Radiotherapy and Oncology 121 (2016) 52–58

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Cardiac and respiration motion

Cardiac and respiration induced motion of mediastinal lymph node targets in lung cancer patients throughout the radiotherapy treatment course

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ARTICLE INFO

Article history:
Received 9 April 2016
Received in revised form 2 July 2016
Accepted 3 July 2016
Available online 2 August 2016

Keywords:
Lung
Intrafraction motion
Interfraction motion
Differential motion
Lymph node

ABSTRACT

Background and purpose: Involved mediastinal lymph nodes (LNs) are often included in the radiotherapy target for lung cancer patients. Their motion may differ from the primary tumor motion, possibly undermining the loco-regional control. This study determines the detailed differential target motion throughout the treatment course.

Material and methods: Ten lung cancer patients with 2–4 fiducial markers implanted in LN targets received IMRT with a daily pre-treatment cone-beam CT (CBCT) scan. Offline, the 3D trajectory of the markers was determined from their projected trajectory in the CBCT projections. Frequency analysis was performed to separate the intrafraction motion into a respiratory and cardiac component. The mean setup error of the markers and the motion range were used to calculate margins required for LN targets when setup is based on soft-tissue match.

Results: Respiration motion was largest in the CC direction and more prominent for more caudal LNs. Cardiac motion was often (73%) largest in the AP direction and tended to be largest for more cranial LNs. Margins for intrafraction motion and daily baseline shifts of LNs were 4.8 mm (LR), 6.0 mm (CC) and 6.7 mm (AP).

Conclusions: Detailed mapping showed that LN motion was in general governed by breathing, but some LNs had substantial cardiac induced motion.

Locally advanced non-small cell lung cancer (NSCLC) radiotherapy suffers from high local failure rates that contribute to low overall survival [1]. Increased radiation doses may improve local control [2], but clinical dose escalation trials have shown significantly increased fatal toxicity [2–4]. Accurate treatment delivery with tight margins is essential, but complicated, as the treatment typically involves both a primary tumor (PT) and involved lymph node (LN) targets that move differently [5]. Intrafraction target motion is caused by respiration and cardiac activity [6], while interfraction target motion is caused by anatomical changes over the treatment course and differences in daily patient positioning [7,8].

Cone-beam computed tomography (CBCT) with soft-tissue tumor matches allows correction for daily tumor position shifts [9], but the LNs may have different shifts. It is important to know both intrafraction and interfraction motion of the LNs relative to the PT in order to design appropriate LN margins. LNs are in general difficult to visualize by CBCT, but may be localized indirectly through neighboring anatomical surrogate structures [10] or more directly by implanted fiducial markers [11].

LN motion has previously been studied by four-dimensional computed tomography (4DCT) [12,13] and 4D-CBCT [11,14]. It gives the position in typically ten different phases measured during a single respiration cycle (4DCT) or averaged over an acquisition time of a few minutes (4D-CBCT). However, if markers are implanted in LNs, their projected 2D trajectory in the raw projection images for CBCT volume reconstruction can be used to obtain their detailed 3D motion trajectory with individual respiration cycle resolution [15]. It gives a much higher time-resolution than 4D-CBCT. This method has previously been applied to extract motion of prostate [16,17], liver [18], pancreas [19], and lung [17] tumors.

In this study, we use the trajectory estimation method to investigate differential time-resolved motion of involved LN targets

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http://dx.doi.org/10.1016/j.radonc.2016.07.015
0167-8140/

during daily CBCT scans throughout the treatment course for ten lung cancer patients. It provides rich information on differential target motion, including intrafraction respiratory and cardiac induced LN motion and daily interfraction shifts of the LNs relative to the PT.

Materials and methods

Patients, treatment planning and image-guidance

Ten lung cancer patients (5 male/5 female), with pathologically proven tumors, treated with chemo-radiotherapy (IMRT) between May 2014 and July 2015 were included in this study. The median patient age was 69 years (range: 50–77 years). Nine patients had NSCLC and received three cycles of cisplatin/carboplatin and vinorelbine concomitant with 60–66 Gy in 30–33 fractions (5 fractions/week). One patient with small-cell lung cancer received four cycles of cisplatin and etoposide concomitant with 45 Gy in 30 fractions (10 fractions/week). Nine patients were treated with radiotherapy for one PT and two or more involved mediastinal LNs. In two patients, the tumor and LNs could not be separated and were treated as one target.

Each patient had for this study 2–4 gold fiducial markers (0.5 mm × 5 mm Visicoils, IBA Dosimetry, Barlett, TN) implanted with ultrasound-guided bronchoscopy (EBUS). Written informed consent was obtained from all patients according to international and national regulations. This study was approved by the institute's medical ethics committee. Supplementary Table 1 (third column) specifies the LN stations with implanted markers following the classification of [20].

A 3 mm slice thickness, free-breathing 4DCT scan acquired with intravenous contrast was used for treatment planning. The internal gross tumor volumes of the PT (GTV-T) and the involved LNs (GTV-N) were delineated on the mid-ventilation (mv) phase of the 4DCT scan using the maximum intensity projection (MIP) thus accounting for respiratory motion [21]. Clinical target volumes (CTV-T_{MIP}, CTV-N_{MIP}) were formed by adding 5 mm margins and correcting for bones and large blood vessels. The CTVs were further expanded to planning target volumes (PTV) by margins of 4 mm (left–right (LR) and anterior–posterior (AP)) and 5 mm (cranio-caudal (CC)) for PTV-T, and 9 mm (LR, AP) and 10 mm (CC) for PTV-N. A free-breathing CBCT scan was acquired with an On-Board Imager system (Varian Medical Systems) and used for daily image-guided setup by automatic registration of the GTV-T to the mv phase of the planning 4DCT.

Post-treatment image analysis

Each setup CBCT scan consisted of approximately 675 projections acquired with 11 Hz frequency during a 360°gantry rotation in 60 s (110 kV, 20 ms, 20 mA, half-fan bow-tie filter). In total, 317CBCT scans were acquired and analyzed.

The centroid position of each marker was obtained in all CBCT projections that included the marker using a semi-automatic template-based segmentation algorithm [22]. In short, a 3D model of each Visicoil was built by co-alignment and back-projection of the 2D marker shape in 4–6 manually selected CBCT projections with large angular separation and good marker contrast. Next, the 3D model was projected into the direction of each CBCT projection to generate 2D templates for automatic template-based marker segmentation [22]. Fig. 1 shows examples of markers in CBCT projections (left) and 2D templates used for marker segmentation (right). The 3D marker model built from the CBCT projections of the first treatment fraction was reused for 2D template generation at subsequent fractions if these 2D templates resulted in robust auto-segmentation. Otherwise, a new 3D marker model was built from the CBCT projections of the subsequent fraction. Each segmentation was visually inspected and manually corrected in case of segmentation errors. The resulting 2D marker trajectory in the CBCT projections was used to estimate the 3D trajectory during the CBCT acquisition using a probability-based method [15].

Stability of markers

Use of fiducial markers as target surrogates requires a stable marker position in the tissue. The stability of the marker orientation and inter-marker distance over the treatment course was investigated. Most of the markers had straight-line shape and thus a well-defined 3D orientation. In order to quantify the orientation stability over the treatment course, the mean 3D orientation at each fraction was determined by auto-segmenting the projected marker shape in 200–600 CBCT projections and fitting the resulting 2D marker orientations to a 3D marker orientation (polar and azimuthal angle). The 3D marker orientation of each fraction was compared with the first treatment fraction. Furthermore, the mean 3D marker positions at each treatment fraction were used to quantify the interfraction stability of all marker-marker distances throughout the treatment course as the mean and standard deviation (SD) of the distances.

Intrafraction motion

The 3D marker trajectories were used to determine motion the range (2nd–98th percentile) of each marker during the setup CBCT at each treatment fraction (example in Fig. 2a). The stability of the motion range from day to day was quantified as the mean and SD over the treatment course. Frequency analysis and Fourier filtering were used to separate the motion at the first three fractions into motion with frequencies below and above 1 Hz. These motion components mainly represented respiratory and cardiac induced motion, respectively. An example is shown in Fig. 2b. The motion ranges (2nd–98th percentile) of the respiratory and cardiac motion components were extracted for the first three fractions. Furthermore, the average waveform of the separated motions was determined by manually selecting a number n of either respiration or cardiac cycles at the first fraction (indicated by arrows in Fig. 2b). Each of the n cycles was scaled in time to the same relative scale from 0% (start of cycle) to 100% (end of cycle), and the average waveform was obtained as the mean position for each time point (Fig. 2c). The mean number of averaged cycles n was 11 for respiratory motion (range: 4–21 cycles) and 16 for cardiac motion (range: 8–21).

Interfraction motion

The mean position of each LN marker at each treatment fraction was used to investigate interfraction differential LN target motion relative to the PT and bony anatomy. First, the position of each LN marker was determined relative to the planned marker position accounting for the couch shift performed between setup CBCT and treatment delivery following the GTV-T soft tissue match. Second, the position of each LN marker was determined relative to an offline bony anatomy match.

This was used to calculate the required CTV-PTV margins to deliver a minimum LN CTV dose of 95% in 90% of the patients with image-guided setup based on both PT match and bony anatomy match as follows [23]:

$$2.5\Sigma_B + 1.64\sqrt{\left(\sigma_B^2 + \frac{A^2}{9} + \sigma_p^2\right)} - \sigma_p$$