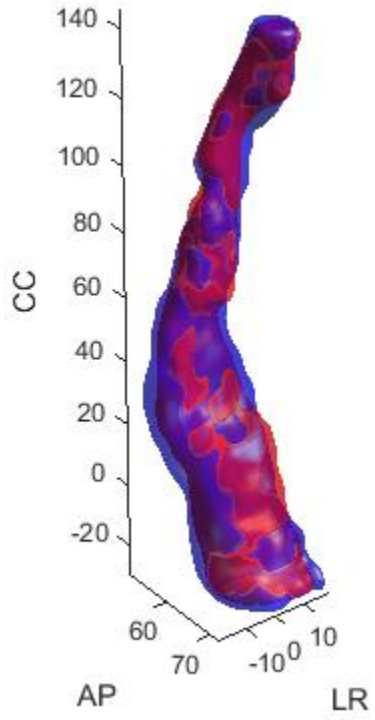
Fontys Paramedische Hogeschool
Medische Beeldvorming en Radiotherapeutische Technieken

Thesis

Inter-fractional deformation of the esophagus in radiotherapy treatment of esophageal cancer



Date: April 2016
Author: Nick van Rijn
Student number: 2115956
Tutor: Esther Bloemen-van Gurp
Commissioning Party: Department of Radiation Oncology, Academic Medical Center Amsterdam

Acknowledgements

This quantitative retrospective study took place in the context of the thesis stage of the course Medische Beeldvorming en Radiotherapeutische Technieken (MBRT) at the Fontys Paramedische Hogeschool located in Eindhoven. It was commissioned by the radiotherapy department of the Academic Medical Center in Amsterdam. The inter-fractional deformation of the esophagus in radiotherapy treatment of esophageal cancer was investigated using three-dimensional kilovolt conebeam computed tomography.

First, I would like to thank Rudie van de Kolk, for giving me the opportunity to do this quantitative study instead of a literature review. Next I would like to thank my supervisor at Fontys, Esther Bloemen-van Gurp for her suggestions and feedback. Of course I would like to thank my supervisors at the AMC in Amsterdam, Tanja Alderliesten, Rianne de Jong and especially Peng Jin. First for their interesting research proposal and secondly for their valuable input and feedback. It is much appreciated. Last but not least I would like to thank my girlfriend Anke, for her feedback and for having to put up with me concentrating on my thesis these past months.

Nijmegen, June 6, 2015,

Nick van Rijn

Abstract

Background: The purpose of this study was to investigate the inter-fractional deformation of the esophagus during radiotherapy treatment of esophageal cancer, using three-dimensional (3D) kilovolt (kV) conebeam computed tomography (CBCT). Additionally, deformation of the aorta and distance between aorta and esophagus were investigated to determine if deformation of the esophagus is influenced by the close presence of the aorta.

Methods and materials: A planning computed tomography (pCT) and five weekly CBCTs were acquired for 13 patients. After bony anatomy registration of CBCT on pCT, the esophagus and the aorta were delineated on every scan for each patient. Delineation of the structures on each CBCT was compared to the delineation on pCT. To analyze deformation, for each structure volume, Dice's Similarity Coefficient (DSC) and surface distance values were obtained for every CBCT.

Results: No significant differences were found over the course of treatment for volume, DSC or surface distance of the esophagus. A significant difference for deformation of the esophagus was found between the three parts of the esophagus and between the four sides of the esophagus. The mean (standard deviation) vector surface distance of the esophagus was 3.29 (1.69) mm. The aorta and the distance between aorta and esophagus showed no significant difference over the course of treatment.

Conclusions: Inter-fractional deformation of the esophagus is not likely to occur during radiotherapy treatment. The deformation of the esophagus was dependent on part of the esophagus and side of the esophagus: larger for the distal part and ventral side and smaller for the proximal part and the dorsal side of the esophagus. Further, it is unlikely that deformation of the esophagus is influenced by deformation of the aorta or the position of the esophagus close to the aorta.

Samenvatting

Achtergrond: Het doel van dit onderzoek was te bepalen in welke mate inter-fractionele deformatie van de oesophagus optreedt tijdens de radiotherapiebehandeling van een oesphaguscarcinoom met behulp van drie-dimensionele (3D) kilovolt (kV) conebeam computed tomography (CBCT). Daarnaast werd de de deformatie van de aorta en de afstand tussen aorta en oesphagus onderzocht om te bepalen of oesophagus deformatie wordt beinvloed door de nabijheid van de aorta.
Methode: Een plannings computed tomography (pCT) en vijf wekelijkse CBCT's werden verkregen voor 13 patiënten. Na een botmatch van de CBCT op de pCT werden de oesophagus en de aorta ingetekend op iedere scan voor iedere patiënt. De intekening van de structuren op iedere CBCT werd vergeleken met de intekening op de pCT. Om de deformatie te bepalen werd voor iedere structuur het volume, Dice's Similarity Coëfficiënt (DSC) en de oppervlakteafstand gemeten op iedere CBCT.
Resultaten: Er werd geen significant verschil gevonden gedurende de behandeling voor het volume, DSC en de oppervlakteafstand van de oesphagus. Er werd een significant verschil gevonden in deformatie van de oesophagus tussen de drie delen van de oesphagus en tussen de vier zijden van de oesophagus. De gemiddelde (standaarddeviatie) vector van oppervlakteafstand was 3.29 (1.69) mm. De aorta en de afstand tussen de aorta en de oesphagus vertoonden geen significant verschil gedurende de behandeling.
Conclusies: Het is niet waarschijnlijk dat inter-fractionele deformatie van de esophagus optreedt gedurende de behandeling. De deformatie van de oesphagus bleek afhankelijk van het deel van de oesphagus en van de zijde van de esophagus: groter voor het distale deel en de ventrale zijde en kleiner voor het proximale deel en de dorsale zijde. Verder is het niet waarschijnlijk dat de deformatie van de esophagus wordt beïnvloed door deformatie van de aorta of de nabijheid van de aorta.

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1 Introduction

Esophageal cancer was diagnosed in 2,369 patients in the Netherlands in 2014. The incidence per 100,000 has been rising over the years with 5.44 in 1990 to 12.81 in 2014. Esophageal cancer is more common in men, which makes up almost 75% of newly diagnosed patients. With a 5-year survival rate of 17% it is one of the most lethal cancers in the Netherlands (1,2).

In the treatment for esophageal cancer, radiotherapy plays an important role. While course of treatment is dependent on resectability of the tumor, radiotherapy is currently recommended in both neoadjuvant and definitive treatment (2–4).
In fractionated external beam radiotherapy for esophageal cancer, systematic and random errors can make a crucial influence on the dose delivery accuracy. These errors, such as delineation uncertainties, intra- and inter-fractional tumor position variation, and setup errors, need to be compensated for. For this reason a safety margin is added onto the clinical target volume (CTV) to form the planning target volume (PTV) (5). However, higher doses in the surrounding healthy tissue and organs at risk (OAR) result in additional toxicity (6). Because of this, the safety margin should be as minimal as possible. Therefore, learning and quantifying these aforementioned errors which determine the safety margin is very important.

The setup accuracy is closely related to immobilization techniques. Hawkins et al. (7) found that setup accuracy can be improved by using three-dimensional (3D) cone-beam computed tomography (CBCT) for patient setup verification compared to two-dimensional (2D) electronic portal imaging devices (EPID). Han et al. (8) showed that further improvement of setup accuracy is possible using a strategy of daily CBCT for patient setup verification. According to Yamashita et al. (9), by using daily CBCT the impact of errors due to setup accuracy on determining the safety margin can be minimized.

Intra-fractional uncertainty is mainly caused by respiratory motion and organ motion (10–16). Zhao et al. (10) concluded that esophageal tumors near the gastroesophageal junction (GEJ) exhibit significant respiration-induced motion, as well as asymmetric and directional changes in shape and volume. They demonstrated that the largest margin is needed in the caudal direction and the smallest margin in the posterior direction. Further studies including esophageal tumors located in different levels of the esophagus showed that the motion of esophageal tumors is highly variable between patients. They also reported that respiration-induced tumor motion is greatest in the cranial-caudal (CC) direction. In addition, this tumor motion is also dependent on the tumor location, with tumors in the distal part of the esophagus showing greater motion compared to tumors in the middle and proximal parts (11–16).
A study by Dieleman et al. (17) analyzed mobility of the esophagus in the left-right (LR) and anterior-posterior (AP) directions during respiration, concluding that the respiration-induced motion of the esophagus can be significant, particularly for the distal part. However, these studies do not take into account tumor motion caused by cardiac motion. As shown by Palmer et al. (18), the magnitude of

esophageal motion near the heart due to cardiac motion can be as significant as that due to respiratory motion. Therefore, anisotropic location-specific margins to compensate the intra-fractional esophageal tumor motion were proposed (18).

The inter-fractional uncertainty refers to position, volume and shape variations of the tumor during the course of treatment. Causes could be the reaction of tissue to irradiation, different daily filling of the stomach or concurrent complications (19).
Several studies have investigated the inter-fractional displacement of esophageal tumors or landmark structures. Wang et al. (20) reported a systematic inter-fractional displacement for the GEJ in the CC direction. Fukada et al. (21) also found a substantial inter-fractional displacement of the esophagus, with a greater magnitude of motion for the distal esophagus in all directions and a greater magnitude of motion in the CC direction in general. However, Yamashita et al. (9) did not find a difference in motion in the AP and LR directions between upper esophagus and lower esophagus. Some other studies reported inter-fractional displacement of the tumor is larger in the CC direction compared to the LR and AP directions. Further, the displacement is also larger for the distal part of the esophagus compared to middle and proximal parts (19,22,23).
Volume and shape variations also contribute to inter-fractional uncertainty. However, only Cohen et al. (24) additionally report on diameter of the esophagus and find that esophageal motion is related to directional shifts of the esophagus rather than changes in esophageal diameter.

Since the CTV in the axial plane is often defined to include the entire esophagus and the peripheral lymph nodes, it is important to take the inter-fractional deformation of the esophagus into account when determining the safety margin. Recently, Jin et al. (23) found there could be a trend of the esophagus moving to the right direction during the treatment, based on movement of markers implanted in the tumor site. It is hypothesized that the reason for this is the aorta constricting movement of the esophagus to the left. If this is indeed the case, minimal movement could be expected in the left direction, making it possible to tighten the currently used safety margin on the left side.

The primary aim of this study is to investigate the inter-fractional deformation of the esophagus that occurs during the course of radiotherapy treatment, with the help of 3D kilovolt (kV) CBCT used for patient setup verification at the department of radiation oncology at the Academic Medical Center (AMC) Amsterdam. The secondary aim is to verify if there is a trend in esophageal movement as observed by Jin et al. (23). The following questions therefore need to be answered:

Primary research question:
To what degree does inter-fractional deformation of the esophagus occur during radiotherapy of esophageal cancer, measured on 3D kV CBCT?

Secondary research questions:

- To what degree is the deformation of the esophagus dependent on direction and region?
- How frequently does the esophagus at the tumor level move in the LR direction over the course of treatment, and is this movement constricted by the presence of the aorta?

2 Methods

This is a quantitative retrospective study. Available computed tomography (CT) and CBCT image sets were used for quantitative analysis of esophageal deformation. This study took place from February 2016 till June 2016 at the department of radiation oncology of AMC Amsterdam.

2.1 Patient selection

In this study patients with esophageal cancer treated between March 2013 and March 2015, that have been included in studies by Machiels et al. (25) and Jin et al. (16,23) were included. Therefore, all patients had 3D-CT, 4D-CT and CBCTs available. Patients were excluded if less than 5 weekly CBCTs were available for a patient. Data of 13 patients were available for analysis.

2.2 Image acquisition

First a 3D planning CT scan (pCT) (LightSpeed RT 16 CT; General Electric Company, Waukesha, WI, USA) was acquired for each patient. All patients were positioned supine with arms up above their heads using an arm support (CIVCO Medical Solution, Rotterdam, The Netherlands) during acquisition. No other immobilization facility was used. The thickness of the axial scan slices was 2.5 mm, and the field of view was between the bottom edge of the mandible and the lower border of the kidneys (23).

For patient setup verification during treatment, CBCTs were acquired using the on-board kilovolt CBCT of the linear accelerator (Elekta Synergy System; Elekta Ltd., Crawley, UK). Patient positioning was identical to patient positioning for the pCT. Following the extended no action level (eNAL) setup correction protocol, a daily CBCT was acquired for the first four fractions for each patient, followed by once-weekly acquisitions. For the fractions without CBCT, patient setup based on the average setup error calculated using the available CBCTs was performed (23).

Of each patient the pCT and 5 CBCT scans were selected for this study. These CBCT scans consisted of the CBCT scans of the first treatment fraction and the approximate weekly follow-up CBCT scans. A total of 78 scans for 13 patients were selected for analysis.

2.3 Structure delineation

Image sets acquired with pCT and CBCT were transferred to VelocityAI software (version 3.1.0, Varian Medical Systems, Inc., Palo Alto, CA, USA). The standard mediastinum setting of window width and window level (WW/WL) of 350/40 was used for delineation of structures on the pCT as seen in Figure 2.1. The esophagus was manually delineated on the axial slices for every other slice, starting from the inlet of the esophagus to the GEJ. The delineations in between slices were automatically interpolated in VelocityAI. These delineations were checked visually and corrected if necessary.
The aorta was delineated on the pCT in the same way for investigating whether is plays a role in the displacement of the esophagus, considering its position adjacent to the esophagus. Delineation of the

aorta started at the top of the aortic arch following the descending aorta to the slice of the most caudal esophagus delineation. Delineations of esophagus and aorta are seen in Figure 2.2.

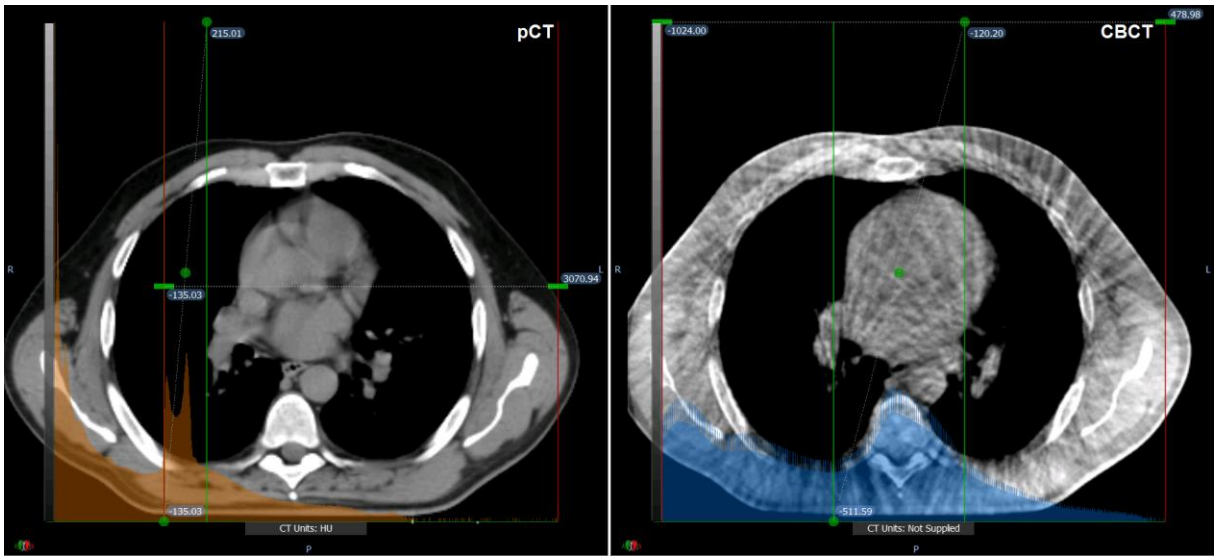

Figure 2.1. Window width and window level settings for pCT (left) and CBCT (right). The pCT has a WW/WL of 350/40. The CBCT has a WW/WL of 380/-315. The poorer image quality of CBCT is clearly visible, showing streak artifacts and a lower spatial resolution.

The grey scale on CBCT does not correlate to Hounsfield Units, therefore the standard mediastinum setting of WW/WL was not sufficient for delineation of structures on CBCT. A WW/WL was chosen for CBCT so the contour of aorta and esophagus were visible and could be followed on the axial slices when scrolling in the CC direction. Generally, the WW/WL on CBCT was around 400/-300, as seen in Figure 2.1. Each CBCT was then rigidly registered to the pCT for each patient using bony anatomy as a reference as seen in Figure 2.3. The pCT was first manually adjusted so the vertebrae roughly matched the CBCT. The auto-registration algorithm of Velocity was then used to precisely match both scans in the region of interest placed on the spine. The esophagus and the aorta were delineated on each CBCT following the same procedure as delineation on pCT, guided by the delineation on pCT when necessary, as seen in Figure 2.2.

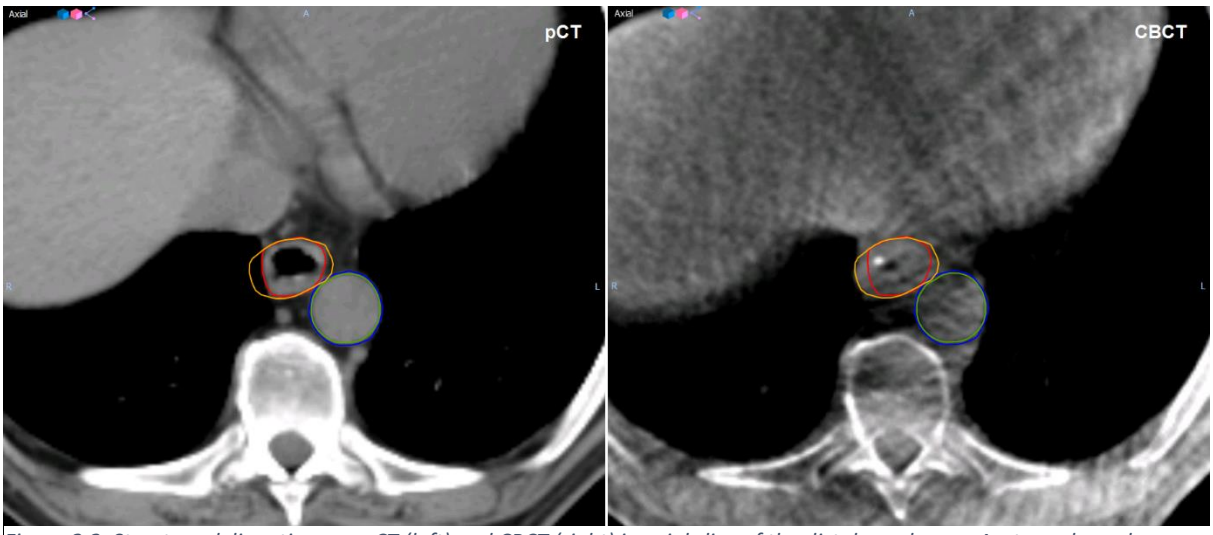

Figure 2.2. Structure delineations on pCT (left) and CBCT (right) in axial slice of the distal esophagus. Aorta and esophagus Delineation of pCT are blue and red, respectively. Aorta and esophagus delineation of CBCT are green and orange, respectively. The poorer image quality of CBCT is clearly visible, showing streak artifacts and a lower spatial resolution.

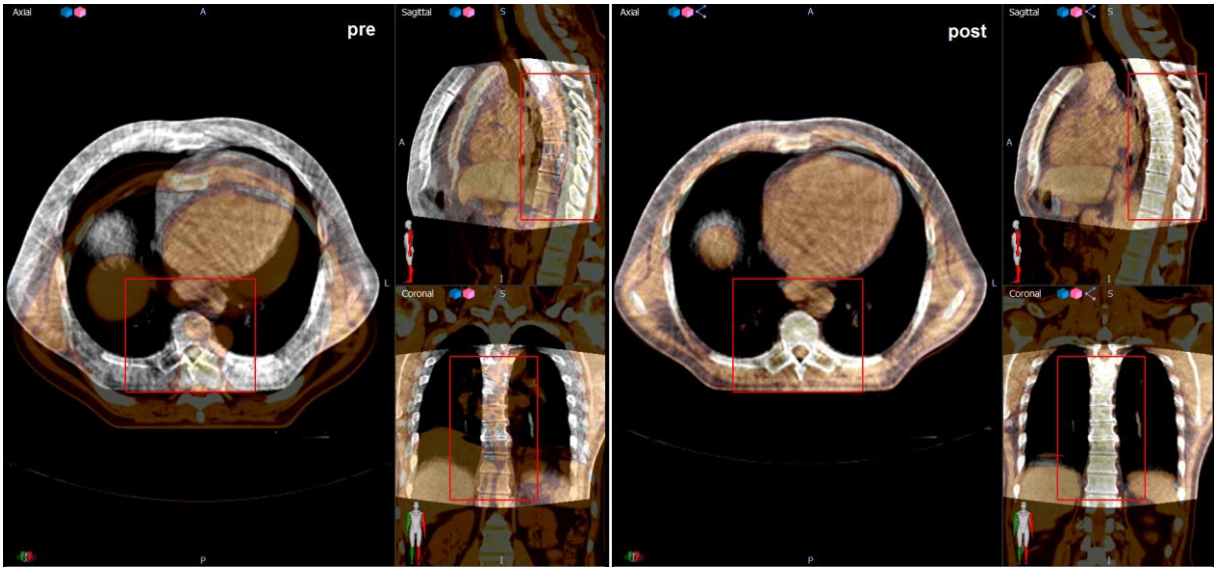

Figure 2.3. The pCT and CBCT before (left) and after (right) bony anatomy registration. The pCT is orange, the CBCT is grey. The red box placed over the spine is the region of interest used by the auto-registration algorithm.

Because of the smaller field of view of the CBCT compared to the pCT and the inter-fractional variation of the structure position in the CC direction within the patients, the pCT and CBCTs structure delineations did not start nor end in the same slice within the same patient. In order to compare these structures, the structure delineations on pCT and CBCT were truncated in the CC direction into the same length for each patient.

The esophagus delineation on pCT and CBCT was divided into the proximal, middle, and distal part for analysis (hereafter they are referred as the three parts of the esophagus). The proximal esophagus ranged from the inlet to the carina, the middle esophagus from the carina to the inferior pulmonary vein and the distal esophagus from the inferior pulmonary vein to the GEJ, as shown in Figure 2.4.

All delineations have been performed according to the delineation atlas used in daily clinical practice (26). All delineations were done by one researcher. Delineations were checked by an experienced radiation therapist. No intra- or inter-observer variability was assessed due to the time limit.

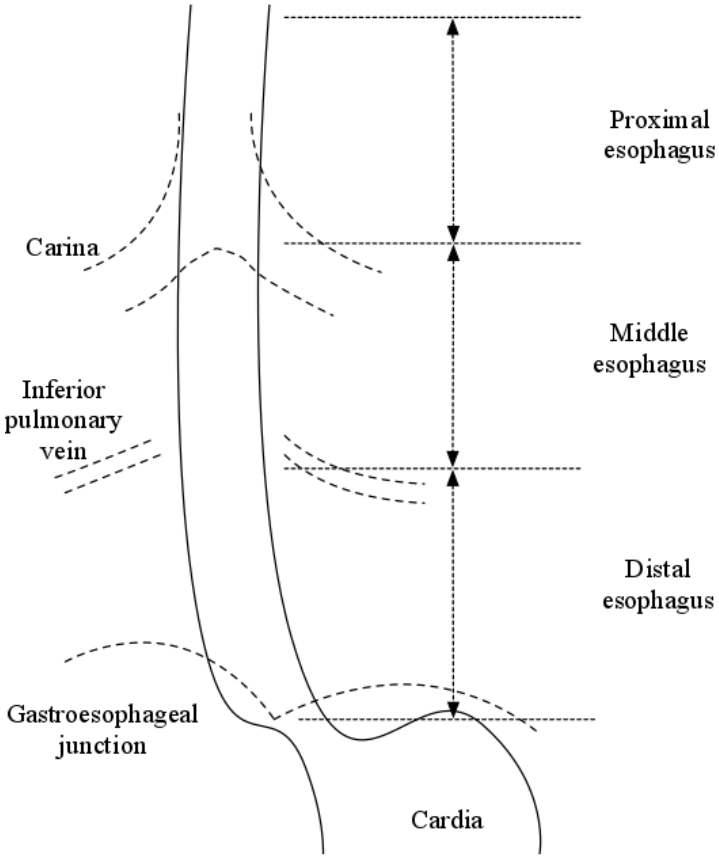

Figure 2.4. Coronal schematic view of the esophagus, divided in proximal, middle and distal part.

2.4 Measurement of deformation

Measurement of deformation of the esophagus was done for the full-length of the esophagus and for each part of the esophagus separately. Measurement of the deformation of the aorta was done only for the full-length of the aorta delineation. The deformation of the esophagus and the aorta was measured using three different methods.

First, the volume of each structure was measured using Velocity. Then the relative volume of every CBCT to its pCT was calculated for every patient.

Second, Dice's similarity coefficient (DSC) was used to measure conformity between two samples. It is calculated using the following formula:

$$DSC = \frac{2(A \cap B)}{A + B}$$

Where A is defined as the volume of the delineation on the pCT, B is the volume of the delineation on CBCT and $A \cap B$ is the volume of overlap between volume of the delineation on pCT and volume of the delineation on CBCT. If DSC is 1, both volumes are the same. If DSC is 0, there is no similarity at all between both volumes. The calculation was done with the help of Velocity.

The third method consisted of measuring the surface distance between the delineations on the CBCTs and the pCT. The structure files of the esophagus and aorta delineations in Velocity were exported to Matlab (R2015a, The MathWorks Inc., Natick, MA, USA). Using a script developed in-house, the corresponding point on the delineation on the CBCT could be found along the perpendicular direction of the reference point of the delineation on the pCT, where the distance between the two points was measured. The mean vector of surface distance (and root mean square of standard deviations) was then calculated for every patient for all structures. Mean, standard deviation, minimum and maximum of surface distance were acquired for the overall structure of each structure in the LR and the AP directions. Furthermore, these values were also calculated for all sides (ventral, dorsal, left and right) of the esophagus structures in the LR and AP direction separately, as seen in Figure 2.5.

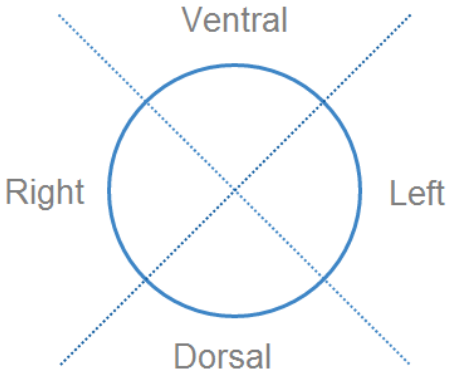

Figure 2.5. Schematic view of division of the esophagus contour (blue circle) into four sides.

Since there were few reference points in or on the esophagus that are clearly visible on both pCT and CBCT images, it was virtually impossible to determine if a particular part of the esophagus had moved in the CC direction. Displacement of the esophagus in the CC direction was therefore not measured.

2.5 Measurement of distance between esophagus and aorta

To determine if movement of the esophagus was constricted by the presence of the aorta, the distance between both structures was measured. The structure files of the esophagus and aorta delineations in Velocity were already exported to Matlab. Using an in-house developed script, the change in distance, compared to the pCT, between the center point line of the esophagus delineation and the center point line of the aorta delineation in the same scan, was measured for pCT and every CBCT for each patient. This resulted in a mean distance between center point lines of the full-length esophagus delineation and aorta delineation. The difference in mean distance between pCT and each CBCT was calculated.

2.6 Statistical analysis

For all patients, the relative volume, DSC, the mean surface distance vector, the mean surface distance in the LR and AP direction were compared between the five weekly CBCT scans (groups) for each structure (full-length esophagus, the three parts of the esophagus and aorta) using statistical tests, to see if a significant change in volume, DSC and mean displacement could be observed over the treatment course. The difference between pCT and CBCT in mean distance between central lines of esophagus and aorta was also compared between the five weekly CBCT scans.

The Shapiro-Wilk test was used to test for normality if more than 30 measurements for a variable were available. The Friedman test was used to compare outcomes between five CBCTs, between three parts and between the four sides. If a significant difference was found, post-hoc two-sample Wilcoxon signed rank tests were used to determine between which groups the difference occurred. Bonferroni correction was performed to all post hoc tests to control the family wise error rate. A one sample Wilcoxon signed test was used to compare a group to a reference value.
All statistical analyses were done using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, N.Y., USA). Results were considered statistically significant for $p < 0.05$, except for the post-hoc Wilcoxon signed rank test where the p value for statistical significance was corrected using the Bonferroni method.

2.7 Ethical aspects

This was a retrospective study using CT and CBCT data that have been used previously in two studies by Jin et al. (16,23). Patients had already given written informed consent for their data to be used for research purposes. Therefore, informed consent was not needed specifically for this study. As this was a retrospective study it was not required to be Wet Medisch-wetenschappelijk Onderzoek (WMO)-compliant. Patient data were anonymized.

3 Results

A total of 78 scans for 13 patients were analyzed. Delineation of the esophagus and aorta on pCT was feasible for all 13 patients. However, it was not possible to delineate the esophagus and/or the aorta on CBCT for four patients. There were three different causes.
In one patient, the anatomy of the aorta, in combination with poor CBCT quality, was indistinguishable from the esophagus for the middle part. In another patient the esophageal anatomy on several CBCTs substantially deviated from anatomy on pCT due to food being lodged in the esophagus, which made it difficult to distinguish the esophagus from other tissue. In the other two patients the overall CBCT quality was insufficient to accurately determine the position of the esophagus, even using the pCT as guidance.

As a result, there were 9 patients (1 female and 8 male) with the aorta and esophagus successfully delineated on CBCT. The tumor was located in the distal esophagus for 7 patients, in the middle esophagus for one patient, and over the full-length of the esophagus for one patient.

3.1 Volume changes

The Figure A1 (Appendix I) summarizes the relative volume for each structure (i.e., aorta, full-length esophagus and the three parts of the esophagus). For all patients, the relative volumes of the aorta on the CBCT were close to the reference volume on the pCT and had a tight spread (median and interquartile range (IQR) of results of all five CBCTs: 0.97, 0.07), indicating the volume of the aorta did not change much. The relative volume was more spread out for the full-length esophagus (1.03, 0.19), indicating greater changes in volume. For the three parts of the esophagus, the changes of the proximal part (0.89, 0.21) were smallest, followed by the distal part (1.03, 0.22) and the middle part (1.02, 0.24).

The relative volumes of the structures were tested for normality and showed a normal distribution for all, except for the proximal esophagus (p=0.000). For the aorta, the relative volume showed no significant difference between the five CBCTs, indicating no significant changes over the treatment course. The same was also found for the full-length esophagus as well as the proximal, middle and distal esophagus, separately. Between the three parts of the esophagus, a significant difference was found for the relative volume between the proximal and the middle part of the esophagus (p=0.009), indicating the relative volume of the esophagus for the proximal part is significantly smaller than the middle part.

3.2 Dice's Similarity Coefficients

As shown in Figure A2 (Appendix II), the DSC of the aorta had a high conformity and a tight spread (median, IQR; 0.90, 0.03), indicating only small deformation. The DSC of the full-length esophagus had less conformity and was more spread out (0.81, 0.06), indicating that it is prone to deformation. For the three parts of the esophagus, the DSC of the proximal esophagus had a tighter spread (0.79,

0.05), compared to the middle esophagus (0.79, 0.09) and the distal esophagus (0.83, 0.09). This indicates that the deformation was larger for the middle and distal part than the proximal part.

The DSC values of the structures were not normally distributed (p<0.05), except for the middle esophagus. For all patients, the DSC of all structures showed no significant difference between the five CBCTs, suggesting no significant change over the course of treatment. A comparison of the DSC between the three parts of the esophagus showed a significant difference (p=0.006) between the proximal and the distal part of the esophagus, confirming that deformation of the esophagus is larger in the distal part than the proximal part.

3.3 Surface distance

An example of 3D representations of the delineated esophagus can be seen in Figure 3.1. These representations show the difference between the delineation on pCT and the delineation on each CBCT.

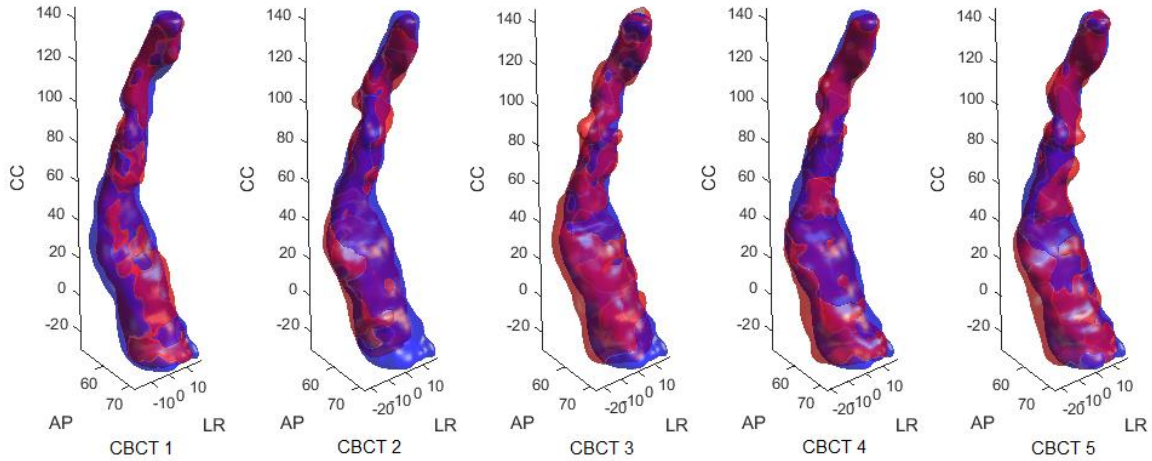

Figure 3.1. 3D reconstruction of surface of esophagus delineation for patient no. 5, who has a distal tumor. The pCT (blue) with the reconstruction of CBCT (red) projected on top of it. It is clearly visible where the CBCT delineation differs from the pCT delineation and that there is a variation between CBCT delineations as well.

Figure A3 (Appendix III) shows the mean vector of surface distance of the full-length esophagus and aorta. For the aorta, the mean and standard deviation (SD) of the vector of surface distance (mean of means, root mean square of SD) were 2.63 mm and 3.26 mm respectively, showing a large spread. For the esophagus, the vector distance of the full-length esophagus (3.29 mm, 1.69 mm) was greater, but had a tighter spread, indicating that the surface distance to the reference was more constant. The vector distance of the proximal part of the esophagus (2.72 mm, 1.40 mm) was smaller and more tightly spread compared to the middle part (3.25 mm, 1.66 mm) and the distal part (3.89, 1.96), showing the largest surface distance in the distal part of the esophagus.

The mean vector of surface distance was found significantly smaller in the proximal part of the esophagus compared to the middle and distal part of the esophagus (p<0.05). Moreover, a significant difference was found in the mean vector of surface distance for the distal esophagus using a one-

sample Wilcoxon signed rank test (p=0.008) compared to the average intra-observer error for esophagus delineation, which was reported to be 3 mm previously (27). This indicates the observed surface distance were far from due to delineation errors.

Further analysis of mean surface distance was done for each structure in the LR and AP directions. For 10 of 42 variables (mean surface distance for aorta per direction, for all esophagus structures per direction and per side) the mean surface distance was not normally distributed (p<0.05). For all structures, in the AP direction no significant difference in mean surface distance was found between the five CBCTs. The same result was found for the mean surface distance between the five CBCTs in the LR direction.

When comparing the three parts of the esophagus, there was no significant difference in mean surface distance between the three parts of the esophagus in the LR direction. However, in the AP direction, there was a significant difference in mean surface distance between the proximal and distal part of the ventral side of the esophagus (p=0.016). As can be seen in the graphs of the surface distance in the LR and AP direction for all structures in Appendix IV, on the ventral side the proximal part of the esophagus (median, IQR: -0.72 mm, 2.33 mm) moved to the posterior, while the distal part (0.46 mm, 1.92 mm) moved to the anterior direction.

When comparing the four different sides of the esophagus, the mean surface distance showed a significant difference between ventral and dorsal side of the proximal esophagus in the LR direction (p=0.000). The Figure 4.1 (Appendix V) shows that the surface distance in the LR direction on the ventral side of the proximal esophagus (-0.02 mm, 1.75 mm) was larger compared to the dorsal side (0.06 mm, 1.52 mm), indicating greater movement for the ventral side.

In the AP direction, a significant difference was found between the right and dorsal side, right and ventral side, left and dorsal side and ventral and dorsal side of the proximal esophagus (p<0.003). As shown in Figure 4.2 (Appendix IV), the dorsal side (0.35 mm, 1.42 mm) of the proximal esophagus moved in the anterior direction, while the ventral side (-0.72 mm, 2.33 mm) moved to the posterior direction. The ventral side also showed greater magnitude of movement compared to the dorsal, left (-0.25 mm, 1.30 mm) and right (0.11 mm, 1.21 mm) side of the proximal esophagus.

In summary, these results suggest that there was no significant change in surface distance over the course of treatment. Moreover, the magnitude of movement was dependent on which part of the esophagus and which side: smaller movement was observed for the proximal part and dorsal side, larger movement for the distal part and the ventral side. Further, the movement in the AP direction was dependent on the side of the esophagus: the ventral side moved to the posterior and the dorsal side moved to the anterior direction.

3.4 Distance between esophagus and aorta

By using the vector distance between the center lines of the full-length esophagus and the aorta on the pCT as a reference, for each patient the mean of the relative vector distance between the two center lines on each CBCT is plotted in Figure 3.2. It shows that the difference in vector distance varies between patients. Statistically, there was no significant difference between the five CBCTs in mean vector distance between the esophagus and the aorta. It indicates that the distance between the aorta and the esophagus did not change significantly over the course of treatment. Furthermore, no significant difference in mean vector distance between the esophagus and the aorta was found for each CBCT group compared to the reference pCT.

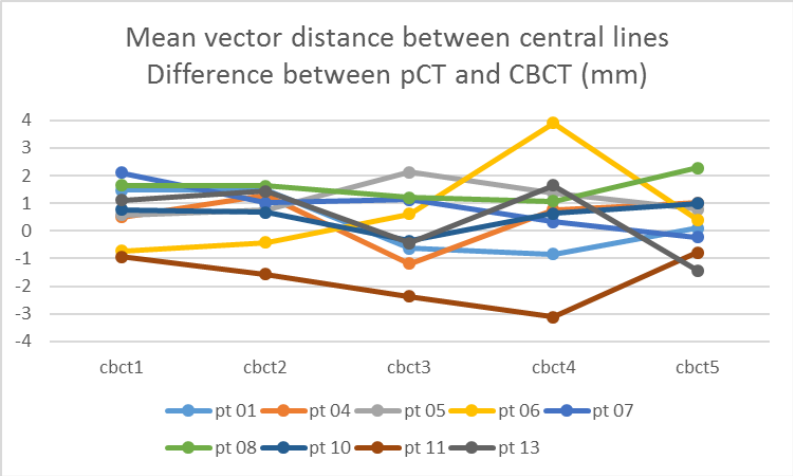

Figure 3.2. Graph of difference between pCT and CBCT for mean vector distance between the central lines of the esophagus and the aorta.

4 Discussion

To improve the safety margins used in external beam radiotherapy of esophageal cancer, it is important to investigate the systematic and random errors that influence the safety margin. Therefore, the inter-fractional deformation of the esophagus over the course of radiotherapy treatment of esophageal cancer was investigated using 3D kV CBCT imaging. The position of the esophagus close to the aorta was also investigated to determine if this influenced the deformation of the esophagus. To determine deformation, volume changes, DSC and surface distance of the esophagus between pCT and CBCT were obtained.

The results show that there was no common tendency in the deformation of the esophagus in the axial plane over the treatment course. The magnitude of deformation was dependent on the part and the side of the esophagus: smaller for the proximal part and the dorsal side, larger for the distal part and the ventral side. The direction of deformation was not dependent on the part or the side of the esophagus in the LR direction. In the AP direction, the direction of deformation was dependent on the side of the esophagus: movement to the posterior for the ventral side of the proximal part, movement to the anterior for the dorsal side of the proximal part. The aorta also showed no significant deformation over the treatment course, and the distance between the aorta and the esophagus did not change significantly over the course of treatment as well.

Delineating the esophagus and the aorta on pCT was done without much effort. However, delineating the esophagus and the aorta on CBCT proved to be challenging. As expected in advance, this was primarily caused by the poor image quality of the CBCTs compared to the pCTs. This led to the time needed for delineation of the structures on a CBCT to be three to four times longer than the time needed for delineation on a pCT. Compared to delineating the esophagus, delineating the aorta on CBCT was relatively easy because its contours were more clearly visible on the CBCTs. In contrast, delineating the esophagus would have been virtually impossible on CBCT without using the delineation on pCT as guidance in some cases. Accordingly, accurate delineation of the esophagus and/or aorta on CBCT was not feasible for four of the 13 patients in this study, as previously described in the “Results” section. Despite this fact, the delineation of the esophagus over the full length in this study allowed to investigate a more complete picture of deformation of the esophagus, compared to the studies by several other authors that have assessed only the esophageal tumor motion (10–16,19,21–23) and a study by Dieleman et al. (17) which investigated respiration induced motion of the esophagus delineating on only five slices spread over the length of the esophagus.

The CBCT was registered to the pCT based on bony anatomy, which was the same as daily setup in the clinic. After the delineations were checked by an experienced radiation therapist, the delineation error was assumed to be minimized. Moreover, the observed values for mean vector of surface distance of the esophagus for the distal part were found significantly larger than the average intra-observer delineation error previously reported by Collier et al. (27), indicating the observed

displacement is far from due to delineation errors. Due to the use of 3D fast pCT and 3D kV CBCT, motion induced by respiration, cardiac activity or peristaltic motion of the esophagus cannot be excluded. Therefore, the obtained inter-fractional deformation of the esophagus is likely caused by a combination of effects of delineation uncertainties, respiratory, cardiac and peristaltic motion, reaction of tissue to irradiation, different daily filling of the stomach and concurrent complications.

Previously, only Cohen et al. (24) have reported on inter-fractional expansion of the esophagus. They have found no significant difference in esophageal diameter between planning CT and pretreatment CT, and they indicated that the inter-fractional motion of the esophagus is therefore not related to changes in diameter of the esophagus. Although they divided the esophagus into a part above and a part below the carina, they have not reported on differences between both parts. The current study found that the volume of the esophagus does not change significantly over the course of treatment, which corresponds with the results reported by Cohen et al. In addition, a difference was found in change of volume between parts of the esophagus, the magnitude of change being larger for the middle and distal part compared to the proximal part of the esophagus.

The use of DSC has not previously been reported in a study investigating the deformation of the esophagus. Because the length of the esophagus was fully delineated in this study, it was possible to use the DSC for easy comparison between pCT and CBCT, combining both the volume changes and the displacement of a structure in one. The results of the DSC for all structures were similar to those found for volume changes and for surface distance.

The mean (SD) vector of surface distance of the esophagus between pCT and CBCT in this study was 3.3 (1.7) mm. This is a little larger than the average esophageal motion between pCT and pretreatment CT of 1.2 (4.7) mm in all directions, previously reported by Cohen et al. (24). An explanation for this lies in the different methods used to obtain these values. Cohen et al. used the diameter and the center point of the esophagus delineation for their measurement, whereas in this study the value was calculated using hundreds of points on the surface of the delineation. Because it is based on data of hundreds of points instead of one point, the mean vector of surface distance of the esophagus between pCT an CBCT should give a more accurate representation of deformation of the esophagus. This could also explain why the mean esophageal motion between pCT and CBCT of 5 (3) mm reported by Yamashita et al. (9) for both the LR and AP direction is larger compared to this study.

No significant difference for deformation of the esophagus in the LR or AP direction over the course of treatment was found. This result is similar to that of a study by Yamashita (9), which also reported no significant difference in inter-fractional motion in the AP or LR directions. Cohen et al. (24) reported greater esophageal motion to the left side, hypothesizing that this was likely related to cardiac motion. However, they did not clarify whether this observed esophagus motion to left was inter-fractional or intra-fractional.

The current study has found a significant difference in deformation of the esophagus between the parts of the esophagus: deformation being larger for the distal and middle part and smaller for the proximal part of the esophagus. However, this significant difference was not found inter-fractionally (between CBCTs). Several studies (10–16) on intra-fractional motion of the esophagus have reported a similar significant difference between the parts of the esophagus, suggesting that the difference in deformation between parts of the esophagus in the current study is likely related to intra-fractional motion of the esophagus.

A significant difference in deformation in the AP direction was found between the sides of the esophagus: deformation being larger for the ventral side and smaller for the dorsal side. The deformation of each side of the esophagus separately has not been reported previously. However, because this significant difference was also not found inter-fractionally (between CBCTs), similar to that of the deformation between the parts of the esophagus, it stands to reason that the significant difference between the sides of the esophagus could also be likely related to intra-fractional motion of the esophagus.

Based on the results of the study of Jin et al. (23) that investigated inter-fractional esophageal tumor position variation using markers, it has been hypothesized that the presence of the aorta could influence the deformation of the esophagus. This has not been reported previously. Therefore, the distance between the aorta and the esophagus was investigated. Because it was unclear whether the aorta deformed over the course of treatment, the deformation of the aorta was also investigated. No significant changes have been found over the treatment course for the aorta, and along with a high conformity this indicates the aorta is a steady structure. The distance between esophagus and aorta has also not shown significant changes over the treatment course. It is therefore considered unlikely that the deformation of the esophagus is influenced by deformation of the aorta or the position of the esophagus close to the aorta.

An important limitation to this study is that the displacement of the structures in the CC direction could not be measured. The reason for this is the lack of reference points in or on the esophagus that are clearly visible on both pCT and CBCT images, which makes it virtually impossible to determine if the esophagus or a part of the esophagus has moved in the CC direction. Further, due to the method used for analyzing the delineations, for each patient the delineations were all truncated in the CC direction into the same length. As a result, any displacement of the structures in the CC direction, or increase or decrease in length of the structures has not been taken into account. This possibly creates differences between pCT and CBCTs, making the obtained volumes, DSC and surface distances of the structures less accurate. This would explain the unexpected large spread for the mean vector surface distance of the aorta (mean of means, root mean square of SD; 2.63 mm, 3.26 mm). This is suspected to be caused by a delineation of the descending aorta being in the same slice as a delineation of the aortic arch due to movement in the CC direction, resulting in large surface distances.

In total 45 CBCTs and 9 pCT have been analyzed. However, these were of only 9 patients, the majority (7) of them having a distal tumor. Since a larger deformation has been found for the distal part of the esophagus, this could very well be due to the fact that the tumor was located distally in most patients. It is recommended for a follow-up study to include more patients with tumors located in the proximal and middle esophagus, to confirm whether the current results also apply to those patients.

This study shows that there was no significant inter-fractional deformation of the esophagus over the course of treatment. Therefore, there is no need to adjust the safety margins used for external beam radiotherapy of esophageal cancer in clinical practice. However, the larger deformation of the distal part of the esophagus and the smaller deformation of the proximal part found in this study as well as previous studies (10–16) should be considered when determining the safety margins, depending on the location of the esophageal tumor.

In summary, this study investigated the inter-fractional deformation of the esophagus during radiotherapy using 3D kV CBCT imaging. No significant change in deformation of the esophagus was found between CBCTs, indicating inter-fractional deformation of the esophagus is not likely to occur. The mean vector of surface distance of the esophagus was 3.29 (1.69) mm. No significant deformation of the esophagus was observed over the course of treatment for either the LR or AP direction. The deformation of the esophagus was found to be dependent on the part of the esophagus and the side of the esophagus, with smaller deformation for the proximal part and dorsal side and larger deformation for the distal part and ventral side of the esophagus. Further, the direction of deformation was dependent on the side of the esophagus in the AP direction. Furthermore, the aorta did not show significant change over the course of treatment and the distance between the esophagus and the aorta showed no significant change as well. It therefore unlikely that the deformation of the esophagus is influenced by deformation of the aorta or the position of the esophagus close to the aorta.

References

1. Integraal Kankercentrum Nederland. Cijfers Slokdarmtumoren [Internet]. Nederlandse Kankerregistratie. 2016 [cited 2016 Feb 25]. Available from: http://cijfersoverkanker.nl/
2. Integraal Kankercentrum Nederland - Werkgroep Oesofaguscarcinoom. Landelijke Richtlijn Oesofaguscarcinoom versie 3.1 [Internet]. Oncoline, richtlijnen oncologische zorg. 2015 [cited 2016 Feb 25]. Available from: http://www.oncoline.nl/oesofaguscarcinoom
3. Berger B, Belka C. Evidence-based radiation oncology: Oesophagus. Radiother Oncol [Internet]. Elsevier Ireland Ltd; 2009;92(2):276–90. Available from: http://dx.doi.org/10.1016/j.radonc.2009.02.019
4. Shapiro J, van Lanschot JJB, Hulshof MCCM, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): Long-term results of a randomised controlled trial. Lancet Oncol [Internet]. Elsevier Ltd; 2015;16(9):1090–8. Available from: http://dx.doi.org/10.1016/S1470-2045(15)00040-6
5. Van Herk M. Errors and Margins in Radiotherapy. Semin Radiat Oncol. 2004;14(1):52–64.
6. Monjazeb AM, Blackstock AW. The impact of multimodality therapy of distal esophageal and gastroesophageal junction adenocarcinomas on treatment-related toxicity and complications. Semin Radiat Oncol [Internet]. Elsevier Inc.; 2013;23(1):60–73. Available from: http://dx.doi.org/10.1016/j.semradonc.2012.09.006
7. Hawkins MA, Aitken A, Hansen VN, McNair HA, Tait DM. Set-up errors in radiotherapy for oesophageal cancers - Is electronic portal imaging or conebeam more accurate? Radiother Oncol [Internet]. Elsevier Ireland Ltd; 2011;98(2):249–54. Available from: http://dx.doi.org/10.1016/j.radonc.2010.11.002
8. Han C, Schiffner DC, Schultheiss TE, Chen YJ, Liu A, Wong JYC. Residual setup errors and dose variations with less-than-daily image guided patient setup in external beam radiotherapy for esophageal cancer. Radiother Oncol [Internet]. Elsevier Ireland Ltd; 2012;102(2):309–14. Available from: http://dx.doi.org/10.1016/j.radonc.2011.07.027
9. Yamashita H, Haga A, Hayakawa Y, Okuma K, Yoda K, Okano Y, et al. Patient setup error and day-to-day esophageal motion error analyzed by cone-beam computed tomography in radiation therapy. Acta Oncol [Internet]. 2010;49(4):485–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20230211
10. Zhao K le, Liao Z, Bucci MK, Komaki R, Cox JD, Yu ZH, et al. Evaluation of respiratory-induced target motion for esophageal tumors at the gastroesophageal junction. Radiother Oncol. 2007;84(3):283–9.
11. Pan C, Kashani R, Hayman J, Kessler M, Balter J. 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. Int J Radiat Oncol Biol Phys. 2004;60(1):S580–1.
12. Patel AA, Wolfgang JA, Niemierko A, Hong TS, Yock T, Choi NC. 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(1):290–6.
13. Yamashita H, Kida S, Sakumi A, Haga A, Ito S, Onoe T, et al. Four-Dimensional Measurement of the Displacement of Internal Fiducial Markers During 320-Multislice Computed Tomography Scanning of Thoracic Esophageal Cancer. Int J Radiat Oncol Biol Phys. 2011;79(2):588–95.
14. Li J, Wang L, Wang X, Zhao Y, Liu D, Chen C, et al. Preliminary study of the internal margin of the gross tumor volume in thoracic esophageal cancer. Cancer / Radiother [Internet]. Elsevier Masson SAS; 2012;16(7):595–600. Available from: http://dx.doi.org/10.1016/j.canrad.2012.05.020
15. Lever FM, Lips IM, Crijns SPM, Reerink O, Van Lier ALHMW, Moerland MA, et al. Quantification of esophageal tumor motion on cine-magnetic resonance imaging. Int J Radiat Oncol Biol Phys [Internet]. Elsevier Inc.; 2014;88(2):419–24. Available from: http://dx.doi.org/10.1016/j.ijrobp.2013.10.036
16. Jin P, Hulshof MCCM, de Jong R, van Hooft JE, Bel A, Alderliesten T. Quantification of respiration-induced esophageal tumor motion using fiducial markers and 4D computed tomography. Radiother Oncol [Internet]. Elsevier Ireland Ltd; 2016; Available from: http://dx.doi.org/10.1016/S0167-8140(15)40540-7\nhttp://linkinghub.elsevier.com/retrieve/pii/S0167814015405407
17. Dieleman EMT, Senan S, Vincent A, Lagerwaard FJ, Slotman BJ, van Sörnsen de Koste JR. Four-dimensional computed tomographic analysis of esophageal mobility during normal respiration. Int J Radiat Oncol Biol Phys. 2007;67(3):775–80.
18. Palmer J, Yang J, Pan T, Court LE. Motion of the esophagus due to cardiac motion. PLoS One. 2014;9(2).
19. Wang JZ, Li J Bin, Wang W, Qi HP, Ma ZF, Zhang YJ, et al. Changes in tumour volume and motion during radiotherapy for thoracic oesophageal cancer. Radiother Oncol [Internet]. Elsevier Ireland Ltd; 2015;114(2):201–5. Available from: http://dx.doi.org/10.1016/j.radonc.2014.12.010
20. Wang J, Lin SH, Dong L, Balter P, Mohan R, Komaki R, et al. Quantifying the interfractional displacement of the gastroesophageal junction during radiation therapy for esophageal cancer. Int J Radiat Oncol Biol Phys [Internet]. Elsevier Inc; 2012;83(2):e273–80. Available from: http://dx.doi.org/10.1016/j.ijrobp.2011.12.048
21. Fukada J, Hanada T, Kawaguchi O, Ohashi T, Takeuchi H, Kitagawa Y, et al. Detection of esophageal fiducial marker displacement during radiation therapy with a 2-dimensional on-board imager: Analysis of internal margin for esophageal cancer. Int J Radiat Oncol Biol Phys [Internet]. Elsevier Inc.; 2013;85(4):991–8. Available from: http://dx.doi.org/10.1016/j.ijrobp.2012.07.2358
22. Wang JZ, Li J Bin, Wang W, Qi HP, Ma ZF, Zhang YJ, et al. Detection of interfraction displacement and volume variance during radiotherapy of primary thoracic esophageal cancer based on repeated four-dimensional CT scans. Radiat Oncol [Internet]. Radiation Oncology; 2013;8(1):224. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4016114&tool=pmcentrez&rendertyp

e=abstract
23. Jin P, van der Horst A, de Jong R, van Hooft JE, Kamphuis M, van Wieringen N, 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 [Internet]. Elsevier Ireland Ltd; 2015;117(3):412–8. Available from: http://dx.doi.org/10.1016/j.radonc.2015.10.005
24. Cohen RJ, Paskalev K, Litwin S, Price RA, Feigenberg SJ, Konski AA. Esophageal motion during radiotherapy: Quantification and margin implications. Dis Esophagus. 2010;23(6):473–9.
25. Machiels M, Van Hooft J, Jin P, Van Berge Henegouwen MI, Van Laarhoven HM, Alderliesten T, et al. Endoscopy/EUS-guided fiducial marker placement in patients with esophageal cancer: A comparative analysis of 3 types of markers. Gastrointest Endosc [Internet]. Elsevier, Inc.; 2015;82(4):641–9. Available from: http://dx.doi.org/10.1016/j.gie.2015.03.1972
26. Kong FM, Ritter T, Quint DJ, Senan S, Gaspar LE, Komaki RU, et al. Consideration of dose limits for organs at risk of thoracic radiotherapy: Atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. Int J Radiat Oncol Biol Phys. 2011;81(5):1442–57.
27. Collier DC, Burnett SSC, Amin M, Bilton S, Brooks C, Ryan A, et al. Assessment of consistency in contouring of normal-tissue anatomic structures. J Appl Clin Med Phys. 2003;4(1):17–24.

Appendices

Appendix I Relative volume

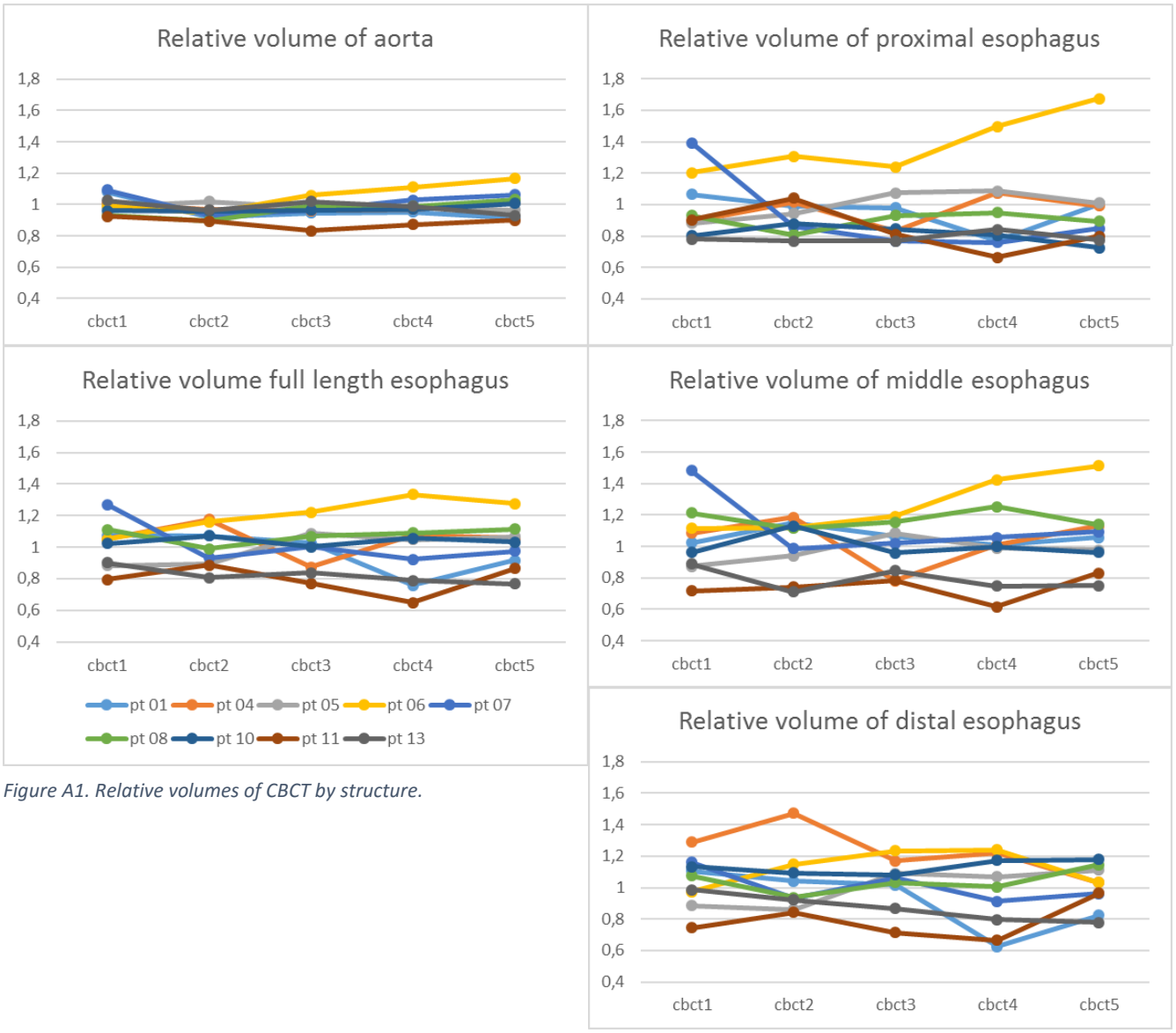

Figure A1. Relative volumes of CBCT by structure.

Appendix II Dice's Similarity Coefficient

Figure A2. Graphs of Dice's coefficient by structure.

Appendix III Mean vector of surface distance

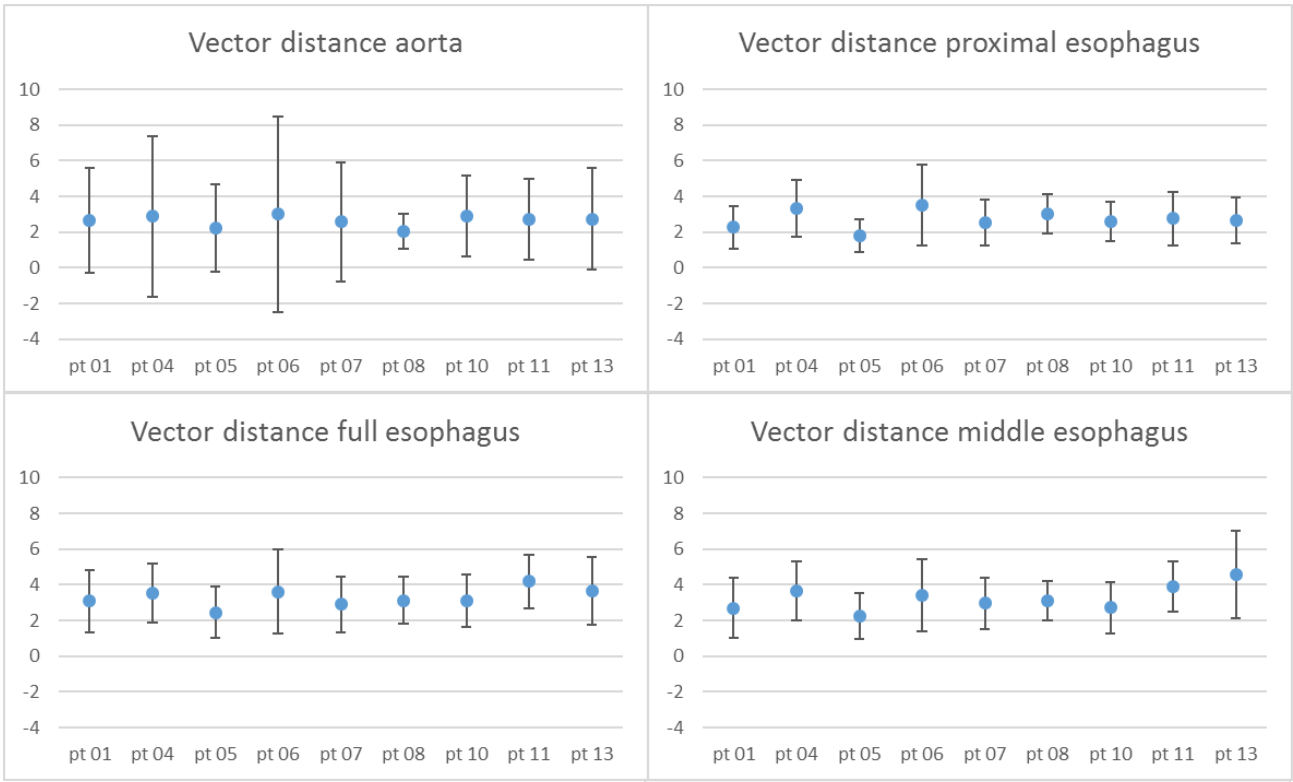

Figure A3. Graph of mean vector of surface distance for every structure in millimeters. Points represent mean vector distance and error bars represent standard deviation.

Appendix IV Mean surface distance in LR and AP directions

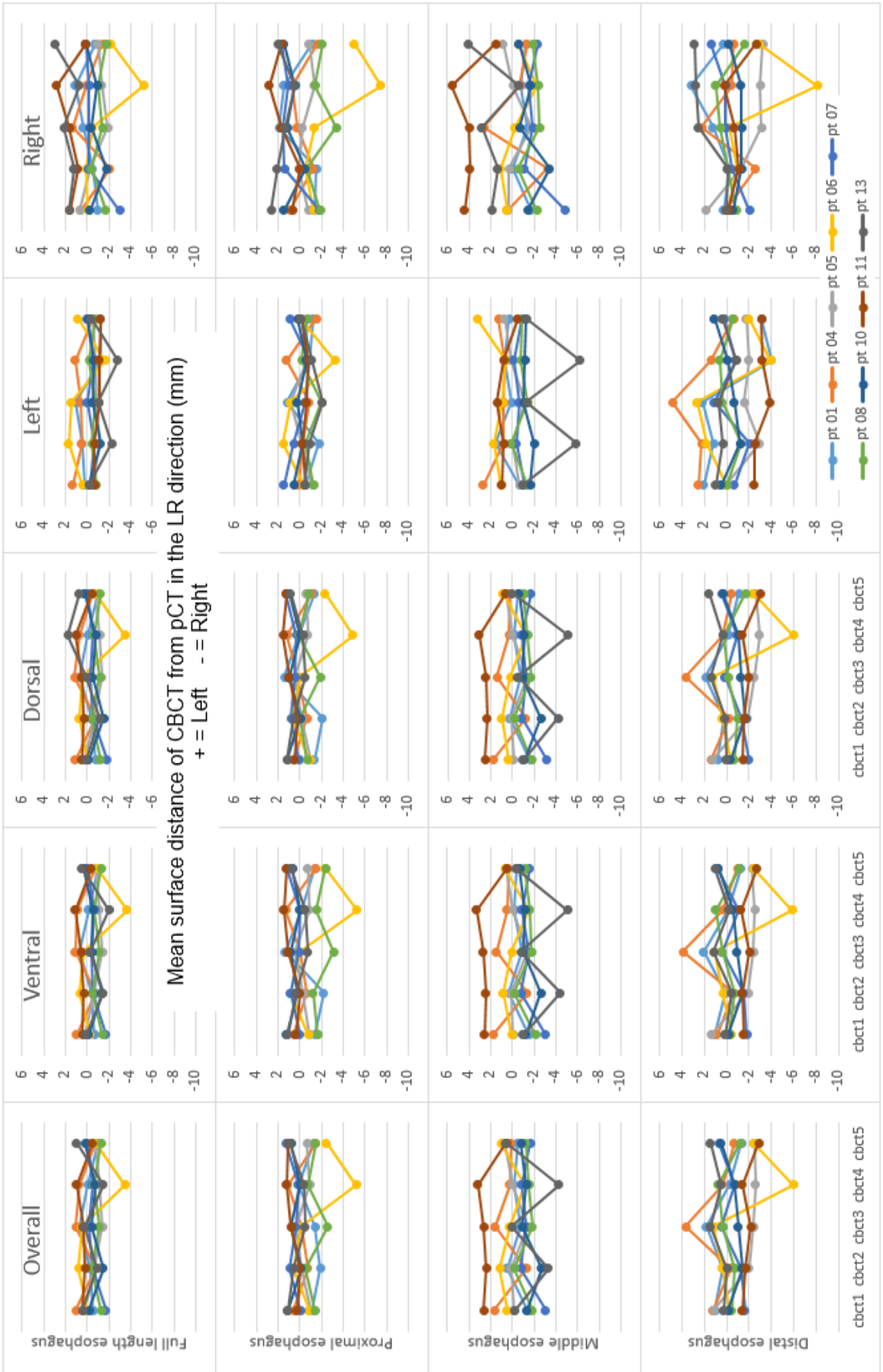

Figure A4.1. Graphs of mean surface distance of the esophagus in the LR direction, sorted by side and part. Distance is in millimeters.

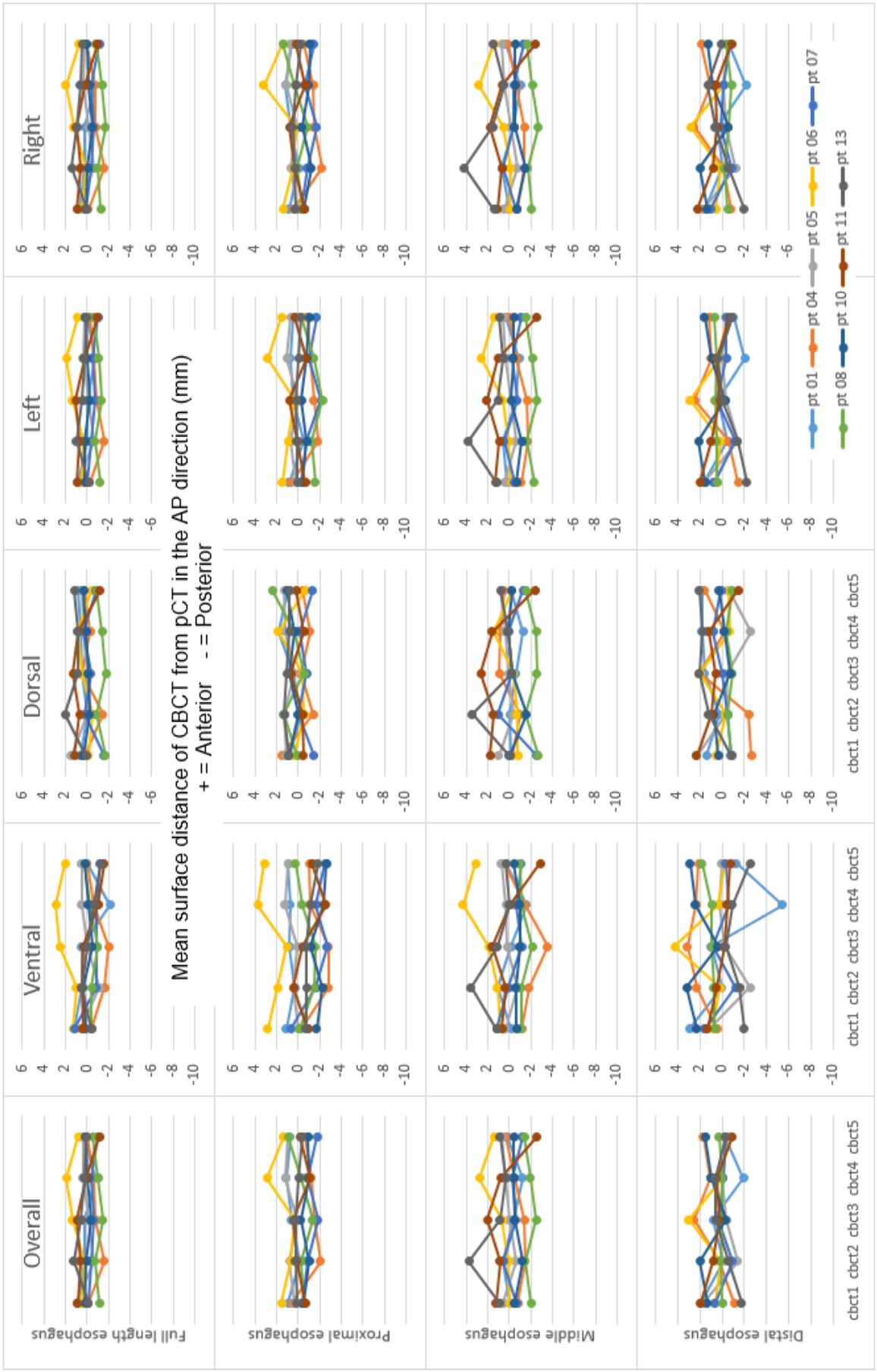

Figure A4.2. Graphs of mean surface distance of the esophagus in the AP direction, sorted by side and part. Distance is in millimeters.