Investigation of intra-fraction stability and inter-fraction consistency of Active Breathing Coordinator (ABC) based deep inspiration breath-holds in left-sided breast cancer.

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Background
Deep inspiration breath-hold (DIBH) has been established as a standard technique to reduce cardiac dose. The amount of the heart exposed to radiation can be significantly decreased when using the DIBH technique during tangential breast irradiation.

Aim
The objective of this study was to investigate the intra breath-hold stability and inter-fraction consistency of patient breath-hold against the threshold as a function of air volumes in the setting of Active Breathing Coordinator (ABC) based DIBH treatment to left-sided breast cancer.

Methods
A total of thirty-four patients treated with external beam radiation treatment (EBRT) to the left breast using the ABC-DIBH device were included. A prescription dose of either 200 cGy (conventional) or 267 cGy (hypofractionation) was administered during 649 fractions, resulting in a total of 4601 breath-hold consistency being evaluated. The amplitude deviation between the baseline threshold and the patient-specific measurement (during each breath-hold) was used to define DIBH stability. The consistency of the breathing amplitudes was used to define reproducibility of breath-holds throughout the entire treatment period. Positional accuracy was measured using orthogonal images.

Results
The average number of breath-hold measured over the course of treatment for each patient measured to be 144 times (58 - 351 times). The average number of breath-hold for each fraction by a patient during the course of treatment was 11 times (7 - 21 times) which included setup imaging and treatment. The total number of times patient has to maintain breath-hold significantly (p value < 0.05) reduced with hypofractionation (104 times; 58 - 170 times) as compared to conventional fractionation (145 times; 58 - 351 times). The average breath-hold threshold was 1.41 L (0.6 - 2.1 L) for all patients. The average translational shifts measured during setup were 0.28 cm ± 0.3 cm, 0.38 cm ± 0.4 cm and 0.21 cm ± 0.3 cm in the lateral, longitudinal and vertical direction.

Conclusion
The average absolute difference in amount of airflow measured against the threshold breath-hold during the course of treatment was within 0.5 L. The frequency of breath-hold was observed to be higher for the first few fractions and decreased over the course of treatment.

Categories: Medical Physics, Radiation Oncology, Oncology
Keywords: image guided radiotherapy, electronic portal imaging device (epid), left-sided breast cancer, deep-inspiration breath-hold, active breathing coordinator

Introduction
Breast cancer is the most prevalent cancer and the leading cause of mortality among women worldwide. One
in four women is diagnosed with breast cancer according to the International Agency for Research on Cancer (IARC) [1]. Breast cancer in Asian females is strongly associated with early onset and a peak incidence rate between 45–49 years [2].

Radiation therapy (RT) after breast-conserving surgery in the early stages of breast cancer is the current treatment of care, as RT has proven to improve local control of the tumor and increase overall survival [3]. Most postoperative patients who undergo breast-conservative surgery require whole breast irradiation (WBI) with or without a tumor bed boost, whereas in low-risk patients, a partial breast irradiation (PBI) method can be used. The need for chest wall irradiation (CWI) is less prevalent until it is used in combination with nodal irradiation or post-mastectomy irradiation (PMI) [4].

Involuntary organ movements, such as respiratory motion during radiotherapy between and within fractions, may cause dose delivery errors due to excess normal tissue being irradiated and missing target volume [5]. Adverse effects such as radiation-induced heart disease and cardiovascular events have been reported in patients with left-sided breast cancer (LSBC) [6-8]. Damage to the heart and lungs due to radiation therapy is the major morbid side effect observed after several years of radiotherapy treatment [4]. An increase of 1 Gy dose in radiotherapy has shown a increased risk of approximately 7% for coronary events; hence, the use of radiotherapy should be assessed for the risk and benefit ratio for toxicity. In addition, newer methods should be used to prevent such conditions with reduced dose exposure to the heart, lungs, and other organs without the presence of tumors [9].

Strategies currently used to reduce the effects of respiratory motion include integration of respiratory motion into the treatment plan, forced shallow breathing by abdominal compression, deep inspiration breath-holding (DIBH), respiratory gating techniques, and four-dimensional computed tomography (4D CT). Traditionally, DIBH techniques are used, which function by separating the heart from the field of irradiation. DIBH works by inflating the lungs and displacing the heart caudally, which can be used to achieve a lower radiation dose to normal intrathoracic tissues. The DIBH technique enables reduction of doses to vital organs while maintaining the recommended dose for the tumor [10,11]. Several studies have reported that DIBH radiotherapy is a potential method for reducing cardiac doses [12-14].

Deep-inspiration breath-hold (DIBH) reduces overlap of the heart and lungs with the treatment fields by taking advantage of organ motion during the respiratory cycle [15]. When compared to free breathing, DIBH significantly lowers the dose to the ipsilateral lung for right-sided treatments and the heart for left-sided treatments [11,16]. Daily patient setup and breath-hold reproducibility, which can be checked using cine portal imaging are crucial for minimizing irradiation of nearby organs at risk without sacrificing treatment of the target volume. To reduce the radiation exposure to the heart, the Active Breathing Coordinator System (ABC) (Elekta, Stockholm, Sweden) was created. By placing a plastic tube with a mouthpiece inside the patient’s mouth, this system enables the patient to breathe through the tube while maintaining their breath-holding ability. In order to track the patient’s breathing pattern, the ABC device is connected to a computer. The reproducibility of the subject lung volume is primarily used to evaluate the effectiveness of the device.

However, DIBH techniques require patient compliance and longer imaging and treatment duration [17]. Throughout the course of therapy, it is necessary to investigate the overall geometric uncertainties, particularly when using various pieces of equipment [18]. Several breath-hold techniques are already available and utilized in normal clinical practice. The instruments used, intra-fraction monitoring, and patient feedback systems differ greatly across these procedures. In general, there is a contrast between voluntary and computer-controlled DIBH approaches, such as surface-guided or spirometry-based systems [15,16,19-21].

Because respiration and breathing pattern differ between patients, tumor locations may also vary throughout each breath-hold treatment fraction. As treatment techniques become more sophisticated through the use of advanced motion management systems, there are uncertainties in the equipment that may impair overall treatment quality. The total geometric uncertainties, especially when more equipment is employed, necessitate investigation during the course of treatment. Furthermore, not many institutions are equipped with automated-gating technique for DIBH based treatment delivery.

Currently, radiotherapy treatment plans for breast cancer are created using two opposing non-divergent isocentric tangent fields along with beam modifiers to homogenize the dose within the target [11,12]. For target-dose homogenization, the tangential field-in-field technique, also known as forward intensity-modulated radiation therapy is employed using multi-leaf collimator (MLC) [15,14].

The objective of this study was to evaluate intra-fraction stability and inter-fraction consistency of patient breath-hold as a function of air volumes and flow in the setting of DIBH based treatment to left-sided breast cancer. The set-up uncertainty was evaluated using portal images.

**Materials And Methods**

**Patient stratification:**
In this retrospective study, 34 consecutive patients diagnosed with left-sided breast cancer who received radiotherapy treatment between September 2022 and May 2023 using the DIBH technique, Active Breathing Coordinator device (Elekta, Stockholm, Sweden), following breast conserving therapy or mastectomy were included. The median age is 46 years old (± 10).

Simulation using ABC-DIBH Device:

A spirometer, which consists of a balloon valve, turbine impeller, and opto-electronic sensor, is used by the ABC system to gauge patients’ respiratory volumes. A patient’s airflow is stopped by the balloon valve at a predetermined breath-hold volume. For a known air volume, the turbine impeller makes one revolution. The opto-electronic sensor tracks rotations and picks up airflow signals.

A GE Discovery CT 590 RT CT scanner (GE Medical Systems, Chicago, IL, USA) was used for simulation using institutional imaging protocols. Patients were simulated in a supine position on a breast board with arms abducted and externally rotated for DIBH using a slice thickness of 5 mm and covered from the mandible to the thorax, which encompassed all normal structures. The DIBH technique was used in patients who were able to hold their breath for 20-30 seconds, at least three times, and was performed using an Active Breathing Coordinator (ABC) device (Elekta, Stockholm, Sweden). Patients received coaching until they could consistently perform deep inspiration breath holding. Subsequently, a breath-hold was used to obtain a CT image in order to enhance the gap between the heart, chest wall, and breast tissue by taking advantage of lung hyperinflation.

The target and organs at risk contouring were delineated by a Consultant Oncologist based on the radiation therapy oncology group (RTOG) guidelines to define the clinical target volume (CTV), which included the entire contralateral chest wall and lymph node region around the collar bone. The organs at risks (OARs) included the ipsilateral lung, contralateral lung, contralateral breast, heart, and spinal cord [22,23].

Radiotherapy Treatment Planning:

Treatment plans were generated using the CMS Monaco (v5.2.11 Elekta, Crawley, UK) treatment planning system (TPS) which utilizes the Collapsed Cone algorithm for three-dimensional conformal therapy (3D CRT) cases. For each patient, the planning target volume (PTV) and various OARs were considered. The goal of the treatment plan was to have 95 % of the PTV covered by at least 90 % of the prescribed dose and less than 95% of the hotspots < 107% of the prescribed dose to be less than 2 c. OAR dose limits were optimized to be as low as possible according to the Quantitative Analysis of Normal Tissue Effects (QUANTEC) guidelines and RTOG protocols [22-25].

Either 5000 cGy in 25 fraction (n = 17) or 4256 cGy in 16 fractions (n = 17) was used. All treatment plans complied with standard quality assurance procedures and departmental planning goals. A bolus was used in the chest wall cases in half fractions (i.e., first seven fractions), and skin involvement was as per the institutional protocols in the respective mentioned fractions.

Image guidance and Treatment Delivery:

Elekta Infinity® (Elekta, Crawley, UK) with an Agility MLC® head was used to deliver all plans. The beam modulator head assembly consisted of 80 leaf pairs for a total of 160 leaves, which were projected at an isocenter width of 5 mm. For all plans, an MV setup image was acquired and registered with digitally reconstructed radiographs to verify the patient setup. The treatment couch corrections in our institution’s DIBH image guidance protocol is based on portal imaging-acquired in anterior and lateral setup images. Following that, the lateral image is used to verify the breath hold level once a week. Daily tangential breast images are collected. For patients with affected lymph nodes, an anterior image is acquired once a week to correct for potential patient rotation. Couch corrections are needed if the position errors of the bony structures in the tangential breast images are greater than 4 mm, if the residual errors of the bony landmarks for the lymph node areas are greater than 4 mm, or if the breath hold level deviates from the planned by more than 4 mm. In order to confirm the accuracy of the corrections, more anterior and lateral orthogonal images are obtained at the following two fractions [26]. Along with setup images, two conformal tangential fields’ continuous portal images (pre-port) were taken every third fraction. The delivery of the treatment and ABC device is controlled manually by the radiation therapist. The treatment is paused on observing a discrepancy of ± 0.5 L in the breath-hold measurement from the threshold level.

Data extraction using ABC-DIBH device:

During CT simulation and treatment delivery, including daily imaging for setup, the ABC was used to record the air volume of every patient. In this study, the breath-hold volume that the ABC recorded during the CT scan was referred to as the reference breath-hold volume. For 3D CRT with traditional fractionation, portal images were acquired. All images were captured while maintaining the pre-set breath-hold setting using ABC device. When the patient’s breathing reached the breath-hold threshold, the radiation therapist activates the therapeutic beam. Every 20 ms, the output data file records the patient’s breathing during imaging and treatment. The actual breath-hold volumes held by the ABC during treatment were compared to the reference breath-hold volume and analyzed as a function of airflow rate.
DIBH stability and reproducibility:

The amplitude deviation between the baseline threshold and the patient-specific measurement (during each breath-hold) was used to define DIBH stability. Throughout the entire treatment period (comparing breath-holds of all treatment fractions), we evaluated the patient-specific inter and intra-fraction DIBH reproducibility. The consistency of the breathing amplitudes was used to define reproducibility between breath-holds in this context. The difference between the minimum and maximum value was calculated and used as a measure of reproducibility. This was done by calculating the breathing amplitudes of all the breath-holds performed on a patient [27,28].

Results

The demographics, prescription doses, clinical characteristics, and staging of the patients assessed in this study are reported in Table 1. The average MU was 611.5 MU (± 147.8 MU) and the average treatment time for each fraction was 25.7 mins (± 1.5 min) respectively. All treatment plans generated in this study met the institutional constraints and objectives and were clinically reviewed and approved by consultant radiation oncologists before treatment. Similarly, all cardiac dose indices obtained using all planning techniques met the limits recommended in the literature.
**Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total Number of Patients N = 31</th>
</tr>
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<tr>
<td><strong>Median Age</strong></td>
<td>46 years (± 10)</td>
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<tr>
<td><strong>ECOG</strong></td>
<td>T1 (n = 7)</td>
</tr>
<tr>
<td></td>
<td>T2 (n = 15)</td>
</tr>
<tr>
<td></td>
<td>T3 (n = 12)</td>
</tr>
<tr>
<td><strong>T Stage</strong></td>
<td>N0 (n = 19)</td>
</tr>
<tr>
<td></td>
<td>N1 (n = 13)</td>
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<tr>
<td></td>
<td>Na1 (n = 2)</td>
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<tr>
<td><strong>N Stage</strong></td>
<td>M0 (n= 34)</td>
</tr>
<tr>
<td><strong>M Stage</strong></td>
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</tr>
<tr>
<td></td>
<td>I-A (n = 4)</td>
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<tr>
<td><strong>AJCC Stage</strong></td>
<td>II-A (n = 9)</td>
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<tr>
<td></td>
<td>II - B (n = 15)</td>
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<tr>
<td></td>
<td>III - A (n = 6)</td>
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<tr>
<td><strong>ER</strong></td>
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<tr>
<td></td>
<td>Positive (n = 24)</td>
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<tr>
<td><strong>PR</strong></td>
<td>Negative (n = 12)</td>
</tr>
<tr>
<td></td>
<td>Positive (n = 22)</td>
</tr>
<tr>
<td><strong>HER-2/neu</strong></td>
<td>Negative (n = 27)</td>
</tr>
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<td>Positive (n = 7)</td>
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**Dosimetric Parameters**

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<tr>
<td>Prescription Dose</td>
<td>5000 cGy / 25# (n = 19)</td>
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<tr>
<td></td>
<td>4256 cGy / 16# (n = 16)</td>
</tr>
<tr>
<td>Total number of Breath-hold (Range)</td>
<td>147.9 (58 – 351)</td>
</tr>
<tr>
<td>Average Breath-hold / fraction (Range)</td>
<td>6.8 (4 – 12.5)</td>
</tr>
<tr>
<td>Threshold</td>
<td>1.4 L (0.6 – 2.1)</td>
</tr>
<tr>
<td>Translational Shift</td>
<td>Lateral = 0.28 cm (± 0.3 cm)</td>
</tr>
<tr>
<td></td>
<td>Longitudinal = 0.38 cm (± 0.4 cm)</td>
</tr>
<tr>
<td></td>
<td>Vertical = 0.21 cm (± 0.3 cm)</td>
</tr>
</tbody>
</table>

**TABLE 1: Patient demographics, tumour characteristics and dosimetric parameters of the selected cohort of patients**

ECOG - Eastern Cooperative Oncology Group; AJCC - American Joint Committee on Cancer; T - tumor; N - node; Tis - tumor in situ; n - number; ER - estrogen receptor; PR - progesterone receptor; HER2 - human epidermal growth factor receptor

Figure 1 illustrates the frequency of breath-hold and consistency of threshold by a patient over the course of treatment. The details from every third fraction have been presented with time (sec) over the volume of air (L). The frequency of breath-hold was observed to be higher for the first fraction (red) and total time recorded for treatment, including setup images, was 36 mins. The consistencies of threshold were maintained within ± 0.5 L from the reference value as shown in Figure 1. The treatment or imaging was interrupted manually on observing a discrepancy in the threshold. The frequency of the breath-hold reduced
after the third fractions and resulted in treatment times lesser than 14 mins.

FIGURE 1: Intra breath-hold stability and inter-fractional consistency of a patient breath-hold during the course of radiotherapy treatment (every third fraction). Each colour represents the breath-hold patterns during every fourth fraction.

A prescription dose of either 200 cGy or 267 cGy was administered during 649 fractions, resulting in a total of 4601 breath-hold being evaluated. The average number of breath-hold measured over the course of treatment for each patient measured to be 144 times (15 - 351 times). The average number of breath-hold per day for each fraction by a patient during the course of treatment was 11 times (7 - 21 times) which included setup imaging and treatment as shown in Figure 2. The total number of times patient has to maintain breath-hold significantly (p value < 0.05) reduced with hypo-fractionation (104 times; 58 - 170 times) as compared to conventional fractionation (145 times; 58 - 351 times).
The ABC recorded the air volumes as a function of airflow rate throughout the entire radiation treatment. During breath holding, each patient showed a range of airflow rates. As a result, the differences in airflow rate during breath-hold were what led to the fluctuations in air volume. Figure 3 illustrates the changes in breath-hold measurement, in terms of minimum and maximum with respect to threshold values, during the course of treatment for each patient against the threshold measurements. The air volume and the reference breath-hold volume determined during the CT simulation were compared. The average breath-hold threshold was found to be 1.41 L/s (0.6 - 2.1 L/s) for all patients. The average absolute difference in amount of airflow measured during the course of treatment that are lesser than breath-hold threshold compliance was 0.43 L/s (0.0 - 1.2 L/s). Similarly, the average absolute difference in amount of airflow difference more than the breath-hold threshold compliance was 0.57 L/s (0.1 - 1.3 L/s). The treatment was interrupted if the measured breath-hold was different to the threshold and the patient would be communicated to adjust the breath-hold for further treatment. The average translational shifts measured during setup were 0.28 cm ± 0.3 cm, 0.38 cm ± 0.4 cm and 0.21 cm ± 0.3 cm in the lateral, longitudinal and vertical direction.
Discussion

Ischemic heart disease is a serious late toxicity associated with adjuvant radiotherapy for breast cancer and is the leading cause of death among breast cancer survivors after 10 years of treatment.

The present study addresses the intra-fraction stability and inter-fraction reproducibility of patient breath-holds during the delivery of ABC based radiotherapy treatment to left sided breast tumors. This study reveals that changes in breath-hold volume, as determined by spirometry, have an impact on target location over the course of radiotherapy. In terms of breathing characteristics like airflow rate, breath-hold time, and threshold, the study found that each patient displayed individual differences. Patient-specific breath-hold settings are essential to increase the accuracy of tumor localization because reproducibility when using breath-hold platforms for radiotherapy is still a concern. Variations in air volume were unavoidable since we set the threshold lower, at around 75% of the maximal breath-hold as recommended by the manufacturer, despite the fact that a consistent breath-hold volume is expected throughout the entire treatment using the ABC breath-hold approach.

Additionally, proper coaching is essential to create a calm environment for treatment because patients’ discomfort can result in rapid breathing or complicated breath-holds. Similarly, we found that the scheduling on the same time every day and communication by the same team member have helped patients to maintain the breath-hold threshold. Longer treatment sessions may cause patients discomfort after repeated breath-holds; as a result, appropriate coaching is needed to maintain the stable breath-hold comfortably.

The measured air volume increased over the course of treatment for the patients receiving conventional fractionation. One of the potential explanations was that as treatment progressed, patients became accustomed to and at ease with the ABC. Further, the ability of the patients to maintain a constant lung volume may have increased as a result of improvements in their ability to breathe during treatment.

Xiao et al. examined over 7200 DIBH cycles using the surface imaging system AlignRT (VisionRT, London, UK). The median of the 5th to 95th percentile range of translational displacement during a single breath-hold or over all breath-holds throughout the course of a single treatment session was investigated. The current study used only the portal images for verification. Similarly, Maria Lutz et al., investigated the internal accuracy of left sided breast cancer treatments using optically monitored DIBH setup with daily IGRT. The study reported a maximum absolute setup error of 16.5 mm.
Moreover, DBIH requires patient adherence to actively breathe-in a predefined threshold volume before every treatment field delivery. The average time spent on breath-hold practice before CT simulation was reported to be 20 minutes [29]. Further, inherent limitations of the technology itself need to be considered, such as an increase in CT simulation time (estimated 45-55 minutes) including coaching and an average increase in daily treatment time of 25 minutes per patient, which may increase the clinical workload.

Limitations:

Continuous portal imaging for position monitoring during treatment delivery has many benefits, however the technique is limited to conformal fields and necessitates the use of x-ray visible markers like the chest wall. The analysis of 3D motion is challenging due to the 2D nature of portal images. The DBIH technique used in this study was limited by manual controlling of the ABC device by the radiation therapist during simulation and treatment.

Conclusions

In this study, we report intra fraction stability and inter fraction reproducibility of patient who received radiotherapy treatment to left-sided breast cancer using DBIH (ABC) device. The average absolute difference in amount of airflow measured during the course of treatment was within 0.5 L. The frequency of breath-hold was observed to be higher for the first fraction and decreased over the course of treatment.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References