

Visually guided inspiration breath-hold facilitated with nasal high flow therapy in locally advanced lung cancer

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ABSTRACT

Background and purpose: Reducing breathing motion in radiotherapy (RT) is an attractive strategy to reduce margins and better spare normal tissues. The objective of this prospective study (NCT03729661) was to investigate the feasibility of irradiation of non-small cell lung cancer (NSCLC) with visually guided moderate deep inspiration breath-hold (IBH) using nasal high-flow therapy (NHFT).

Material and methods: Locally advanced NSCLC patients undergoing photon RT were given NHFT with heated humidified air (flow: 40 L/min with 80% oxygen) through a nasal cannula. IBH was monitored by optical surface tracking (OST) with visual feedback. At a training session, patients had to hold their breath as long as possible, without and with NHFT. For the daily cone beam CT (CBCT) and RT treatment in IBH, patients were instructed to keep their BH as long as it felt comfortable. OST was used to analyze stability and reproducibility of the BH, and CBCT to analyze daily tumor position. Subjective tolerance was measured with a questionnaire at 3 time points.

Results: Of 10 included patients, 9 were treated with RT. Seven (78%) completed the treatment with NHFT as planned. At the training session, the mean BH length without NHFT was 39 s (range 15–86 s), and with NHFT 78 s (range 29–223 s) ($p = .005$). NHFT prolonged the BH duration by a mean factor of 2.1 (range 1.1–3.9s). The mean overall stability and reproducibility were within 1 mm. Subjective tolerance was very good with the majority of patients having no or minor discomfort caused by the devices. The mean inter-fraction tumor position variability was 1.8 mm (-1.1–8.1 mm; SD 2.4 mm).

Conclusion: NHFT for RT treatment of NSCLC in BH is feasible, well tolerated and significantly increases the breath-hold duration. Visually guided BH with OST is stable and reproducible. We therefore consider this an attractive patient-friendly approach to treat lung cancer patients with RT in BH.

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Background and purpose

Due to breathing, lung tumors and surrounding organs move, and this may pose a challenge for radiotherapy (RT) treatments. Methods taking motion into account, such as internal target volume (ITV) or midventilation/midposition approaches using a 4D-CT may result in larger margins, potentially leading to higher normal tissue doses and toxicity [1]. Breath-holding is an attractive strategy to minimize movements during RT as this may lead to a more reliable target coverage with smaller margins, and together with the larger lung volumes with lower densities, IBH may decrease the normal lung tissue doses and toxicity, and in some cases allows for curative treatment of larger lung tumors without exceeding dose-constraints [2–4]. In addition, proton RT might benefit from IBH, as anatomical shifts caused by breathing can lead to severe over- and underdosage [5].

However, the lung function of lung cancer patients may be impaired (e.g. because of chronic obstructive pulmonary disease (COPD), or as a direct result of the disease), making it potentially difficult to treat them in IBH. Techniques supporting IBH might make it a feasible approach for those with a less favorable performance status.

A widely used technique for BH assistance is active breathing control (ABC), but BH durations are usually rather low, around 20 s [6–8]. A second example is high frequency percussive ventilation (HFPV) that administers small volumes of air at high pressure and frequency resulting in prolonged BHs of 5–10 min [9], but this device requires trained personnel, and evidence for safety is very little so far. Parkes *et al.* used a simple mechanical ventilator where pre-oxygenation was administered with mechanically induced hypocapnia through a facemask [10]. The mean BH duration in 30 volunteers was 6 min [11], but a substantial blood pressure rise

was seen and therefore caution has to be taken in patients with cardiovascular comorbidity [12].

In this study, we investigated the use of nasal high-flow therapy (NHFT), a simple noninvasive system, providing controlled oxygen concentrations and low levels of positive pressure *via* a nasal cannula (Fisher&Paykel Healthcare Ltd, Auckland, New Zealand) [13]. A nasal cannula might be more patient-friendly compared to a mouthpiece or facemask used in the previously mentioned methods [9–12]. NHFT is increasingly used as ventilatory support and improves oxygenation in diverse patient groups. It was shown to be safe in the home setting and in several clinical situations and patient populations, such as in neonatal and pediatric intensive care, in COPD patients, and in apneic conditions under general anesthesia [14–16]. This device has however, to the best of our knowledge, never been used in the context of BH-support in RT. We hypothesized that supporting BH with NHFT will allow robust RT treatments of moving targets in a broad patient population allowing BHs that are longer, stable and reproducible during a whole treatment course, and will be well tolerated by the patients.

Material and methods

Patients

In this prospective study (NCT03729661), non-small cell lung cancer (NSCLC) patients with locally advanced stage III or oligometastatic disease treated with radical intent RT were included. Exclusion criteria were performance status WHO >2, hypercapnic COPD patient ($=\text{PaCO}_2 > 45 \text{ mmHg}$). The institutional ethics committee approved the study.

Preparation

After having signed informed consent, a training session of 45 min was planned to familiarize the patients with the devices, define the voluntary BH level and test the maximal duration of a BH without and with NHFT (Figure 1(A)). NHFT was administered with Optiflow™ nasal high flow therapy using the AIRVO device (Fisher&Paykel). This noninvasive system administers low levels of positive pressure *via* a nasal cannula. We administered the airflow at a volume of 40 L/min with 80% of oxygen, at a temperature of 34 °C. Patients were immobilized supine in treatment position on a chest board (MacroMedics®, Waddinxveen, The Netherlands) with the arms above the head. They were instructed to breathe in and hold their breath to a level that felt comfortable. The chosen moderate IBH level was provided to the patient through visual feedback with virtual reality (VR) goggles using an OST system installed in the CT (Sentinel from C-RAD®, Uppsala, Sweden) and treatment room (Catalyst HD from C-RAD®). The BH level was measured with OST at the xiphoid process. The width of the BH gating window, corresponding to the IBH level, was set at 3 mm. Patients performed at least two voluntary BHs without NHFT, followed by at least two BHs with NHFT, with the instruction to hold the breath as long as possible (Figure 1(A)). After every BH,

patients indicated when they were ready for the next BH, and after start of NHFT there was at least one minute of rest before starting BH. After training session, two planning CT-scans were performed, one in BH with NHFT, and one 4D-FDG-PET/CT scan in free breathing (FB). The first was used for planning the treatment with NHFT, the latter to create a back-up plan if needed. Throughout all sessions (training and treatment), a transcutaneous CO₂-meter (TCM4® from Radiometer) with ear sensor was used to continuously monitor transcutaneous carbon dioxide tension (tcpCO_2), oxygen saturation (SpO_2) and heart rate (HR).

For each patient, the predicted forced expiratory volume in 1 s (FEV1) was obtained with spirometry in upright sitting position.

Treatment planning

The prescribed RT dose was 60 Gy in 2 Gy fractions for concurrent chemoradiation, and 57.75–66 Gy in 2.75 Gy for sequential chemoradiation or RT alone. The planning target volume (PTV) margin in the BH plan with NHFT was 8 mm for the primary tumor, and 5 mm for lymph nodes. For the back-up plan in FB individual PTV-margins for the primary tumor were calculated based on the 4D-CT, and were on average 8.3, 9.1 and 8.3 mm in left-right (LR), cranio-caudal (CC) and anterior-posterior (AP) directions respectively [1]. Treatment techniques consisted of volumetric modulated arc therapy or a hybrid technique with AP-PA beams and arcs (using Eclipse TPS version 15.5), which were delivered with a linear accelerator (Truebeam, Millenium™ 120-leaf MLC, Varian, Palo Alto, USA).

Treatment

Patients were imaged and treated in IBH, supported by NHFT, with visual feedback from OST system using VR goggles. An IBH cone-beam CT (CBCT) was used for daily image guidance with registration based on carina or bones at the discretion of the treating radiation-oncologist. In contrast to the training session, for the treatment, patients were instructed to hold their breath for the time it felt comfortable and stable.

The imaging or treatment beam was interrupted as soon as the BH level moved outside the 3 mm tolerance window, which was done mainly manually for the first 5, and automatically for the last 4 patients when this interface between linac and OST became available.

The number of BHs needed per session was recorded. The thoracic surface was monitored continuously by the OST system and compared with an initially acquired reference surface using a surface threshold of 12 mm. A new baseline was taken at the beginning of each fraction and the gating window was automatically set at a relative distance from this baseline by the Catalyst software. After couch translations an update of the actual live image may be necessary. Also the isocenter position and reference surface (body contour) were retrieved from the DICOM-RT plan and structure files. The Catalyst software predicted the isocenter position

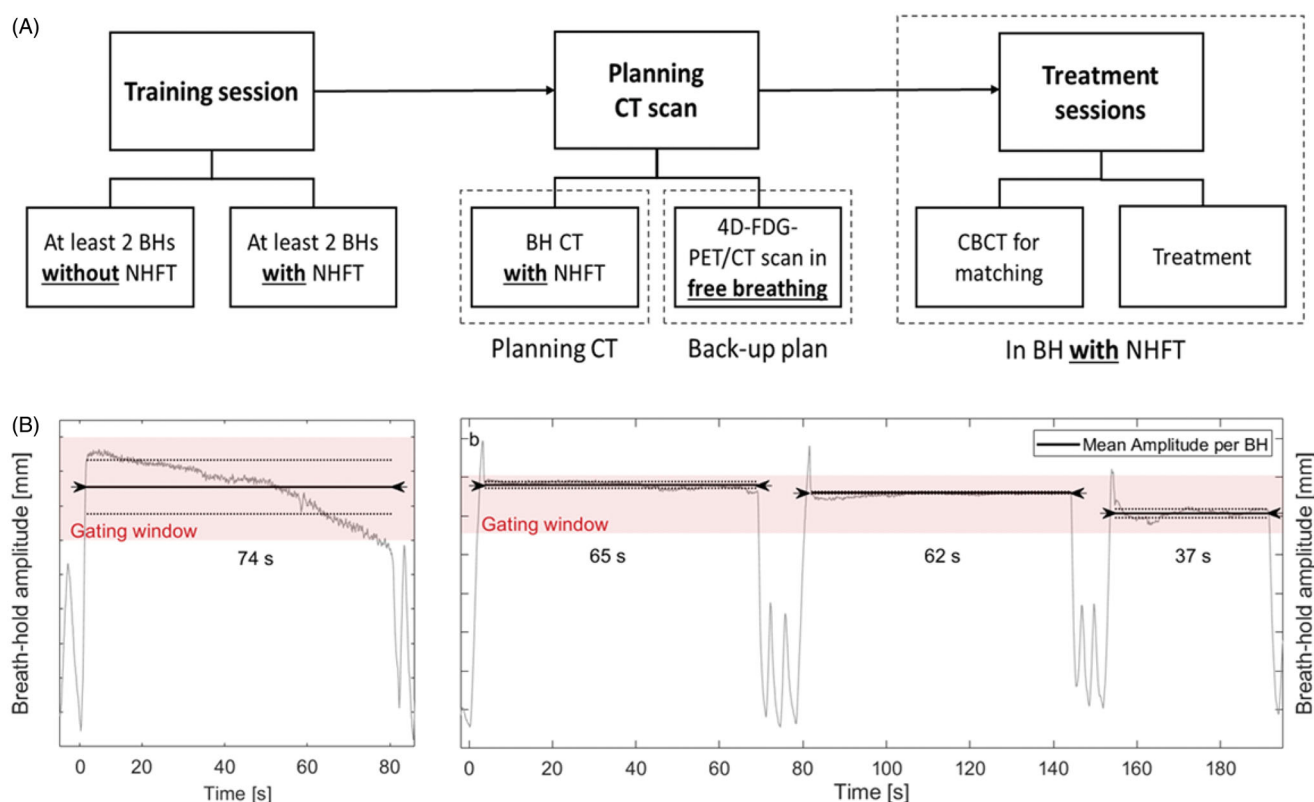


Figure 1. (A) Flow chart of the study. (B) Examples of BHs in two patients where the BH signal, monitored by the OST system is represented by the gray line. The pink area shows the gating window of 3 mm. The black line indicates the level of the mean amplitude per BH, and the dotted line is the \pm SD. The arrows on the black line show the BH length (x-axis). The beginning and end of each BH were defined manually. Overshoots at the beginning of a BH as seen in (B), were excluded, and the signal was included from the local minimum on. The graph on the left shows an example of an unstable BH, but with the signal still within the gating window. The second patient on the right has three very stable BHs with small intra-BH SD. The change in level of the black line between BHs represents the reproducibility. BH: breath-hold; CBCT: cone-beam CT; NHFT: nasal high-flow therapy.

instantaneously based on the live surface and was calculated and visualized using a threshold tolerance of 5 mm for potential isocenter shifts.

Analyses

The primary endpoint was feasibility of the treatment, defined as the proportion of patients able to complete the whole treatment (CT-scan and treatment sessions) in BH with NHFT. Sample size calculation is based on the approach for a single stage phase II clinical trial, where the aim is to determine a confidence interval (CI) around the primary endpoint that excludes the threshold for poor feasibility while containing the aim for good feasibility [17]. The poor feasibility threshold is set at 33% while 75% would constitute good feasibility. Inclusion of 9 patients is sufficient for this purpose. If 6 or more patients complete the treatment successfully, the lower border of the 95% CI (from alpha 0.05) will exclude 0.33, showing a feasible treatment. If less than 6 patients complete the treatment successfully, the upper border of the 80% CI (from power 0.80) will exclude 0.75, making the treatment not feasible. Taking into account a dropout of 10%, the sample size was defined at 10 patients. Reasons for failure resulting in stopping of the treatment with NHFT may be subjective intolerance of NHFT, unable to perform a BH, unstable BH, unreproducible BH, or patient refusing further treatment with NHFT.

Secondary endpoints were subjective tolerance, increase in maximal BH length during training session, stability and reproducibility of BH, and daily BH-depth. Subjective tolerance was measured at 3 time points (after training session, first and last treatment fraction) using a questionnaire with 6 items to be scored on a 5-point scale from 0 (no discomfort) to 5 (maximal discomfort): general discomfort, discomfort from nasal cannula, goggles, ear clip, dry throat or BH. Differences in BH length during the training session were calculated with a Wilcoxon Signed Rank Test, with a p -value ≤ 0.05 considered significant. The correlation of FEV1 with BH length was calculated with the Spearman's rank correlation coefficient.

The stability (or intra-BH variability) and reproducibility (or inter-BH variability) were calculated using OST. For stability, first the standard deviation (SD) of the amplitude of each BH was calculated, and this was averaged over all BHs per patient. For the reproducibility, the mean amplitude of each BH was first calculated, and for each patient the SD was then calculated over all BHs (Figure 1(B)). For overall stability and reproducibility, these results were averaged over all patients. BHs for imaging and treatment were analyzed together.

Differences in total lung volumes between planning FB-CT (represented by the 50% exhale phase of the 4D-CT) and IBH-CT were analyzed using a Wilcoxon Signed Rank Test.

To analyze the interfractional differences in daily BH depth we used an AP distance as a surrogate because the

Table 1. Patients' characteristics.

	N = 10
Mean age (years) (range)	67 (60–74)
Gender	
Male	6
Female	4
WHO performance status	
0	3
1	5
2	2
Stage (TNM 8)	
Stage IIIA	3
Stage IIIB	3
Stage IIIC	2
Stage IVA	1
Stage IVb	1
Primary tumor location	
Upper lobe	8
Middle lobe	0
Lower lobe	2
FEV1 (%pred): mean (range)	66 (24–94)
Smoking status	
Never smoker	0
Former smoker	6
Active smoker	4
Treatment (n = 9) ^a	
Concurrent chemoradiotherapy	6
Sequential chemoradiotherapy	2
Radiotherapy alone	1
Lung volume (n = 9) ^a	
Free breathing (L) (mean) (range)	4.1 (2.1–5.7)
Breath hold (L) (mean) (range)	6.1 (4.1–8.0)
Relative increase (%) (mean) (range)	150 (114–200)

FEV1: Forced expiratory volume in 1 s.

^a1 patient was upstaged to stage IVc at planningCT and was not treated with RT.

lungs are not fully imaged on the daily CBCT due to the limited field-of-view. This daily AP distance was obtained by doing a 3D CBCT-CT match both on the spine and on the sternum, and subtracting the resulting AP numbers from each other. Finally, the daily positions of the primary tumor were analyzed by measuring the displacement vector of the primary tumor relative to the matching structure (carina or bones). For this study, all CBCT matches were re-done offline.

Results

Patients' characteristics & feasibility

Between March and December 2019, 10 NSCLC patients signed informed consent, but one was excluded after training session due to diagnosis of diffuse metastases on the planningCT. Table 1 shows patients' characteristics. Seven out of 9 patients (78%) completed the whole treatment with NHFT as planned. The remaining two (22%) (patients 1 and 5) asked for a FB treatment with the backup plan for 2 and 3 fractions, at a dose of 40 Gy and 54 Gy, respectively, because of worsened condition due to chemoradiotherapy side effects.

BH length

During training session, the mean BH length without NHFT was 39 s (range 15–86 s;SD 21 s), and significantly increased with NHFT to 78 s (range 29–223 s;SD 57 s) ($p = .005$) (Figure

2). The BH duration increased by a mean factor of 2.1 (range 1.1–3.9; SD 0.9) with NHFT. Two out of 10 patients (20%) were able to perform a BH of >90 s, and 5 (50%) performed a BH of >60 s with NHFT (Figure 2). The boxplots in Figure 2 represent the maximal BH length per session, and it shows that despite the different BH instructions, most patients can reproduce the BH length of the training session during treatment. The overall mean maximal BH length during treatment was 65 s (range 36–107 s;SD 25 s) (Figure 2). FEV1 did not correlate with BH length, both without and with NHFT (correlation coefficients: 0.2 and 0.1, respectively) (Figure 2).

The mean number of BHs needed to perform one CBCT was 1.7 (range 1.2–2.5) and to deliver RT 3.7 (range 2.2–6.1). The mean beam-on time per fraction was 3.0 min (range 2.2–4.6 min). Individual patient data is shown in Supplementary file B.

Stability and reproducibility

Stability and reproducibility of all patients are represented in Figure 3. The mean and median overall stability were 0.34 mm and 0.33 mm respectively, range 0.17–0.49 mm. The mean and median overall reproducibility were 0.43 mm and 0.45 mm respectively, range 0.17–0.68 mm.

The average of the mean displacement vector of the primary tumor relative to the matching structure per patient was 1.8 mm (range –1.1–8.1 mm;SD 2.4 mm) (Figure 4(A)). These differences were ≤ 8 mm (which is the PTV margin for the primary tumor), except for patient 1 who had an outlier of 10 mm, and patient 6 where differences up to 32 mm were seen due to atelectasis disappearance. Replanning resulted in small differences for the rest of the treatment.

The mean lung volume increased significantly from 4.1 L in FB to 6.1 L with BH ($p = .008$), with a relative increase of on average 150% (Table 1).

The interfractional difference in BH depth, based on the mean differences in AP match results (spine and sternum) per patient between planning CT and daily CBCT, was on average 1.2 mm (range: –1.6–4.2 mm;SD 1.4 mm) (Figure 4(B)).

Subjective tolerance

Overall, the subjective tolerance to the treatment was excellent (Supplementary file A). The majority of patients had no (score 0) or minor (score 1–2) discomfort throughout the treatment. Only two patients scored discomfort 3 at training session (because of the goggles, or a dry throat), and none had a score of 4 or 5.

Physiological parameters

The average of the mean tcpCO₂ per patient was 34 mmHg (SD 3 mmHg;range 27–38 mmHg). The mean change in tcpCO₂ per session (=maximum minus minimum) per patient was 6 mmHg (SD 2 mmHg;range 4–8 mmHg). The average of the mean HR per patient was 79 bpm (SD 6 bpm;range 60–96 bpm). The mean change in HR per session (maximum minus minimum) per patient was 13 bpm (range 6–25 bpm).

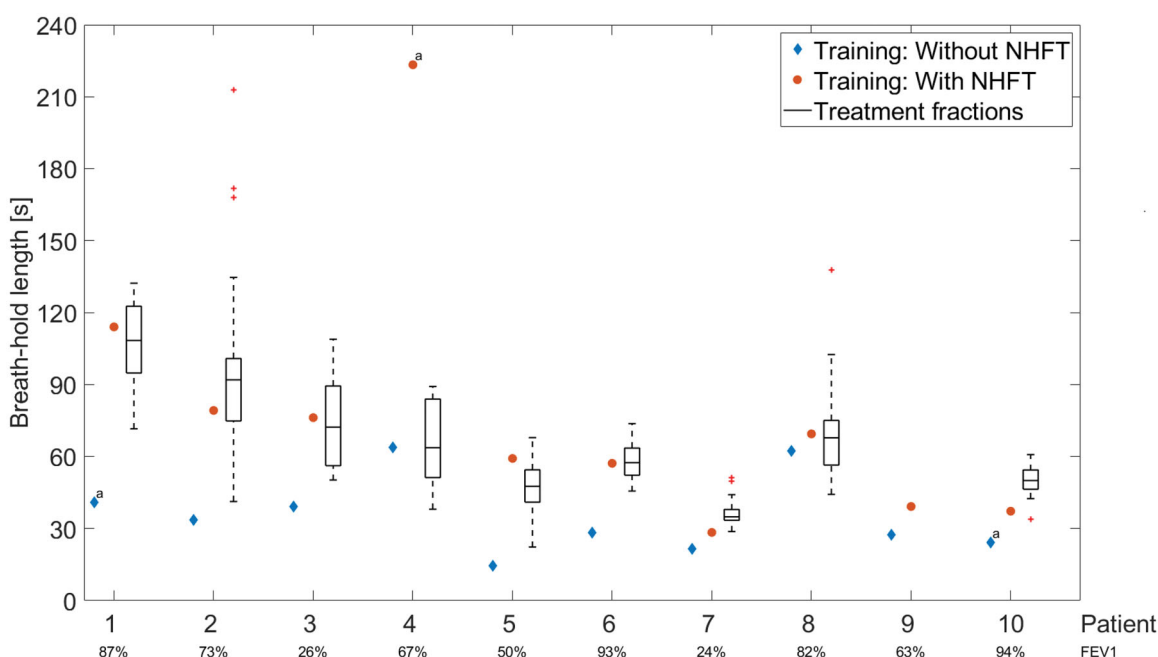


Figure 2. Maximal BH length during *training session* without (blue diamond) and with NHFT (red circles) per patient: instruction was to hold the breath as long as possible. Boxplots show the longest BH per fraction for the whole *treatment* per patient: instruction was to hold the breath as long as it felt comfortable and/or stable. FEV1 of each patient is shown below the graph. Patient 9 was excluded from the study after the training session. For patient 4, a NHFT BH extending to 223 s was observed, but this BH was unstable according to the OST signal, and may have been caused by the absence of the goggles for the patient for that BH. NHFT: nasal high-flow therapy. ^aWithout visual feedback.

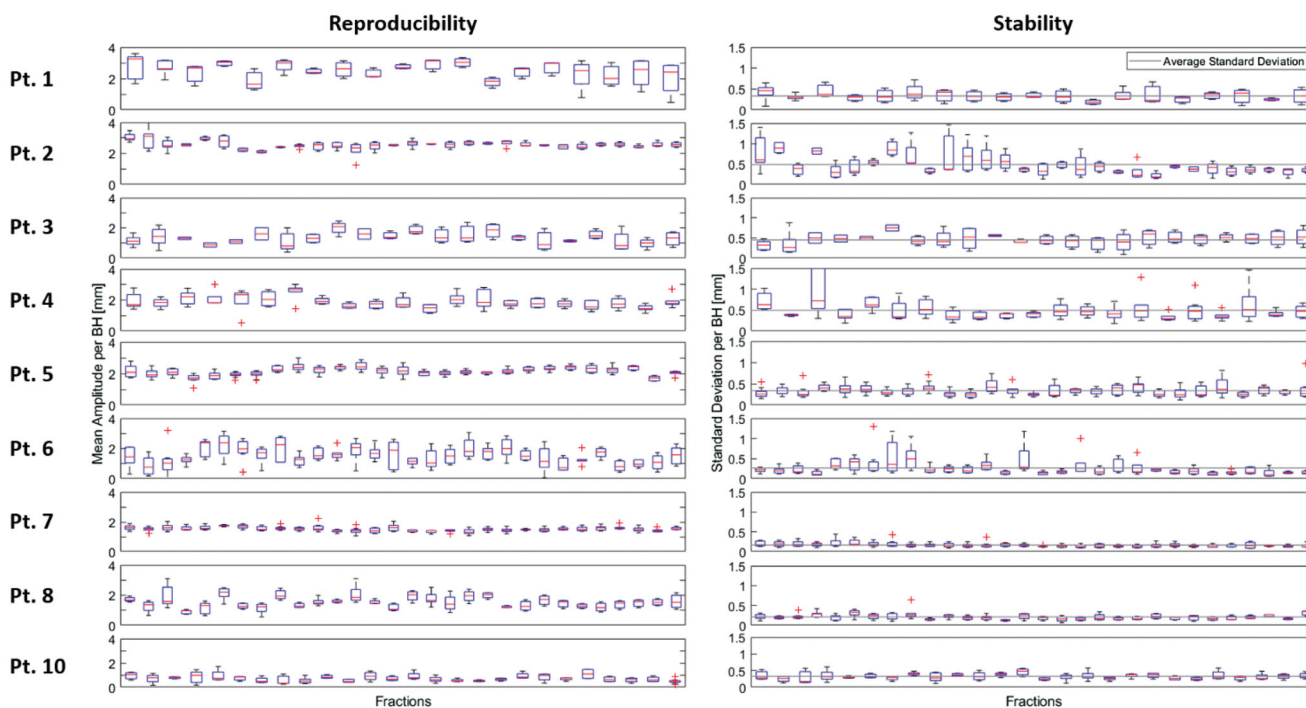


Figure 3. Reproducibility and stability for 9 patients (patient 9 was excluded after the training session). Patients 7 and 8 have the most stable BHs, and patient 7 also has the most reproducible BHs as can be seen in the low variability within and between fractions. BH: breath-hold.

We did not observe significant desaturation, with mean minimum SpO₂ ranging between 97–99% (Supplementary file B).

Discussion

We showed that IBH supported with nasal high flow therapy (NHFT) in locally advanced NSCLC patients treated with RT

was feasible, with 78% of patients completing the whole treatment as planned. Only two patients (22%) were treated with the back-up FB plan for 2 and 3 fractions respectively. Because of chemoradiation side effects, they didn't feel well enough to perform several BHs. Furthermore, subjective tolerance to the treatment in our study was very good (Supplementary file A). Compared to other studies the compliance was higher. In the study of Giraud *et al.*, a

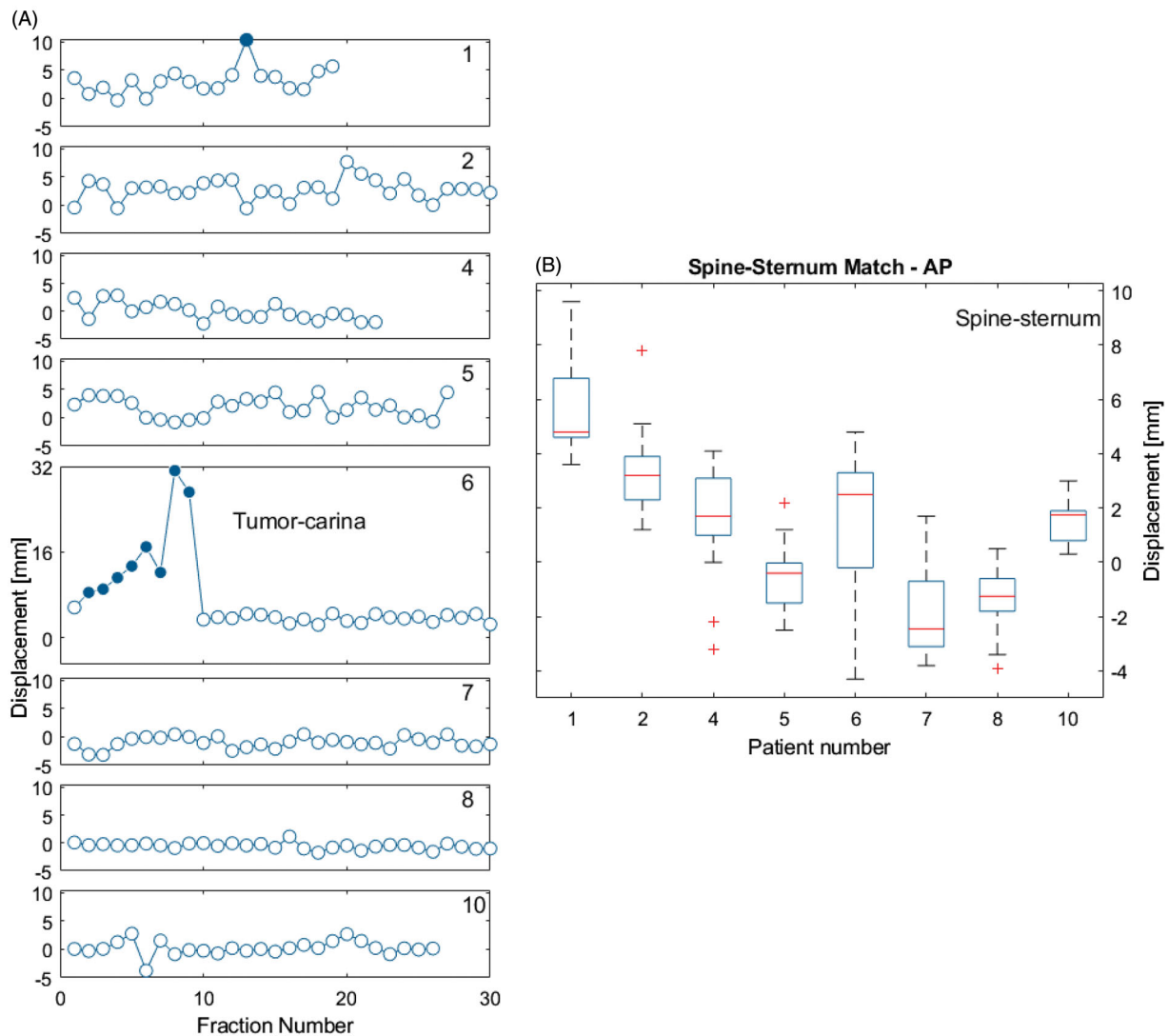


Figure 4. (A) 3D shift vectors of the primary tumor in eight patients for all fractions, obtained by calculating the difference between the daily CBCT match on carina (or bones for patient 1) and match on the primary tumor. Open dots are sessions with a shift of ≤ 8 mm and solid blue dots > 8 mm. Patient 6 had sessions with a large shift in the first part of the treatment, due to disappearance of atelectasis. Patient 3 is not shown here because he had no primary tumor, only lymph nodes. (B) Difference in AP distance (spine-sternum 3D match results) between daily CBCT and planning CT. This measure is considered a surrogate for the daily BH depth or lung volume.

compliance of 88% was reported using a spirometer for BH, but according to their definition of compliance, this would be 100% in our study [4]. Josipovic *et al.* reported that 86% could start visually-guided IBH treatment, and 63% terminated the whole treatment as planned [18].

In general, reported BH durations are rather short, around 20 s, resulting in many BHs per session and longer treatment sessions [7]. During training sessions the mean maximal BH duration in our study increased significantly from 39 s without to 78 s with NHFT (Figure 2), with an increase of on average factor 2.1. Half of the patients were even able to hold their breath for more than one minute. Most patients were able to reproduce the BH length from the training session during treatment, despite the different BH instructions between training and treatment (Figure 2). In some patients, there was even an increased BH length during treatment, suggesting a learning curve.

Potential explanations why addition of nasal airflow with extra oxygen through a nasal cannula worked, can be found

in the study of Parke *et al.* [19], where with NHFT through a nasal cannula in healthy volunteers, the airway pressures and the end-expiratory lung volumes increased, suggesting that with high flows the functional residual capacity increases. Another potential explanation is the washout of CO_2 in BH caused by the high airflow, resulting in suppression of the breath stimulus.

The mean overall stability and reproducibility measured with OST were within 1 mm (Figure 3). For stability, the median SD of the BH level was 0.33 mm. Regarding reproducibility, the median SD of the mean amplitudes was 0.43 mm.

Because an external marker is not always a good surrogate for the daily position of the lung tumor, we measured the daily lung tumor position on the CBCT relative to the matching structure [20]. Overall, we found an acceptable reproducibility with a mean change in tumor position of 1.8 ± 2.4 mm. In the majority of the sessions the displacement was within the PTV margin of 8 mm, except for one patient where an atelectasis disappeared causing a primary tumor

shift (Figure 4(A)). Inter-fraction variability for the tumor position has previously mainly been evaluated on a few (often 3 to 5) repeated CT scans, whereas in our study we evaluated the position of the primary tumor in all treatment fractions [18,21–24]. Brock *et al.* reported a mean interfraction change in tumor position between pretreatment and midtreatment of 5.1 mm (CC), 3.6 mm (LR) and 3.5 mm (AP), with the largest difference 16.6 mm [25]. In the pilot study of Josipovic *et al.*, the median differences in tumor position between 3 BH CTs were 2.5 mm, 4.1 mm and 2.4 mm, and in their subsequent study with 72 patients, 1.0 mm, 0.9 mm and 1.3 mm, respectively [18,22]. All these studies, including ours, used a visual feedback system as it has been shown to increase reproducibility not only for FB, but also for BH treatments [26,27].

Unfortunately, we have no information on the intra-fraction tumor position changes, as we did not use imaging during or immediately after delivery. Other studies showed that IBH reduces, but not eliminates tumor motion, and that tumor motion can be influenced by cardiac motion [21,23,28]. Yoshitake *et al.* showed a low residual motion of the tumor (1.3 mm (LR), 1.5 mm (AP) and 2.0 mm (CC)) in 16 lung cancer patients treated with stereotactic ablative radiotherapy in visually-guided BH [23]. Rydhog *et al.* found similar numbers in locally advanced lung cancer patients with residual motions of 1.4 mm, 1.2 mm and 2.1 mm, measured during visually guided BH through implanted liquid markers injected in lymph nodes or tumors [21]. Furthermore, IBH significantly reduced marker movements, and this movement was not significantly different anymore between fractions compared with FB [21].

In our study, PTV margins were still comparable to those used in FB treatments. But when considering reducing the PTV-margins for treatments in BH, this residual motion has to be taken into account. Interestingly, also the intrafractional baseline shifts reported by Rydhog *et al.* were very small with means of -0.3 mm (AP), 0.0 mm (LR) and 0.5 mm (CC) with total time between measurements around 15 min [21]. In both studies the BH length was only around 20 s, raising the question whether these results can be extrapolated to longer BHs. Since the BH durations in our study were only a bit longer, around 1 min, it seems therefore acceptable to do so. However, for longer BHs of 5 to 20 min as studied by several other groups, this question is more pressing [9,11,28].

Audiovisual feedback not only improves the reproducibility, but also the consistency of a BH, being the differences in lung volumes per BH [26]. Because the lungs are not fully imaged on the daily CBCTs we measured in 3 D the AP distance between spine and sternum as a surrogate for the lung volume, and showed reproducible BH depths (mean 1.2 mm, range -1.6 – 4.2 mm), except for patient 1 where a systematically deeper BH was seen compared with the planning CT (Figure 4(B)).

To evaluate the safety during NHFT, we monitored $tpCO_2$, heart rate and SpO_2 , and changes in these parameters per fraction. Although the parameters could vary within a fraction, they remained within normal limits. One of the limitations of this study is that we did not measure the blood pressure during training session or treatment. Parkes *et al.*

has shown that with prolonged BHs, systolic blood pressure may rise without change in heart rate and this rise cannot be prevented by pre-oxygenation [12]. Therefore, caution has to be taken in patients with cardiovascular morbidity, especially when longer BH of several minutes are performed [10].

We chose a simple method (Optiflow™ nasal high flow therapy) that is cheap, easy to use and simple to implement. Moreover, the flow is administered through a nasal cannula and not through a face mask, which is less cumbersome for patients. And since BHs were stable and reproducible, we believe that with several BHs per session a high treatment accuracy can be achieved, especially in proton treatments for non-small cell lung cancer with large tumor motion in FB. With protons, anatomy shifts due to breathing can lead to considerable over- or underdosage because the proton range is much more sensitive to density changes compared with photons [5,29,30].

In conclusion, NHFT for BH in RT treatment of NSCLC is feasible and well tolerated, even without extensive training, and significantly increased the BH duration. Visually guided BHs with surface scanning were stable and reproducible. Furthermore, this technique is easy to use by radiotherapy technicians, comfortable for patients and not expensive. We therefore consider this an attractive approach to irradiate lung cancer patients in IBH that can be introduced in daily clinical practice, both for photon and proton therapy.

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Disclosure statement

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All other coauthors have nothing to disclose.

Data availability statement

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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