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Intrafraction esophageal motion in patients with clinical T1N0 esophageal cancer

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ABSTRACT

Aim: To investigate the intrafraction movement of the esophagus using fiducial markers.
Background: Studies on intrafraction esophageal motion using the fiducial markers are scarce.
Materials and methods: We retrospectively analyzed patients with clinical T1N0 esophageal cancer who had received fiducial markers at our hospital between July 2007 and December 2013. Real-Time Position Management System to track the patient's respiration was used, and each patient underwent three-dimensional computed tomography of the resting expiratory and inspiratory level. We used the center of the marker to calculate the distance between the expiratory and inspiratory breath-holds, which were measured with the radiotherapy treatment planning system in three directions: left–right (LR), superior–inferior (SI), and anterior–posterior (AP). The movements at each site were compared with the Kruskal–Wallis analysis and Wilcoxon rank sum test with a Bonferroni correction.
Results: A total of 101 patients with 201 fiducial markers were included. The upper, middle and lower thoracic positions had 40, 77, and 84 markers, respectively. The mean absolute magnitudes of the shifts (standard deviation) were 0.18 (0.19) cm, 0.68 (0.46) cm, and 0.24 (0.24) cm in the LR, SI, and AP directions, respectively. From the cumulative frequency distribution, we assumed that 0.35 cm LR, 0.8 cm SI, and 0.3 cm AP in the upper; 0.5 cm LR, 1.55 cm SI, and 0.55 cm AP in the middle; and 0.75 cm LR, 1.9 cm SI, and 0.95 cm AP in the lower thoracic esophagus covered 95% of the cases.
Conclusions: The internal margin based on the site of esophagus was estimated.

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1. Background

Esophageal cancer is one of the most common gastrointestinal malignancies in the United States, with 18,170 new cases and 15,450 deaths expected in 2013 alone.[1] The incidence of esophageal adenocarcinomas has increased in Western countries, though the frequency of esophageal squamous cell carcinoma (SCC) varies considerably among geographic regions.[2,3]

Radiotherapy plays a primary role in multimodality treatment for patients with esophageal carcinoma. Definitive chemoradiotherapy is an established therapeutic option for patients with carcinoma of the esophagus.[4–6]

Modern three-dimensional techniques allow better visualization of the organ at risk in radiation treatment planning. However, the radiation oncologist often has difficulty in contouring the gross tumor volume and internal target volumes (ITV) of clinical T1N0 esophageal cancer due to its flatness and the invisibility of its motion on computed tomography (CT) images. Fiducial markers can minimize the impact of locational distinction and anatomic motion. Estimations of both the intrafraction and interfraction motions of esophageal cancer are needed to avoid administration of an overdose to normal tissues and an underdose to the tumor. The purpose of this study was to determine the extent of the internal margin of each site of primary esophageal cancer that was determined from our intrafraction motion data.

2. Materials and methods

2.1. *Patient characteristics*

Between July 2007 and December 2013, consecutive patients with clinical T1N0 esophageal cancer who had undergone endoscopic insertion of fiducial markers at our hospital were selected for this study. All patients had histologically proven SCC. The fiducial markers were placed in the normal esophageal wall close to the oral and anal sides of the primary tumor. No adverse effects associated with the placement were observed. We eliminated the markers at the cervical and abdominal esophagus from the study.

2.2. *Esophageal localization and shift*

On the same day when the markers were inserted, the patients underwent three-dimensional CT using Real-Time Position Management System (Varian Medical Systems, Palo Alto, CA, USA) at the resting expiratory and inspiratory levels for radiotherapy treatment planning. All CT data were exported to the radiotherapy planning system (RTPS), Eclipse (Varian Medical Systems, Palo Alto, CA, USA). The CT origins of the two phases were similar. The CT slice thickness of CT was 1–3 mm. We divided the markers' sites into three groups (the upper, middle, and lower thoracic esophagus) according to the TNM Staging Atlas (UICC 2009).[7] The fiducial markers were delineated manually by a single radiation oncologist (S. S.) and the other oncologist (Y. I.) reconfirmed the contouring. To obtain left-right (LR; x-axis), superior–inferior (SI; y-axis), and anterior–posterior (AP; z-axis) shifts, we acquired the x-, y-, and z-coordinates of the center of each marker at the resting expiratory and inspiratory phases using the RTPS.

2.3. *Data analysis*

To estimate the internal margin based on the site of the esophageal cancer, we evaluated the cumulative frequency distribution. We used the Kruskal–Wallis test followed by the Wilcoxon rank sum test with Bonferroni corrections to compare the motion by the site. A p-value < 0.017 was considered significant. Data were analyzed using SPSS Version 21.0 (IBM Corp., Armonk, NY, USA).

3. Results

A total of 201 fiducial markers of 101 patients were included in our study. Forty markers were located in the upper, 77 in the middle, and 84 in the lower thoracic esophagus. The mean absolute amplitude of movement (standard deviation) was 0.18 (0.19) cm, 0.68 (0.46) cm, and 0.24 (0.24) cm in the LR, SI, and AP directions, respectively. The movement of the lower thoracic esophagus was significantly larger than that of the other sites in all the directions ($p < 0.017$). The mean absolute amplitudes of the upper, middle, and lower thoracic esophagus in the SI direction were 0.41 cm, 0.65 cm, and 0.84 cm, respectively. No significant differences were found between the upper and middle thoracic esophagus both in the LR ($p = 0.97$) and AP ($p = 0.038$) directions. The movement difference between the upper and middle thoracic esophagus in the SI direction was significant ($p < 0.001$). The cumulative frequency distribution of each motions showed that 0.35 cm LR, 0.8 cm SI, and 0.3 cm AP in the upper; 0.5 cm LR, 1.55 cm SI, and 0.55 cm AP in the middle; and 0.75 cm LR, 1.9 cm SI, and 0.95 cm AP in the lower thoracic esophagus covered 95% of the cases (Fig. 1).

4. Discussion

This study estimated the measurement of the esophagus at three sites (Ut, Mt, and Lt) in three directions (LR, SI, and AP), and the internal margin. Fiducial markers are often used as a surrogate for the tumor location in radiation therapy for esophageal cancers. We quantitatively estimated the tumor movement using the motion of the fiducial markers at the resting expiratory and inspiratory phases on the RTPS. Few studies on intrafraction esophageal motion using the fiducial markers have been reported. Hashimoto et al. first analyzed the motion of the esophagus using markers to evaluate the feasibility of real-time monitoring.[8] Yamashita et al. also used markers to investigate the three-dimensional movement.[9]

Our study showed that the mean absolute amplitude of movement/standard deviation was 0.18/0.19 cm, 0.24/0.24 cm, and 0.68/0.46 cm in the LR, AP, and SI directions, respectively. The SI motion was significantly larger than that in the other directions. This result concurs with existing data. In a series of 13 patients, Hashimoto et al. reported that while the esophageal motions (median/standard deviation) in the LR and the AP directions were 0.35/0.18 and 0.4/0.26 cm,

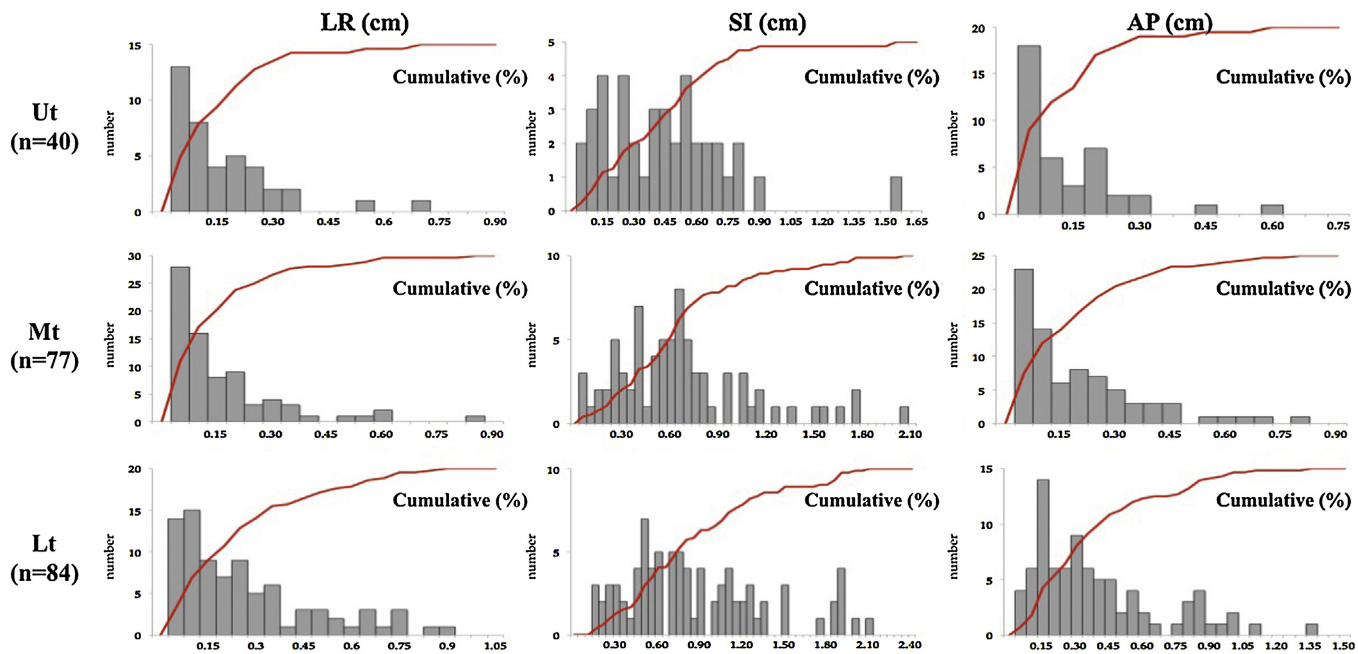

Fig. 1 – Cumulative frequency distribution of fiducial markers in the three directions at the three thoracic sites.

the SI motion was 0.83/0.38 cm.[8] Yaremko et al. showed that the LR, the AP, and the SI movements were 0.13/0.006, 0.23/0.01, and 0.71/0.02 cm, respectively, in a series of 31 patients.[10]

We proposed the internal margin of the LR, the AP, and the SI directions at the three sites. Yamashita et al. concluded that the internal margin requirements were 0.2 LR, 0.15 AP, and 0.43 cm SI in the upper; 0.24 LR, 0.3 AP, and 0.74 cm SI in the middle; and 0.68 LR, 0.66 AP, and 1.38 cm SI in the lower thoracic esophagus in a series of 12 patients (22 markers).[9] We estimated a much longer internal margin in all directions at all three sites. In a series of 29 patients, Dieleman et al. reported that the margins were 0.5 LR and 0.5 AP in the upper; 0.7 LR and 0.6 AP in the middle; and 0.9 LR and 0.8 cm AP in the lower esophagus.[11] Patel et al. concluded that the minimum radiation field margins required to cover the internal target volume of 95% of the primary esophageal cancers were 0.75 LR, 0.75 AP, and 1.5 cm SI directions.[12] Our results were consistent with this study, as it was considered that the majority of the population in this study (83%) had lower thoracic esophageal cancer.

Our study had some limitations. The delineation of the fiducial markers had some influence on the degree of the motion, and the beam-hardening artifacts affected the contouring of the fiducial markers. In our study, one oncologist delineated the fiducial markers and another oncologist reviewed them. The respiratory phase also had a potential, and we used CT with Real-Time Position Management System to avoid increasing the errors. We may underestimate the impact of heart beat or aortic pulsation. Few studies have been reported about the influence of cardiac motion on the tumors or organs of the thoracic cavity. Seppenwoolde et al. referred to the motion of the lung tumor located near the heart or attached to the aortic arch.[13] Palmer et al. concluded that cardiac pulsation resulted in displacements of 0.5–1.0 cm for some parts of the esophagus, depending on the patient and location.[14]

To our knowledge, this is the first report limited to clinical T1N0 and the thoracic tumors alone. In particular, our data are useful for determination of the internal margin for definitive radiotherapy of clinical T1N0 esophageal cancers of the thorax. Additionally, we included a large number of subjects for analysis, which further strengthened the study. An attempt at intensity-modulated radiation therapy (IMRT) for esophageal cancer has been made. Vieillevigne and colleagues examined the feasibility of dose escalation using IMRT for thoracic esophageal cancer.[15] In an era of high-precision external beam radiotherapy, the data of intrafraction and interfraction motion must be mandatory for carcinoma of other sites as well as of the esophagus. In the report of Cvek et al., they estimated intrafraction and interfraction motion of liver tumors.[16]

Our data will also help plan radiotherapy treatments for esophageal carcinoma in clinical situations.

5. Conclusions

Intrafraction motion occurred predominantly in the SI direction. We estimated that 0.35 cm LR, 0.8 cm SI, and 0.3 cm AP in the upper, 0.5 cm LR, 1.55 cm SI, and 0.55 cm AP in the middle, and 0.75 cm LR, 1.9 cm SI, and 0.95 cm AP in the lower thoracic esophagus covered 95% of the cases (Fig. 2).

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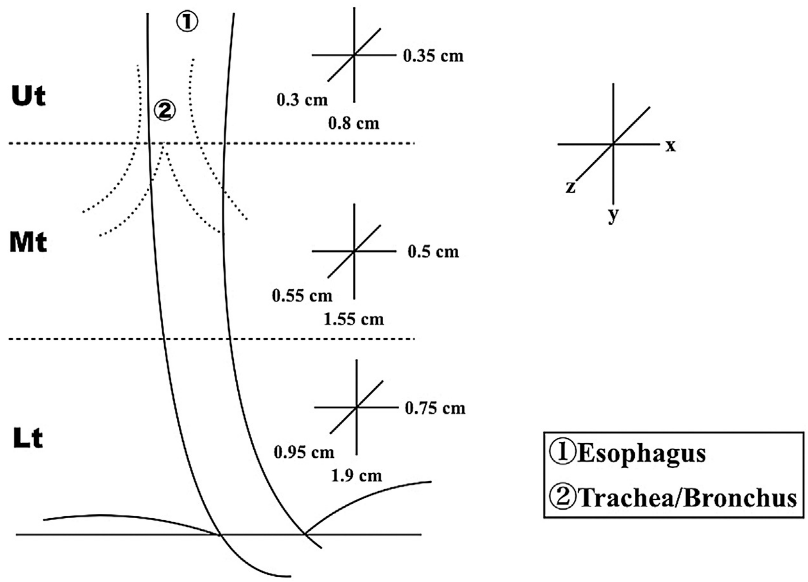

Fig. 2 – Our estimation of intrafraction motion of three sites of esophagus. Ut = upper thoracic esophagus; Mt = middle thoracic esophagus; Lt = lower thoracic esophagus; *x*-axis = left–right; *y*-axis = superior–inferior and z-axis = anterior–posterior.

Conflict of interest

All authors declare no conflict of interest associated with this manuscript.

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