of Esophageal Tumor Motion and Investigation of Different Image-Guided Correction Strategies

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Abstract

Purpose: To accurately quantify esophageal tumor position variability and to optimize image guided correction strategies.

Material and Methods: Esophageal cancer patients receiving chemoradiotherapy (41.4-50.4 Gy in 23-28 fractions combined with carboplatin plus paclitaxel) were included in a prospective cohort study (NCT02139488). Gold fiducial markers were inserted into the esophageal tumors during diagnostic endoscopic ultrasound. Four-dimensional (4D) planning computed tomography (CT) and daily 4D cone beam (CB) CT scans were acquired. Each CBCT was registered to the planning CT using different regions of interest (bone; 3D), and carina, diaphragm, clinical target volume (CTV), and fiducial markers (4D) for alignment and using the fiducial markers as the true tumor position. Subsequently, a planning target volume (PTV) margin accounting for residual uncertainties, including the average respiratory motion, was calculated for each of these registrations.

Results: Fifty-six patients with tumors located in the proximal (n = 1), mid (n = 7), or distal esophagus (n = 25) or at the gastroesophageal junction (n = 23) were included. The average peak-to-peak respiratory tumor motion was 0.20, 0.92, and 0.34 cm on the planning CT in left−right (LR), cranial−caudal (CC), and anterior−posterior (AP) directions, respectively. The required PTV margin with average motion amplitude, depending on the correction strategy used for image guidance, ranged from 0.8 cm to 1.0 cm, 1.1 cm to 1.6 cm, and 0.7 cm to 0.9 cm in LR, CC, and AP direction, respectively. A registration based on the CTV resulted in the smallest PTV margins (0.8, 1.1,

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and 0.7 cm in LR, CC, and AP direction, respectively). For bone registration the calculated PTV margins were 1.0, 1.3, and 0.7 cm in LR, CC, and AP directions, respectively. The registration based on the diaphragm increased PTV margins.

Conclusions: Substantial and anisotropic position variability of esophageal tumors was observed during radiation therapy, and nonuniform margins should be considered. Cranial-caudal PTV margins need to be larger than those commonly used. Target positioning during image-guided radiotherapy could be improved with a CTV registration-based correction strategy.

Introduction

Esophageal cancer is the sixth leading cause of cancer-related death worldwide.[1] Multimodal treatment strategies comprising neoadjuvant chemoradiotherapy (nCRT) plus surgery or definitive chemoradiotherapy (dCRT) have improved survival of patients with locally advanced esophageal cancer.[2-4]

For optimal irradiation of esophageal cancer, accounting for geometric uncertainties such as respiratory motion and day-to-day position variability of the tumor is required. To compensate for these uncertainties, planning target volume (PTV) margins are applied. Frequently these margins are generous, isotropic, and equal for all patients. Consequently, organs at risk adjacent to the CTV are exposed to high levels of irradiation, resulting in increased risk of toxicity of the heart or lungs.[5,6] Detailed knowledge of the position variability, respiratory motion, and identification of the region of interest (ROI) could improve target alignment in esophageal cancer irradiation.

Image guided radiation therapy (IGRT) has been developed to reduce geometric uncertainties by acquiring images before treatment and making corrections accordingly. Cone beam computed tomography (CBCT) is currently the state of the art IGRT imaging modality. However, its image quality is lower than diagnostic CT. Bone registration is feasible on CBCT and currently widely used for esophageal radiation therapy setup. Fiducial markers, placed during endoscopic ultrasound (EUS), can facilitate esophageal tumor localization on CBCT and have been safely implemented in mediastinal and upper abdominal tumors.[7,8] Although fiducial markers optimize the visibility on CBCT, studies on fiducial-based registration reported conflicting data, and currently a fiducial-based registration is not recommended for clinical practice.[9]

Therefore, a more robust correction strategy, preferably without fiducial markers, is needed to optimize IGRT. In this study we explored correction strategies on bone, carina, diaphragm, and CTV for IGRT alignment of esophageal tumors. The aims were to quantify interfraction, intrafraction, and respiratory motion variability and to investigate the effect of these image-guided correction strategies on the required PTV margins.

Materials and Methods

From April 2014 until February 2018 a single center prospective cohort study (NCT02139488) included patients with esophageal cancer who were planned for curative chemoradiotherapy. Chemoradiotherapy regimen consisted of 41.4 Gy (for nCRT) or 50.4 Gy (for dCRT) in 1.8 Gy fractions concurrently given with weekly intravenous paclitaxel (50 mg/m^2) and carboplatin (AUC 2 mg/mL/min). All included patients underwent diagnostic endoscopy and EUS with fiducial marker placement before the start of treatment. Patients were excluded from the analysis if all fiducials were lost before the planning CT (pCT) or if none of the fiducials were visible on 4-dimensional (4D) CBCT.

Written informed consent was obtained in all patients according to the International Conference of Harmonization/Good Clinical Practice and national and local regulations. This study was approved by the institute's medical ethical committee.

Staging and marker placement procedure

Staging procedures included a contrast enhanced CT-thorax/abdomen, ^{18}fluorodeoxyglucose positron emission tomography CT scan, an endoscopy, and EUS. The endoscopy (Olympus GIF-H180/H190) and EUS (Pentax EG3870UTK/EG3270UK) were performed under conscious sedation (fentanyl and midazolam). After endoscopic and endosonographic staging, sterile gold fiducial markers (0.35 × 5.0 mm; Visicoil, RadioMed, Barlett, TN) were implanted using a 22-gauge cytology EUS needle (Cobra, Sonotip). The goal was to insert 3 fiducial markers in the tumor (proximal, central, and distal) under EUS guidance. If the tumor was stenotic leading to a no-pass during EUS, the distal fiducial was placed as distal as possible or only 2 fiducials were inserted. No prophylactic antibiotics were prescribed.

Location of the tumor and fiducials were classified according to the American Joint Committee on Cancer manual into 4 subgroups based on their location: proximal, midthoracic, distal, and gastroesophageal junction (GEJ).[10]

Image acquisition

All patients received a 4DCT (Siemens, Somatom sensation open, Erlangen, Germany) with intravenous contrast (3-mm slice thickness) after fiducial insertion. Oral contrast was not administered to ensure visibility of the fiducial markers. Patients were positioned supine and stabilized with an armrest (ThoraxSupport, MacroMedics, Waddinxveen, The Netherlands). A midposition pCT scan was subsequently reconstructed from the 4DCT scan for delineation and dose calculation.[11,12] The GTV was contoured on the pCT by the radiation oncologist with all diagnostic information of diagnostic CT, positron emission tomography CT, endoscopy, or EUS with fine-needle aspiration, reflecting clinical practice. Before December 2016 the clinical target volume (CTV) was defined as follows: the CTV comprised the GTV, extended with a 35-mm cranial-caudal (CC) margin and a 5-mm margin in the transverse plane and was extended to include all pathologic lymph nodes. The CTV delineation into the gastric mucosa could be limited to 20 mm. From December 2016 onwards, the clinical delineation protocol was modified according to the adaptations in the national standard; the CTV included the esophageal GTV with circumferential borders restricted to the periesophageal fat. The periesophageal fat was delineated for 30 mm in CC direction from the GTV or extended to include all pathologic lymph nodes. The isotropic CTV to PTV margin in all directions was 10 mm for the first and 12 mm for the second period.

Daily 4D-CBCT scans (Synergy 4.6, Elekta Ltd, Crawley, UK; augmented with in-house developed software) were acquired and bony anatomy registration was used for online setup error correction. Once a week, an additional 4D-CBCT scan was performed immediately after treatment delivery to quantify the intrafraction motion. The imaging dose per scan was approximately 2 cGy.

Tumor position variability analysis

The acquired CBCT images were registered to the pCT by experienced IGRT technologists using chamfer registration algorithm (for bony anatomy; 3D) and each fiducial marker individually (4D) or gray-value registration (for carina, diaphragm, or CTV; all 4D). The chamfer registration algorithm segments high densities in the pCT scan and CBCT scan inside the region of interest and minimizes their distance, and the gray value registration uses all gray value information inside the region of interest to optimize the similarity between the images. For the following regions of interest, a rectangular-shaped clipbox was used: the bony anatomy, carina, diaphragm, and the fiducial markers with a rectangular clipbox per fiducial. The CTV was registered using a shaped region of interest (Fig 1). For readability, the different regions of interest for registration will now be referred to as bone registration, carina registration, and so on. For the CTV registration the fiducials were erased from the mask to ensure the fiducials did not influence the CTV registration.

To the day-to-day positional variability of the esophageal tumors, the 4D registration results were converted to 3D misalignments by time averaging the displacements per phase in the left−right (LR), CC, and anterior−posterior (AP) direction. Interfraction variability was quantified in terms of grand mean (GM), standard deviation of the patient specific systematic errors (Σ), and root mean square of patient specific random errors (σ).[13] Peak-to-peak breathing amplitudes were calculated from the minimum and maximum displacements in the 4D registration over the breathing phases in 3 directions for both pCT and for all 4D-CBCT scans. The interfraction variability was quantified by the fiducial registration corrected for the bone registration that was driving the clinically applied online couch correction. The intrafraction variability was quantified by subtracting the interfraction displacement from the posttreatment marker registration.

To determine which registration resulted in the smallest PTV margins for IGRT setup, the difference between all registrations and the average of the marker registration was calculated, thus assessing the residual error relative to the fiducial markers for each registration.

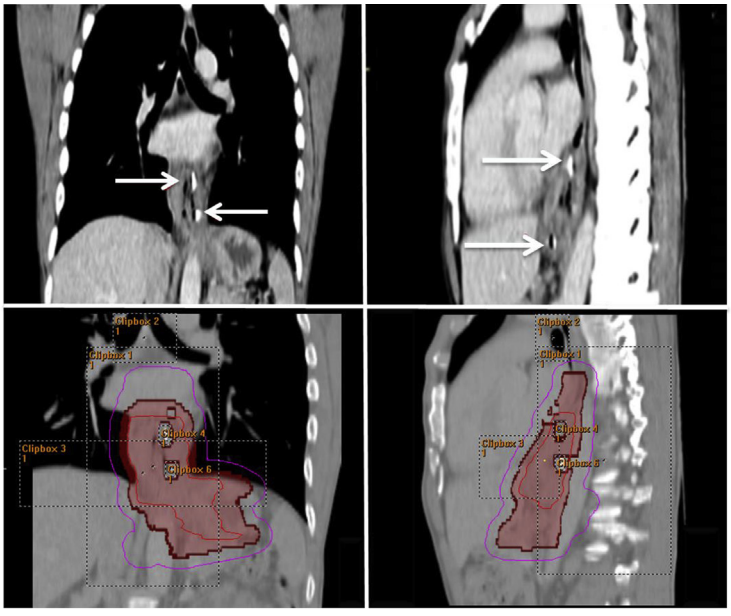
Statistical analyses were performed using SPSS (IBM Corp, Armonk, NY, version 22) and Excel (Microsoft Corp, Redmond, WA, version 14.6.5). Amplitudes of the pCT and CBCT, and comparison of the interfraction variation of the different registrations with the bone registration were tested by Wilcoxon sign-rank test and paired t test. Results with $P < .05$ were considered to be significant.

Margins

Subsequently, the required PTV margin (M) for the different ROI registrations was determined according to the nonlinear van Herk formula.[13,14] The input parameters include the peak-to-peak respiratory amplitude of the tumor (A), the systematic errors ($\sum$: the overall standard deviations of the systematic errors) and random errors (σ: the overall standard deviation of the random errors). Margins were calculated for all patients and per tumor location separately.

$$M = 2.5 \times \Sigma + \beta \times \sqrt{\sigma^2 + \sigma_p^2} - \beta \times \sigma_p$$

$$\Sigma = \sqrt{\Sigma^2_{interfraction\ motion} + \Sigma^2_{intrafraction\ motion}}$$



Abbreviations: CT=computed tomography, CBCT= cone beam computed tomography, CTV= clinical target volume, PTV= planning target volume.

Figure 1 Planning computed tomographic scan with fiducial markers (white arrows, 2 upper figures) and cone beam computed tomographic scans (lower figures) with clinical target volume registration (brown mask) and planning target volume (pink) contours and the different clipboxes used for registration of the different region of interest. Clipbox 1: bone; 2: carina; 3: diaphragm; 4 and 5: fiducials. (A color version of this figure is available at https://doi.org/10.1016/j.prro.2019.11.012.)

$$\sigma = \sqrt{\sigma^2_{interfraction\ motion} + \sigma^2_{intrafraction\ motion} + (0.36 \times A)^2}$$

where β is a factor that depends on the prescription dose level (1.64 for 95%) and σ_p a parameter that reflects the penumbra width. Because esophageal tumors tend to border both to lung and mediastinal tissue, σ_p was conservatively chosen to reflect the penumbra in water ($\sigma_p = 0.32$ cm). Margins to cover the CTV with 95% of the prescribed dose for 90% of the patients were calculated to account for the residual geometric uncertainties for the different regions for registration and corrections, for the complete patient group, and per tumor location specific. The average peak-to-peak amplitude of the tumor on the pCT was used for margin calculations of the complete patient group and per tumor location separately.

Marker stability

Using the average marker position as a surrogate of the tumor position assumes that the position of the markers relative to the tumor is constant. For all fractions, the individual marker position was compared with the center of mass of the fiducials and quantified in terms of systematic and random errors.

Results

Sixty-eight eligible patients signed informed consent for this prospective study. Twelve patients were excluded from this analysis for the following reasons. In 7 patients, all inserted fiducial markers were lost. In 3 patients, attenuation of subdiaphragmatic soft-tissue caused poor visibility of all fiducial markers prohibiting daily 4D registration in all phases. One patient withdrew from the study, and in another patient the 4D-CT reconstruction failed. A total of 56 patients (40 male) with a median age of 64 (range, 37-84) years were included in this analysis. Most patients (91%) were treated with neoadjuvant chemoradiotherapy (Table 1).

Per patient, a median of 3 fiducials was inserted in the tumor. In 16 out of 56 patients, tumor stenosis hampered passage of the EUS probe to the distal border, resulting in fiducials in tumor at the proximal border, middle part, and as distal as possible. This most distal fiducial was located at a median of 2 cm cranial of the distal tumor border, as determined during endoscopy. No adverse events related to the EUS fiducial insertion procedure (ie, no infection, perforation, bleeding) occurred. Out of 152 implanted fiducials, 126 were visible on the pCT (all 126 located in the esophageal tumor mass) and 118 on the first CBCT (Table 1). In total, 115 out of 118 fiducials that were identified on the first CBCT remained visible during the complete treatment period. However, 7 of these 115 fiducials were not visible in all 4D-CBCT phases, which prohibited 4D-CBCT registration. Figure 2 shows the location of the 108 inserted fiducials in 56 patients. A total of 1453 4D-CBCT scans were evaluable, or on average 26 per patient.

Table 1 Baseline characteristics of patients included in this analysis

Patient characteristics	(n = 56)
Age, median (range), y	64 (37; 84)
Sex	
Male	40
Female	16
Histology	
Adenocarcinoma	46
Squamous cell carcinoma	9
Adenosquamous	1
Location of the primary tumor	
Proximal esophagus	1
Middle esophagus	7
Distal esophagus	25
Gastroesophageal junction	23
Stage*	
IB	4
IIA	10
IIB	10
IIIA	15
IIIB	14
IIIC	3
Radiation dose	
41.4 Gy (23 × 1.8 Gy)	51
50.4 Gy (28 × 1.8 Gy)	5
No. of fiducials inserted at EUS	
1 fiducial	1
2 fiducials	16
3 fiducials	37
4 fiducials	2
Total no. of fiducials (median/patient)	
No. of inserted fiducials EUS	152 (3)
No. of fiducials at planning CT	126 (2)
No. of fiducials visible on first CBCT	118 (2)
No. of fiducials visible on last CBCT	115 (2)
No. of fiducials visible on last CBCT in all 4D-phases	108 (2)

Abbreviations: 4D = 4-dimensional; CBCT = cone beam computed tomography; CT = computed tomography; EUS = endoscopic ultrasonography.

* According to the seventh edition of the tumor-node-metastasis classification.

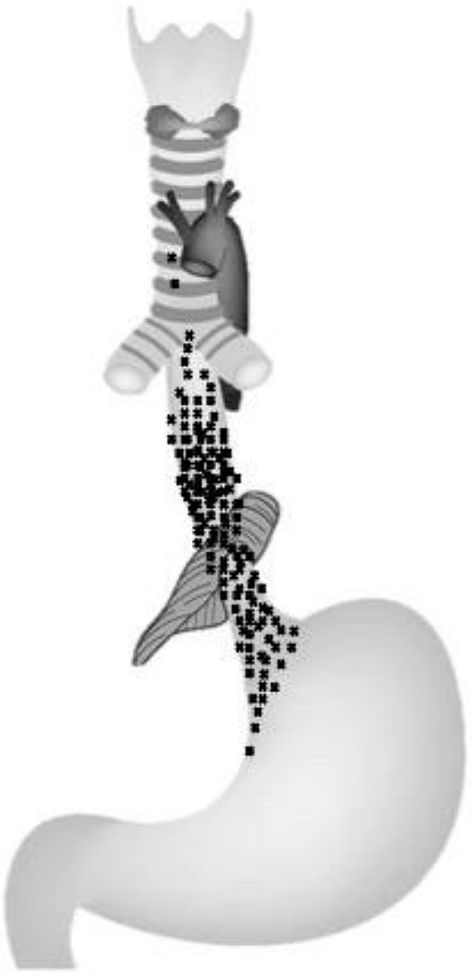


Figure 2 Representation of the locations of the 108 fiducials markers of 56 patients at the planning computed tomographic scan. Each "X" reflects one fiducial.

Marker stability

The individual marker position compared with the center of mass over the treatment period showed a systematic and random error of 0.09 and 0.08 cm, respectively.

Interfraction variability

The systematic interfraction variation of tumor position relative to the bone registration was 0.24, 0.27, and 0.17 cm in the LR, CC, and AP directions, respectively, whereas the random baseline variation was 0.35, 0.47, and 0.26 cm, respectively. The residual interfraction variability for correction strategies based on the different registrations (bone registration, carina registration, diaphragm registration, and CTV registration) are shown in Table 2. The largest systematic error was seen in CC direction. The CTV registration reduced the systematic error of the tumor in LR ($P < .001$) and CC ($P = .049$) direction. The carina registration reduced the systematic error in the CC direction ($P < .001$) but significantly increased in AP direction ($P = .02$), whereas the diaphragm registration significantly increased the systematic error in both CC ($P = .01$) and AP ($P < .001$) directions.

Intrafraction variability

The average (range) peak-to-peak amplitude of the esophageal tumor on the pCT was 0.20 (0.1-0.6), 0.92 (0.2-2.3), and 0.34 (0.0-1.2) cm in LR, CC, and AP, respectively (Table 3). The average peak-to-peak

Table 2 Interfraction tumor position variability relative to the different registrations

Variability	LR (cm)	CC (cm)	AP (cm)
Bone registration			
GM	0.07	−0.13	0.05
Σ	0.24	0.27	0.17
σ	0.35	0.47	0.26
Carina registration*			
GM	0.03	−0.17	−0.18
Σ	0.25	0.23†	0.23‡
σ	0.35	0.38†	0.33‡
Diaphragm registration*			
GM	−0.01	0.08	-0.14
Σ	0.24	0.34‡	0.23‡
σ	0.34	0.54	0.38‡
CTV registration*			
GM	−0.03	−0.03	−0.01
Σ	0.21†	0.24†	0.18
σ	0.29†	0.35†	0.27

Abbreviations: Σ = systematic error; σ = random error; AP = anterior-posterior; CC = cranial-caudal; cm = centimeters; CTV = clinical target volume; GM = grand mean; LR = left-right; ROI = region of interest; SD = standard deviation.

This table shows the interfraction tumor position variability relative to the different registrations. The grand mean (GM), SD of systematic errors (Σ), root mean square of random errors (σ) of the bone, carina, diaphragm and CTV-registration–based setup strategy.

* Systematic and random errors of carina registration, diaphragm registration, and CTV registration were compared with bone registration. Numbers marked with a double dagger (‡) represent statistical significant increase and marked with dagger (†) represent statistical significant decrease of the registration compared with the bone registration.

Table 3 Amplitudes of the fiducial marker motion measured on the 4D-planning CT and 4D-CBCT for all patients and intrafraction fiducial marker variability between pretreatment and posttreatment CBCT

Variability	LR (cm)	CC (cm)	AP (cm)
Amplitudes pCT			
Average	0.20	0.92	0.34
Standard deviation	0.12	0.37	0.22
Range	0.1-0.6	0.2-2.3	0.0-1.2
Average (range) of amplitudes on pCT by tumor location			
Mid + proximal	0.15 (0.1-0.2)	0.73 (0.2-1.4)	0.15 (0-0.4)
Distal	0.22 (0.1-0.6)	0.97 (0.5-1.7)	0.38 (0.1-0.8)
GEJ	0.20 (0.1-0.5)	0.93 (0.5-2.3)	0.38 (0.1-1.2)
Amplitudes CBCT			
Average	0.17	0.88	0.31
Standard deviation	0.07	0.35	0.16
Range	0.06-0.43	0.13-1.84	0.04-0.64
Amplitude difference pCT and CBCT			
GM	0.03	0.02	0.03
Σ	0.13	0.35	0.19
σ	0.13	0.19	0.18
Intrafraction position variability			
GM	0.06	0.02	−0.11
Σ	0.14	0.19	0.09
σ	0.23	0.19	0.17

Abbreviations: Σ = systematic error; σ = random error; 4D = 4-dimensional; LR = left-right; AP = anterior-posterior; CBCT = cone beam computed tomography; CC = cranial-caudal; cm = centimeters; GEJ = gastroesophageal junction; GM = grand mean; pCT = planning computed tomography.

amplitude of the tumor during treatment was 0.17, 0.88, and 0.31 cm, respectively, not significantly different from the pCT ($P = .07$, $P = .49$, $P = .27$, respectively). The group mean amplitude difference between pCT and CBCT during treatment was 0.03, 0.02, and 0.03 cm in LR, CC, and AP, respectively, whereas the systematic/random amplitude difference was 0.13/0.13, 0.35/0.19, and 0.19/0.18 cm, respectively.

Margins

Margins per registration and per tumor location, calculated with the average breathing amplitude, are presented in Table 4. The bone registration requires a PTV margin of 1.0 cm in LR, 1.3 cm in CC, and 0.7 cm in AP direction. The CTV registration resulted in the smallest PTV margins, with a LR, CC, and AP margin of 0.8, 1.1, and 0.7 cm, respectively. An increase of the required margins was seen with the diaphragm registration. Differences in PTV margins were seen between the different tumor locations. For bone registration the LR, CC, and AP PTV margins of the GEJ tumor required 1.1, 1.4, and 0.8 cm; for distal esophageal tumors this was 0.9, 1.4, and 0.6 cm; and for mid and proximal tumors the calculated margins were 0.7, 0.9, and 0.4 cm, respectively. For CTV registration these PTV margins for GEJ tumors were 1.1, 1.2, and 0.9 cm; for distal tumors 0.7, 1.2, and 0.6 cm; and for mid and proximal tumors were 0.4, 0.7, and 0.5 cm in LR, CC, and AP, respectively.

Amplitude of motion influenced the PTV margins. In the hypothetical situation that there is no amplitude motion, calculated PTV margins for the CTV registration strategy were 0.8, 1.0, and 0.7 cm for LR, CC, and AP, respectively. The required PTV margin increased with larger amplitude motion. The influence of amplitude motion on PTV margins of a CTV registration is presented in Figure E1 (available online at https://dooi.org/10.1016/j.prro.2019.11.012).

Table 4 PTV margins for different registration strategies for all patients and separately per tumor location

	All patients (n = 56)			GEJ (n = 23)			Distal (n = 25)			Mid + Prox (n = 8)		
	margin (cm)			margin (cm)			margin (cm)			margin (cm)		
	LR	CC	AP	LR	CC	AP	LR	CC	AP	LR	CC	AP
Correction strategy												
Bone	1.0	1.3	0.7	1.1	1.4	0.8	0.9	1.4	0.6	0.7	0.9	0.4
Carina	1.0	1.1	0.9	1.2	1.2	1.0	1.0	1.2	0.8	0.6	0.7	0.7
Diaphragm	1.0	1.6	0.9	1.2	1.5	1.1	0.8	1.6	0.8	0.9	1.5	1.0
CTV	0.8	1.1	0.7	1.1	1.2	0.9	0.7	1.2	0.6	0.4	0.7	0.5

Abbreviations: AP = anterior-posterior; CC = cranial-caudal; cm = centimeters; CT = computed tomography; CTV = clinical target volume; GEJ = gastroesophageal junction; LR = left-right.
The average marker position was taken as a surrogate of the tumor position, and margins were calculated with the average breathing amplitude of the CTV region of interest on the planning CT.

Discussion

Interfraction and intrafraction motion of esophageal tumors were analyzed in 56 patients on daily pretreatment and weekly posttreatment 4D-CBCT scans by using fiducial markers. Substantial and anisotropic tumor motion variability was observed, indicating that anisotropic PTV margins should be considered. This study showed that PTV margins could be reduced with a CTV registration and carina registration compared with bone registration.

The different registration strategies in relation to the fiducials in the primary tumor (GTV) were investigated. Accurate alignment of both CTV and GTV is required for optimal irradiation, especially when SIB techniques are applied. Although a GTV registration could potentially reduce systematic and random errors even further, appropriate CTV coverage is required for the success of the treatment. Therefore, a CTV registration was investigated. Furthermore, motion of the lymph nodes at distance of the GTV was not assessed in this study, as markers were inserted in the primary tumor only. In patients with lung cancer, differential motion between tumor and lymph nodes was observed, and a carina based setup was shown to be beneficial.[15] For esophageal cancer, a carina registration was previously explored in 24 patients and registration was feasible in 95% of the CBCT scans.[16] An increase of the systematic and random error with a carina registration was observed, resulting in larger PTV margins. In the present series, the carina registration significantly increased the systematic and random error in AP direction relative to a bone registration, leading to an increase of the AP margin. Unfortunately, sample sizes for analysis of subgroups per tumor location were too small for strong conclusions. Future studies should investigate whether location-specific correction strategies could be beneficial.

Diaphragm registration was explored because the diaphragm is adjacent to the distal esophagus and GEJ. Unfortunately, registration on the diaphragm resulted in increased positioning uncertainty. The diaphragm deforms during inspiration and the semicircle flattens to a straighter shape. A rigid registration on this deforming diaphragm might lead to rotations and possibly explains its decreased accuracy for setup.

Overall, respiratory motion amplitude was largest in the cranial−caudal direction, and the magnitude of motion depended on the tumor location. Previous studies found similar results; motion of tumors located below the diaphragm showed a larger motion than thoracic tumors.[17-19] Additional individualization of PTV margins is needed owing to these differences in amplitude motion between tumor locations. For most patients with esophageal cancer, radiation therapy is currently delivered after bone setup correction. To improve esophageal cancer radiation therapy a marker-based setup seems an obvious approach and is currently standard of care in other tumor sites (eg, prostate cancer or bladder cancer).[20,21] However, we used fiducial markers for localization of the tumor but advocate a registration without fiducial markers for esophageal IGRT for the following reasons. First, although we did not experience adverse events of the fiducial insertion in our cohort, others reported adverse events in 4 out of 30 patients with esophageal cancer.[22] Second, the present study shows that in 10% of the patients all fiducials were detached and only 76% (115 out of 152) of the fiducials remained visible until the last CBCT. Jin et al reported similar results; only 60% (60 out of 101) of the fiducials remained visible on CBCT during the complete treatment period.[9] And last, esophageal marker displacement was observed in a selection of patients, caused by tumor shrinkage, marker migration, or shape variation of the esophagus and proximal stomach. Likewise, Liu et al[18] reported a moderate correlation between fiducials and primary tumor motion, but results were patient specific, and differential fiducial motion was observed. Therefore marker-based registration was only suitable in a selection of patients. Jin et al also found considerable fluctuations of the pairwise distance of the fiducial markers owing to tissue deformation and concluded that a marker-based registration was not feasible for clinical use.[9] Hence, the

invasiveness of EUS insertion, frequent detachment of fiducial markers, and possible fiducial displacements stresses the need for IGRT setup correction strategy without fiducial markers for esophageal cancer.

Our results show that the required PTV margins are still substantial, even with state-of-the art esophageal IGRT. Furthermore, in the present series, the 4D-CT was reconstructed as a midposition CT. Treatment volumes will increase even further without a 4D technique or with an internal target volume strategy instead of a midposition strategy.[23] Notably, the random error was larger than the systematic error, indicating that anatomic variation, deformation, or tumor response might have influenced these errors. Furthermore, other uncertainties, such as marker surrogate error, rotations, and delineation errors, were not included in the margin calculation. PTV margins should be increased even more to account for these uncertainties. Cranial−caudal PTV margins need to be larger than nowadays commonly used. Future studies should analyze whether improved soft tissue contrast and daily replanning (eg, with a magnetic resonance imaging Linac) is feasible for esophageal cancer. With ongoing improvements in MR image acquisition (eg, with the 4D-MR technique) further improvements in image quality of the esophageal tumor are expected. With the aim to further reduce margins and thus normal tissue toxicity, treatment delivery after online adaptive planning on the magnetic resonance imaging Linac may further improve accurate dose delivery.

For patients treated with dCRT, local in-field recurrence still occurs in about half of the patients[24] and currently phase II and III prospective dose escalation trials are including patients for simultaneous integrated boost GTV boost strategies.[25,26] In these studies, isotropic PTV margins to the (internal) CTV and (internal) GTV of 0.5 and 0.3 cm, respectively,[26] and 1.0 cm and 1.0 cm, respectively,[25] are applied. For a substantial group of patients, these margins are too small to ensure complete target coverage, especially in CC direction. Accurate delivery without geometric miss of this additional boost is essential for the success of these trials. Also, with pathologic complete response rates of 23% to 49%[27] there is a trend toward the development of organ-preservation strategies for the clinical complete responders after nCRT.[28,29] For these patients who may be cured by chemoradiotherapy alone, a geometric miss could potentially lead to noncomplete response and inevitably lead to esophagectomy. Therefore, an accurate setup correction strategy is needed for both operable and inoperable esophageal cancer patients treated with chemoradiotherapy.

Conclusions

In this prospective study we observed substantial and anisotropic position variability of the esophageal tumor during radiation therapy. Variability was largest in the cranial−caudal direction. Cranial−caudal PTV margins need to be larger than nowadays commonly used to ensure target coverage. Margins were calculated to compensate for the interfraction and intrafraction variability and need to be increased even further to compensate for other uncertainties such as target definition or marker surrogate errors. To further improve esophageal IGRT, anisotropic patient specific margins should be considered. IGRT setup correction with a CTV registration is promising for further improving treatment accuracy in esophageal cancer.

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Supplementary data

Supplementary material for this article can be found at https://doi.org/10.1016/j.prro.2019.11.012.

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;49:1374-1403.
2. Gwynne S, Hurt C, Evans M, et al. Definitive chemoradiation for oesophageal cancer—a standard of care in patients with non-metastatic oesophageal cancer. *Clin Oncol (R Coll Radiol)*. 2011;23:182-188.
3. Shapiro J, van Lanschot JJB, Hulshof M, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (cross): Long-term results of a randomized controlled trial. *Lancet Oncol*. 2015;16:1090-1098.
4. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: An updated meta-analysis. *Lancet Oncol*. 2011;12:681-692.
5. Beukema JC, van Luijk P, Widder J, et al. Is cardiac toxicity a relevant issue in the radiation treatment of esophageal cancer? *Radiother Oncol*. 2015;114:85-90.
6. Lin SH, Zhang N, Godby J, et al. Radiation modality use and cardiopulmonary mortality risk in elderly patients with esophageal cancer. *Cancer*. 2016;122:917-928.
7. DiMaio CJ, Nagula S, Goodman KA, et al. EUS-guided fiducial placement for image guided radiation therapy in GI malignancies by using a 22-gauge needle (with videos). *Gastrointest Endosc*. 2010;71:1204-1210.
8. Schaake EE, Belderbos JS, Buikhuisen WA, et al. Mediastinal lymph node position variability in non-small cell lung cancer patients treated with radical irradiation. *Radiother Oncol*. 2012;105:150-154.
9. 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;117:412-418.
10. Rice TW, Blackstone EH, Rusch VW. 7th edition of the AJCC cancer staging manual: Esophagus and esophagogastric junction. *Ann Surg Oncol*. 2010;17:1721-1724.
11. Wolthaus JW, Sonke JJ, van Herk M, et al. Reconstruction of a time-averaged midposition CT scan for radiotherapy planning of lung cancer patients using deformable registration. *Medical Physics*. 2008;35:3998-4011.
12. Kruis MF, van de Kamer JB, Belderbos JS, et al. 4D CT amplitude binning for the generation of a time-averaged 3D midposition ct scan. *Phys Med Biol*. 2014;59:5517-5529.
13. van Herk M. Errors and margins in radiotherapy. *Semin Radiat Oncol*. 2004;14:52-64.
14. van Herk M, Remeijer P, Rasch C, et al. The probability of correct target dosage: Dose-population histograms for deriving treatment margins in radiotherapy. *Int J Radiat Oncol Biol Phys*. 2000;47:1121-1135.
15. Schaake EE, Rossi MM, Buikhuisen WA, et al. Differential motion between mediastinal lymph nodes and primary tumor in radically irradiated lung cancer patients. *Int J Radiat Oncol Biol Phys*. 2014;90:959-966.
16. Machiels M, Jin P, van Gurp CH, et al. Comparison of carina-based versus bony anatomy-based registration for setup verification in esophageal cancer radiotherapy. *Radiat Oncol*. 2018;13:48.
17. Jin P, Hulshof MC, de Jong R, et al. Quantification of respiration-induced esophageal tumor motion using fiducial markers and four-dimensional computed tomography. *Radiother Oncol*. 2016;118:492-497.
18. Liu F, Ng S, Huguet F, et al. Are fiducial markers useful surrogates when using respiratory gating to reduce motion of gastroesophageal junction tumors? *Acta Oncol*. 2016;55:1040-1046.
19. Yaremko BP, Guerrero TM, McAleer MF, et al. Determination of respiratory motion for distal esophagus cancer using four-dimensional computed tomography. *Int J Radiat Oncol Biol Phys*. 2008;70:145-153.
20. Pos F, Bex A, Dees-Ribbers HM, et al. Lipiodol injection for target volume delineation and image guidance during radiotherapy for bladder cancer. *Radiother Oncol*. 2009;93:364-367.
21. van der Heide UA, Kotte AN, Dehnad H, et al. Analysis of fiducial marker-based position verification in the external beam radiotherapy of patients with prostate cancer. *Radiother Oncol*. 2007;82:38-45.
22. 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;82:641-649.
23. Jin P, Machiels M, Crama KF, et al. Dosimetric benefits of mid-position compared with internal target volume strategy for esophageal cancer radiation therapy. *Int J Radiat Oncol Biol Phys*. 2019;103:491-502.
24. Welsh J, Settle SH, Amini A, et al. Failure patterns in patients with esophageal cancer treated with definitive chemoradiation. *Cancer*. 2012;118:2632-2640.
25. Hulshof MC. Dose escalation study for inoperable esophageal cancer patients. Nederlands trial register (http://www.trialregister.nl). NTR3532, 2012.
26. Welsh JW, Seyedin SN, Allen PK, et al. Local control and toxicity of a simultaneous integrated boost for dose escalation in locally advanced esophageal cancer: Interim results from a prospective phase I/II trial. *J Thorac Oncol*. 2017;12:375-382.
27. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *New Engl J Med*. 2012;366:2074-2084.
28. Noordman BJ, Spaander MCW, Valkema R, et al. Detection of residual disease after neoadjuvant chemoradiotherapy for oesophageal cancer (presano): A prospective multicenter, diagnostic cohort study. *Lancet Oncol*. 2018;19:965-974.
29. Noordman BJ, Wijnhoven BPL, Lagarde SM, et al. Neoadjuvant chemoradiotherapy plus surgery versus active surveillance for oesophageal cancer: A stepped-wedge cluster randomised trial. *BMC Cancer*. 2018;18:142.