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FULL PAPER

Deep inspiration breath hold in locally advanced lung cancer radiotherapy: validation of intrafractional geometric uncertainties in the INHALE trial

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Objectives: Patients with locally advanced non-small cell lung cancer (NSCLC) were included in a prospective trial for radiotherapy in deep inspiration breath hold (DIBH). We evaluated DIBH compliance and target position reproducibility.

Methods: Voluntary, visually guided DIBHs were performed with optical tracking. Patients underwent three consecutive DIBH CT scans for radiotherapy planning. We evaluated the intrafractional uncertainties in the position of the peripheral tumour, lymph nodes and differential motion between them, enabling PTV margins calculation. Patients who underwent all DIBH imaging and had tumour position reproducibility <8 mm were up-front DIBH compliant. Patients who performed DIBHs throughout the treatment course were overall DIBH compliant. Clinical parameters and DIBH-related uncertainties were validated against our earlier pilot study.

Results: 69 of 88 included patients received definitive radiotherapy. 60/69 patients (87%) were up-front DIBH compliant. DIBH plan was not superior in seven patients and three lost DIBH ability during the treatment, leaving 50/69 patients (72%) overall DIBH compliant.
The systematic and random errors between consecutive DIBHs were small but differed from the pilot study findings. This led to slightly different PTV margins between the two studies.

Conclusions: DIBH compliance and reproducibility was high. Still, this validation study highlighted the necessity of designing PTV margins in larger, representative patient cohorts.

Advances in knowledge: We demonstrated high DIBH compliance in locally advanced NSCLC patients. DIBH does not eliminate but mitigates the target position uncertainty, which needs to be accounted for in treatment margins. Margin design should be based on data from larger representative patient groups.

INTRODUCTION

During deep inspiration breath hold (DIBH), the lungs are inflated, the heart position changes and the respiratory motion is mitigated compared with free breathing (FB). The major advantage of DIBH for lung cancer radiotherapy is the changed anatomy that enables dose reduction compared with FB through larger lung volume and increased distance between the tumour and the heart.[1–4] DIBH is a simple, cost-efficient technique that can be implemented without any detriment to other organs or to the target. DIBH is routinely used for patients with breast cancer[5–9] and mediastinal lymphoma.[10] Its use in locally advanced non-small cell lung cancer (NSCLC) has been limited. Studies reporting on lung radiotherapy in DIBH have included few patients, but have shown good patient compliance and dosimetric benefits.[3,11,12]

DIBH in modern radiotherapy is delivered either based on breathing volume, measured with spirometer, or based on optical surface tracking, with or without optical markers.[13]

For both methods, patient compliance is important for reproducible treatment delivery. Visual feedback of the patient's DIBH level improves the reproducibility.[6,14] Most studies on lung cancer radiotherapy in DIBH used spirometry-based devices,[3,11,12] except for a small cohort treated at our institution,[15] where surface tracking with an optical marker was used.

We previously evaluated geometric uncertainties in the position of the target in voluntary visually guided optical tracking-based DIBH for locally advanced NSCLC in a pilot study of 17 patients treated in FB, but extensively imaged in DIBH during their treatment course[16,17] and in 15 patients treated in DIBH or FB.[15] In both studies, the patient compliance to voluntary visually guided DIBH and geometric reproducibility of anatomical structures in DIBH were promising.

The purpose of the current work was to evaluate the patient compliance and geometric uncertainty in DIBH in a larger, less-selected cohort, treated prospectively in DIBH and hence validate the previously published data on geometric uncertainties.[16]

METHODS AND PATIENTS

Patients referred for radiotherapy for locally advanced NSCLC, aged >18 years and performance status ≤2, were candidates for the INHALE trial (ClinicalTrials.gov identifier NCT02540499), upon signing the informed consent. The inclusion period was May 2015 to December 2017.

Respiratory coaching and image acquisition

Prior to their PET/CT radiotherapy planning scan, the patients met for a 15-min DIBH coaching session. The DIBH level was individually set to a comfortable level, and the patients were trained to hold their breath for 20 s. The width of the gating window, corresponding to the DIBH level, was 2.5–3.0 mm. Respiratory motion was monitored with an optical surface tracking system (Real-time Position Management system, RPM^{TM}, Varian Medical Systems Inc., USA) from a marker placed at the xiphoid process. The chosen DIBH level and gating window width were provided to the patient through visual feedback during respiratory coaching, all imaging and treatment sessions, as described earlier.[6]

Patients were immobilised on a chest board (ConChest, Candor ApS, Denmark). As part of imaging for radiotherapy treatment planning, the patients underwent a whole body FDG PET/CT in FB, with the addition of a PET/CT in DIBH covering the tumour region, on the day of respiratory coaching. A day or two later the patients underwent a 4DCT and three consecutive CT scans in three consecutive visually guided DIBHs during the same scan session. All scans were acquired with the patient in the treatment position. All CT images were reconstructed with 2-mm plane separation and 0.98-mm pixel size.

Patient compliance

DIBH compliance was evaluated in several steps. First, patients were categorized as *up-front DIBH compliant*, if 1, they could hold three consecutive DIBHs of 20 s within the set DIBH level during the DIBH coaching session; 2, they performed all planned imaging in DIBH; and 3, the position variation of the tumour on consecutive DIBH CTs was <8 mm along any single axis, which was 50% more than the largest tumour position variation found in the pilot study.[16] All up-front DIBH compliant patients underwent comparative treatment planning with volumetric modulated arc therapy, delivering 66 Gy in 33 fractions. The patients proceeded with radiotherapy in DIBH, if the DIBH plan had at least 1 Gy lower mean dose to the heart and/or the lungs compared with the FB plan, but without detriment to the target. If the patient was treated in DIBH and able to perform DIBHs throughout the treatment course, the patient was categorized as *overall DIBH compliant*.

Reproducibility of DIBH and treatment margins

PTV margins need to include the geometric uncertainties in the position of the target structures: the peripheral tumour, the involved lymph nodes and the differential motion between the tumour and the nodes. If carina is used as a lymph nodes surrogate, the uncertainty in its position relative to the nodes needs to be included in margins as well.

We evaluated the intrafractional geometric uncertainties in DIBH from the reproducibility of the target structures between the three consecutive DIBH-CT scans: the first DIBH-CT was considered as reference and the second and the third DIBH-CTs were rigidly registered onto this first DIBH-CT as described below. The translations performed for each image registrations were considered as a difference between the scans.

In all patients, three sets of registrations were performed, based on the primary tumour (T), the mediastinal lymph nodes (N) and the carina. All registrations were performed by single observer in image registration platform within Aria (v.13.6, Varian Medical Systems Inc., USA). Fixed window/level settings were used for each registration: lung setting for T (HU range: −1000 to 0) and abdominal setting for N and carina (HU range: −125 to 250). The intraobserver and interobserver uncertainties of the manual registration process on the tumour and carina were <1 mm.[16]

The intrafractional uncertainties in the position of the T, N and carina were evaluated from the rigid registrations of the three DIBH-CTs, based on T, N and carina, respectively. The intrafractional differential motion between T and N was evaluated from the differences between the registrations on T and N. The uncertainty of carina as a surrogate for N (*i.e.,* differential motion between the N and carina) was evaluated from the differences between the registrations on carina and N.

The maximal deviation in the positions of T and N between the three DIBHs for each patient was compared with the patient's FB respiratory motion amplitude of T and N.

All intrafractional uncertainties were expressed in terms of group mean, systematic and random errors, enabling calculation of PTV according to van Herk,[18] which we—based on[19]—considered to be appropriate for low-density lung tissue:

$$margin_{PTV} = \alpha\Sigma + \beta\sigma - \beta\sigma_p$$

where Σ represents all systematic errors, σ represents all random errors and σ_p is the width of the penumbra. We anticipated daily image guidance with cone beam CT (CBCT) registered on the target.[20] Additional uncertainties, included in the margin calculation, were interfractional differential motion between T and N,[16] lack of 6D corrections,[21] image registration uncertainty[22] and penumbra width. All systematic and random errors were added in quadrature. For a 90% coverage of the CTV in 90% of patients, $\alpha = 2.5$ and $\beta = 1.28$.[23]

Clinical parameters, DIBH-related uncertainties and PTV margins from the INHALE trial were compared with the previously published pilot study.[16] Both descriptive and non-parametric statistics were applied. Association between variables was evaluated with Pearson correlation coefficient. A two-sided p-value < 0.05 was considered as level of significance.

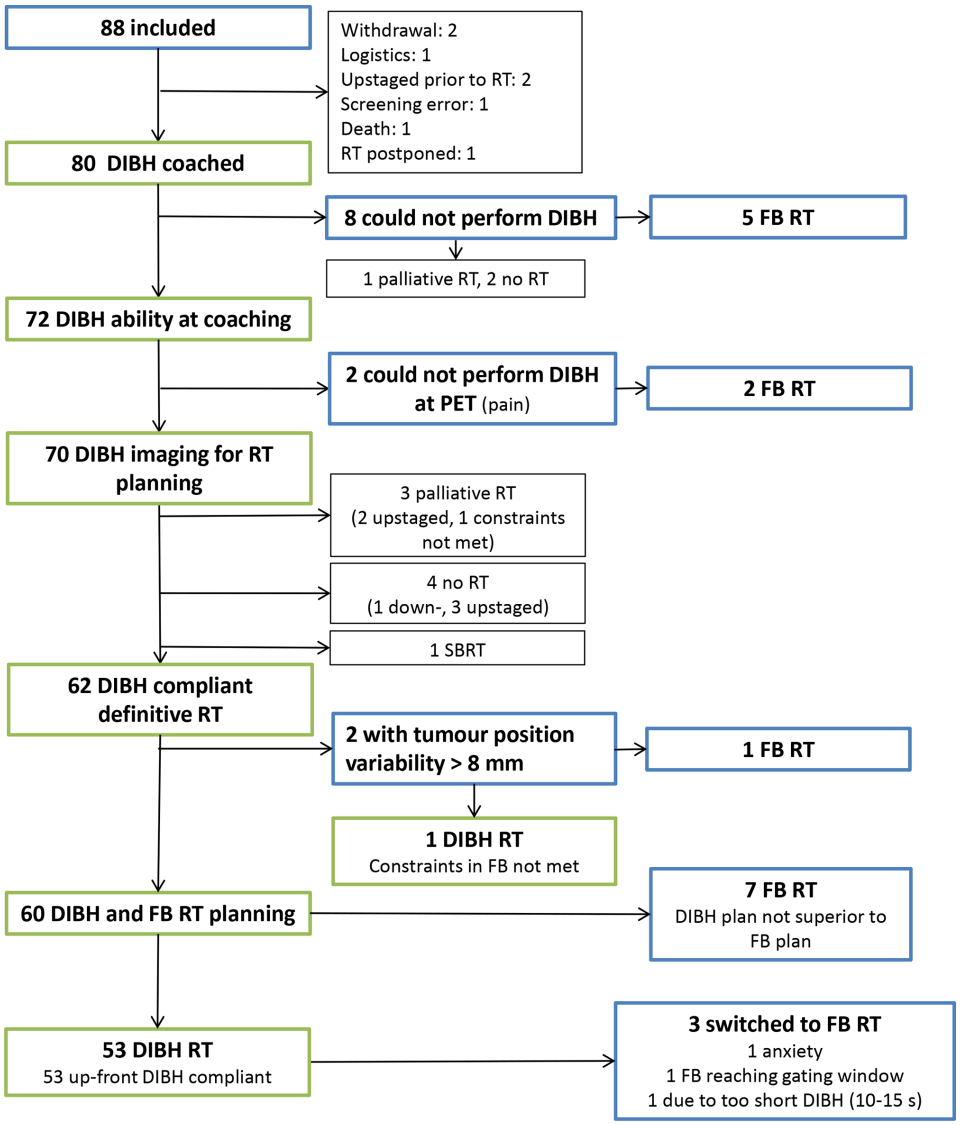
RESULTS

Patient compliance and clinical data

88 patients were included in the INHALE trial upon signing the informed consent (Figure 1). 80 patients attended the DIBH coaching session, scheduled 10–14 days after inclusion. 72 of 80 patients (90%) were able to perform DIBH of 20 s during the coaching session, six could only hold a shorter DIBH (5–15 s), one did not comprehend the instructions and in one the achieved DIBH level was only 2 mm above FB inspiration level and DIBH could therefore technically not be feasible for treatment with RPM™. 70 patients completed all imaging in FB and DIBH; the treatment intent was maintained in 62 of these patients (five were upstaged, two downstaged and one received palliative radiotherapy, since the risk organs constraints could not be met in either FB or DIBH) and in 69 of all patients.

In two patients, the tumour position between consecutive DIBH-CTs deviated >8 mm and they were categorized as

Figure 1. Flow chart of the INHALE trial



non-DIBH compliant, resulting in 60 out of 69 patients (87%) being *up-front DIBH compliant*. DIBH treatment plan was superior to FB plan in 53 patients, who proceeded with radiotherapy in DIBH. Three patients lost their DIBH compliance; this occurred during the first few treatment fractions. Hence, 50 of the 69 patients (72%) treated with definitive intent were *overall DIBH compliant*. In one of the patients with tumour position deviation >8 mm, the risk organs constraints in FB could not be met. This patient received radiotherapy in DIBH with an extended PTV margin to accommodate for the large intrafractional deviation of the target.

Median lung volume increased 55% in DIBH compared with FB (range 20–168%, $p < 0.001$, Wilcoxon signed-rank test). Clinical parameters are presented in Table 1.

Reproducibility of DIBH

Geometric uncertainties were evaluated based on data from 65 patients, *i.e.* all patients who underwent DIBH imaging and were not upstaged after the PET/CT findings. 14 patients had a peripheral tumour component only, 50 patients had both a peripheral tumour and involved lymph nodes and one patient had only central disease.

Median values of patients' maximal position deviations between the three DIBHs were 0.9 –1.3 mm for T and 0.8–1.3 mm for N (Table 2). Median FB amplitudes were 1.6–2.6 mm for T and 2.4–4.6 mm for N.

The extent of maximal deviations in the position of the tumour between the three DIBHs was weakly correlated with the extent of tumour's motion in FB in the same direction: $r = 0.26$ ($p < 0.05$) in left–right (LR), and $r = 0.32$ ($p < 0.02$) in anterio–posterior (AP) direction. After removing three influential outliers (using Cooks' distance on a residuals *vs* leverage plot), we found no correlation between the tumour position deviations in DIBH and tumour motion in FB in cranio–caudal (CC) direction ($r < 0.01$, $p = 0.95$). 64% of the tumours were adherent to the thoracic wall. We found no difference between the tumour motion in FB and whether the tumour was adherent to the thoracic wall or not ($p = 0.27$, Mann–Whitney U-test). For the nodes, there was no correlation ($p > 0.2$) between their maximal positional deviations in DIBH and FB motion (Supplementary Figure 1).

The positions of T, N and the carina were highly reproducible between the consecutive DIBHs, with median position deviations between the consecutive DIBHs within ±0.3 mm (Supplementary Figure 2)(Supplementary Figure 2). Depending on the direction, the position of T deviated ≤3 mm between the consecutive DIBHs in 89–91% of cases, the position of N deviated ≤3 mm in 90–96% of cases and the position of the carina deviated ≤3 mm in 85–99% of cases (Table 2).

Median differential motion between T and N was ≤0.1 mm, with 90–94% of deviations ≤ 3 mm, depending on direction. Median differential motion between N and carina was ≤0.1 mm, with 85–94% of deviations ≤ 3 mm. There was no correlation ($r = 0.13$, $p = 0.36$) between the uncertainty of using the carina as a surrogate for N and the distance between carina and N (distances ranged from 0–72 mm).

For all the structures and differential motion, deviations > 3 mm were most frequent in the CC direction.

The correlations of the position deviations between T, N and carina between the consecutive DIBHs were statistically significant ($p < 0.001$), with highest correlation between them all in the CC direction (r: 0.77–0.78) and between N and carina in all directions (r: 0.75–0.80). Details on Figure 2.

PTV margin calculation

The evaluation of systematic and random uncertainties was based on data from 63 patients, *i.e.* excluding the two patients with tumour deviation ≥8 mm, since they were not DIBH compliant.

Group mean, systematic and random errors are shown in Table 3. All group mean values were ≤0.4 mm, and systematic and random errors were <1.4 mm. The resulting PTV margins were 4.1–5.6 mm for a simple target, with either peripheral or mediastinal tumour component alone. For complex targets, with both a peripheral tumour and mediastinal lymph nodes, the margins depended on the image guidance strategy. If daily CBCT was registered on the peripheral tumour, margins for the nodes also included the differential motion between them and were 8.0–11.5 mm. If the CBCT was registered on the lymph nodes, the uncertainty due to the differential motion was instead added to the margins for the peripheral tumour, which were 7.4–10.8 mm. Details are presented in Table 4, along with margins calculated based on results from the pilot study.[16]

DISCUSSION

We evaluated DIBH compliance and geometric uncertainties in visually guided optical tracking-based DIBH radiotherapy for locally advanced NSCLC, in a larger cohort of patients treated in a prospective trial. The results confirmed that for a majority of patients, the position of the peripheral tumour, the involved lymph nodes and the carina was highly reproducible (median differences ≤ 1.3 mm) between the consecutive DIBHs.

The DIBH compliance was high, 87% of the patients were up-front DIBH compliant and 72% overall DIBH compliant. Including the patients, in which the plan in DIBH was dosimetrically equal with the FB plan, the overall DIBH compliance could potentially increase to 78%. This is at the lower edge of DIBH compliance found in other studies. With the exception of the French STIC 2003 study,[3] all other studies were small with <20 patients[12,16,25–28] and as such potentially biased in patient selection. Our experience during patient accrual for the pilot study[16] was that ~10% of the patients, who declined study participations did so due to self-reported lack of ability to perform DIBH; therefore, there was a risk of a biased cohort in terms of patient compliance. In the pilot study, all 17 patients were categorized as up-front compliant and one patient lost compliance during the study period (6%).[16]

Table 1. Clinical patient data

	INHALE	Pilot study	*p*-value
Number of evaluable patients	72	17	
Lung volume increase in DIBH relative to FB (median, (range))*	55% (20–168%)	60% (35–108%)	0.43[a]
Gender	M: 38 (52.8%)	M: 6 (35.3%)	0.30[b]
	F: 34 (47.2%)	F: 11 (64.7%)	
Smoking status	Current: 18 (25.0%)	Current: 8 (47.1%)	0.33[c]
	Former: 49 (68.0%)	Former: 9 (52.9%)	
	Never: 3 (4.2%)	Never: 0 (0.0%)	
	Unknown: 2 (2.8%)		
Smoking status in pack years (median, (range))	Current: 40 (0.5–100)	Current: 47.5 (15–70)	0.70 [a]
	Former: 40 (26–80)	Former: 40 (10–70)	
	Unknown: 2		
Age (median, (range))	66 (49–85)	67 (45–79)	0.85[a]
Performance status**	PS 0: 32 (44.4%)	PS 0: 7 (41.2 %)	0.83[c]
	PS 1: 39 (54.2%)	PS 1: 10 (58.8 %)	
	PS 2: 1 (1.4%)	PS 2: 0 (0 %)	
FEV1(%) (median, (range))	78 (36–127)	67 (44–100)	**0.046**[a]
Stage***	IA: 1 (1.4%)	IA: 0 (0.0 %)	0.13[c]
	IB: 0 (0.0 %)	IB: 0 (0.0 %)	
	IIA: 2 (2.8 %)	IIA: 2 (11.8%)	
	IIB: 5 (6.9%)	IIB: 0 (0.0 %)	
	IIIA: 30 (41.7 %)	IIIA: 3 (17.6%)	
	IIIB: 31 (43.0%)	IIIB: 11 (64.7%)	
	IV: 3 (4.2%)	IV: 1 (5.9%)	
Histology	SCC: 26 (36.1%)	SCC: 8 (47.1%)	0.22[b]
	Adeno: 45 (62.5%)	Adeno: 8 (47.1%)	
	Both: 1 (1.4%)	Other: 1 (5.9%)	
GTV volume [ml](median, (range))	65.5 (4.1–388.9)	71.3 (32.6–749.2)	0.37[a]
Tumour site****	RUL: 27 (37.5%)	RUL: 7 (41.2%)	**0.03** [c]
	RML: 5 (6.9%)	RML: 1 (5.9%)	
	RLL: 5 (6.9%)	RLL: 0 (0.0%)	
	LUL: 29 (40.3%)	LUL: 3 (17.6%)	
	LLL: 4 (5.6%)	LLL: 4 (23.5%)	
	Central: 4 (5.6%)	Central: 4 (23.5%)	
Chemotherapy regime	Cis/vino: 40 (58.0%)	Data not available	
	Carbo/vino: 23 (33.3%)		
	None: 4 (5.8%)		
	Unknown: 2 (2.9%)		

(Continued)

Table 1. (Continued)

DIBH, deep inspiration breath hold; F, female; FB, free breathing; FEV1, forced expired volume in the first second; LLL, left lower lobe; LUL, left upper lobe; M, male; PS, performance status; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; SCC, squamous cell carcinoma; adeno, adenocarcinoma.
Clinical patient data from patients participating in INHALE and in the pilot study [16]. For INHALE, it is the data from the 72 patients, which were not upstaged after the PET/CT; i.e. patients, where the curative treatment intent could be maintained as planned (69 patients), the two downstages patients treated with either surgery or stereotactic body radiotherapy and the one patient, treated with semi-palliation due to failure of meeting risk organs constraints. For the pilot study, it is the data from all 17 included patients.
[a]Mann–wilWhitney test
[b]Chi-squared contingency table
[c]Fischer exact probability test
[d]patients, who were imaged in DIBH (65 in INHALE, 17 in pilot study)
[e]according to Eastern Cooperative Oncology Group (ECOG) scale of performance
[f]according to union for International Cancer Control (UICC) TNM classification, seventh edition
[g]sum of locations: 74 in INHALE (two patients had tumours extending in RUL and RML), 18 in pilot study (one patient had tumour extending in both left lobes)

As opposed to other studies evaluating DIBH compliance in patients with locally advanced NSCLC, we included several levels of DIBH compliance, and only treated patients in DIBH, who had a dosimetric benefit of DIBH, and the variation of the tumour position between consecutive DIBHs was within prespecified limits. Only 2/65 patients (3%) exceeded these limits. These two patients also had substantial FB tumour motion and lower lobe tumours. In FB, tumours close to the diaphragm tend to move more than tumours in other locations.[29] Median FB tumour motion for INHALE patients with lower lobe tumours was 9.5 mm in CC direction; one of these patients also had substantial deviations in tumour position between the DIBHs (7.6 mm in CC direction), while in all other lower lobe tumours, their position deviated <2 mm. We found no apparent correlation between FB tumour motion and its position deviation within consecutive DIBHs in the CC direction and only weak correlation in the AP and LR directions. Since very few patients (6/65) had extreme FB tumour motion (>10 mm), any general conclusion should be taken with caution.

Acquiring several CT scans in consecutive DIBHs as part of the treatment planning is therefore advisable to evaluate the tumour variation between the DIBHs in each patient.

The carina, often used as a surrogate for mediastinal lymph nodes position,[16,24,30] was stable within the consecutive DIBHs. The small differential motion relative to the nodes supports carina's suitability as a surrogate for the nodes in daily image guidance. However, the residual uncertainty between the position of the carina and the lymph nodes needs to be included in the PTV margins.

The intrafractional differential motion between N and T exceeded 3 mm in 8% of patients; this is comparable to 13% in

Table 2. Maximal deviations in the positions of anatomical structures between the three deep inspiration breath-hold CTs

	X [mm] – LR			Y [mm] – AP			Z [mm] – CC		
	median (range)			median (range)			median (range)		
	% deviations < a threshold			*% deviations < a threshold*			*% deviations < a threshold*		
	≤2 mm	≤3 mm	≤5 mm	≤2 mm	≤3 mm	≤5 mm	≤2 mm	≤3 mm	≤5 mm
Tumour	0.9 (0–7.2)			1.3 (0–7.7)			1.0 (0–14.3)		
	87.5	*90.6*	*98.4*	*76.6*	*89.1*	*93.8*	*79.7*	*89.1*	*93.8*
Lymph nodes	0.8 (0–5.4)			1.3 (0–5.7)			1.1 (0–9.1)		
	92.0	*96.0*	*98.0*	*80.0*	*94.0*	*94.0*	*70.0*	*90.0*	*94.0*
Carina	0.7 (0–3.7)			1.2 (0–4.2)			1.5 (0–7.2)		
	92.3	*96.9*	*100*	*90.8*	*98.5*	*100*	*63.1*	*84.6*	*96.0*
Differential motion: T *vs* N	0.7 (0.1–7.6)			1.2 (0.2–4.9)			1.1 (0–7.1)		
	85.5	*92.3*	*98.1*	*76.9*	*94.2*	*100*	*73.1*	*90.4*	*96.2*
Differential motion: N *vs* C	0.7 (0–5.7)			0.9 (0–6.2)			1.2 (0–8.8)		
	92.5	*94.0*	*98.5*	*82.1*	*92.5*	*98.5*	*74.6*	*85.1*	*91.0*

AP, anterior–posterior; CC, cranio–caudal; LR, left–right; N, lymph nodes; T, peripheral tumour.

Figure 2. Differential motion between different structures on consecutive DIBHs. The lines represent the linear fit between the variables. Notice longer axes lengths for data presented in cranio–caudal direction. T-peripheral tumour, N-lymph nodes, L-R-left–right, A-P- anterio–posterior and C-C-cranio–caudal.

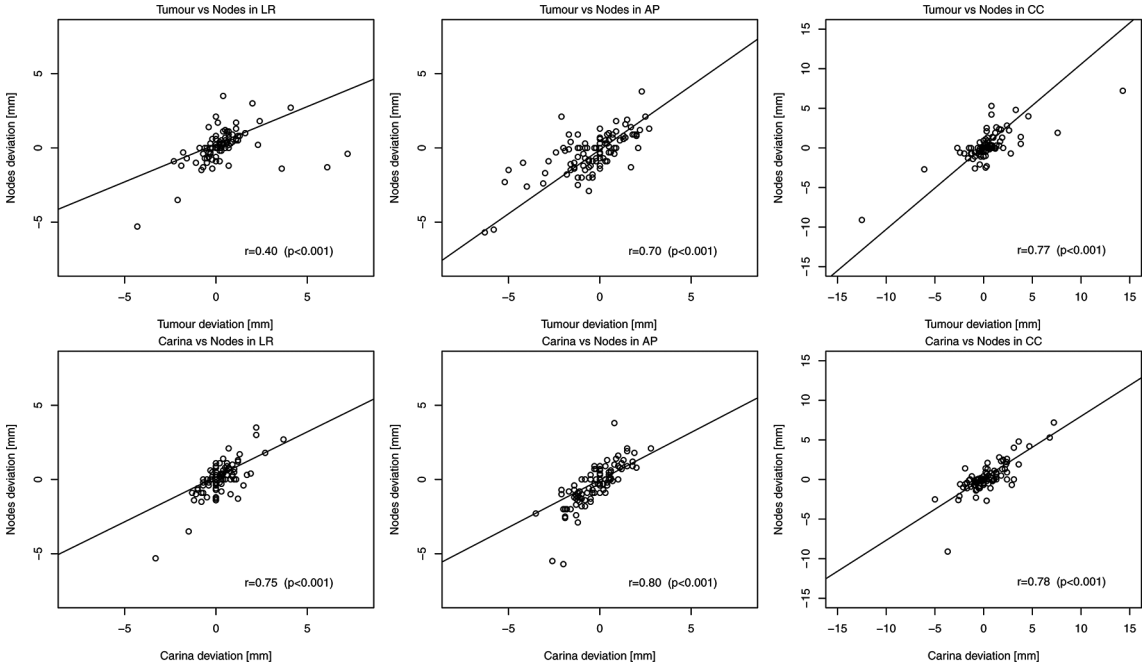


Table 3. Group mean, systematic and random errors

		X [mm] – LR	Y [mm] – AP	Z [mm] – CC
Uncertainty in T	M	0.1	−0.3	0.4
	Σ	1.3	1.2	1.1
	δ	0.9	1	1
Uncertainty in N	M	0.1	−0.3	0.3
	Σ	1	1.1	1.2
	δ	0.7	0.9	1
Uncertainty in C	M	0.2	−0.2	0.3
	Σ	0.8	0.9	1.4
	δ	0.6	0.7	1.2
Differential motion: T *vs* N	M	0.1	−0.1	0.2
	Σ	1.2	1	1.2
	δ	0.9	0.9	1
Differential motion: T *vs* C	M	0	−0.1	0
	Σ	0.9	1	1.4
	δ	0.7	0.8	1.1
Differential motion: C *vs* N	M	0.1	0.1	0
	Σ	0.6	0.6	0.9
	δ	0.5	0.6	0.8

Σ, systematic error; δ, random error; AP, anterior–posterior; C, carina; CC, cranio–caudal; LR, left–right; M, group mean; N, lymph nodes; T, peripheral tumour.

Table 4. Margins, depending on tumour location and image-guided radiotherapy strategy

	INHALE			Pilot studya		
PTV marginsa	X [mm] – LR	Y[mm] - AP	Z [mm] - CC	X [mm] - LR	Y[mm] - AP	Z [mm] - CC
T – T site only	4.2	5.2	4.2	2.9	4.7	3.6
N – N site only	4.1	5.6	4.8	5.6	6.8	6.0
T – *T* + N site (IGRT on N)	10.8	7.4	10.1	9.9	6.6	9.7
N – *T* + N site (IGRT on N)	4.1	5.6	4.8	5.6	6.8	6.0
T – *T* + N site (IGRT on T)	4.2	5.2	4.2	2.9	4.7	3.6
N – *T* + N site (IGRT on T)	11.5	8.0	11.2	11.8	8.5	11.7

[a]In the pilot study,[16,17] margins for the N site were based on carina registration and included the differential motion between carina and the nodes, as evaluated by Schaake et al.[24] The pilot study-based margins presented here differ slightly from previously published values,[16,17] since we added the additional uncertainty of the image registration process,[21] which was not available at the time of the original publication.

spirometry-assisted DIBH.[11] Compared with spirometry-assisted DIBH, based on 17 patients,[11] the systematic error due to differential motion was doubled, the random error was equal in LR and AP and halved in CC. Still, all these errors were <1.2 mm.

There were two clinical parameters, which differed significantly between the INHALE and the pilot study patient Groups[16]: tumour site, where central and left lower lobe tumours were over-represented in the pilot study group (p = 0.03), and forced expired volume in 1 s (FEV1%), which was higher in the INHALE group (78% *vs* 67%, p = 0.046).

The systematic and random errors in the position of the peripheral tumour differed sub mm between the two cohorts, and the resulting margins were within the same order of magnitude. Margins, based on the INHALE patients, were 0.4 –1.3 mm larger for T, depending on direction and image guidance strategy. For N, INHALE-based margins were 1.2–1.5 mm smaller, if CBCT was registered on N and 0.3–0.5 mm smaller for complex targets, where CBCT was registered on T. The difference in margins for N may be partly due to use of carina as a surrogate for N in the pilot study, combined with literature-based data for the uncertainty of carina as surrogate for N in FB radiotherapy.[24] While margin differences may seem minor, they still emphasize the necessity of choosing representative, not too small patient cohorts, when evaluating uncertainties for margin design. This would particularly be important, if patients with larger variation in tumour position were treated in DIBH.

One of the drawbacks of our study is that we evaluated the intrafractional geometric uncertainties based on three consecutive DIBHs only, while it typically takes 7–9 DIBHs of 20 s to deliver a treatment fraction: three for acquisition of the DIBH CBCT for image guidance,[22] and 4–6 for delivery of two partial or full volumetric modulated arc therapy. However, we have earlier evaluated the intrafractional uncertainty in DIBH from the pretreatment CBCT and post-treatment fluoroscopy, with the 4–6 DIBHs needed for the treatment in between, and showed very high intrafractional DIBH stability, with no target position differences exceeding 4 mm.[15] Similarly, Ottosson et al[28] evaluated the intrafractional DIBH reproducibility from pretreatment and post-treatment CBCTs and demonstrated that 85% of intrafractional differences were within 2 mm for a single direction. Median 3D differences were 2.8 mm, which is larger than ~1.5 mm we observed. The patients in their study were treated in FB and trained to a higher DIBH (median 85% lung volume increase), which was challenging to reproduce throughout the treatment course.[28] We recommend a more moderate and comfortable DIBH level to increase reproducibility and avoid bending of the back.

Another drawback of our study may be that we only evaluated DIBH reproducibility during imaging for treatment planning. Interfractional changes in the position of the target relative to the bones are corrected for daily with the CBCT registered on the target.[20] Other studies have not shown any trend in intrafractional reproducibility of the tumour during the DIBH treatment course.[16,26] The interfractional differential motion between the peripheral tumour and the lymph nodes needs to be accounted for in the margins.[16,24] During the ~7 weeks of radiotherapy, anatomical changes will occur, both as tumour shrinkage, but also changes in the normal tissue, like pleural effusion and atelectasis. These anatomical changes can have an impact on the position of the target, in FB[31] as in DIBH,[11] but will be intercepted by the use of adaptive strategies in modern radiotherapy for locally advanced NSCLC.

CONCLUSION

We showed high overall DIBH compliance (>75%) in a larger unselected cohort of patients with locally advanced NSCLC. Position of the peripheral tumour, the lymph nodes and differential motion between them was reproducible in consecutive DIBHs; however, the residual uncertainties need to be included in the PTV margins.

PTV margins for DIBH radiotherapy for locally advanced NSCLC remained within the same magnitude after analysing the INHALE data compared with the earlier pilot study.

CONFLICT OF INTEREST STATEMENT

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