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Tumor motion

Geometric uncertainties in voluntary deep inspiration breath hold radiotherapy for locally advanced lung cancer

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ABSTRACT

Background and purpose: Deep inspiration breath hold (DIBH) increases lung volume and can potentially reduce treatment-related toxicity in locally advanced lung cancer. We estimated geometric uncertainties in visually guided voluntary DIBH and derived the appropriate treatment margins for different image-guidance strategies.

Material and methods: Seventeen patients were included prospectively. An optical marker-based respiratory monitoring with visual guidance enabled comfortable DIBHs, adjusted to each patient's performance. All patients had three consecutive DIBH CTs at each of the treatment fractions 2, 16 and 31. DIBH reproducibility was evaluated as inter- and intra-fractional variations in lung volume, tumour position and differential motion between primary tumour and mediastinal lymph nodes.

Results: Lung volume increased by median 60% in DIBH. Inter- and intra-fractional lung volume variations were median 2.1% and 1.1%, respectively.

Inter- and intra-fractional uncertainties in 3D tumour position were 4.8 ± 2.8 mm and 1.7 ± 1.4 mm (mean ± SD). Inter- and intra-fractional differential motion was 4.8 ± 3.3 mm and 0.0 ± 1.1 mm.

Conclusions: For single targets, visually guided voluntary DIBH radiotherapy is highly reproducible provided an image-guidance strategy with tumour registration is performed. If the primary tumour is separated from the mediastinal lymph nodes, inter-fractional differential motion remains a challenge and margins must be adapted to reflect the image registration strategy.

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Deep inspiration breath hold (DIBH) radiotherapy is well established for breast cancer [1–3] and also used in mediastinal lymphoma [4]. In DIBH the lungs are inflated and the heart is pushed posteriorly and inferiorly minimising the radiation dose to these organs and thus risk of treatment related toxicity [5]. Furthermore, DIBH radiotherapy for lung cancer holds the potential for curative treatment of larger tumours because the increased lung volume enables easier fulfilment of dose constraints [6].

The first studies on DIBH radiotherapy for lung cancer were reported over a decade ago [7,8], but the technique has not gained wide implementation. Published studies on DIBH radiotherapy for locally advanced non-small cell lung cancer (NSCLC) originate from just four clinics [9–15]. The only larger scale study published, reporting on national experience with 203 patients treated in DIBH [16], focused on treatment toxicity and did not evaluate geometrical uncertainties, which are of major concern in DIBH. Inter- and intra-fractional variations in tumour position as well as in total lung volume will impact the accumulated dose to the target and the healthy lung. Application of forced spirometry-assisted DIBH system (where a valve actively blocks the patient's respiration at a pre-defined level) implies that the reproducibility of the lung volume translates into a stable position of the tumour within the lungs [17]. However, tumour baseline shifts of up to 25 mm have been reported [13].

Voluntary DIBH with visual guidance and optical respiration monitoring has only been reported for small peripheral lesions in stereotactic body radiotherapy (SBRT) [18,19]. However, tumours treated with SBRT are geometrically less complex than locally advanced disease, where differential motion between the primary tumour and the mediastinal lymph nodes occurs: reported systematic and random variations in differential motion for free breathing (FB) were 2.1–2.5 mm [20], and slightly larger in forced spirometry-assisted DIBH, 2.0–3.6 mm [14].

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Since voluntary DIBH has been reported more comfortable than forced DIBH [21], we hypothesise that the geometric uncertainties in locally advanced NSCLC would be reduced compared to forced spirometry-assisted DIBH. We report on the inter- and intra-fractional reproducibility of the tumour and the lymph nodes position in voluntary DIBH. We also estimate the impact of these uncertainties on the treatment margins for image-guided radiotherapy (IGRT) in voluntary DIBH and recommend an IGRT strategy for DIBH radiotherapy.

Materials and methods

Seventeen patients were prospectively included upon signing an informed consent (local ethics committee approval nr. H-2-2011-153). The patients were referred for radiotherapy of locally advanced NSCLC in FB.

Image acquisition

Patients were immobilised in a chest board (ConChest, Candor Aps). Standard imaging for radiotherapy planning at our institution includes FB PET/CT, 4DCT and a voluntary DIBH-CT (referred later as DIBH0). For this study, the patients underwent additional imaging sessions on each of the days of treatment fractions 2, 16 and 31 with three CT-scans in three consecutive DIBHs (referred later as DIBH2.1, DIBH2.2 etc., see Supplementary Fig. 1) and one DIBH-CBCT. A complete CBCT acquisition takes one minute and was split into three DIBHs of 20 s. DIBH-CTs were performed without contrast enhancement, in a helical scan mode (pitch 1.2) and reconstructed with pixel size 0.98 mm and 2 mm plane separation. The present report focuses on the analysis of the DIBH-CTs.

Respiratory motion was monitored with Real-time Position Management system (RPM™, Varian Medical Systems Inc.), using an infra-red camera to track the respiratory signal from an optical marker placed at the xiphoid process. The DIBH level was individually set to a comfortable level during a 15 min coaching session prior to the treatment planning session. The chosen DIBH level was provided to the patient through visual feedback for all imaging sessions, as described in [1].

Feasibility was defined as the patient being able to perform six consecutive DIBHs of $\geqslant$20 s duration at all points during the treatment course, with the DIBH amplitude reaching the predefined level. The reproducibility of DIBH was evaluated as variations in lung volume, tumour position and differential motion between the primary tumour and the mediastinal lymph nodes.

Reproducibility of lung volume

Lung volume was delineated using automatic delineation tools in Eclipse™ treatment planning system (version 11.0.31, Varian Medical Systems Inc.), with manual exclusion of trachea and main bronchi. Inter-fractional variations in DIBH lung volume were evaluated from the DIBH2.1, DIBH16.1 and DIBH31.1 scans compared to the DIBH0. Intra-fractional DIBH lung volume variations were evaluated from the three daily consecutive DIBH-CTs (i.e. DIBHx.1, DIBHx.2 and DIBHx.3).

Reproducibility of tumour position

To evaluate the inter-fractional reproducibility of tumour and carina position in DIBH, for each session x, DIBHx.1 was registered to DIBH0 on bony anatomy, with focus on the spine at the levels of the tumour or the carina. Image registration was also performed on the tumour and the carina. Inter-fractional tumour and carina position uncertainty was evaluated from differences between the registrations on the bony structures and on the tumour or on the carina, respectively.

Intra-fractional reproducibility was defined as the reproducibility between three consecutive DIBHs: DIBHx.2 and DIBHx.3 were registered to DIBHx.1 with focus on either the tumour or the carina. Intra-fractional uncertainty in the position of the tumour or the carina was evaluated from differences between the registrations on the tumour or on the carina, respectively.

Differential motion between tumour and mediastinal nodes

Patients with central tumours were excluded from this analysis. Differences between the inter- and intra-fractional registrations on the tumour and the carina (used as a surrogate for the mediastinal nodes) were used to evaluate the inter- and intra-fractional differential motion.

Inter- and intra-observer variation

Image registrations were rigid, applying 3D translations only, and using predefined settings: Hounsfield units between −1000 and 250 for the tumour and carina registrations, and between −125 and 225 for the bone registration. This manual process mimicked typical clinical procedures, but might be prone to observer uncertainties, with a potential impact on the evaluation of geometrical uncertainties. In order to evaluate the image registration uncertainty, all registrations were first performed twice by the same observer and once by a second observer. The standard deviation (SD) of the differences between two repeated sets of registrations by the same observer was considered a measure of the intra-observer variation in image registration, on tumour, carina and bony anatomy respectively. The SD of the differences between the two sets of registrations of two different observers was considered a measure of the inter-observer variation in image registration.

Data analysis and margin calculation

Intra- and inter-fractional tumour and carina position deviations were expressed in terms of group mean, systematic and random errors [22]. Planning target volume (PTV) margins were calculated accordingly, including also uncertainties for lack of 6D corrections [23] and compared to our clinically applied margins for FB radiotherapy, based on extent of tumour motion, baseline shift and lack of 6D corrections [22,23].

Results

Patients' characteristics are presented in Table 1. All 17 patients could initially effortlessly perform six consecutive DIBH of $\geqslant$20 s (three for the three DIBH-CTs and three for one DIBH-CBCT). One patient (#12) left the study on day 16 for lack of DIBH compliance (inability to reach the predefined DIBH level). Three patients left the study prematurely, due to a decrease in general performance (#2), distant metastases (#8) and own wish to omit imaging at 31st fraction (#11). Due to either logistic or technical issues, we lack one CT image set from patients #3, #6, #16 and #17.

Altogether, sixteen DIBH0 and 40 complete image sets from triple DIBH-CT sessions were available for the analysis.

Reproducibility of lung volume

Lung volume increased in DIBH by 60% (median; range 35–108%, $p < 0.0003$, Wilcoxon signed rank test) compared to FB. Variations in DIBH lung volume were small: 2.1% (0.3–4.6%) inter-fractionally and 1.1% (0.1–5.6%) intra-fractionally.