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Quantifying the Interfractional Displacement of the Gastroesophageal Junction during Radiation Therapy for Esophageal Cancer

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Abstract

Purpose—Accounting for *interfractional* changes in tumor location improves accuracy of radiation treatment delivery. The purpose of this study is to quantify the *interfractional* displacement of the gastro-esophageal junction (GEJ) based on standard treatment setup in patients with esophageal cancer undergoing radiation therapy.

Methods and Materials—Free-breathing four-dimensional computed tomography (4D-CT) datasets were acquired weekly from 22 patients during treatment for esophageal adenocarcinoma. Scans were registered to baseline (simulation) 4D-CT scans by using bony landmarks. The distance between the center of the GEJ contour on the simulation scan and the mean location of GEJ centers on subsequent scans was used to assess changes in GEJ location between fractions; displacement was also correlated with clinical and respiratory variables.

Results—Mean absolute random error (range) was 1.69 mm (0.11–4.11 mm) in the lateral direction, 1.87 mm (0.51–4.09 mm) anterior-posterior (AP), and 3.09 mm (0.99–6.16 mm) superior-inferior (SI). Mean absolute systemic GEJ displacement between fractions was 2.88 mm lateral (5 mm in 14%), mostly leftward; 2.90 mm (5 mm in 14%) AP, mostly anterior; and 6.77 mm (1 cm in 18%) SI, mostly inferior. Variations in tidal volume and diaphragmatic excursion during treatment correlated strongly with systematic SI GEJ displacement ($r=0.964$, $p<0.0001$; and $r=0.944$, $p<0.0001$, respectively) and moderately with systematic AP GEJ displacement ($r=0.678$, $p=0.0005$; $r=0.758$, $p<0.0001$, respectively). Systematic displacement in the inferior direction resulted in higher-than-intended doses (60 Gy) to the GEJ, with increased hot-spot to the adjacent stomach and lung base.

Conclusion—We found large (>1-cm) interfractional displacements in the GEJ in the SI (especially inferior) direction that was not accounted for when skeletal alignment was alone used

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for patient positioning. Because systematic displacement in the SI direction had dosimetric impact and correlated with tidal volume, better accounting for depth of breathing is needed to reduce interfractional variability.

Keywords

Esophageal cancer; 4D-CT; interfraction displacement

INTRODUCTION

Esophageal carcinoma is relatively rare but deadly, causing 2% of all cancer-related deaths (1). Despite advances in diagnosis and treatment, the overall 5-year survival rate has improved from 3% to only 15% since the mid-1970s (1). Currently, radiotherapy (RT), surgery, and chemotherapy are the main forms of treatment for esophageal cancer. Precise definition of RT fields is crucial for RT planning; however, accurate dose delivery, by three-dimensional conformal RT (3D-CRT) or especially by intensity-modulated RT (IMRT), is limited by the physiologic motion of tumor and critical organs.

Intrafractional esophageal motion can be attributed mostly to respiration, cardiac activity, and peristalsis (2). Lorchel et al (3) first evaluated esophageal tumor motion during respiration in 8 patients. Two similar studies from MD Anderson (4,5) used 4D computed tomography (CT) to quantify the intrafractional motion of gastroesophageal junction (GEJ) tumors in 25 and 31 patients; the mean displacements of the center of the gross tumor volume (GTV) in the superior-inferior (SI) plane were 8.7 mm and 7.1 mm. A subsequent study at Massachusetts General Hospital (6) found that distal esophageal tumors moved more than proximal or mid-esophageal tumors, with mean displacements of 8.9 mm SI and 3.3 mm anterior-posterior (AP). Thus the International Commission on Radiation Units and Measurements (ICRU) recommends establishing an internal margin, in addition to the setup margin, around the clinical target volume (CTV) to account for respiration-induced tumor motion (7, 8).

Although the extent of *intrafractional* motion has been well documented, studies of *interfractional* esophageal motion have been limited. Most patients with esophageal cancer are treated while “free breathing,” with standard laser-tattoo or skeletal alignment used for patient positioning before delivery of each fraction. However, this technique does not account for skin mobility, anatomical changes, or respiratory-related motion of the esophagus between fractions. Failure to account for *interfractional* changes in tumor location can compromise treatment margins and the dose delivered (9), thereby affecting clinical outcomes such as locoregional control, survival, and toxicity to normal surrounding tissues.

The purpose of this study was to assess whether standard treatment set-up based on skeletal landmarks is adequate to account for potential variations in internal organ position, both systematic and random, between delivery of RT fractions for free-breathing patients with esophageal cancer. Specifically, we used 4D-CT for treatment simulation and weekly during treatment delivery to document movement of the GEJ in the lateral, AP, and SI directions. We also assessed whether various clinical or respiratory variables could account for the extent of *interfractional* GEJ motion in these three directions.

METHODS AND MATERIALS

Patient selection

Twenty-five patients with pathologically confirmed esophageal cancer already enrolled in an institutional review board-approved study of tumor motion at MD Anderson Cancer Center were selected for analysis. Three patients who did not have weekly 4D-CT scans adequate for determining *interfractional* GEJ displacement were excluded. Thus, the 4D-CT simulation scans and weekly scans of 22 patients constituted the dataset for this study. All eligible patients had adenocarcinoma, and all were to undergo either definitive or neoadjuvant chemoradiotherapy.

CT image acquisition

For each patient, natural (free) -breathing 4D-CT image datasets were acquired at the time of treatment simulation and weekly just before radiation delivery by using one of two commercial CT scanners (Discovery ST [GE Medical Systems, Waukesha, WI] and MX8000-IDT [Philips Medical Systems, Andover, MA]). Each of the 4D-CT sets was sorted into 10 phases per respiratory cycle using Varian's Real-time Position Management system [RPM™, Varian Medical Systems, Palo Alto, CA]. Information from each CT dataset was then transferred to a commercial radiation treatment planning system (Pinnacle Radiation Treatment Planning Software v 8.2 [Philips, Inc., Madison, WI]).

GEJ contouring

The first 4D-CT dataset, typically that used for treatment planning/simulation, was considered the reference dataset. The GEJ was contoured manually by one radiation oncologist on the reference dataset corresponding to end-expiration (respiratory phase 50%). This GEJ contour was then propagated onto each of the weekly 4D-CT datasets (also corresponding to respiratory phase 50%) and manually moved to the correct anatomical locations. The reference datasets (phase 50%) and each of the weekly datasets (phase 50%) were then fused using bony landmarks for comparison. Fusions were performed using the vertebral spine as the primary reference for alignment because this structure is the most likely to be stationary during respiratory and cardiac cycles. The lungs were also contoured on the reference dataset (phase 50%) and on each weekly dataset (phase 50%) to calculate tidal volume. Geometric centroids were automatically placed at the center of the GEJ contour on the reference dataset and each of the weekly datasets.

Definitions and data analysis

Interfraction displacement was defined as the difference between the GEJ centroid on the reference dataset and that on the weekly scans (both obtained at respiratory phase 50%). All weekly scans were registered to the simulation scans by using bony landmarks; thus the difference in the position of the GEJ centroid represents variations in the soft tissue target relative to bony structures. The interfractional systematic uncertainty/displacement in GEJ location for each patient was then determined as the mean distance between the locations of the GEJ center on the weekly datasets subtracted from the location of the GEJ center on the reference dataset. The random error for each patient was defined as the standard deviation of this mean distance. The calculations of interfractional systematic uncertainty in GEJ location were calculated in the lateral, AP, and SI directions, as well as combined in quadrature to obtain the absolute magnitude of three-dimensional (3D) GEJ excursion.

To test for correlations between the systematic displacement in each of the three directions and clinical/respiratory variables (height, weight, body mass index, delta-tidal volume, vertical diaphragmatic excursion), the interfractional GEJ displacements were plotted

against the clinical/respiratory variables. Spearman correlation coefficients (r) and coefficients of determination (R^2) were calculated using Microsoft Excel 2002.

The dosimetric impact of *interfractional* systematic uncertainty was estimated for two patients with the largest SI displacement of the GEJ by generating DVHs using a 4D dose calculation and accumulation process. In this process, the isocenter was first positioned based on skeleton registration of the weekly 4DCT to the original planning CT. Then the original plan was re-calculated on each phase of the 4D CT set. Deformable image registration was performed between each phase and the reference end-of-expiration phase (10). The resulting displacement vector field was used to map each dose distribution from the phase of interest to the reference phase and then averaged voxel-by-voxel (each phase has equal time interval in the 4D-CT scan). To calculate the cumulative dose from week to week, we used the same deformable mapping process to map the cumulative weekly dose to the planning CT (end-of-expiration phase). The resulting DVHs were then compared with DVHs in the original plan.

RESULTS

Patient characteristics

Characteristics of the 22 patients are summarized in Table 1. The median age at diagnosis was 62 years, and 20 patients (91%) were male. All 22 patients had histologically confirmed adenocarcinoma of the esophagus; tumors in 21 patients were in the distal esophagus (including the GEJ), and the other tumor was in the middle third of the esophagus. Four patients (18%) received definitive chemoradiation therapy, and 18 (82%) received neoadjuvant chemoradiation followed by surgery. Radiation in all cases was delivered as IMRT to a total dose of 50.4 Gy.

Set-up displacements

Table 2 summarizes the *interfractional* mean and mean absolute systematic uncertainty, the mean and mean absolute random error, and the maximum displacements in each direction for the 22 patients. *Interfractional* systematic uncertainties were largest in the SI direction and smallest in the lateral direction. The *interfractional* systemic uncertainties in GEJ location were as follows: 2.88 mm (range 0.86–6.94 mm) in the lateral direction, 2.90 mm (range 1–7.88 mm) in the AP direction, 6.77 mm (range 2.10–16.94 mm) in the SI direction, and 8.63 mm (range 3.27–20.02 mm) in the 3D direction. The GEJ was displaced in the lateral direction by 5 mm in 14% of cases and by 10 mm in 0%; in AP, 14% 5 mm and 0% 10 mm; and in SI, 64% 5 mm and 18% 10 mm (not shown). The largest excursion in the SI direction was 1.76 cm.

Figure 1 shows the *interfractional* systematic displacements in GEJ location in the SI, AP, and lateral directions throughout the course of treatment for all 22 patients. Leftward GEJ displacement occurred slightly more frequently than rightward displacement. In contrast, *interfractional* systemic displacements in the AP and SI directions occurred predominantly in the anterior and inferior directions. Supplementary Figure 1 shows the frequency of *interfractional* systemic displacements in the SI, AP, and lateral directions, summarized for the 22 patients. Again, large displacements were noted to occur more frequently in the SI direction compared to the AP and lateral directions. Moreover, the extent of displacement between fractions varied substantially among patients in all three directions.

Correlation of GEJ displacement and clinical/respiratory variables

We hypothesized that part of the variation in GEJ location between fractions may be caused by inconsistencies in patients' respiration between treatment fractions. We correlated

interfractional systematic displacements in each patient with interfractional differences in tidal volume and vertical diaphragmatic displacement, as well as the patients' height, weight, and body mass index. Interfractional systematic displacement in the SI direction correlated strongly with interfractional change in tidal volume ($r=0.9635$) and vertical diaphragmatic displacement ($r=0.9437$) (Table 3, Fig. 2), as well as weakly with total absolute tidal volume ($r=0.424$), suggesting that larger lungs may be associated with greater target excursion (data not shown). Modest positive correlations were also noted between interfractional systematic displacement in the AP direction and interfractional change in tidal volume ($r=0.678$) and vertical diaphragmatic displacement ($r=0.758$). No significant correlations were found between interfractional systematic displacement in any of the three directions with patient height, weight, or body mass index. In addition, there were no statistically significant correlations found between interfractional systematic displacement in any of the three directions with absolute change in weight, relative weight change (defined as the absolute value of the patient's weight gain or loss at the end of treatment, divided by the patient weight at the beginning of treatment), and change in BMI (data not shown).

Dosimetric impact of interfractional systematic displacement

To demonstrate the dosimetric impact of interfractional systematic displacement (especially in the SI direction, where excursions were largest), we selected two patients, one with the largest GEJ excursion in the inferior direction (Fig. 1, patient 12) and the other with the largest superior excursion (Fig. 1, patient 1). For patient 1, who had the largest superior systematic displacement, systemic uncertainty in the superior direction resulted in better tumor coverage (Fig. 3A-C). For patient 12, who had the largest inferior systematic displacement, the CTV was underdosed, but this underdosing was minimal when 1-cm PTV margins were used (Fig. 3D-F). Interfractional systematic uncertainty in the inferior direction resulted in the GEJ area being exposed to higher than expected (>60 -Gy) doses. However, these "hot spots" also included coverage of nearby normal structures, including the stomach and the lower lobes of the lung. The clinical sequelae of this exposure for patient 12 manifested as grade 2 odynophagia (requiring acetaminophen and hydrocodone [Lortab]), grade 2 nausea (requiring prochlorperazine [Compazine]), grade 2 anorexia/early satiety (requiring a dietary consultation), and grade 1 radiation pneumonitis. Overall, however, there were no statistically significant correlations found between interfractional displacement and the severity of various treatment toxicities including radiation pneumonitis, stricture, dysphagia, or esophagitis (data not shown).

To determine whether the large systematic uncertainty seen was an artifact of the weekly 4D-CT imaging that was performed in one room and the treatments in another (i.e., whether the patient's depth of breathing during the 4D-CT scans was different than during the treatment), we compared the MV portal x-rays taken immediately before actual treatment with digitally reconstructed radiography from the simulation CT scans. As an example the portal images for patient 12 revealed a large inferior displacement with diaphragmatic flattening, indicating a larger positive change in the inspiration volume at week 5 (Fig. 3G,H), similar to what was observed on the weekly 4D-CT images. We conclude that the large systemic uncertainties seen were not an artifact, and indeed reflect the patients' systemic alteration in GEJ position due to differences in the depth of breathing from week to week.

DISCUSSION

In this study of interfractional displacement of the GEJ in patients with esophageal cancer, we found marked interfractional displacement of the GEJ in the SI direction (absolute mean 6.77 mm, maximum displacement 17.6 mm) and smaller interfractional displacements in the AP and lateral directions (absolute means 2.90 mm and 2.88 mm). In addition,

interfractional changes in tidal volume and in vertical diaphragmatic excursion were found to correlate strongly with systematic displacement of the GEJ in the SI direction and moderately with systematic displacement in the AP direction, but not with systematic displacement in the lateral direction. Interfractional systematic displacement in the superior direction resulted in better tumor coverage, because the tumor moved into the radiation field. However, interfractional systematic displacement in the inferior direction resulted in higher-than-expected doses to the GEJ because of decreased attenuation of the radiation beams. These hot spots also affected exposure of the normal stomach and lung. While underdosing of the CTV was minimal, this presumed a 10-mm PTV margin in the inferior direction. Our findings thus justify at least a 10-mm inferior PTV margin; however, 5-mm PTV margins may be adequate for superior, lateral, and AP margins.

Although the extent of intrafractional motion of GEJ tumors has been well established (3–6, 11–13), reports of interfractional displacement have been limited. The first study of interfractional esophageal motion was reported in abstract form in 2005 (14) and has yet to be published. That study used a CT-on-rails system to analyze daily shifts in the esophagus in the AP and lateral directions for six patients with lung cancer and showed an average daily shift of <1 mm in all measured directions, supporting a correction of 2–5 mm for internal esophageal motion in all directions. However, the sample size was small and the study included patients with lung cancer rather than esophageal cancer. Another group (15) also used CT-on-rails to study eight patients with esophageal cancer and found mean absolute esophageal displacement of 3.2 mm below and 4.2 mm above the carina in the lateral direction and a mean absolute AP displacement of 2.8 mm posterior below and 3.9 mm posterior above the carina. A third study (16) using cone-beam CT to analyze esophageal shifts in 20 patients with esophageal cancer showed similar 5-mm shifts in the lateral direction and 5-mm shifts in the AP direction. Our findings are different in that we found relatively smaller AP and lateral displacements of the GEJ and we specified displacement of the GEJ rather than the whole esophagus. Moreover, none of the prior studies addressed interfractional esophageal motion in the SI direction.

We also report the interfractional distal esophageal positioning relative to skeletal alignment and compared esophageal motion between fractions with respiratory variables. Our findings suggest that substantial changes occur in the position of the distal esophagus, not only within fractions (as demonstrated elsewhere) but also between fractions as related to respiration. For most of the subset of patients with large interfractional SI displacements, the tidal volumes on the weekly scans were larger than on the simulation scans (except for one patient whose weekly tidal volumes were consistently smaller). The reasons for this are unclear. Nevertheless, our results do agree with those of others (4,5) that the largest respiration-related GEJ/distal-esophageal displacements occur in the SI direction (inferior > superior), followed by those in the AP direction (anterior > posterior, most likely because of obstruction by the vertebrae and descending aorta), and smallest in the lateral direction (left > right, perhaps related to cardiac motion).

Our findings have a number of clinical implications. The substantial inter-fractional SI displacement of the GEJ despite weekly skeletal alignment (the current standard treatment setup) raises several concerns. First, the precise delineation of the GTV/CTV/PTV is crucial for RT planning/delivery and hence for optimal clinical outcomes. Large interfractional displacements of the GEJ, such as we observed, could compromise appropriate treatment margins and negatively affect radiation dose delivery. For example, our discovery of large inferior GEJ displacements (maximum 17.6 mm) on a week-to-week basis, could result in geometric miss or underdosing of the GTV/CTV if inferior margins are inadequate. Fortunately for all the patients on this study, the CTV and PTV margin inferiorly were within proximal portions of the stomach or into the celiac axis, and therefore there was no

underdosing in this area. This is especially important given the precision required by IMRT to safely deliver high doses of radiation to the PTV means that substantial displacement of esophageal tumors could result in unnecessary irradiation of adjacent normal structures and hence increased treatment toxicity. In support of this hypothetical risk, we did find increased hot spot coverage of adjacent normal stomach and lung, when evaluating the dosimetric impact of interfractional GEJ displacement in the inferior direction.

In addition, our findings suggest that better means of accounting for breathing are needed to reduce the extent of interfraction esophageal motion. As our data demonstrates, week-to-week variations in absolute tidal volumes can result in changes in esophageal tumor location that were not corrected for by skeletal alignment alone during treatment set-up. Although various ways of compensating for respiration-correlated tumor motion, including respiratory-gated radiotherapy, respiratory tracking techniques, and active breathing control via spirometry have been widely used in the treatment of lung cancer, they have not been used for esophageal cancer. Such techniques warrant further consideration. Another option to reduce interfraction esophageal motion would be to monitor changes on weekly portal films to assess movement of the diaphragm as a surrogate for potential GEJ tumor movement (Fig, 3G,H). Patients with consistent deviations in diaphragmatic displacement may require radiation re-planning, given the near-perfect correlation between changes in diaphragmatic displacement and tidal volume and changes in GEJ position. Comparing weekly portal films offers an easier and faster way to gauge potential changes in tumor location. Now with the modern LINACs, low dose weekly cone beam CT is an additional option to help monitor these systemic changes. Our results support a move towards adaptive RT, particularly for treatment with IMRT, in which precise and reproducible set-up is critical for accurate dose delivery.

Our study has some limitations, including the potential for methodologic errors in assessing interfraction esophageal motion, such as correcting the setup error only by linear translation (as is done by the Pinnacle system) and not accounting for possible rotational changes; the relatively small number of patients, particularly for studying clinical implications; and the fact that not all 22 patients in the data analysis had GEJ tumors, rendering some discussion points theoretical in nature.

CONCLUSIONS

Our results suggest that the location of the GEJ could not be reliably reproduced on a weekly basis using standard treatment setup with skeletal alignment. Because systematic displacement in the SI direction can be marked, can influence treatment dosimetry, and correlates strongly with tidal volume, measures to better account for breathing to reduce interfraction displacements are suggested. Additional studies with larger numbers of patients are needed to confirm these results and to assess their clinical implications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Feig, B.; Berger, DH.; Fuhrman, GM., editors. The M.D. Anderson Surgical Oncology Handbook. Philadelphia, PA: Lippincott Williams and Wilkins; 2006. p. 367-390.

2. Hasimoto T, Shirato H, Kato M, et al. Real-time monitoring of a digestive tract marker to reduce adverse effects of moving organs at risk (OAR) in radiotherapy for thoracic and abdominal tumors. *Int J Radiat Oncol Biol Phys.* 2005; 61:1559–1564. [PubMed: 15817362]
3. Lorchel F, Dumas JL, Noel A, et al. Esophageal cancer: determination of internal target volume for conformal radiotherapy. *Radiother Oncol.* 2006; 80:327–332. [PubMed: 16959345]
4. Zhao KL, Liao Z, Bucci MK, et al. Evaluation of respiratory-induced target motion for esophageal tumors at the gastro-esophageal junction. *Radiother Oncol.* 2007; 84:283–289. [PubMed: 17716759]
5. 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. [PubMed: 17855008]
6. Patel A, Wolfgang J, Niemierko A, et al. Implications of respiratory motion as measured by four-dimensional computed tomography for radiation treatment planning of esophageal cancer. *Int J Radiat Oncol Biol Phys.* 2009; 74:290–296. [PubMed: 19362248]
7. ICRU Report 50: Prescribing, Recording, and Reporting Photon Beam Therapy. Bethesda, MD: ICRU Publications; 1993. International Commission on Radiation Units and Measurements (ICRU).
8. ICRU Report 62: Prescribing, recording, and reporting photon beam therapy (supplement to ICRU Report 50). Bethesda, MD: ICRU Publications; 1999. International Commission on Radiation Units and Measurements (ICRU).
9. Hui Z, Zhang X, Skarschall G, et al. Effects of interfractional motion and anatomic changes on proton therapy dose distribution in lung cancer. *Int J Radiat Oncol Biol Phys.* 2008; 72:1385–1395. [PubMed: 18486357]
10. Wang H, Dong L, O'Daniel J, Mohan R, Garden AS, Kian Ang K, Kuban DA, Bonnen M, Chang JY, Cheung R. Validation of an accelerated 'demons' algorithm for deformable image registration in radiation therapy. *Phys Med Biol.* 2005; 50(12):2887–2905. [PubMed: 15930609]
11. Pan CC, Kashani R, Hayman JA, et al. Intra- and inter- fraction esophagus motion in 3D-conformal radiotherapy: implications for ICRU 62 definitions of internal target volume and planning organ at risk volume [Abstract]. *Int J Radiat Oncol Biol Phys.* 2004; 60(Suppl 1):S580–S581.
12. Guerrero T, Zhang G, Huang TC, et al. Intrathoracic tumour motion estimation from CT imaging using the 3D optical flow method. *Phys Med Biol.* 2004; 49:4147–4161. [PubMed: 15470929]
13. Dieleman EM, Senan S, Vincent A, et al. Four-dimensional computed tomographic analysis of esophageal mobility during normal respiration. *Int J Radiat Oncol Biol Phys.* 2007; 67:775–780. [PubMed: 17293234]
14. Sasidharan S, Allison R, Jenkins T, et al. Interfraction esophagus motion study in image guided radiation therapy (IGRT) [Abstract]. *Int J Radiat Oncol Biol Phys.* 2005; 63(Suppl 1):S91–S92.
15. Cohen RJ, Paskalev K, Litwin S, et al. Esophageal motion during radiotherapy: quantification and margin implications. *Dis Esophagus.* 2010; 23:473–479. [PubMed: 20095993]
16. Yamashita H, Haga A, Hayakawa Y, et al. Patient setup error and day-to-day esophageal motion error analyzed by cone-beam computed tomography in radiation therapy. *Acta Oncologica.* 2010; 49:485–490. [PubMed: 20230211]

Highlights

The accuracy of radiation delivery needs to account for tumor motion and setup uncertainties. This is particularly true for gastroesophageal junction (GEJ) tumors, since this is an area with large amounts of uncertainty due to respiratory motion. We gauged the reproducibility in the setup of the GEJ using bony alignment compared to weekly 4DCT imaging on 22 patients undergoing chemoradiation treatment. We found for many patients there were substantial inferior displacement of the GEJ (≥ 1 cm in 18%) in the interfractional displacement that is highly correlated to the end-tidal volume. This could be assessed using daily or weekly portal imaging. These results suggest that bony alignment is inadequate for accurate setup for the treatment of GEJ tumors. Accurate setup needs to account for the depth of respiratory volume.

Figure 1.

Box-and-whisker plots showing interfractional systematic displacement for each patient in the lateral (A), anterior-posterior (AP) (B), and superior-inferior (SI) (C) directions. The band at the middle represents the median; the bottom and top of the box represent the 25th and 75th percentiles. The whiskers indicate the lowest datum still within 1.5 interquartile range (IQR) of the lower quartile and the highest datum still within 1.5 IQR of the upper quartile. Xs indicate outliers of maximum displacements. Positive numbers indicate left, anterior, and inferior displacement; negative numbers indicate right, posterior, and superior displacement.

Figure 2. Differences in weekly measurements of tidal volume (panels A-C) and vertical diaphragmatic excursion (panels D-F) plotted against interfractional displacements in three dimensions.

Figure 3.

Dosimetric impact of systematic error for two patients with large superior (panels A-C) or inferior (panels D-F) displacements of the gastroesophageal junction (GEJ). A-C, original treatment plan (with 1-cm planning target volume [PTV] margins) (A), week 5 treatment plan (B) and normalized dose-volume histograms (C) for patient 1, who had large superior displacement of the GEJ. Dotted lines indicate dose distribution on the original treatment plan; solid lines, dose distribution on week 5. D-F, original treatment plan (with 1-cm PTV margins) (D), week 5 treatment plan (E), and normalized dose-volume histograms (F) for patient 12, who had large inferior GEJ displacement. Dotted lines indicate the original treatment plan; thick solid lines, the cumulative dose distribution; and thin solid lines, the individual weekly dose distributions for patient 12. G and H, portal films for patient 12, obtained at simulation (G) and at week 5 (H). Brown, gross tumor volume (GTV); cyan, clinical tumor volume (CTV); purple, heart; white, hot spots.

Table 1

Patient, tumor, and treatment characteristics

Characteristic	Number
No. of Patients	22
Sex, <i>n</i> (%)	
Male	20 (91)
Female	2 (9)
Age, median, years (range)	62.3 (41.1–81.0)
Height, median, cm (range)	179.1 (154.9 – 188.9)
Weight, median, kg (range)	94.0 (61.5 – 135.3)
Body mass index, median, kg/m ² (range)	28.9 (20.2 – 39.9)
Tumor histology, <i>n</i> (%)	
Adenocarcinoma	22 (100%)
Squamous cell carcinoma	0 (0%)
Disease stage, <i>n</i> (%)	
I	2 (9%)
II	6 (27%)
III	10 (45%)
IV	2 (9%)
Unknown	2 (9%)
Tumor location, <i>n</i> (%)	
Upper	0 (0%)
Mid	1 (4%)
Distal	21 (96%)
Treatment, <i>n</i> (%)	
Definitive chemoradiation	4 (18%)
Neoadjuvant chemoradiation + surgery	18 (82%)
Concurrent chemotherapy, <i>n</i> (%)	
Yes	22 (100%)
No	0 (0%)
Radiation Dose, Gy (%)	50.4 (100%)

Table 2

Summary of the *interfractional* systematic uncertainty, random error, and maximum displacement of the gastroesophageal junction for 22 patients being treated for esophageal cancer

Direction	Mean Systematic Uncertainty, cm (range)	Mean Absolute Systematic Uncertainty, cm (range)	Mean Random Error, cm (range)	Mean Absolute Random Error, cm (range)	Maximum Displacement, cm
Lateral	0.092 (-0.510 to 0.694)	0.288 (0.086 to 0.694)	0.212 (0.035 to 0.411)	0.169 (0.011 to 0.411)	1.35
Antero-posterior	0.145 (-0.592 to 0.788)	0.290 (0.100 to 0.788)	0.231 (0.080 to 0.409)	0.187 (0.051 to 0.409)	1.38
Superior-inferior	0.443 (-1.028 to 1.694)	0.677 (0.210 to 1.694)	0.409 (0.099 to 0.854)	0.309 (0.099 to 0.616)	1.76
Distance		0.863		0.301	
(3D vector)	Not applicable	(0.327 to 2.002)	Not applicable	(0.130 to 0.652)	2.16

Table 3

Overall correlation between systematic displacements and delta-tidal volume, vertical diaphragmatic excursion, height, weight, and BMI

	Delta Tidal Volume			Diaphragmatic Displacement			Height			Weight		
	<i>r</i>	<i>p</i>	<i>R</i> ²	<i>r</i>	<i>p</i>	<i>R</i> ²	<i>r</i>	<i>p</i>	<i>R</i> ²	<i>r</i>	<i>p</i>	<i>R</i> ²
Direction of displacement												
Lateral	0.014	0.945	0.0002	0.124	0.583	0.0153	0.239	ns	0.057	0.135		
	ns	0.0182	0.065	ns	0.0042							
AP	0.678	0.0005	0.459	0.758	<0.0001	0.574	0.0141	ns	0.0002	0.147		
	ns	0.0215	0.139	ns	0.0194							
SI	0.964	<0.0001	0.928	0.944	<0.0001	0.891	0.0748	ns	0.0056	0.205		
	ns	0.0419	0.198	ns	0.0393							

Abbreviations: *r*, Pearson's correlation coefficient; *p*, correlation significance based on two-tailed *p* values; *R*², coefficient of determination; ns, not significant; AP, anterior-posterior; SI, superior-inferior