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Deep-inspiration breath-hold in lung

Target position uncertainty during visually guided deep-inspiration breath-hold radiotherapy in locally advanced lung cancer

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ABSTRACT

Purpose: The purpose of this study was to estimate the uncertainty in voluntary deep-inspiration breath-hold (DIBH) radiotherapy for locally advanced non-small cell lung cancer (NSCLC) patients.
Methods: Perpendicular fluoroscopic movies were acquired in free breathing (FB) and DIBH during a course of visually guided DIBH radiotherapy of nine patients with NSCLC. Patients had liquid markers injected in mediastinal lymph nodes and primary tumours. Excursion, systematic- and random errors, and inter-breath-hold position uncertainty were investigated using an image based tracking algorithm.
Results: A mean reduction of 2–6 mm in marker excursion in DIBH versus FB was seen in the anterior-posterior (AP), left–right (LR) and cranio-caudal (CC) directions. Lymph node motion during DIBH originated from cardiac motion. The systematic- (standard deviation (SD) of all the mean marker positions) and random errors (root-mean-square of the intra-BH SD) during DIBH were 0.5 and 0.3 mm (AP), 0.5 and 0.3 mm (LR), 0.8 and 0.4 mm (CC), respectively. The mean inter-breath-hold shifts were −0.3 mm (AP), −0.2 mm (LR), and −0.2 mm (CC).
Conclusion: Intra- and inter-breath-hold uncertainty of tumours and lymph nodes were small in visually guided breath-hold radiotherapy of NSCLC. Target motion could be substantially reduced, but not eliminated, using visually guided DIBH.

Most lung tumours move during respiration [1] and adapting the radiotherapy treatment to different types of motion is an on-going challenge [2]. Current practice during radiotherapy is to account for the resulting tumour position uncertainty by expanding the planning target volume (PTV), thus ensuring that the prescribed dose is delivered to the target [3–5]. Therefore, the PTV includes healthy tissue, which may increase the risk of radiotherapy-related toxicity [6]. During deep-inspiration breath-hold (DIBH) radiotherapy [7,8] the lung tissue inflates and expands, causing a relatively large part of the normal tissue to move outside of the treated volume and potentially resulting in fewer side effects [7]. Using DIBH has shown to improve image quality and registration uncertainty in cone beam computer tomography (CT) [9]. Safe DIBH requires a signal to trigger the radiation, usually accommodated by an external marker. In order to deliver radiotherapy with a small uncertainty and to reduce PTV margins, it is crucial that the external surrogate signal accurately corresponds to the internal tumour position, which should be verified with image-guidance [10].

Previous investigations on intra-BH position uncertainty are based on patients receiving stereotactic body radiotherapy for small tumours over 3–5 fractions, using fiducial or external markers [10–12]. Previous studies on intra-BH reproducibility focused on the position of the diaphragm or sternum, and not the lung tumour itself [7,12]. DIBH reduces, but does not eliminate, tumour motion [13], and tumour motion arising from e.g. cardiac motion has been noted [14]. Motion still occurs both during BH (intra-BH tumour position uncertainty) and between consecutive BHs (inter-BH tumour position uncertainty) [11]. The intra-BH tumour position uncertainty has not yet been investigated for patients with locally advanced non-small cell lung cancer (NSCLC) treated with definitive radiotherapy [15–17]. The inter-BH reproducibility of the primary tumour has been evaluated with repeated

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CT imaging [10,11,13,18], but inter-BH reproducibility of the lymph nodes has not yet been investigated, therefore further investigations are warranted. Using active motion-management techniques, such as DIBH, has also shown superior dose coverage and better organ sparing compared to margin management techniques [19].

In this study, we have implanted liquid fiducial markers into lung tumours and affected lymph nodes; and recorded fluoroscopic images during a course of definitive radiotherapy to estimate the DIBH related motions and uncertainties. We evaluated the intra- and inter-BH tumour position uncertainty for primary tumours and lymph nodes in patients with locally advanced NSCLC. Additionally, we establish the systematic and random errors during DIBH.

Materials and methods

Patients, treatment, delivery and image acquisition

Fifteen patients with NSCLC referred for concomitant chemo-radiotherapy with 66 Gy in 33 fractions, 5 fractions per week, were included in an investigation of a novel liquid fiducial marker at our institution [20,21]. The prospective study was approved by the regional ethics committee (H-1-2013-133) and Danish Health and Medicines Authority (2013113675), and registered at ClinicalTrials.gov (identifier NCT02447900). Informed consent was obtained from all patients prior to inclusion. Patients were injected with the liquid fiducial marker BioXmark® (Nanovi Radiotherapy A/S, Lyngby, Denmark) in metastatic lymph nodes and, if possible and feasible, also in or near the primary tumour using either endoscopic ultrasound or endobronchial ultrasound equipment [21].

Patients were planned in both free breathing (FB) and DIBH. The best plan regarding target coverage and doses to organs at risk was chosen for treatment. Two Volumetric Modulated Arc Therapy (VMAT) beams of 6 MV delivered by a linear accelerator (Novalis/TrueBeam™ STx, Varian Medical Systems, Palo Alto, CA, USA) was used for treatment. Respiration was monitored with Real-time Position Management™ (RPM) system, (Varian Medical Systems, Palo Alto, CA, USA), with an external surrogate placed on the xiphoid process. The gating level was set individually, based on the breathing performance of the patient during a coaching session prior to the CT scanning. A visual feedback system guided the patient's BH level during imaging and treatment. DIBH cone-beam CT (CBCT) was used for daily image guidance with tumour-based registration. Projections for the DIBH-CBCT were acquired only when the patient was inside the gating window.

Series of anterior and lateral kilovoltage (kV) fluoroscopies with 15 Hz frame rate were collected after the treatment fractions number 2, 16 and 30, in the same couch position as for the treatment delivery. A 20 s FB fluoroscopy and two 10–15 s DIBH fluoroscopies were acquired at both imager angles (Fig. 1), resulting in six fluoroscopies from each fraction. The automatic brightness control function of the TrueBeam™ STx was applied during imaging, using exposure parameters varying between 70–90 kV and 35–60 mA.

Marker segmentation

The fluoroscopic images were retrieved from the TrueBeam™ service mode in DICOM format. Image based segmentation of the liquid fiducial marker was performed in Matlab (Version 2013b, Mathworks Inc., Natwick, USA) using in–house developed software. A template-based image-tracking algorithm with 2D normalized cross-correlation [22], was used to segment the implanted liquid fiducial markers in the fluoroscopic images (Matlab Version 2013b, Mathworks Inc., Natwick, USA). The marker positions were manually defined as image templates in one image and this was subsequently used to extract the marker position during the entire FB fluoroscopy. For DIBH fluoroscopies, an image template from the middle of the first fluoroscopy from each fraction was used to segment the liquid marker in both DIBH fluoroscopies acquired from the same gantry angle (Fig. 1). The segmented marker position was visually inspected and manually corrected if the automatic localization procedure was deemed unsuccessful. The vertebra position in the fluoroscopies was inspected in order to check if any gross intra-fraction patient movement occurred between repeated BH fluoroscopies.

Free breathing and breath-hold excursion

Marker excursion in all three cardinal axes (anterior-posterior (AP), left–right (LR) and cranio-caudal (CC)) was determined for both FB and DIBH data sets as the difference between the marker's minimum and maximum position (Fig. 1). As the CC excursion was measured twice in FB and four times in DIBH (in both anterior and lateral fluoroscopy) the maximum of these two or four excursions was reported. The differences in excursion between fractions, for both FB and DIBH, were compared using a Wilcoxon signed rank test in order to evaluate potential significant changes in the marker excursion over the course of radiotherapy. Wilcoxon signed rank test was also applied for comparison of excursions between FB

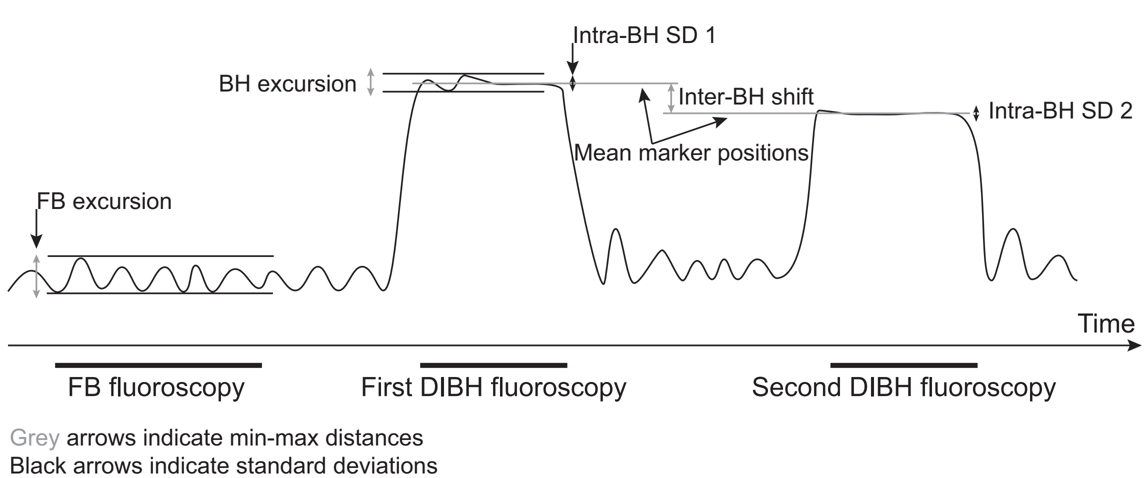

Fig. 1. Schematic of breathing motion and fluoroscopic images acquired anteriorly and laterally with measured quantities presented. Thick black lines indicate time points where fluoroscopy image acquisitions were performed. Grey arrows indicate min–max distance measured and black arrows indicate standard deviations measured. BH: breath-hold, SD: standard deviation, FB: free breathing, DIBH: deep-inspiration breath-hold.