Deep inspiratory breath-hold radiotherapy for left-sided breast cancer: Initial experience with Active Breathing Coordinator™ in a regional hospital

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Abstract

Introduction: Deep inspiratory breath-hold (DIBH) has become standard in radiotherapy for left-sided breast cancer to reduce the heart dose. This study evaluated breath-hold stability and reproducibility using Elekta’s Active Breathing Coordinator™ (ABC) and its effectiveness and feasibility in left-sided breast cancer patients undergoing radiotherapy. Methods: Eligible patients were planned with free breathing (FB) and DIBH protocols. DIBH treatment was considered if the mean heart dose (MHD) was ≥2 Gy on the FB plan. Those who proceeded with DIBH treatment were enrolled for the pilot study. Electronic portal images of DIBH treatment beams were taken using the movie-exposure mode for breath-hold stability and reproducibility analysis. DIBH effectiveness in heart dose reduction and impact on simulation and treatment durations were compared with FB protocol. Results: Out of 56 eligible patients, 15 proceeded with DIBH treatment. The mean difference of patient setup within a single breath-hold was 0.4 mm; between different breath-holds of the same beam 1.1 mm and between different days 2.6 mm. DIBH reduced the MHD by 47% and the mean left anterior descending artery (LAD) dose by 35%. DIBH took longer time than FB in simulation and treatment. At least 14% of the eligible patients did not tolerate DIBH during simulation. Conclusions: ABC leads to stable and reproducible breath-holds and results in significant heart dose reductions. It may not be tolerated by all patients and has resource implications.

Introduction

Although radiotherapy improves local control and disease-specific survival for patients with early-stage breast cancer,1–5 cardiotoxicity can occur. Modern conformal radiation techniques may have decreased heart doses, but evidence is suggestive of a small residual risk.6 Deep inspiratory breath-hold (DIBH) has been shown to effectively decrease heart doses and is widely used with radiotherapy for left-sided breast cancer.7,8 Two common methods for DIBH are voluntary and machine-assisted. In voluntary DIBH, the patient holds the breath voluntarily and the radiation beam is gated using a sensor device placed on the patient’s chest wall. In machine-assisted DIBH, the patient uses a spirometer device that allows monitoring as well as stopping the airflow once the patient’s inhaled volume reaches a set threshold, causing the patient to hold their breath to maintain this volume.

This pilot study aims to evaluate breath-hold stability and reproducibility as well as effectiveness and feasibility...
of DIBH using Elekta’s (Elekta AB, Stockholm, Sweden) Active Breathing Coordinator\textsuperscript{TM} (ABC) R3 in left-sided breast cancer patients undergoing breast or chest wall radiotherapy in our institution.

**Methods**

**Patient selection**

A protocol was designed and received ethics approval (Northern A Health and Disability Ethics Committee, Reference: 15/NTA/149). The aim was to enrol 15 consecutive patients who proceeded with DIBH radiotherapy, from January 2016. The last patient was enrolled in January 2018. Patients with left-sided breast cancer who required radiotherapy after breast-conserving surgery or mastectomy were eligible to participate. Patients were excluded if they were older than 70 years in this initial pilot, as we aimed to target the treatment to the most at risk and thus most likely to benefit before we expanded it to include others. We also excluded those needing nodal irradiation in this pilot, as our monoisocentric technique for nodal treatments required more quality assurance to proceed with DIBH. Those with any significant respiratory illness were also excluded.

The eligible patients underwent simulation using both free breathing (FB) and DIBH techniques. A training session on ABC device was given prior to CT. A written information sheet and a video clip on ABC treatment were also provided. Patients who did not tolerate DIBH at simulation proceeded with FB protocol. Their data were kept for DIBH uptake and tolerability analysis.

Our institution changed the policy mid-way through the recruitment period and only FB scans were performed for local patients, who were recalled for DIBH training and scan if their mean heart dose (MHD) on FB plan exceeded 2 Gy. Out-of-town patients still underwent both FB and DIBH simulations.

If the MHD was $\geq 2$ Gy on the FB scan and there was $\geq 5\%$ improvement in the MHD with DIBH, the DIBH plan was used for treatment. An acceptable MHD was not well defined in the literature; however, 2 Gy was chosen as it reflected international practice at the time.\textsuperscript{9,10}

**Planning and treatment**

Plans were generated using Elekta Monaco\textsuperscript{®} planning system. Three-dimensional conformal radiotherapy was used with parallel-opposed tangent beams modified with virtual wedges and segments to comply with the ICRU dose homogeneity of 95–107\% for the target volume. The dose delivered was either 42.5 Gy in 16 fractions or 40 Gy in 15 fractions to ICRU reference point. Cavity boost radiation was permitted but not included in the dose analyses of this study. Mid-lung distance (MLD); the distance between the chest wall and the posterior edge of the treatment field at the central axis) and heart distance in tangent field (HDTF; the maximum perpendicular distance between the heart border and the tangent field edge) were measured from the plans.

Electronic portal imaging (EPI) was used for treatment. Tolerance was determined by MLD: treatment proceeded if MLD difference was 5 mm or less from the plan. If this was not met, the patient and equipment was reset up, re-imaged and treated if satisfactory. If the MLD variation was over 5 mm in the first three fractions requiring reset up, the treating clinician was informed and it was decided whether to re-coach the patient and continue with the treatment, revert to FB or re-plan for DIBH. If EPI for the first three days was stable, it was then repeated weekly, otherwise more frequently.

**Breath-hold analyses**

For the first three fractions, portal images of all treatment beams were taken using the movie-exposure mode in iViewGT version 3.4.1 (Elekta AB, Stockholm, Sweden). Separate movies were created for each breath-hold. Portal images exported from iView were analysed using ImageJ version 1.48v\textsuperscript{11} by measuring the distance from field edge to patient surface near the superior and inferior edges and at the middle of the portal image.

Using the iView image timestamps, the breathing traces recorded by ABC, and the treatment records on Elekta MOSAIQ\textsuperscript{®}, images were matched to particular breath-holds. Only images which could be conclusively grouped were included in analysis.

- **Stability of breath-hold.** By comparing the patient setup measurements from within a single breath-hold (i.e. separate frames of the same movie exposure), patient movement while in a breath-hold was analysed. This was quantified by comparing patient setup measurements of individual frames to the first frame in the same breath-hold.

- **Repeatability of breath-holds.** By comparing the patient setup measurements taken from the same beam during the same treatment, but in different breath-holds, the repeatability of patient position for different breath-holds was analysed. This was quantified by averaging the patient setup measurements for each breath-hold and calculating the difference between matching breath-holds.

- **Repeatability of setup.** By comparing patient setup measurements from the same beam on different days, the day-to-day patient setup variability was analysed.
This was quantified by averaging the patient setup measurements for each breath-hold and comparing these average measurements to the first day’s treatment for the same beam.

- To assess the uncertainty in the measurement technique, iView images were also taken using an Alderson Rando Phantom treated with four identical tangential beams with the gantry and multileaf collimator (MLC) reset between deliveries. The resulting images were analysed in the same way as the clinical data, with the resulting measurements grouped into ‘within beam’ and ‘between beams’. The within beam analysis gives an estimate of the uncertainty introduced by the imaging and measurement process, and the between beams analysis estimates the combination of this plus the uncertainty introduced by the machine setup.

Contouring cardiac structures

Prior to the study, a heart and vessel contouring education session was conducted with a radiologist for the radiotherapy staff and a contouring guide was generated. The heart and the left anterior descending artery (LAD) were contoured on FB and DIBH scans for each patient. The dosimetric analyses were performed based on delineation of the structures by the original contourer. Two other independent practitioners also contoured the structures for evaluation of inter-observer consistency.

Time comparison

Times taken for education, CT and treatment sessions with DIBH were measured by radiation therapists. The equivalent times for 15 contemporaneous right-sided breast cancer patients simulated and treated using standard FB protocol during the study period were also measured for comparison.

Statistical methods

For heart and lung dose comparison between DIBH and FB plans, P-value was derived via paired t-test when continuous data are normally distributed, or Wilcoxon signed-rank test when normality assumption is violated. Relationship between MHD and HDTF was evaluated using Pearson correlation coefficient and further quantified via fitting a linear regression model.

For assessment of inter-observer variability of cardiac structure contouring and the potential effect on reported doses to critical structures, the heart and LAD doses derived from delineations by three independent contourers were analysed using a single-measurement, consistency, 2-way mixed-effects intraclass correlation coefficient (ICC) model, namely ICC(3,1).12,13 The following recommendation was used for interpretation of consistency: ICC greater than 0.9 is considered excellent; between 0.75 and 0.9 good; between 0.5 and 0.75 moderate and less than 0.5 poor.14

Results

Patient characteristics

Between January 2016 and January 2018, 56 patients were eligible for consideration of DIBH. Of those, 15 patients consented and were enrolled on the DIBH pilot protocol. Table 1 summarises patient characteristics and their diagnosis and treatment.

Setup and breath-hold analysis

Stability & reproducibility

The number of breath-holds per daily fraction of radiation ranged between 7 and 21. These numbers include breath-hold attempts needed to set up the patient prior to beam on, for example, to set to treatment source-to-surface distance (SSD), check isocentre SSD, check light fields to

Table 1. Demographics, stage and treatment details of the DIBH patients (n = 15).

| Age (years) | Range | Median |
|-------------|-------|--------|
| Cardiac risk factors (no.) | Pre-existing cardiac disease 0 | Smoking history 2 |
| Diabetes 0 | Hypertension 1 |
| Hyperlipidaemia 0 | Family history 5 |
| Surgery (no.) | Breast conserving 13 |
| Mastectomy 2 | T Stage (no.) |
| Tis 2 | T1 9 |
| T2 4 | N Stage (no.) |
| N0 13 | N1 2 |
| Neoadjuvant (no.) | Chemotherapy 2 |
| Adjuvant (no.) | Chemotherapy 4 |
| Endocrine therapy 7 | Radiation Volume and Dose (no.) |
| Whole breast 13 | 40Gy/15# 11 |
| 42.5Gy/16# 2 | Cavity Boost (10Gy/4#) 4 |
| Chest wall 2 | 40Gy/15# 2 |
breast borders and obtain EPI images. Extra breath-holds were done as required to correct setup.

**Breath-hold stability**

We obtained 281 portal images from individual breath-holds, covering 73 different breath-holds from 9 patients. From these, 628 individual measurement comparisons were extracted. The mean absolute difference between a given portal image frame and the first frame from that breath-hold was 0.4 mm with a standard deviation of 0.5 mm (Table 2). Images from the other six patients were unavailable within iView following their treatment and could not be properly analysed due to being deleted.

**Breath-hold repeatability**

We identified 27 instances where a single beam was split over multiple breath-holds, involving 6 different patients. From these, 79 individual measurement comparisons were extracted. The mean absolute difference between the patient setup measurements in different breath-holds was 1.1 mm, with a standard deviation of 1.2 mm (Table 2).

**Setup repeatability**

We identified 65 instances of portal images covering the same beam on different days, involving 9 patients. From these, 191 individual measurement comparisons were extracted. The mean absolute difference between patient setup measurements on different days was 2.6 mm with a standard deviation of 2.4 mm (Table 2).

**Uncertainty estimate**

The mean difference seen between phantom setup measurements acquired in the same movie-exposure was 0.07 mm, with a standard deviation of 0.2 mm. The largest difference seen was 0.5 mm. When comparing phantom setup measurements from different exposures, the mean absolute difference seen was 0.7 mm with a standard deviation of 0.8 mm. The largest difference seen was 2.3 mm.

**Mid-Lung distance tolerance**

MLD measured on treatment was in tolerance (i.e. 5 mm or less different from planned) in 11 out of 15 patients. Four patients had one fraction with MLD out of tolerance (Table S1). Two were resolved on re-coaching with DIBH, and 2 had adjustment for the best match to borders and lung with confirmation of adequacy of treatment with treating radiation oncologists. All were able to complete the prescribed DIBH treatment with subsequent treatments within tolerance.

**Organs at risk**

**Heart**

Compared with FB plans, DIBH reduced MHD by 1.14 Gy (47%) and maximum heart dose by 4.1 Gy (9%). The mean and maximum LAD doses also decreased by 7.43 Gy (35%) and 8.6 Gy (20%), respectively. The heart dose-volumes were also significantly reduced by DIBH (Table S2).

A statistically significant linear correlation was demonstrated between MHD and HDTF in FB plans (Fig. 1). From this regression model, the following is derived: MHD (Gy) = 0.1303 + 1.9216 × HDTF (cm).

**Inter-observer consistency of heart doses**

Individual heart and LAD doses derived from delineations by the three contourers were plotted as shown in Figures S1 and S2. ICC is also shown for each plot. The best consistency was demonstrated for the maximum LAD doses for both FB and DIBH plans and the MHD of DIBH plans. The mean LAD doses for FB plans showed the least consistency. For the MHD on FB plans (Figure S1c), despite moderate consistency, the MHD

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**Table 2.** Magnitude of differences between patient measurements taken from portal images.

| Magnitude of difference | Percentage of cases |
|-------------------------|---------------------|
|                         | Breath-hold Stability\(^a\) | Breath-hold Repeatability\(^b\) | Setup Repeatability\(^c\) |
| Less than 1 mm          | 85.7%                | 54.4%                | 28.8%                |
| Less than 2 mm          | 98.9%                | 82.3%                | 53.9%                |
| Less than 3 mm          | 99.7%                | 93.7%                | 72.3%                |
| Less than 4 mm          | 99.7%                | 97.5%                | 80.6%                |
| Less than 5 mm          | 100%                 | 97.5%                | 85.3%                |
| Less than 6 mm          | 100%                 | 100%                 | 88.5%                |
| Less than 7 mm          |                      |                      | 92.7%                |
| Less than 8 mm          |                      |                      | 95.8%                |
| Less than 9 mm          |                      |                      | 98.0%                |
| Less than 10 mm         |                      |                      | 100%                 |
| Mean Difference         | 0.4 mm               | 1.1 mm               | 2.6 mm               |
| Standard Deviation      | 0.5 mm               | 1.2 mm               | 2.4 mm               |

\(^a\)Comparison of measurements within a single breath-hold.

\(^b\)Comparison of measurements from different breath-holds of the same beam on the same day.

\(^c\)Comparison of measurements from the same beam on different days.
threshold (2 Gy) set by our department for consideration of DIBH treatment has been met in all doses except one, suggesting that the clinical implications of inter-observer variation were minimal.

**Lung**

Patients have larger absolute lung volumes with DIBH than FB as expected (Table S3). There was no statistically significant difference in lung dose-volumes between DIBH and FB.

**Table 3.** Time spent on education, simulation CT and treatment for 15 DIBH patients and 15 contemporaneous right-sided breast cancer patients treated with standard FB protocol.

| TIME (minutes) | Education | Simulation CT | Average Treatment Duration<sup>1</sup> |
|---------------|-----------|---------------|--------------------------------------|
|               | DIBH     | FB<sup>3</sup> | DIBH     | FB<sup>3</sup> | DIBH     | FB<sup>3</sup> |
| Minimum       | 24       | 13            | 23       | 16.2          | 19.9     | 8            |
| Maximum       | 45       | 33            | 50       | 30            | 36.5     | 18           |
| Mean          | 33.9     | 20.2          | 34.7     | 23.7          | N/A      | N/A          |

DIBH: Deep inspiratory breath-hold; FB: free breathing.
<sup>3</sup>Right-sided breast cancer patients.
<sup>1</sup>Average value of all daily treatment durations for each patient.

**Time comparison**

Education and CT took on average 14 min (68%) and 11 min (46%) longer, respectively, in DIBH than FB (Table 3). The average duration of DIBH treatment sessions for each individual ranged between 19.9 and 36.5 min, compared to 8 and 18 min in FB.

**DIBH uptake**

Of the 56 patients eligible for consideration of DIBH, 15 (27%) patients proceeded to DIBH treatment. The remaining 41 (73%) were treated using FB protocol instead (Table 4). In 35 of these 41 patients, DIBH was not required as MHD below 2 Gy was achieved in FB plan by simple modifications such as border change and MLC shielding. From those, 2 were local patients who did not get recalled for DIBH simulation due to low MHD on FB plans as per the new department policy (Figure S3); the other 33 patients were simulated with FB and DIBH, 4 of whom did not tolerate DIBH during simulation. Six patients had MHD above 2 Gy despite adjustments but did not receive DIBH treatment due to reasons shown in Table 4. Overall, 8 (14%) of the total 56 patients did not tolerate DIBH. The actual figure could be slightly higher as there were 2 local patients simulated with FB only.
Breath-hold reproducibility in ABC has been demonstrated in other studies using different methods and appears comparable to voluntary DIBH.15-17

DIBH reduced the MHD by 47% and the mean LAD dose by 35% in our study. Our results are only from those with MHD > 2 Gy in FB plans with a small sample size, though they seem comparable to other ABC DIBH trials.8 Our linear regression modelling shows a promise in prediction of MHD with a known HDTF value, as per Figure 1. MHD threshold of 2 Gy approximates to HDTF 0.9730 ± 1 cm with extrapolation. As this result is only derived from a small sample with MHD > 2 Gy, further larger studies are required to confirm this correlation before HDTF can be used to screen patients at simulation to identify those unlikely to meet criteria for DIBH.

Inter-observer consistency of heart and LAD doses from three contourers was mostly satisfactory, except for the mean LAD doses on FB mode, with the ICC of 0.4644. One possible reason for this is geospatial variation of LAD delineations along its course due to its poor visibility on CT.18-22 Intravenous contrast or cardiac contouring guidelines may not necessarily improve LAD dose consistency.20,21

Thirty-five (63%) of the eligible patients did not require DIBH as MHD was kept below the threshold with planning modifications. Other studies report higher DIBH uptake (38–72%) but with different eligibility criteria, for example, heart dose-volumes or heart volume in field.23,24 ‘Ideal threshold’ of MHD for offering DIBH is unknown. The MHD constraint recommended by guidelines for breast tangential radiotherapy varies from 2 to 4 Gy,10,25,26 though ideally should be as low as achievable, as the risk of coronary event has been shown to increase linearly with MHD with no minimum threshold.10,25

DIBH is more time-consuming than FB as shown in Table 3. It would take longer depending on patients’ anxiety or willingness, their ability to follow instructions, staff experience and equipment reliability. Times may get shorter with training and experience but will remain greater than standard planning and treatment slots. It is also noted at least 14% of the eligible patients did not tolerate DIBH during simulation. Another trial similarly quoted that 19% of eligible patients did not tolerate ABC.24

We suggest the development of patient selection process for DIBH according to patient tolerability, cardiac risk factors, cancer prognosis27 and patient-specific dosimetric variables such as HDTF as an easily measurable surrogate for MHD. Also, based on the safety and tolerability of DIBH demonstrated in the pilot, our department is expanding the eligibility to include breast cancer patients with nodal treatments and other malignancies.

Discussion

Radiotherapy has been shown to improve breast cancer local control and survival,1-3 but does carry a long-term risk of heart disease, which is correlated with the mean dose to the heart.9 DIBH has been tested and proven to be effective in reducing the heart dose in breast cancer patients in many institutions over the last decade.8 Our pilot study assessed stability and reproducibility of breath-holds using ABC and its effectiveness and feasibility.

The ABC unit was able to immobilise the patient in a stable breath-hold position: in 99% of cases, the patient moved by 2 mm or less while in breath-hold. This suggests that potential issues such as breathing around the mouthpiece or through the nose have not been seen at our centre. The use of ABC with pre-defined inhalation volumes and suitable patient coaching also lead to a reproducible breath-hold. We found that when a patient had to pause mid-beam, they were able to obtain the same position in a second breath-hold to within 2 mm in 82% of cases and 4 mm in 98% of cases. The MLD was in tolerance for most treatment fractions, also suggesting excellent reproducibility. For context, our day-to-day setup variation introduced a mean change in patient position of 2.6 mm, with less than a 5 mm change in 85% of cases. From the uncertainty analysis performed with the Rando Phantom, it was found that the imaging and measurement technique was robust and did not introduce any significant errors. This in turn suggests that the differences in patient setup measured are almost entirely caused by real changes in patient setup.

Table 4. Patients who did NOT proceed with DIBH radiotherapy (n = 41).

| Reason for no DIBH | Mean (Gy) | Median (Gy) | Range (Gy) |
|--------------------|-----------|-------------|------------|
| Struggled to maintain breath-hold | 1.52 | 1.50 | 0.70–3.69 |
| Psychological/panic | | | |
| Unspecified | | | |
| Unable to be recalled for DIBH simulation | | | |
| Not specified | | | |
| Unable to tolerate DIBH (4) | 6 | | |

These patients did not require DIBH as MHD was below threshold; however, there were four patients who did receive DIBH simulation but were unable to tolerate DIBH.

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In conclusion, ABC DIBH used for left-sided breast or chest wall irradiation in our pilot study demonstrated stable and reproducible breath-holds and significant heart dose reductions, but may not be tolerated by some patients and has resource implications.

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Conflicts of Interest

None.

Ethics Approval Statement

A protocol was designed and received ethics approval (Northern A Health and Disability Ethics Committee, Reference: 15/NTA/149).

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### Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Appendix S1** Supporting Information