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Tumor motion

Quantification of respiration-induced esophageal tumor motion using fiducial markers and four-dimensional computed tomography

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ABSTRACT

Background and purpose: Respiration-induced tumor motion is an important geometrical uncertainty in esophageal cancer radiation therapy. The aim of this study was to quantify this motion using fiducial markers and four-dimensional computed tomography (4DCT).

Materials and methods: Twenty esophageal cancer patients underwent endoscopy-guided marker implantation in the tumor volume and 4DCT acquisition. The 4DCT data were sorted into 10 breathing phases and the end-of-inhalation phase was selected as reference. We quantified for each visible marker ($n = 60$) the motion in each phase and derived the peak-to-peak motion magnitude throughout the breathing cycle. The motion was quantified and analyzed for four different regions and in three orthogonal directions.

Results: The median(interquartile range) of the peak-to-peak magnitudes of the respiration-induced marker motion (left–right/anterior–posterior/cranial–caudal) was 1.5(0.5)/1.6(0.5)/2.9(1.4) mm for the proximal esophagus ($n = 6$), 1.5(1.4)/1.4(1.3)/3.7(2.6) mm for the middle esophagus ($n = 12$), 2.6 (1.3)/3.3(1.8)/5.4(2.9) mm for the distal esophagus ($n = 25$), and 3.7(2.1)/5.3(1.8)/8.2(3.1) mm for the proximal stomach ($n = 17$).

Conclusions: The variations in the results between the three directions, four regions, and patients suggest the need of individualized region-dependent anisotropic internal margins. Therefore, we recommend using markers with 4DCT to patient-specifically adapt the internal target volume (ITV). Without 4DCT, 3DCTs at the end-of-inhalation and end-of-exhalation phases could be alternatively applied for ITV individualization.

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The incidence of esophageal cancer has increased rapidly in the past decades [1,2]. Currently esophageal cancer is the eighth most common cancer worldwide [3]. Radiation therapy (RT) with concurrent chemotherapy has demonstrated benefits for patients with operable or inoperable esophageal cancer [4,5]. To generate the planning target volume (PTV) for RT of esophageal cancer, apart from the delineation uncertainty and interfractional tumor position variation, the uncertainty of respiration-induced tumor motion also needs to be taken into account. Although an active breathing control or a breath-holding technique could reduce this uncertainty, so far these techniques have been applied only in a few clinical RT trials for esophageal cancer [6,7]. Four-dimensional (4D) computed tomography (CT) was developed to facilitate the inspection of respiration-induced anatomical motion [8], however it has not yet commonly replaced the conventional 3D "snapshot" CT for the treatment planning for esophageal cancer RT [4,9]. Therefore, it is necessary to quantify the respiration-induced tumor motion prior to incorporating this uncertainty into the internal margin [10].

With the aid of 4DCT, most of the previous studies used gross tumor volume (GTV) delineation for the quantification of respiration-induced esophageal tumor motion [11–14]. However, without fiducial markers, the delineation of the primary tumor volume on CT may not be accurate even if ^{18}F-fluorodeoxyglucose-positron emission tomography is present [15]. Only one study placed large metal clips near the primary tumors as markers for motion quantification [16]. This was a rather small study, though, since only 12 patients with in total 22 markers were included.

Endoscopy-/endoscopic ultrasound (EUS)-guided implantation of various types of small fiducial markers in the esophagus has recently been successfully performed [17–19] which aided the quantification of interfractional esophageal tumor position

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variation [20]. Consequently, in this retrospective study we included 20 esophageal cancer patients with in total 69 fiducial markers in the primary tumor volume. By the use of 4DCT data and fiducial markers, we aimed to quantify the respiration-induced motion of the primary tumors located in different esophagus regions throughout the breathing cycle. In addition, we assessed the inter-observer variability in the motion quantification for method validation.

Materials and methods

Patients and markers

A previous prospective pilot study included 30 esophageal cancer patients who underwent endoscopy-/EUS-guided implantation of three different types of markers for evaluating and comparing the feasibility and benefits of marker implantation [19]. In this retrospective study, we included 20 patients with esophageal cancer between July 2013 and March 2015. Eighteen patients were from the cohort of the pilot study who had given additional informed consent for 4DCT acquisition; the other two patients were included after the pilot study ended. As described in [19], two different types of gold markers and one gel-based marker were used: solid marker (Cook Medical, Limerick, Ireland; or in-house manufactured), flexible coil-shaped marker (Visicoil; IBA Dosimetry, Bartlett, TN, USA), and hydrogel marker (TraceIt; Augmenix Inc., Waltham, MA, USA). For each patient, 2–6 markers of the same type were superficially placed in the submucosal layer at the cranial/caudal tumor borders and preferably the center of the primary tumor. In total 69 markers were implanted. For gastroesophageal junctional tumors, the marker at the caudal border could be placed in the cardia or fundus of the stomach. The detailed procedure of marker implantation and the appearance of the three types of markers in the CT scans were described in [19]. An overview of patient and marker characteristics is presented in Supplementary Table A1. According to the American Joint Committee on Cancer staging manual [21], all markers were classified into four subgroups based on the marker locations in the 3D planning CT scans as done in [20]: the proximal esophagus, middle esophagus, distal esophagus, and proximal stomach.

4DCT acquisition

For all patients, in addition to the 3D planning CT, a 4DCT was acquired using a LightSpeed RT 16 CT scanner in cine mode (General Electric Company, Waukesha, WI, USA). All 20 free-breathing patients were positioned supine with arms up above the head using an arm support (CIVCO Medical Solutions, Rotterdam, The Netherlands). No other immobilization devices were used. The axial thickness of the 4DCT scan slices was 2.5 mm and the in-plane resolution was 1.0 mm × 1.0 mm.

Based on the monitored breathing signal by the Real-time Position Management system (Varian Medical System, Palo Alto, CA, USA), the 4DCT data acquired in one breathing cycle were automatically sorted into 10 bins using the Advantage 4D software (General Electric). The image data in each bin were reconstructed into a 3DCT scan, representing one breathing phase throughout the breathing cycle, where phase 0% denotes the end of inhalation and phase 50% approximately denotes the end of exhalation.

Marker identification and motion quantification

Using the X-ray Volume Imaging (XVI) software (Elekta Ltd., Crawley, UK), the markers on each of the reconstructed 3DCT scans were manually identified by two observers (R.d.J. and P.J.). The reconstructed 3DCT scan of phase 0% (i.e., the end of inhalation) was selected as the reference scan. One trained radiation therapist (R.d.J.) manually registered for each patient the individual markers visible in each reconstructed 3DCT scan of phases 10–90% to the corresponding markers in the reference scan. It was done by only altering the translations in XVI to align the centers of the two markers visually (example: Supplementary Fig. A1). Based on the outcomes of the individual marker registrations, we calculated for each breathing phase the motion of each marker relative to its position in the reference. Then we derived for the individual markers the peak-to-peak magnitude of the respiration-induced motion that indicates the maximum marker position difference throughout the breathing cycle. All results were measured in the 3D vector distance, as well as in the left–right (LR), anterior–posterior (AP), and cranial–caudal (CC) directions, where the positive values indicate the left, anterior, and cranial direction, respectively.

Because of the elongated shape of the esophagus and the manner of motion of diaphragm and abdomen induced by respiration, the tumor motion could be direction- and location-dependent. Hence, we applied the Friedman test with Wilcoxon signed-rank test to compare the peak-to-peak magnitude of marker motion between the three orthogonal directions (LR, AP, and CC). Further, we applied the Kruskal–Wallis test with Dunn's test to compare that between the four marker subgroups (i.e., markers located in the proximal esophagus, middle esophagus, distal esophagus, and proximal stomach). Holm adjustment was performed to all the post hoc tests. In this study, all the statistical analyses were performed using R software [22]. The significance level was set at 0.05.

Inter-observer variability

To validate the marker-registration procedure and the quantification of the marker motion, the inter-observer variability was assessed. The second observer (P.J.) repeated all the marker registrations and derived the motion quantifications independently. For the three types of markers and all markers separately, the

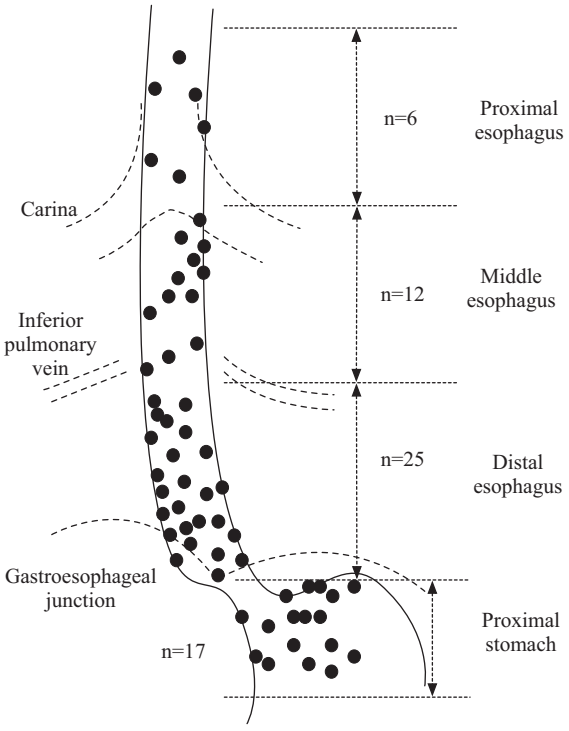

Fig. 1. Illustration of the locations of all the 60 visible markers in the 20 patients. The filled circle denotes a marker.