

ORIGINAL ARTICLE

## Patient setup error and day-to-day esophageal motion error analyzed by cone-beam computed tomography in radiation therapy

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### Abstract

Little has been reported on the errors of setup and daily organ motion that occur during radiation therapy (RT) for esophageal cancer. The purpose of this paper was to determine the margins of esophageal motion during RT. *Methods and materials.* The shift of the esophagus was analyzed in 20 consecutive patients treated with RT for esophageal cancer from November 2007. CT images for RT planning were used as the primary image series. Computed tomography (CT) images were acquired using an Elekta Synergy System, equipped with a kilovoltage-based cone-beam CT (CBCT) unit. The subsequent CBCT image series used for daily RT setup were compared with the primary image series to analyze esophageal motion. CBCT was performed before treatment sessions a total of 10 times in each patient twice a week. The outer esophageal wall was contoured on the CBCT images of all 200 sets. *Results.* In the 200 sets of CBCT images, the mean (absolute)  $\pm$  standard deviation (SD) of setup errors were  $2 \pm 2$  mm (max, 8 mm) in the lateral direction,  $4 \pm 3$  mm (max, 11 mm) in the longitudinal direction, and  $4 \pm 3$  mm (max, 13 mm) in the vertical direction. Additionally, the mean  $\pm$  SD values of daily esophageal motion comparing the CBCT with RT planning CT were  $5 \pm 3$  mm (max, 15 mm) in the lateral direction and  $5 \pm 3$  mm (max, 15 mm) in the vertical direction. *Conclusions.* Our data support the use of target margins (between the clinical target volume and planning target volume) of 9 mm for day-to-day esophageal motion and 8 mm for patient setup in all directions, respectively.

Inter-fraction and intra-fraction motion of critical structures is a significant concern when patients undergo intensity modulated radiation therapy (IMRT). Improper dose modulation can be a result of anatomical motion among other factors. Overdosage to normal tissues can cause toxicity, while underdosage can lead to tumor progression. Image guided radiation therapy (IGRT) has been used in an attempt to minimize the impact of this motion.

Esophageal motion can be attributed to peristalsis, respiratory action, and cardiac action [1]. However, it was not addressed in reviews on inter-fraction and intra-fraction organ motions during RT [2]. Only the limited amount of data is available on the esophageal movement in patients undergoing RT planning [1,3]. The majority of patients with esophageal cancers are treated during free respiration. Thus, cone-beam computed tomography (CBCT) scans acquired during free respiration could provide

relevant data on respiration-induced motion. Dieleman et al. [4] performed four-dimensional CT analysis of esophageal mobility during normal respiration and concluded that the distal esophagus showed more mobility than other parts. Thus, they derived margins of mobility for use in treatment planning that can encompass all movement. The present study analyzed the patient setup error and day-to-day esophageal motion during IGRT. The 20 consecutive patients in this study represent the largest analysis heretofore conducted of daily inter-fraction esophageal movement during free respiration.

### Materials and methods

#### Subjects

In this study, both patient setup error and inter-fraction daily shifts of the esophagus were analyzed in 20

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consecutive patients with stage I-IVB esophageal cancer treated with chemoradiation with curative intent between November 2007 and May 2008 in University of Tokyo Hospital, Tokyo, Japan. The entire thoracic esophagus in all 20 cases was included within the radiation field. Ten sets of computed tomography (CT) images from each patient were acquired using an Elekta Synergy System (Elekta Ltd, Crawley, UK), equipped with a kilovoltage (kV)-based CBCT unit [5].

The clinical and demographic data of the 20 patients are shown in Table I. The 6th edition of the American Joint Committee on Cancer TNM staging system [6] was used. For each patient, the CT images for RT planning (slice thickness of 5 mm, index of 1 mm, helical pitch of 15, and beam pitch of 15/16) acquired in free respiration by a large-bore CT system (Aquilion/LB, Toshiba, Tokyo, Japan) without any contrast media one or two days before treatment were used as the primary image series. The subsequent CBCT image series (slice thickness of 5 mm) used for daily RT setup were then compared to the primary image series to analyze inter-fraction esophageal motion. CBCT was performed before treatment sessions a total 10 times in each patient: one set of images was acquired twice a week during an overall RT duration of five weeks. The patient setup for RT treatment was carried out daily without referring to the previous data on setup error generated by CBCT and only the automatic bony landmark matching was carried out each time. However, because the CBCT imaging performed after this bone-matching

registration (i.e. after correcting for the setup error) was used in the comparison, only day-to-day esophageal motion was taken into account. Automatic matching of anatomic bony landmarks was carried out and part of the image set for the matching was removed (e.g. shoulders, which are easily moved). A bony co-registration based on a window around the vertebral column was used for esophageal treatment since the esophagus is a posterior structure in close proximity to the vertebral column. Only an arm support was used as an immobilization device.

#### CBCT imaging

To generate a set of CBCT images, the typical patient dose was 15.1 mGy (120 kV, 40 mA, 40 ms, 640 frames, 360° data collection), based on the weighted CT dose index (CTDI<sub>w</sub>), and this radiation dose was expected to have almost no effect on the total dose in the treatment. The outer esophageal wall was contoured on the CBCT images of all 200 sets from the esophageal orifice to the esophago-gastric junction under the mediastinal window setting (window width, 350 HU; window level, 40 HU). Only one radiation oncologist (HY), who was experienced with the RT planning system and had utilized it for routine planning, was involved in the contouring process.

#### Measurements method

After bone-matching registration, the primary and pre-treatment CT image series were fused and compared

Table I. Patient and tumor characteristics.

Case No.	Gender	Age (y)	Primary Site	Clinical Tumor Stage	Clinical Nodal Stage	Clinical Metastasis Stage	AJCC Stage
1	M	78	Lt	3	1	0	III
2	M	81	Mt	1	0	0	I
3	F	70	Lt	3	1	1b	IVB
4	M	64	Ut	1	0	0	I
5	M	73	Lt	3	1	1b	IVB
6	M	67	Ut	2	0	0	IIA
7	M	53	Lt	2	0	0	IIA
8	M	72	Ut	3	1	0	III
9	F	79	Ut	3	1	0	III
10	M	80	Lt	3	1	0	III
11	M	90	Lt	3	1	0	III
12	M	78	Mt	4	1	1b	IVB
13	M	73	Ut	1	1	0	IIB
14	M	74	Mt	4	1	0	III
15	F	62	Mt	1	0	0	I
16	M	68	Lt	2	0	0	IIA
17	M	55	Ut	4	1	1a	IWA
18	M	73	Mt	1	0	0	I
19	M	64	Ut	1	0	0	I
20	M	67	Lt	3	1	1b	IVB

Abbreviations: AJCC=American Joint Committee on Cancer; F=female; Lt=lower thoracic; M=male; Mt=middle thoracic; Ut=upper thoracic; y=years.

using a Pinnacle<sup>3</sup> treatment-planning workstation (Philips Healthcare, Andover, MA, USA; ADAC, Milpitas, CA, USA). A case with the outer esophageal wall contoured on the CBCT image is shown in Figure 1. Inter-fraction motion was measured using approximately 50 axial CT images of 5-mm slices from the esophageal inlet to the esophago-gastric junction. The measurements were done in the anterior-posterior and right-left (lateral) directions on all slices and then the maximum deviation between esophageal walls delineated in the each CBCT after the bone matching registration and the planning CT images across all scans were used. Therefore, all values of the inter-fraction motion were positive.

The formalism of Stroom et al. for margin derivation [7] ( $= 2.0\sigma + 0.7\sigma$ ) and van Herk et al. [8] ( $= 2.5\sigma + 0.7\sigma$ ) were used to evaluate the values as margin for setup error and daily esophageal motion error. However, another new optimization algorithm for the determination of treatment margins around moving and deformable targets like esophagus in radiotherapy proposed by Redpath & Muren [9] was not used this time.

## Results

### Setup errors

In the 200 sets of CBCT images, the mean and SD values of the patient setup errors were 0 +/- 2 mm in the lateral direction, 0 +/- 3 mm in the longitudinal direction, and 0 +/- 4 mm in the vertical direction.

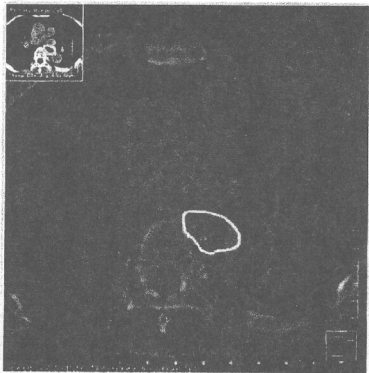


Figure 1. CBCT image of the middle thoracic region, scanned under free respiration and processed after transferring data onto a Pinnacle<sup>3</sup> workstation for planning of RT. A case with the outer esophageal wall contoured on the CBCT images (sky-blue contour).

The composite (all) SD was defined simply as the average of the individual SDs in each direction. The value of SD ( $=\Sigma$ ) of the absolute value of the setup error in all 200 data was 2 mm (lateral), 3 mm (longitudinal), and 3 mm (vertical), respectively. The mean of the absolute value of the setup error in all 200 data was 2 mm (max, 8 mm) in the lateral direction, 4 mm (max, 11 mm) in the longitudinal direction, and 4 mm (max, 13 mm) in the vertical direction (Table II). Based on the setup error for each patient, the maximum of SD was 4 mm in the lateral direction (case no. 14), 6 mm in the longitudinal direction (case no. 7), and 6 mm in the vertical direction (cases 5 and 18). The frequencies of setup errors >2 mm on the lateral, longitudinal, and vertical axes were 48%, 60%, and 73%, respectively, and the frequencies of errors >5 mm were 11%, 31%, and 30%, respectively. The patient setup error was corrected only by parallel translation, so the lag of rotation was not considered. According to the formalism of Stroom for margin derivation, the evaluation value as margin for setup error was 4 mm of right-left direction, 6 mm of dorsal-ventral direction, and 6 mm of cranio-caudal direction, and additionally, according to van Herk 5 mm, 8 mm, and 8 mm (Table II).

### Esophageal motion errors

Additionally, the means  $\pm$  SD's of daily esophageal motion comparing the CBCT with RT planning CT were 5 +/- 3 mm (max, 15 mm) in the lateral direction and 5 +/- 3 mm (max, 15 mm) in the vertical direction (Table III). A maximum shift in the lateral direction was found at the upper thoracic site in 79 sets (39.5%), at the middle thoracic site in 63 sets (31.5%), and at the lower thoracic site in 58 sets (29.0%). Moreover, there were shifts on the left side in 136 sets (68.0%) and on the right side in 64 sets (32.0%). A maximum shift in the vertical direction was found at the upper thoracic site in 49 sets (24.5%), at the middle thoracic in 80 sets (40%), and at the lower thoracic in 71 sets (35.5%). The motion was the same in the upper or the lower esophagus. Also, shifts were noted to the anterior direction in 88 sets (44.0%) and to the posterior direction in 112 sets (56%). Based on each patient's daily esophageal motion, the maximum SD was 4 mm in both vertical

Table II. Setup error in three dimension.

Direction	Right-left	Dorsal-ventral	Cranio-caudal
Mean (Absolute)	2 mm	4 mm	4 mm
$\Sigma$ (systematic error)	2 mm	3 mm	3 mm
Max	8 mm	11 mm	13 mm
$\delta$ (random error)	0 mm	1 mm	1 mm
Stroom [30]	4 mm	6 mm	6 mm
van Herk [31]	5 mm	8 mm	8 mm

Table III. Organ motion error.

Direction	Right-left	Dorsal-ventral
mean	5 mm	5 mm
SD	3 mm	3 mm
max	15 mm	15 mm
95%*	10 mm	11 mm
$\sigma$	1 mm	2 mm
Stroom [30]	7 mm	7 mm
van Herk [31]	8 mm	9 mm

\*Margin value covering 95% of data.

(cases 6 and 11) and lateral directions (case 3). According to Stroom, the evaluation value as margin for daily organ motion error was 7 mm of right-left direction and 7 mm of dorsal-ventral direction, and additionally, according to van Herk, 8 mm and 9 mm (Table III).

### Clinical results

Though the median follow up time has been only nine months, six patients (30%) have died of esophageal cancer and two patients (10%) who are still alive have loco-regional and/or distant recurrences of esophageal cancer. To date, there has been no non-hematological toxicity of grade 3 and acute or sub-acute esophagitis or pneumonitis.

### Discussion

#### Brief summary of main points

In this study patient setup error and inter-fraction motion of the esophagus were examined during RT in 20 patients. To our knowledge, this is the first report of the study of inter-fraction esophageal motion during day-to-day RT in patients with esophageal cancer. In fact, corrections for the setup errors have already been made in our method using CBCT and thus the setup errors are pertinent for our patients. The interesting aspect of our data is the remaining internal organ motion of the esophagus. In this study, the inter-fraction error was defined as the difference between day-to-day esophageal positions after eliminating daily setup error. This inter-fraction error included tumor motion due to the patient's random movement, cardiac motion, peristaltic motion and respiratory motion (i.e. intra-fraction motion).

#### Main findings in relation to other studies

The kV CBCT was used for determining setup error in this study. The different interaction mechanisms of kV photons with tissues and image transducers offer improved imaging compared with megavoltage (MV) photons. This capability enhances the localization of target volumes and adjacent organs at risk

during treatment compared with MV electronic portal imaging. The scatter component should not have as much an impact with MV CBCT compared with kV CBCT. The use of MV photos for imaging is a departure from the general preference for kV beams in imaging. The visibility of large low-contrast objects in tomographic images depends on the contrast-to-noise ratio. Contrast is determined by the differential attenuation of the beam through different bodily tissues. Most importantly, the image sequence from rotation fluoroscopy can be used in filtered back-projection to reconstruct an x-ray volumetric image. Recently, Xu et al. [10] utilized CBCT measurements before and after treatment in the same day in order to detect intra-fraction tumor position errors (including 19 head and neck, 25 thoracic and 10 abdominal-pelvic tumors). Guckenberger et al. [11] used CBCT scanning for the evaluation of setup errors and demonstrated the feasibility of its use in day-to-day clinical practice.

Esophageal movement was not addressed in an earlier review on inter-fraction and intra-fraction organ motion during RT [2]. In our study, the daily esophageal motion were  $5 \pm 3$  mm (max, 15 mm) in the left-right direction and  $5 \pm 3$  mm (max, 15 mm) in the antero-posterior direction. These values were almost similar to those of the following previous reports. Measurements of lower esophageal sphincter pressure during quiet respiration revealed lateral esophageal motion of  $6 \pm 2$  mm in the abdominal portion and  $4 \pm 1$  mm in the thoracic region [12]. Cine-fluoroscopic barium swallow images of the esophagus in 51 patients undergoing catheter ablation for atrial fibrillation indicated that lateral shifts of more than 20 mm occurred in a majority of patients [13]. Daily online CT images in a study of six IGRT-treated patients were reported to show maximal motion in the distal esophagus, and indicated that margins of 2–5 mm could account for all motion [14]. A study of esophageal positions at the extreme phases of respiration in six patients suggested that a margin of 5–6 mm was sufficient to account for variations in organ position [15]. Hashimoto et al. [1] analyzed the motion during quiet respiration in 13 patients with implanted fiducial markers inserted into the esophageal wall and it was  $4 \pm 2$  mm,  $8 \pm 4$  mm, and  $4 \pm 3$  mm for the medio-lateral, cranio-caudal, and antero-posterior directions, respectively. According to Dieleman et al. [4], margins that would have incorporated all esophageal movement in the medio-lateral and dorso-ventral (anterior-posterior) directions were 5 mm proximally, 7 mm and 6 mm in the mid-esophagus, and 9 mm and 8 mm in the distal esophagus, as determined by 4D-CT. According to Guerrero et al. [16], the displacement of the esophageal tumors,



which estimated from breath-hold CT imaging using the 3-D optical flow method, was non-uniform and up to 14 mm.

#### *Limitations of this study*

The possible sources of methodological errors in assessing inter-fraction esophageal motion in this study could involve (a) inaccurate contouring of the outer esophageal wall on CBCT and/or planning CT images (i.e. human error), (b) mistakes in fusing CBCT images after correcting setup errors on the planning CT image on the Pinnacle<sup>3</sup> workstation because the form or relative position of the chest wall and/or vertebral bone might be different, (c) correcting the setup error only by parallel translation, and not considering the lag of rotation and the longitudinal displacement could not be evaluated with our method, and, therefore, the error in the longitudinal direction was also detected as the error in the left-right or anterior-posterior directions, (d) the difference in the speed at which free breathing scans were acquired with the conventional CT and the CBCT, and (e) the CBCT is a slow scan over approximately 2 minutes and it therefore blurs the intra-fraction motion which is predominantly respiratory motion with a period of about 4 seconds. The probability of the first error (a) was minimized by having only a single experienced radiation oncologist (i.e. not multiple clinicians) contouring the outer esophageal wall and by expanding the image significantly. The other potential errors (b and c) were not formally evaluated in this study; however, images displayed on the Pinnacle<sup>3</sup> workstation were checked to make sure they were not significantly out of position after they were fused (Figure 1). The slow scan blurs the esophageal outline and makes accurate delineation more difficult (e). So in this study, only the intra-fraction esophageal motion during treatment could not be extracted.

In this study, the margin recipes of Stroom [7] and van Herk [8] were used in order to evaluate errors of setup and daily esophageal motion. In addition, Redpath & Muren [9] proposed a new optimization algorithm for the determination of treatment margins around moving and deformable targets like bladder or esophagus in radiotherapy. The algorithm is completely empirical and is based on an iterative method of determining margins around the planning clinical target volume (CTV) to provide the optimum coverage of the envelope of CTV positions observed during treatment. The major advantage with this approach is that it can be used on non-solid organs, circumventing any assumptions on the nature of the geometrical uncertainties. In this study, this empirical approach was not used. Therefore, our

chosen method may be the limitation to detect the structure of the esophageal wall and this may not be the ideal approach. We are currently planning to introduce this empirical algorithm for determining margin of CTV.

#### *Impact of the findings for future work*

In our study, the motion was the same in the upper or the lower esophagus but this is contrary to the findings of other authors such as Dieleman et al. [4]. The reason may be that the whole thoracic esophagus was analyzed which was difficult to identify the esophageal tumor on the CBCT. It may be necessary to determine whether the movement of the tumor bearing part of the esophagus was the same as the parts without gross tumor involvement. This is a problem for future study.

The present study is the first study to evaluate inter-fraction esophageal motion with patients in the supine position on the linear accelerator bed during RT and under free respiration. It cannot be concluded from this study who requires CBCT or whether every patient needs CBCT imaging. The change in mean esophageal position arising from twice-weekly imaging of individual patients was very small. This finding could be interpreted to mean that target volume coverage was fully adequate and that therefore costly daily imaging is not required.

In the present study, the patient setup error was not small, and therefore using twice-weekly CBCT might not be enough to reach the levels of target margin confidence. In the era of modern IGRT systems, the daily registration performed using CBCT was assumed to be necessary in order to minimize the setup error. The use of IGRT with CBCT will most likely benefit treatments such as IMRT for head and neck cancer, prostate cancer [17,18], or breast cancer; stereotactic RT for lung cancer or brain tumor; and patients with tumors commonly associated with organ motion, such as gastric cancer or urinary bladder cancers.

#### **Conclusions**

Both the patient setup error and day-to-day esophageal movements were detected in every patient in this study. The highest amounts of motion were distributed across various sites in the esophagus. However, the amount of motion did not appear to be clinically significant provided an appropriate internal target volume was considered. Our data support the use of target margins of 9 mm for day-to-day esophageal motion and 8 mm for patient setup error of motions in all directions. Also, when using daily kV CBCT during RT in order to minimize the setup error, only

day-to-day motion of esophagus should be considered since it was found to be so small that the radiation field for esophageal cancer can be reduced.

**Declaration of interest:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

**References**

[1] Hashimoto T, Shirato H, Kato M, Yamazaki K, Kurauchi N, Morikawa T, 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;61:1559-64.

[2] Langen KM, Jones DT. Organ motion and its management. *Int J Radiat Oncol Biol Phys* 2001;50:265-78.

[3] Kahn D, Zhou S, Ahn SJ, Hollis D, Yu X, D'Amico TA, et al. "Anatomically-correct" dosimetric parameters may be better predictors for esophageal toxicity than are traditional CT-based metrics. *Int J Radiat Oncol Biol Phys* 2005;62:645-51.

[4] Dieleman EM, 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;67:775-80.

[5] Amer A, Marchant T, Sykes J, Czajka J, Moore C. Imaging doses from the Elekta Synergy X-ray cone beam CT system. *Br J Radiol* 2007;80:476-82.

[6] AJCC (American Joint Committee on Cancer) Cancer Staging Manual, 6th ed. Greene, FL, Page, DL, Fleming, ID, et al., editors. New York: Springer-Verlag; 2002. pp. 223-40.

[7] Stroom JC, Heijmen BJ. Geometrical uncertainties, radiotherapy planning margins, and the ICRU-62 report. *Radiother Oncol* 2002;64:75-83.

[8] van Herk M, Remeijer P, Rasch C, Lebesque JV. The probability of correct target dosage: Dose-population

histograms for deriving treatment margins in radiotherapy. *Int J Radiat Oncol Biol Phys* 2000;47:1121-35.

[9] Redpath AT, Muren LP. An optimisation algorithm for determination of treatment margins around moving and deformable targets. *Radiother Oncol* 2005;77:194-201.

[10] Xu F, Wang J, Bai S, Li Y, Shen Y, Zhong R, et al. Detection of intrafractional tumour position error in radiotherapy utilizing cone beam computed tomography. *Radiother Oncol* 2008;89:311-9.

[11] Guckenberger M, Meyer J, Vordermark D, Baier K, Wilbert J, Flentje M. Magnitude and clinical relevance of translational and rotational patient setup errors: A cone-beam CT study. *Int J Radiat Oncol Biol Phys* 2006;65:934-42.

[12] Welch RW, Gray JE. Influence of respiration on recordings of lower esophageal sphincter pressure in humans. *Gastroenterology* 1982;83:590-4.

[13] Good E, Oral H, Lemola K, Han J, Tamirisa K, Igic P, et al. Movement of the esophagus during left atrial catheter ablation for atrial fibrillation. *J Am Coll Cardiol* 2005;46:2107-10.

[14] Sasidharan S, Allison R, Jenkins T, Wolfe M, Mota H, Sibata C. Interfraction esophagus motion study in image guided radiation therapy (IGRT). No. 152. Proceedings of the 47th Annual ASTRO Meeting. *Int J Radiat Oncol Biol Phys* 2005;63(Suppl):S91-S92.

[15] Giraud P, Yorke E, Ford EC, Wagman R, Mageras GS, Amols H, et al. Reduction of organ motion in lung tumors with respiratory gating. *Lung Cancer* 2006;51:41-51.

[16] Guerrero T, Zhang G, Huang TC, Lin KP. Intrathoracic tumour motion estimation from CT imaging using the 3D optical flow method. *Phys Med Biol* 2004;49:4147-61.

[17] Pinkawa M, Pursch-Lee M, Asadpour B, Gagel B, Piroth MD, Klotz J, et al. Image-guided radiotherapy for prostate cancer. Implementation of ultrasound-based prostate localization for the analysis of inter- and intrafraction organ motion. *Strahlenther Onkol* 2008;184:679-85.

[18] Guckenberger M, Flentje M. Intensity-modulated radiotherapy (IMRT) of localized prostate cancer: A review and future perspectives. *Strahlenther Onkol* 2007;183:57-62.

PHYSICS CONTRIBUTION

FOUR-DIMENSIONAL MEASUREMENT OF THE DISPLACEMENT OF INTERNAL FIDUCIAL MARKERS DURING 320-MULTISLICE COMPUTED TOMOGRAPHY SCANNING OF THORACIC ESOPHAGEAL CANCER

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**Purpose:** To investigate the three-dimensional movement of internal fiducial markers placed near esophageal cancers using 320-multislice CT.

**Methods and Materials:** This study examined 22 metal markers in the esophageal wall near the primary tumors of 12 patients treated with external-beam photon radiotherapy. Motion assessment was analyzed in 41 respiratory phases during 20 s of cine CT in the radiotherapy position.

**Results:** Motion in the cranial–caudal (CC) direction showed a strong correlation ( $R^2 > 0.4$ ) with the respiratory curve in most markers (73%). The average absolute amplitude of the marker movement was  $1.5 \pm 1.6$  mm,  $1.6 \pm 1.7$  mm, and  $3.3 \pm 3.3$  mm in the left–right (LR), anterior–posterior (AP), and CC directions, respectively. The average marker displacements in the CC direction between peak exhalation and inhalation for the 22 clips were 1.1 mm (maximum, 5.5 mm), 3.0 mm (14.5 mm), and 5.1 mm (16.3 mm) for the upper, middle, and lower thoracic esophagus, respectively.

**Conclusions:** Motion in primary esophagus tumor was evaluated with 320-multislice CT. According to this study, 4.3 mm CC, 1.5 mm AP, and 2.0 mm LR in the upper, 7.4 mm CC, 3.0 mm AP, and 2.4 mm LR in the middle, and 13.8 mm CC, 6.6 mm AP, and 6.8 mm LR in the lower thoracic esophagus provided coverage of tumor motion in 95% of the cases in our study population. © 2011 Elsevier Inc.

Intrafraction motion, Computed tomography, Esophageal cancer, Internal margin.

INTRODUCTION

Interfraction and intrafraction motion of critical structures is a significant concern when patients undergo intensity-modulated radiotherapy. Improper dose modulation can be a result of anatomical motion. Overdosage to normal tissues can result in toxicity, whereas underdosage can lead to tumor progression. Image-guided radiotherapy has been used in an attempt to minimize the impact of anatomic motion.

The thoracic esophagus is more mobile than the proximal (cervical) esophagus because it passes through the less-confining space of the mediastinum. This is especially true in the region of the diaphragm, where the relatively unconstrained esophagus can be subjected to considerable respiratory diaphragmatic motion. Although esophageal motion can be attributed to peristalsis, respiratory action, and cardiac action (1), it was not addressed in reviews on interfraction and intrafraction organ motions during radiotherapy (2). Information on esophageal motion is scarce because of the limited amount of data available on this organ's movement in patients

undergoing radiotherapy planning (1, 3). The majority of patients with esophageal cancers are treated during free respiration. Thus, the 320-multislice CT (320MSCT) acquired during free respiration could provide relevant data on respiration-induced motion. Dieleman *et al.* (4) performed four-dimensional (4D) CT analysis of esophageal mobility during normal respiration and concluded that the distal esophagus showed more mobility than other parts. Moreover, they derived margins of mobility for use in treatment planning that can encompass all movements.

Recently, 4D-CT simulation has enabled CT data acquisition to be gated to the respiratory cycle (5–7). This approach enables esophageal motion to be tracked over the entire length of the organ and at all phases within the respiratory cycle. The present study analyzed the three-dimensional movement of internal fiducial markers near esophageal cancers using 320MSCT. The 12 patients in this study represent the largest analysis heretofore conducted of interfraction esophageal movement during free respiration.

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## METHODS AND MATERIALS

### 320-Multislice CT scanner

A 320-slice volumetric CT scanner (320-slice Aquilion ONE; Toshiba Medical Systems, Otawara, Tokyo) was used to scan the esophageal metal clips for 20 s (8–10). Images were collected on a clinical multidetector CT scanner. Images were acquired in volume mode (16 cm z coverage per rotation). Images were reconstructed at slice thicknesses of 1 mm (with 1-mm slice intervals). The 320MSCT has  $512 \times 512$  (transverse)  $\times$  320 (cranial-caudal [CC]) elements, each approximately  $0.5 \text{ mm} \times 0.5 \text{ mm}$  at the center of rotation. The 160-mm total beam width allows the continuous use of several collimation sets. Superior to inferior (SI) coverage is 160 mm per rotation. The detector element consists of a  $\text{Gd}_2\text{O}_2\text{S}$  ceramic scintillator and a single-crystal silicon photodiode, as used for MSCT.

Instructions for quiet free breathing were reviewed by a physician. All scans were performed under free-breathing conditions. After several minutes' rest, volumetric cine scanning was started without the patient being informed to avoid any psychosomatic effect on breathing. Scan conditions were 120 kV, 50 mA, 0.5 s per rotation,  $160 \text{ mm} \times 0.5 \text{ mm}$  slice collimation, and 20.0 s acquisition time. Continuous scan mode was used. Field of view size was set LL ( $= 500 \text{ mm}$ ). When these protocols were used, CT dose index volume was 110 mGy, dose length product was  $1770 \text{ mGy} \cdot \text{cm}$ , and effective dose (dose length product  $\times 0.017$ ) was 30 mSv. In other words, a three-dimensional image 16 cm in length was acquired every 0.5 s.

### Patients

Intrafraction motions of the esophagus were analyzed in 12 patients with thoracic esophageal cancer treated with radiotherapy between July and November 2009 at University of Tokyo Hospital, Tokyo, Japan.

The clinical and demographic data of the 12 patients (11 male, 1 female) are shown in Table 1. All of the tumors were pathologically diagnosed as esophageal squamous cell carcinoma. The median age was 72 years (range, 56–86 years). The sixth edition of the American Joint Committee on Cancer TNM staging system (11) was used. The 320MSCT was performed after placement of a metal clip (EZ endoclip, HX-610-090; Olympus, Tokyo, Japan) in the normal esophageal wall near the primary tumor for one time in each

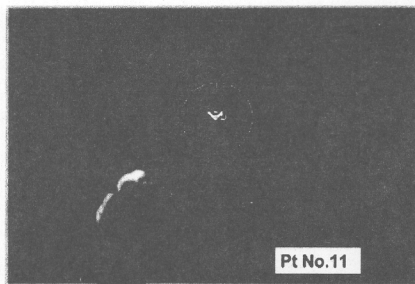


Fig. 1. Contouring of metal clip and center of gravity of each metal clip, performed on a Pinnacle<sup>3</sup> workstation.

patient. The clip is cylindrically structured after closing the wings. The length is approximately 10 mm, and the diameter is approximately 2 mm. The primary site in the esophagus was upper thoracic for 3 patients, middle for 5 patients, and lower for 4 patients (Table 1). Each tumor had one or two fiducial markers, and 22 markers in 12 patients were analyzed. The flat board (CABMO21A) was used in place of a body mat, to flatten the superior surface of the patient table. In this way, patients were placed in the same position as for radiotherapy.

Written informed consent was obtained from all patients before the treatment was initiated. This study was approved by the institutional review board of Tokyo University (no. 2613).

### Metal clip and lung delineation

One or two metal clips and bilateral lung delineation was performed for each timing and each patient (total 41 sets each metal clip) on a Pinnacle<sup>3</sup> treatment-planning workstation (Philips Healthcare, Andover, MA; ADAC, Milpitas, CA). The delineation was performed semiautomatically. The lower auto-contour threshold

Table 1. Patient characteristics

Patient no.	Sex	Age (y)	Primary tumor location	Location Clip 1		Location Clip 2	
				incisor tooth	incisor tooth	incisor tooth	incisor tooth
				cm	Ut/Mt/Lt	cm	Ut/Mt/Lt
1	M	67	Mt	27	Mt	35	Lt
2	M	66	Ut	19	Ut	29	Mt
3	F	79	Ut	20	Ut	21	Ut
4	M	68	Ut	22	Ut	25	Mt
5	M	82	Mt	26	Mt	30	Mt
6	M	74	Lt	32	Mt	40	Lt
7	M	70	Lt	34	Lt	36	Lt
8	M	79	Lt	37	Lt	40	Lt
9	M	56	Mt	18	Ut	—	—
10	M	81	Mt	29	Mt	31	Mt
11	M	86	Mt	30	Mt	32	Mt
12	M	57	Lt	43	Lt	—	—

Abbreviations: Ut = upper thoracic; Mt = middle thoracic; Lt = lower thoracic; M = male; F = female.

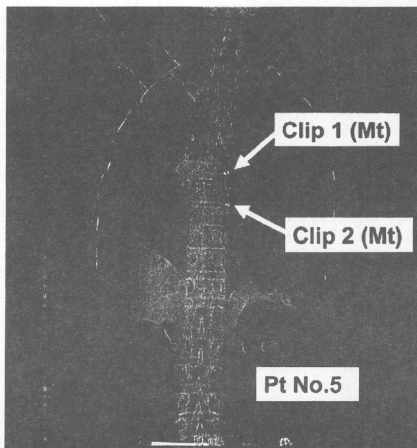


Fig. 2. Position of metal clips (Patient 5).

Table 2. Relationship between marker position and respiratory curve for each patient

Patient no.	$R^2$ of Clip 1 with lung volume			$R^2$ of Clip 2 with lung volume			Respiration frequency during 20 s
	x (RL)	y (AP)	z (CC)	x (RL)	y (AP)	z (SI)	
1	0.31	<0.2	0.77	0.34	0.71	0.76	5.0 (regular)
2	<0.2	<0.2	0.36	<0.2	<0.2	0.47	7.0 (regular)
3	<0.2	0.45	0.47	<0.2	0.79	0.82	5.0 (regular)
4	<0.2	0.6	0.48	<0.2	<0.2	0.48	6.5 (irregular)
5	0.31	0.36	0.71	0.570	0.86	0.61	8.0 (regular)
6	0.67	0.8	0.93	0.68	0.7	0.97	6.5 (regular)
7	<0.2	<0.2	0.31	<0.2	<0.2	0.31	6.5 (irregular)
8	<0.2	<0.2	0.76	0.4	0.52	0.78	8.5 (regular)
9	<0.2	<0.2	<0.2	—	—	—	7.0 (irregular)
10	<0.2	<0.2	0.36	<0.2	<0.2	0.33	9.5 (regular)
11	0.38	0.88	0.61	0.26	0.81	0.66	6.0 (irregular)
12	0.81	0.9	0.97	—	—	—	5.5 (regular)

Abbreviations: RL = right-left; AP = anterior-posterior; CC = crano-caudal.

was set at 1400 Hounsfield units for the metal clips (Fig. 1) and 800 Hounsfield units for the lung. The coordinates (x, y, and z) of the center of gravity of each metal clip were calculated automatically on a Pinnacle<sup>3</sup> workstation (Fig. 1). Positive directions were right to left on the x-axis, from posterior to anterior on the y-axis, and from superior to inferior on the z-axis.

#### Statistical methods

Using a Wilcoxon signed ranked test, with a level of significance of  $\alpha = 0.05$ , we compared the measured changes in right and left lung volumes and in average CT intensity due to respiration. We also calculated  $R^2$  values (decision coefficient, i.e., the square of correlation coefficient) to assess the possible correlation between metal clip displacements and bilateral lung volume only within the scan range of 16 cm in the CC direction, not the full length of the lung. Histograms and cumulative distribution curves were generated for the entire set of calculated slice-by-slice centroid displacements, in each of the x (right-left [RL]), y (anterior-posterior [AP]), and z (SI) directions. From these displacement data the 95th percentile displacements were determined in all x, y, and z directions.

## RESULTS

In the procedure of marker insertion, no patient experienced symptomatic complications. Positions of the 22 metal markers are shown in Table 1. Upper, middle, and lower thoracic positions had 5, 10, and 7 clips, respectively (Fig. 2). There was no apparent migration or dislocation of the markers until after the 320MSCT was performed.

Motion in the CC direction (z-axis) showed a strong correlation ( $R^2 > 0.4$ ) with the respiratory curve for most markers (16 of 22 markers, 73%) (Table 2). Especially in 9 clips (41%), a very strong correlation ( $R^2 > 0.7$ ) was shown with the respiratory curve (Fig. 3). For the LR (x-axis) and AP (y-axis) directions, 5 clips (23%) and 11 clips (50%), respectively, also showed a strong correlation ( $R^2 > 0.4$ ) with the respiratory curve (Table 2). In the CC direction, 5 of 7 clips (71%) showed a strong correlation ( $R^2 > 0.4$ ) with the respiratory curve in the lower, 8 of 10 clips (80%)

in the middle, and 3 of 5 clips (60%) in the upper thoracic esophagus.

The respiratory curve for 20 s, which was obtained using bilateral lung volume within the scan range per 0.5-s image-set per each patient, showed a regular sine curve in 8 patients and an irregular one in the other 4 patients (Fig. 4 and Table 2). There was no relationship between age and regular (average, 73.1 years; median, 76.5 years) or irregular (average, 70 years; median, 69 years) respiratory curves. The respiration frequency during 20 s ranged from 5.0 cycles (4 s per cycle) to 9.5 cycles (2.1 s per cycle), with median values of 6.5 cycles and 3.1 s per cycle (Table 2).

The average amplitudes of the marker from the minimum values, which were the most right, posterior, and caudal position in the LR, AP, and CC directions per each clip, respectively, for each patient are shown in Table 3. The average  $\pm$  SD amplitude from the minimum of the marker movements was  $1.5 \pm 1.6$  mm (maximum, 11.7 mm),  $1.6 \pm 1.7$  mm (maximum, 10.8 mm), and  $3.3 \pm 3.3$  mm (maximum, 16.3 mm) in the LR, AP, and CC directions,

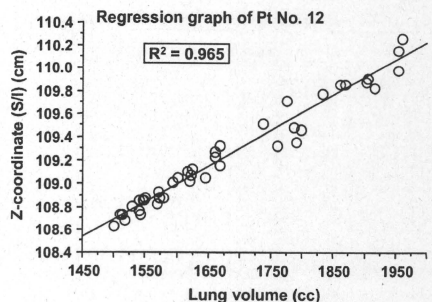


Fig. 3. Correlation of metal clip motion with respiratory curve (Patient 12).



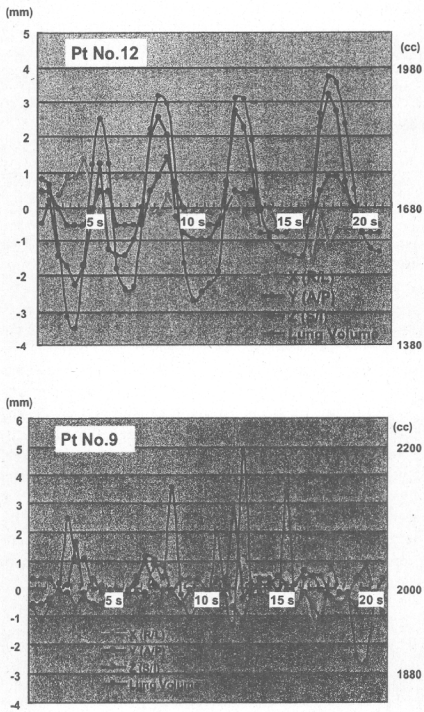


Fig. 4. Metal clips' centroid trajectories in all 41 phases for 20 s of the four-dimensional CT scans. (A) Patient 12. (B) Patient 9. R/L = right-left; A/P = anterior-posterior; S/I = superior-inferior.

respectively (Tables 3 and 4). The average amplitude from the minimum in the CC direction was found to be significantly larger in the lower thoracic compared with the middle ( $p < 0.0001$ ) and upper ( $p < 0.0001$ ) by the Wilcoxon test.

The average marker displacements in the CC direction between peak exhalation and inhalation were 3.2 mm (range, 0.7–5.5 mm), 6.4 mm (range, 1.5–14.5 mm), and 10.3 mm (range, 4.0–16.3 mm) for the upper, middle, and lower thoracic esophagus, respectively (Fig. 5 and Tables 2 and 4).

The 95th percentile values from the cumulative distributions (Fig. 6) were used to define minimum margins to account for gross tumor volume motion during treatment planning. The values of the CC direction were 4.3 mm, 7.4 mm, and 13.8 mm in the upper, middle, and lower thoracic esophagus, respectively (Table 5). For the axial margin, the values were 2.0 mm, 3.0 mm, and 6.8 mm in the upper, middle, and lower thoracic esophagus, respectively. According to Stroom *et al.* (12), the evaluation values as margin for esophageal motion error in the CC direction were 2.68 mm, 5.69 mm, and 9.10 mm in the upper, middle, and lower thoracic esophagus, respectively. Additionally, evaluation values of 3.28 mm, 6.99 mm, and 11.20 mm (Table 5) were reported by van Herk *et al.* (13). As for the axial margin, the values were 1.54 mm, 2.21 mm, and 4.55 mm by Stroom's formula and 1.89 mm, 2.71 mm, and 5.60 mm by van Herk's formula in the upper, middle, and lower thoracic esophagus, respectively.

## DISCUSSION

The literature describing esophageal tumor motion is limited. Lorchel *et al.* (14) reported measurements of esophageal tumor motion acquired by CT scans during inspiratory and expiratory breath-hold for a series of 8 patients. Dieleman *et al.* (4) analyzed healthy esophageal motion using normal-breathing 4D-CT in 29 patients with non-esophageal thoracic malignancies. In two recently published

Table 3. Average amplitudes of marker from minimum values for each patient

Patient no.	n	Clip 1 (mm)									Clip 2 (mm)								
		LR			AP			CC			LR			AP			CC		
		Mean	SD	Max	Mean	SD	Max	Mean	SD	Max	Mean	SD	Max	Mean	SD	Max	Mean	SD	Max
1	41	0.2	0.2	0.4	0.9	0.4	1.5	4.8	1.6	6.7	1.2	0.4	2.0	1.2	0.8	3.5	8.0	2.8	10.8
2	41	0.6	0.3	1.0	0.2	0.2	0.5	0.2	0.2	0.7	0.4	0.4	1	0.5	0.1	0.5	0.8	0.4	1.5
3	41	0.9	0.3	1.4	0.5	0.4	0.9	1.9	1.3	4.8	1.60	0.6	3.0	0.5	0.5	1.9	2.3	1.4	5.5
4	41	0.0	0.0	0.0	0.1	0.3	1.5	0.4	0.3	1.0	0.1	0.3	1.0	0.0	0.0	1.0	0.6	1.8	1.8
5	41	0.9	0.3	1.0	0.7	0.4	1.9	3.5	1.2	4.0	0.7	0.4	1.0	0.5	0.6	2.0	3.5	1.2	4.7
6	41	1.7	0.8	3.7	1.6	1.0	4.0	3.8	2.3	8.6	3.8	1.6	6.9	3.1	2.0	7.2	4.6	2.9	10.2
7	41	1.1	0.8	3.9	3.0	1.3	5.8	1.7	1.3	4.0	2.4	1.2	5.9	2.6	1.1	5.8	2.1	1.7	5.2
8	41	4.0	2.0	7.3	3.8	1.9	8.8	3.7	2.7	10.0	5.5	2.1	11.7	4.6	2.5	10.8	5.7	4.1	15.3
9	41	1.5	0.4	2.5	1.2	0.5	2.0	0.8	0.7	3.8	—	—	—	—	—	—	—	—	—
10	41	1.5	0.6	2.9	2.4	0.6	3.0	2.7	1.2	4.5	1.4	0.9	2.9	1.2	0.6	2.9	2.6	1.3	4.8
11	41	1.2	0.6	2.3	0.9	1	3.4	3.5	4.1	12.5	0.7	0.5	2.0	1.4	1.6	5.3	3.9	4.6	14.5
12	41	1.5	0.8	2.5	2.7	1.8	6.8	10.2	4.6	16.3	—	—	—	—	—	—	—	—	—
Total	492	1.5	1.6	11.7	1.6	1.7	10.8	3.3	3.3	16.3	—	—	—	—	—	—	—	—	—

Abbreviations: CC = cranial-caudal; Max = maximum. Other abbreviations as in Table 2.

"Total" is the SD for all 12 patients.



Table 4. Relationships between average amplitude and primary tumor location

Parameter	n	LR (mm)				AP (mm)				CC (mm)			
		Mean	Max	$\Sigma$	$\sigma$	Mean	Max	$\Sigma$	$\sigma$	Mean	Max	$\Sigma$	$\sigma$
Total	902	1.5	11.7	1.6	1.9	1.6	10.8	1.7	2.4	3.3	16.3	3.3	5.0
Ut	205	0.9	3.0	0.7	0.2	0.6	2.0	0.5	0.2	1.1	5.5	1.2	0.4
Mt	410	0.9	3.7	0.7	0.2	1.0	5.3	1.0	0.3	3.0	14.5	2.6	0.7
Lt	287	2.8	11.7	2.1	0.5	3.0	10.8	2.0	0.6	5.1	16.3	4.2	1.0

Abbreviations:  $\Sigma$ , systematic error;  $\sigma$ , random error. Other abbreviations as in Tables 1–3.

studies by Zhao *et al.* (15) and Yaremko *et al.* (16), normal-breathing 4D-CT was used to characterize the motion of tumors at the gastroesophageal junction in 25 and 31 patients, respectively. Patel *et al.* (17) evaluated the motion of malignancies in the upper ( $n = 1$ ), mid- ( $n = 4$ ), and lower ( $n = 25$ ) esophagus of 30 patients using normal-breathing 4D-CT. Moreover, they measured the motion of pathologically enlarged or positron emission tomography–positive celiac region lymph nodes. As far as could be determined, this is the first report of the three-dimensional movement of the esophageal wall measured in the radiotherapy positions using internal fiducial markers, except for one report by Hashimoto *et al.* (1), which had only a single marker. In the previous reports that evaluated esophageal tumor motions using 4D-CT (14–17), a radiation oncologist contoured the volume of the primary tumor and/or lymph nodes as shown on several

respiratory-phase CT images, and its motions were analyzed. However, in this study, because the motions of 22 metal clips were analyzed and the contouring was performed semi-automatically using the threshold CT value, the human error of contouring is less than in the previous reports, and the same position coordinate is provided whoever performs the contouring. Moreover, in this study, because the continuous cine-mode shooting for 20 s under free breathing was performed over 16 cm in the CC direction using the 320MSCT, no respiratory monitoring system like the Real-Time Positional Management (RPM) (Varian Medical Systems, Palo Alto, CA) or the AZ-733V system (Anzai Medical, Tokyo, Japan) was used, and the respiratory curves were made using the change of lung volume for each respiratory phase. Although Patel *et al.* (17) analyzed the motion of upper ( $n = 1$ ) and middle ( $n = 4$ ) thoracic esophageal tumors

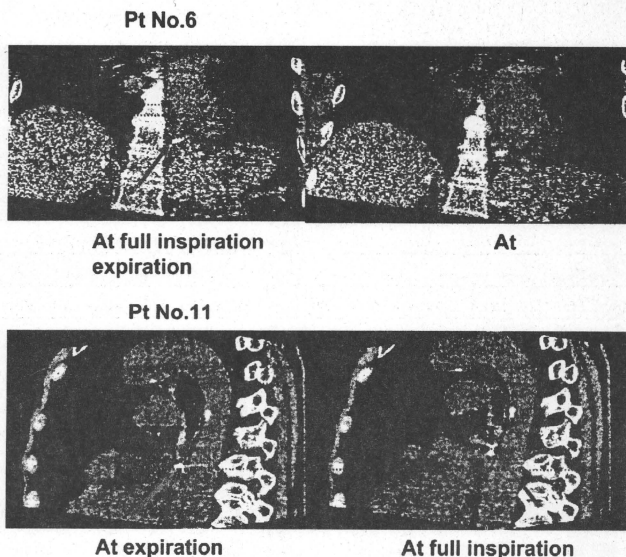


Fig. 5. Four-dimensional CT images of end-expiration and end-inspiration taken during normal breathing. (A) Coronal of Patient 6. (B) Sagittal of Patient 11.

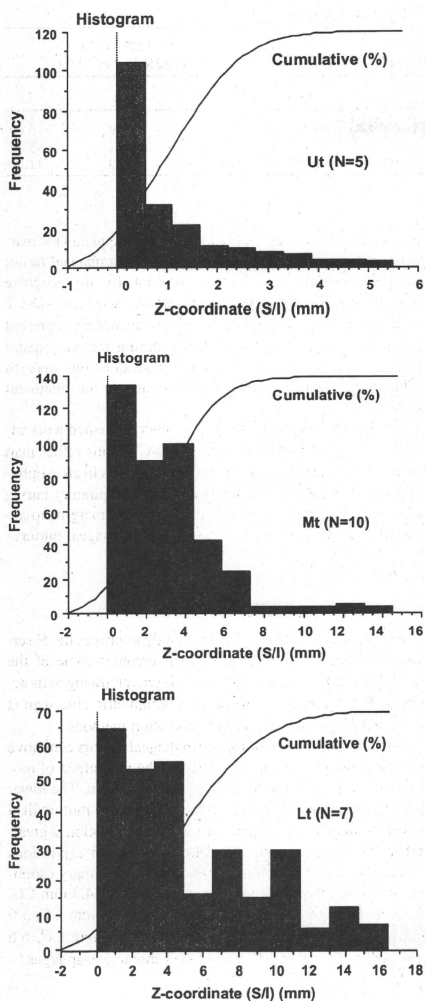


Fig. 6. Cumulative distribution of metal clips in the cranial-caudal direction. (A) Upper thoracic, (B) middle thoracic, (C) lower thoracic. S/I = superior-inferior.

in addition to the lower for the first time, our study evaluated more cases with upper (5 clips) and middle (10 clips) thoracic esophageal cancer. The present study can serve as the basis for the determination of the internal margins of thoracic esophageal cancers.

Measurements of lower esophageal sphincter pressure during quiet respiration revealed lateral esophageal motions of  $6.0 \pm 2.0$  mm in the abdominal portion and  $4.0 \pm 1.0$  mm in the thoracic region (18). Cine-fluoroscopic barium-swallow images of the esophagus in 51 patients undergoing catheter ablation for atrial fibrillation indicated that lateral shifts of more than 20 mm occurred in a majority of patients (19). Daily online CT images in a study of 6 patients treated with image-guided radiotherapy showed maximal motion in the distal esophagus and indicated that margins of 2.0–5.0 mm could account for all motion (20). A study of esophageal positions at the extreme phases of respiration in 6 patients suggested that a margin of 5.0–6.0 mm was sufficient to account for variations in organ position (21). Motion during quiet respiration for thoracic and abdominal tumors was analyzed in 13 patients with implanted fiducial markers, and the predominant source of motion was found to be respiration, whereas motion resulting from cardiac action was of far smaller magnitude (1). The means  $\pm$  SD of motion of fiducial markers inserted into the esophageal wall using a fluoroscopic real-time tumor tracking system were  $3.5 \pm 1.8$  mm,  $8.3 \pm 3.8$  mm, and  $4.0 \pm 2.6$  mm for the LR, CC, and AP directions, respectively (1). Lorchel *et al.* (14) proposed an internal target volume (ITV) margin of 10 mm, because 95% of CTV movements were  $<10$  mm on the basis of the measurements of tumor motion in the various locations. Zhao *et al.* (15) reported measurements of mean peak-to-peak gross tumor volume centroid motion of  $3.9 \pm 2.7$  mm in the LR,  $3.8 \pm 2.3$  mm in the AP, and  $8.7 \pm 4.7$  mm in the CC directions, based on scans of 25 patients. Asymmetric margins were recommended because of variations in tumor boundaries and deformation: 10 mm left, 8 mm right, 11 mm anterior, 6 mm posterior, 10 mm superior, and 16 mm inferior. Yaremko *et al.* (16) measured the following values for mean (SE) tumor motion among 31 patients: CC 7.1 (0.2) mm, AP 2.3 (0.1) mm, and LR 1.3 (0.06) mm; and they concluded that a radial margin of 8 mm and an axial margin of  $\pm 18$  mm would provide distal esophageal tumor motion coverage for 95% of the cases. Patel *et al.* (17) concluded that the minimum radiation field margins required to cover the ITV of 95% of the primary tumors were 15 mm, 7.5 mm, and 7.5 mm in the CC, AP, and LR dimensions, respectively. Similarly, ITV coverage of 100% of celiac-region lymph nodes could be achieved with CC, AP, and LR margins of 22.5 mm, 10 mm, and 7.5 mm, respectively. According to Dieleman *et al.* (4), margins that would have incorporated all esophageal movement in the LR and AP directions were 5.0 mm proximally, 7.0 mm and 6.0 mm in the middle esophagus, and 9.0 mm and 8.0 mm in the lower esophagus, as determined by 4D-CT. A comparable lateral motion of 6.8 mm and a maximum CC motion of 14 mm have been reported in patients with primary esophageal tumors (1, 22, 23). This latter value is also comparable to our maximum values, which were 16.3 mm in the CC direction and 11.7 mm and 10.8 mm in the LR and AP direction, respectively.

In our study, the CC motion was significantly larger in the lower than in the upper or middle esophagus, and this is

Table 5. Intrafractional esophageal motion error

Direction	95th percentile			2.0 $\Sigma$ + 0.7 $\sigma$ (Stroom <i>et al.</i> [12])			2.5 $\Sigma$ + 0.7 $\sigma$ (van Herk <i>et al.</i> [13])		
	Ut	Mt	Lt	Ut	Mt	Lt	Ut	Mt	Lt
LR (mm)	2.0	2.4	6.8	1.54	1.54	4.55	1.89	1.89	5.60
AP (mm)	1.5	3.0	6.6	1.14	2.21	4.42	1.39	2.71	5.42
CC (mm)	4.3	7.4	13.8	2.68	5.69	9.10	3.28	6.99	11.20

Abbreviations as in Tables 1, 2, and 4.

consistent with the findings of other authors, such as Dieleman *et al.* (4). In addition to the lower thoracic, even the middle or upper thoracic esophagus also showed a strong correlation ( $R^2 > 0.4$ ) with the respiratory curve at a high rate in this study.

We are aware of the concern that may be raised about radiation exposure to patients during the continuous cine-mode shooting for 20 s using the 320MSCT procedure. The continuous shooting for 20 s may be too long for patients with a regular respiratory cycle. Actually, however, there were some patients with an irregular respiratory cycle, and for these patients the continuous shooting for 20 s was considered necessary to obtain sufficient data about respiratory motion. With our protocol, the dose of radiation exposure from 320MSCT for 20 s was approximately 40–50 mGy at the skin surface, which is approximately 1% of the total isocenter dose of radiotherapy for esophageal cancer. Because all 12 patients in this study were given radiotherapy for curative intent, the radiation exposure by 320MSCT was considered to be within the allowable range. A secondary concern in this study is the blurring for 0.5 s that occurs in imaging because the time response remains at 0.5 s. As for a very quick movement of <0.5 s, the error may occur in the evaluation of the motion. Because the typical breathing period of a patient is approximately 3–5 s, the data are acquired for roughly every 10% of the respiratory cycle in this study, which is comparable to what typical 4D-CTs acquire using RPM or the Anzai belt. Finally, there might be a problem regarding the resolution of the reading system. Because the resolution is 512  $\times$  512 segments in the transverse, there is a limit to the resolution of reading power. Therefore, although the motion can be traced in a patient with a broad movement to a certain extent, the data will show a poor resolution in a patient with only a small movement. The small sample size of 12 patients and 22 metal clips limits our ability

to make firm recommendations regarding adequate ITV margin expansions, although prior studies of esophageal tumor motion had similar sample sizes. Additionally, we recognize that the measurements of organ motion based on 4D-CT taken on the day of simulation may not accurately represent the magnitude of motion occurring during the subsequent daily radiation treatments. Practical considerations make it difficult to obtain multiple 4D scans during the treatment course.

Strengths of our study relative to other published work include the use of normal-breathing 4D-CT scans rather than breath-holding techniques, inclusion of tumors in all esophageal locations, and the comparison with a respiratory curve. Our study provides reasonable guidelines for margins to account for respiratory motion of primary esophageal tumors.

## CONCLUSIONS

In conclusion, 320MSCT significantly improves the observation of tumor displacement and overcomes some of the limitations of present CT methods. Moreover, owing to its accurate determination of the margin, volumetric cine scan is a useful complement to current irradiation methods.

We have shown that primary esophageal tumors can move substantially with respiration and that the magnitude of motion can vary significantly from patient to patient. The lower primary tumors seem to have greater respiratory motion than upper- or middle-esophageal tumors, and the motion is greatest in the CC direction. The following margin expansions were proposed to allow for >95% motion of primary esophageal tumors (removing the 5% outlier values): 4.3 mm CC, 1.5 mm AP, and 2.0 mm LR in the upper, 7.4 mm CC, 3.0 mm AP, and 2.4 LR in the middle, and 13.8 mm CC, 6.6 mm AP, and 6.8 mm LR in the lower thoracic esophagus.

## REFERENCES

1. Hashimoto 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.
2. Langen KM, Jones DT. Organ motion and its management. *Int J Radiat Oncol Biol Phys* 2001;50:265–278.
3. Kahn D, Zhou S, Ahn SJ, *et al.* "Anatomically-correct" dosimetric parameters may be better predictors for esophageal toxicity than are traditional CT-based metrics. *Int J Radiat Oncol Biol Phys* 2005;62:645–651.
4. 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.
5. Ford EC, Mageras GS, Yorke E, *et al.* Respiration-correlated spiral CT: A method of measuring respiratory-induced anatomic motion for radiation treatment planning. *Med Phys* 2003;30:88–97.
6. Vedam SS, Keall PJ, Kini VR, *et al.* Acquiring a four-dimensional computed tomography dataset using an external respiratory signal. *Phys Med Biol* 2003;48:45–62.

7. Pan T, Lee TY, Rietzel E, *et al.* 4D-CT imaging of a volume influenced by respiratory motion on multi-slice CT. *Med Phys* 2004;31:333–340.
8. Silverman JD, Paul NS, Siewerdsen JH. Investigation of lung nodule detectability in low-dose 320-slice computed tomography. *Med Phys* 2009;36:1700–1710.
9. Coolens C, Breen S, Purdie TG, *et al.* Implementation and characterization of a 320-slice volumetric CT scanner for simulation in radiation oncology. *Med Phys* 2009;36:5120–5127.
10. Kroft LJ, Roelofs JJ, Geleijns J. Scan time and patient dose for thoracic imaging in neonates and small children using axial volumetric 320-detector row CT compared to helical 64-, 32-, and 16-detector row CT acquisitions. *Pediatr Radiol* 2010;40:294–300.
11. Greene FL, Page DL, Fleming ID, *et al.*, editors. American Joint Committee on Cancer Cancer staging manual. 6th ed. New York: Springer-Verlag; 2002. p. 223–240.
12. Stroom JC, Heijmen BJ. Geometrical uncertainties, radiotherapy planning margins, and the ICRU-62 report. *Radiother Oncol* 2002;64:75–83.
13. 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.
14. Lorchel F, Dumas JL, Noël A, *et al.* Esophageal cancer: Determination of internal target volume for conformal radiotherapy. *Radiother Oncol* 2006;80:327–332.
15. Zhao KL, Liao Z, Bucci MK, *et al.* Evaluation of respiratory-induced target motion for esophageal tumors at the gastroesophageal junction. *Radiother Oncol* 2007;84:283–289.
16. 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.
17. Patel AA, Wolfgang JA, 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.
18. Welch RW, Gray JE. Influence of respiration on recordings of lower esophageal sphincter pressure in humans. *Gastroenterology* 1982;83:590–594.
19. Good E, Oral H, Lemola K, *et al.* Movement of the esophagus during left atrial catheter ablation for atrial fibrillation. *J Am Coll Cardiol* 2005;46:2107–2110.
20. Sasidharan S, Allison R, Jenkins T, *et al.* Interfraction esophageal motion study in image guided radiation therapy (IGRT) (Abstr.). *Int J Radiat Oncol Biol Phys* 2005;63(Suppl.):S91–S92.
21. Giraud P, Yorke E, Ford EC, *et al.* Reduction of organ motion in lung tumors with respiratory gating. *Lung Cancer* 2006;51:41–51.
22. 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.
23. Tsunashima Y, Sakae T, Shiyama Y, *et al.* Correlation between the respiratory waveform measured using a respiratory sensor and 3D tumor motion in gated radiotherapy. *Int J Radiat Oncol Biol Phys* 2004;60:951–958.



