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Original article

Systematic intrafraction shifts of mediastinal lymph node targets between setup imaging and radiation treatment delivery in lung cancer patients

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ABSTRACT

Background and purpose: Internal target motion results in geometrical uncertainties in lung cancer radiotherapy. In this study, we determined the intrafraction motion and baseline shifts of mediastinal lymph node (LN) targets between setup imaging and treatment delivery.

Material and methods: Ten lung cancer patients with 2–4 fiducial markers implanted in LN targets received intensity-modulated radiotherapy with a daily setup cone-beam CT (CBCT) scan used for online soft-tissue match on the primary tumor. At a total of 122 fractions, 5 Hz fluoroscopic kV images were acquired orthogonal to the MV treatment beam during treatment delivery. Offline, the 3D trajectory of the markers was determined from their projected trajectory in the CBCT projections and in the intra-treatment kV images. Baseline shifts and changes in the respiratory motion amplitude between CBCT and treatment delivery were determined from the 3D trajectories.

Results: Systematic mean LN baseline shifts of 2.2 mm in the cranial direction (standard deviation (SD): 1.8 mm) and 1.0 mm in the posterior direction (SD: 1.2 mm) occurred between CBCT imaging and treatment delivery. The mean motion amplitudes during CBCT and treatment delivery agreed within 0.2 mm in all directions.

Conclusions: Systematic cranial and posterior intrafraction baseline shifts between CBCT and treatment delivery were observed for mediastinal LN targets. Intrafraction motion amplitudes were stable.

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Radiotherapy for lung cancer patients is subject to substantial motion, influencing the accuracy of the treatment delivery [1]. Accurate dose delivery with tight margins is essential for optimal target coverage and normal tissue sparing, but it is also complicated, as the treatment typically involves both a primary tumor and involved mediastinal lymph node (LN) targets that move individually [2]. The tumor and LN positions may vary between treatment fractions (interfraction), within one treatment fraction (intrafraction), and also within delivery of the treatment fields (intra-treatment). Interfraction baseline shifts for tumor and LNs originate from variations in daily patient positioning [2,3] and anatomical changes during the treatment course [4–6]. Intrafraction baseline shifts may occur between setup imaging, e.g. cone-beam computed tomography (CBCT), and the end of the delivery of the treatment fraction [2,7]. These shifts come from internal target motion and/or patient movement during treatment. Additionally, the amplitude of the intrafraction respiratory and cardiac induced motion may vary from day to day [8–10]. The intrafraction motion has been investigated in a number of studies, typically based on additional 3D CBCT [11], 4D CBCT [2] or 4DCT scans [12], that show baseline shifts and motion amplitude variations. However, very little information on the LN motion during the actual treatment delivery has been reported. Schaake et. al. [2] have published a study on intrafraction motion using pre- and post-treatment CBCT scans once a week, but observation of intrafraction and intra-treatment motion amplitudes and positional changes require time-resolved intra-treatment imaging. For this purpose implanted fiducial markers in LNs serve perfectly, as the position of these markers has been shown to be stable during the treatment course [9].

In a previous study based on 10 lung cancer patients with implanted fiducial markers, the detailed 3D target motion of multiple involved mediastinal LN targets throughout the treatment course was determined from daily setup CBCT projections acquired before the actual treatment delivery [9].

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This study investigates the 3D LN motion in fluoroscopic X-ray images acquired *during* treatment delivery for the same patient group. This gives a direct measurement of geometric errors during treatment delivery and allows for determination of intrafraction baseline shifts or motion amplitude changes between CBCT setup imaging and treatment delivery.

Methods and materials

Patients, image guidance, and image acquisition

This study was based on motion data from 10 lung cancer patients treated between May 2014 and July 2015, following our protocols for non-small-cell lung cancer (NSCLC) (9 patients, 60–66 Gy in 30–33 fractions, 5 fractions/week) and small-cell lung cancer (SCLC) (1 patient, 45 Gy in 30 fractions, 10 fractions/week). The study was approved by the regional ethics committee, and all patients gave written informed consent. The patient characteristics, treatment planning, and image-guided setup have been described in detail previously [9]. Each patient had 2–4 gold fiducial markers (0.5 mm × 5 mm Visicoils, IBA Dosimetry, Barlett, TN) implanted in mediastinal LN targets with ultrasound-guided bronchoscopy (EBUS). The motion of 28 markers was analyzed in this study. IMRT treatment plans with 5–8 fields were made in the mid-ventilation phase of a 4DCT planning scan. Patients were positioned on a thorax board with their arms above the head. Daily CBCT scans were acquired for patient setup using soft tissue matching on the primary tumor [13]. The CBCT scans were reconstructed from ~670 2D kV images acquired at 11 Hz during a full 1-min gantry rotation. During treatment field delivery, fluoroscopic kilovoltage (kV) images (100 kV, 40–50 mA, 9–30 ms) were acquired at 5 Hz perpendicular to the treatment beam with an On-Board Imager system (Varian Medical Systems, Palo Alto, USA). The source-to-detector distance was set to 180 cm, rather than 150 cm used for the setup CBCT, to reduce cross-scatter from the MV treatment beam onto the kV imager. For some patients, the impact of MV cross-scattering was reduced by triggered read-out of unexposed kV frames in-between the exposed frames [14]. The intra-treatment kV imaging was performed at the first three fractions and afterwards at every third fraction, i.e. at fractions 1, 2, 3, 6, 9, …, 27, 30 (33). Some deviations from this imaging scheme occurred due to clinical practice or technical problems. Furthermore, for three patients, intra-treatment imaging was omitted for 1–2 non-coplanar fields that were delivered at the end of the treatment fraction and made deployment of the kV imager infeasible. The intra-treatment imaging was performed at a total of 122 fractions.

Intra-fraction motion measurement

As described in [9], the 3D trajectory of each marker during CBCT acquisition was estimated by segmenting the marker position in each CBCT projection and transforming the resulting 2D motion in the CBCT projections to 3D motion in patient coordinates by the probability-based method [15] used in kilovoltage intrafraction monitoring (KIM) [16]. In the current study, the marker segmentation was extended to the intra-treatment kV images by use of the same algorithm for template-based marker segmentation [17]. The same 3D marker model [9,17] was used for segmentation in CBCT projections and intra-treatment kV images to ensure that the same position within each marker was segmented in both image types. All segmentations were visually verified and manually corrected in case of segmentation errors. The 3D trajectory of each marker during treatment delivery was determined in the accelerator coordinate system by applying the probability-based 3D trajectory estimation method [15] to the intra-treatment kV images.

Intra-fraction motion analysis

The intra-treatment 3D marker motion was used to calculate the time-resolved 3D positional error of each LN marker during treatment delivery by comparison with the planned marker position relative to the isocenter. This error originated from interfraction LN shifts relative to the primary tumor, online tumor match errors, couch shift inaccuracies, and intrafraction LN baseline shifts in the time interval between the setup CBCT and treatment delivery. Next, the expected error from the setup CBCT was calculated from the 3D marker motion during the CBCT by correcting for the online couch shift that was applied between CBCT and treatment delivery. This error did not include couch shift inaccuracies and intrafraction baseline shifts. Finally, the intrafraction LN baseline shift was calculated for each marker at each imaged fraction as the difference between the actual intra-treatment mean error and the mean error expected from the CBCT. This baseline shift calculation assumed that couch shift inaccuracies were negligible. For both the setup errors measured during treatment delivery, the errors expected from CBCT and the intrafraction baseline shifts, the grand mean (M) and the standard deviation (SD) of the systematic (Σ) and random (σ) errors of the LN marker positions were calculated from the mean and SD values for each marker averaged per fraction [18].

Besides intrafraction baseline shifts, the intrafraction motion amplitude was calculated for each marker at each fraction as the 2nd to 98th percentile motion span in each direction during the CBCT scan and during delivery of each treatment field. The intra-treatment motion amplitude was calculated as the mean amplitude for the imaged treatment fields. The CBCT motion amplitude and the intra-treatment motion amplitude were compared with the marker motion amplitudes between the exhale phase and inhale phase of the planning 4DCT scan.

Statistics

A non-parametric Wilcoxon-signed rank test was utilized to test for statistical significance of baseline shifts. Pearson's correlation test was used to test for significant correlations between the waiting time from CBCT acquisition to treatment field delivery start and the magnitude of the baseline shifts. A significance level of $p < 0.05$ was assumed.

Phantom validation

The use of CBCT projections and intra-treatment kV images to estimate internal marker motion and baseline shifts was validated by performing the same CBCT imaging, couch shifts, and kV imaging for a motion phantom as applied at the first fraction for each patient. A moving phantom (Varian Medical Systems) with a gold marker embedded in a Styrofoam block simulated respiratory motion using a rotating disc and a platform with a period of approximately 9 s and peak-to-peak amplitudes of left–right (LR): 1 mm, cranio-caudal (CC): 11 mm, and anterior-posterior (AP): 34 mm. In ten experiments, corresponding to the ten patients, a CBCT scan was first acquired of the motion phantom with the same couch position as at the patients' first fraction. Next, the same couch shift was applied as at the first fraction followed by 30 s kV fluoroscopy at the same imaging angles as used for intra-treatment imaging of the patients.

The recorded images were analyzed in the same way as the clinical images. First, the embedded marker was segmented in all images. Next, the 3D motion was estimated for the CBCT and for

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