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Original article

Changes in tumour volume and motion during radiotherapy for thoracic oesophageal cancer

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ABSTRACT

Background and purpose: Variations of target volume and position were important factors in correction of radiotherapy planning. The purpose was to investigate the changes in volume and motion of oesophageal cancer during radiotherapy using four-dimensional computed tomography (4D-CT).

Methods and materials: In total, 109 enhanced 4D-CT data sets were acquired for 38 patients throughout treatment. Gross tumour volumes (GTVs) were outlined on each data set. Variations in volume, motion, and position were calculated for GTV and internal GTV (IGTV) during treatment.

Results: GTV (25%, $P < 0.01$) and IGTV (27%, $P < 0.01$) had decreased significantly when measured at the twentieth fraction. Larger intrafractional GTV centre shifts ($P < 0.01$) were observed in the superior–inferior direction (median value of 3.1 mm) compared with the right–left and anterior–posterior directions (1.6 mm and 1.4 mm, respectively). The interfractional shift of the IGTV centre was not significant during radiotherapy. The overlap ratios of the targets decreased for both GTV and IGTV during treatment.

Conclusions: Variations in GTV and IGTV centre shifts were not significant throughout treatment. However, tumour volume decreased significantly by the twentieth fraction. Finally, changes in oesophageal tumour volume and motion may decrease the overlap ratio for GTV and IGTV during radiotherapy.

Determination of tumour and target volumes is crucial in the treatment planning of radiotherapy for oesophageal cancer. The planning target volume (PTV) of the tumour is defined as the internal target volume (ITV) plus the set-up margin [1]. Reasonable modifications to the PTV during radiotherapy could decrease toxicity to organs at risk. At present, image-guided radiotherapy has been widely used to minimise the impact of the set-up margin. Therefore, the ITV, which is primarily influenced by respiration, cardiac activity, and peristalsis [2], is the main factor used in determining the PTV. Therefore, variations in tumour volume and motion during radiotherapy are worth investigating. Accurate measurement of the ITV during radiotherapy may determine the patient-specific margin.

Four-dimensional computed tomography (4D-CT) delivering time-resolved three-dimensional (3D) data sets has been used to explicitly measure tumour motion and to determine the ITV [3–5]. This technique can demonstrate both spatial and temporal anatomic changes at planning and delivery of radiotherapy, thereby improving the characterisation of target mobility [6]. 4D-CT is one of the most widely applied techniques to determine the individual target area affected by organ motion.

To date, several studies on the movement of oesophageal tumours measured by 4D-CT have been published [1,7–9]. However, most of these studies measured tumour motion only at the pre-treatment stage, and tumour motion, along with tumour size, shape, and position, may also change during radiotherapy. Therefore, a single 4D-CT data set acquired before treatment may not adequately account for variations to the target during the course of treatment. There have been no prior studies investigating the nature of changes of oesophageal cancer during radiotherapy using repeated 4D-CT. The present study assessed intrafraction variations in the displacement of the GTV, the interfractional position variations in IGTV, the interfraction variations in volume, and the overlap ratio for the GTV_{50} (the respiratory phases to end expiration) and internal gross tumour volume (IGTV) using 4D-CT during radiotherapy.

Materials and methods

Patient characteristics

Thirty-eight patients who had visited the centre from August 2011 to September 2013 and had pathologically confirmed

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thoracic oesophageal cancer were considered eligible for 3D conformal radiotherapy or intensity-modulated radiotherapy. The patients received a prescription dose of 50–60 Gy, 5 times a week (dose of 2 Gy per fraction). All patients completed the simulation 4D-CT scan and the tenth fractional scan, and 33 patients completed the twentieth fractional scan. Enhanced 4D-CT scanning was performed at each treatment session. In all, 109 enhanced 4D-CT data sets were acquired for 38 patients throughout treatment. Patients with poor pulmonary function or pre-existing respiratory problems were excluded. All patients in our study received regular breathing training. Written informed consent was obtained from all patients before the treatment was initiated. Patient characteristics are listed in Supplementary Table 1.

CT data acquisition

Every patient underwent a 4D-CT scan on a 16-slice CT scanner (Philips Brilliance Bores CT, Netherlands). Using a vacuum bag, all patients were scanned in the supine position with arms stretched over the head, followed by laser alignment. Metal marks were applied to the laser cross-marked points on the bilateral axial midline and the anterior midline. The 4D-CT images were reconstructed using a thickness of 3 mm, and all scans were acquired during free breathing without any breathing control. During the 4D-CT image acquisition, the patient's respiration was monitored using the Real-Time Position Management Respiratory Gating System (Varian Medical Systems, Palo Alto, CA), and a signal was sent to the scanner to label each CT image with a time tag. GE Advantage 4D software (GE Healthcare, Waukesha, WI) sorted the reconstructed 4D-CT images into ten respiratory phases labelled as 0–90% based on these tags, with 0% (GTV_0) corresponding to end inspiration and 50% (GTV_{50}) corresponding to end expiration.

GTV delineation and motion determination

Based on bony landmarks, all 4D-CT data sets for each patient were registered to the reference 4D-CT scan (simulation/first 4D-CT scan) using software tools in the radiation treatment-planning system. For each 4D-CT data set, the primary tumour (considered as the GTV) was contoured manually by a single radiation oncologist using the mediastinal window and level setting. The full respiration GTV centre positions were acquired by the Varian Eclipse 8.6 treatment planning system, and the magnitude of 3D peak-to-peak motion was calculated. The 95th percentile values from the cumulative distributions were used to define minimum margins to account for GTV motion during treatment planning. The GTV_{50} acquired from the first, second, and third 4D-CT scan were named GTV1, GTV2, and GTV3, respectively; this naming convention was also applied to IGTV.

Definition of the degree of inclusion and the matching index

In order to further evaluate target variation, we also detected variations in degree of inclusion (DI) [5,10] and matching index (MI) [11–13] during radiotherapy. The definitions of DI and MI are outlined in the Supplementary material.

Statistical analysis

Three-dimensional shifts and shifts in the same direction at different locations during the same fraction were analysed using the Kruskal–Wallis *H* and Mann–Whitney *U* tests. The shift of the GTV centre in the same direction among all fractions, the variation of tumour volumes during treatment, the variation in IGTV centre, and the variation in DI and MI during radiotherapy were analysed using the Friedman and Wilcoxon signed-ranked tests. The correlation between target motion vectors and DI and MI were evaluated using the Spearman test. *P* values < 0.05 were considered statistically significant. All statistical analyses were performed using the SPSS software package 13.0.

Results

Fig. 1 shows the intrafractional variations of the GTV centre for all patients during radiotherapy. Larger shifts ($P < 0.01$) were observed in the superior–inferior (SI) direction (median value of 3.1 mm) compared with the right–left (RL) and anterior–posterior (AP) directions (1.6 mm and 1.4 mm, respectively). Shifts of the intrafractional GTV centre for upper, middle, and lower thoracic oesophageal tumours are summarised in Supplementary Table 2. Shifts in the SI direction were also larger than those in the RL and AP direction in different locations ($P < 0.01$). However, the shift of the GTV centre in the same direction among the three sessions did not reach statistical significance ($P > 0.05$). According to this study, 2.5 mm RL, 2.3 mm AP, 5.0 mm SI, and 5.5 mm 3D vector total; 2.3 mm RL, 2.1 mm AP, 4.9 mm SI, and 5.4 mm 3D vector in the upper; 2.4 mm RL, 2.3 mm AP, 4.1 mm SI, and 4.7 mm 3D vector in the middle; and 2.5 mm RL, 2.5 mm AP, 5.4 mm SI, and 6.3 mm 3D vector in the lower thoracic oesophagus provided coverage of tumour motion in 95% of the cases in our study population.

Fig. 2 shows the variations of interfractional IGTV centre for all patients. The IGTV centre shifts in the SI direction (3.0 mm for the 10th fraction, 3.6 mm for the 20th fraction) were greater than those in the RL (1.2 mm for the 10th fraction, 1.6 mm for the 20th fraction) and AP (1.4 mm for the 10th fraction, 2.0 mm for the 20th fraction) directions. Our results showed that shifts at the twentieth fraction were larger than those at the tenth fraction (based only on values); however, the shift variations of the IGTV centre were not significant during radiotherapy ($P > 0.05$). The results of the upper, middle, and lower locations are listed in Supplementary Table 3. Shifts in the SI direction were also larger than those in the RL and AP direction in upper, middle, and lower locations ($P < 0.01$).

Tumour volumes (GTV_{mean} and IGTV) tended to decline over the entire treatment course (Fig. 3). The GTV_{mean} decreased by 10% at the 10th fraction and 25% at the 20th fraction. The IGTV decreased by 10% at the 10th fraction and 27% at the 20th fraction. The GTV_{mean} and IGTV were observed to have decreased significantly by the 20th fraction ($P < 0.05$). The results in the upper, middle, and lower locations are listed in Supplementary Table 4. The GTV_{mean} and IGTV also tended to decline over the entire treatment course in different locations.

For all tumours, target DI tended to decrease during radiotherapy. The median values of ($GTVn \cap GTV1$)/GTV1 were 0.76 and 0.64 ($P < 0.01$) [$n = 2, 3$], respectively; those of ($IGTVn \cap IGTV1$)/IGTV1 were 0.81 and 0.67 ($P < 0.01$), respectively. The variations of DI for the upper, middle, and distal locations are summarised in Supplementary Table 5. The DI exhibited a downward trend in different locations.

For all tumours, MI tended to decrease for each target during radiotherapy. The median values of MI for GTV_{50} were 0.63 and 0.57 ($P < 0.01$), respectively, and those for IGTV were 0.68 and 0.59 ($P < 0.01$), respectively. The results for the upper, middle, and lower locations are summarised in Supplementary Table 6. The MI also exhibited a downward trend in different locations.

For all tumours, the 3D vector negatively correlated with ΔDI (the change in DI from the primary target to a subsequently acquired target); GTV: $r = -0.37$, $P < 0.01$; IGTV: $r = -0.39$, $P < 0.01$) and ΔMI (the change in MI); GTV: $r = -0.46$, $P < 0.01$; IGTV: $r = -0.44$, $P < 0.01$).

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