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Scientific Article

Prospective Randomized Trial Comparing 2 Devices for Deep Inspiration Breath Hold Management in Breast Radiation Therapy: Results of the BRAVEHeart Trial

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Purpose: The Breast Radiotherapy Audio Visual Enhancement for sparing the Heart (BRAVEHeart) trial prospectively randomized patients with left-sided breast cancer to 1 of 2 deep inspiration breath hold biofeedback devices: a novel chest surface tracking system and an abdominal block tracking system. The primary hypothesis was that the accuracy of chest tracking would be higher than that of abdominal tracking as the chest is a more direct surrogate of the breast target.

Methods and Materials: Patients with left-sided breast cancer were treated in deep inspiration breath hold with intensity modulated radiation therapy delivery. Patients were randomized to either the novel chest surface system or abdominal block system for active management of breath hold with visual feedback. On both trial arms, the unallocated system was monitored passively. A total of 239,296 cine electronic portal imaging device images were analyzed retrospectively to extract the chest wall position. Treatment accuracy was quantified as the deviation of the internal chest wall during treatment relative to the planned position from the digitally reconstructed radiograph. The correlation between motion of the external surrogate and internal chest wall was calculated per-breath hold. Ease of use was assessed with questionnaires for both radiation therapists and patients and appointment length recorded.

Results: Data from 26 participants were available for analysis. No difference was found in delivered treatment accuracy between arms. Across all patients and fractions, the median correlation between internal chest wall movement and external surrogate was 0.69 for the

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Ethics approval allows for the public sharing of anonymized data via a public repository.

BRAVEHeart clinical trial (NCT02881203). Approval was granted by the Northern Sydney Local Health District Human Research Ethics Committee for this study and all patients provided written informed consent.

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chest surface and 0.17 for the abdominal block. Patients found it easy to follow visual feedback from both systems. No difference was found in appointment length between arms.

Conclusions: No statistical evidence was found for superior treatment accuracy, satisfaction, or appointment length for the novel chest surface tracking device compared with the abdominal block system. During deep inspiration breath hold, the median per-breath hold correlation of internal chest wall movement to the motion of the chest surface was higher than the median correlation of the abdominal block to the chest surface.

Background

Radiation therapy to the left breast carries a greater risk of dose to the heart leading to increased morbidity and mortality.[1-3] Deep inspiration breath hold (DIBH) mitigates this impact by physically increasing separation between the breast target and the heart.[4-7] Many studies have demonstrated a reduction in heart dose and accompanying cardiac side effects with DIBH compared with free breathing.[6,8-13] Nissen and Appelt[10] using intensity modulated radiation therapy with tangential photon fields, the radiation therapy technique used in this study, showed a reduction in median heart dose of 48%.

Most DIBH management strategies gate the treatment beam if an external surrogate moves beyond a specified tolerance. Technologies to monitor breath hold depth include laser monitoring of tattoos,[14,15] spirometry-measured inspiration volume,[16] infrared camera and reflector block,[17] fiducial markers,[18] or a 3-dimensional surface point cloud.[19,20]

Although it has been shown that audio-visual feedback to the patient improves reproducibility and stability of breath holds,[20-23] there is uncertainty in how external surrogate motion relates to motion of the internal, dosimetrically important volumes. Jensen et al[14] demonstrated a technique to assess intrafraction motion of the internal chest wall by capturing cine images from the electronic portal imaging device (EPID). Doebrich et al[24] used cine EPID imaging to perform a dosimetric analysis of DIBH using only a single midline intensity profile to determine chest wall position. Delombaerde et al[25] compared the external surface monitored with AlignRT (Vision RT) to cine EPID monitoring of internal chest wall for spirometer-regulated DIBH (n = 7), finding a correlation between internal and external motion of $R^2 = 0.38$ ($P < .01$).

Best external surrogate monitoring point has been reviewed in recent studies. Lutz et al[26] compared 5 cm to the right of the xiphoid process to the inferior part of the sternum for DIBH managed with Real-time Position Management (RPM) system (Varian). The authors showed a significantly reduced interfield random shift for the sternum (1.7 mm vs 0.9 mm, $P < .005$). Conroy et al[17] extracted chest wall from cine EPID images at 3 levels across the chest: superior, mid, and inferior. They found strong correlations between chest wall and breast surface at superior and mid position ($R^2 = 0.90$ and 0.83, respectively), but only moderate at inferior position ($R^2 = 0.36$).

The primary aim of the Breast Radiotherapy Audio Visual Enhancement for sparing the Heart (BRAVE-Heart) trial was to prospectively measure the accuracy of treatment delivery under DIBH with visual feedback for 2 regions of interest—comparing tracking of the chest surface at the sternal tattoo to monitoring a block placed on the abdomen near the xiphoid process.

Secondary aims investigating patient and staff perception of the DIBH management devices and appointment length are also reported below.

Methods

Women with left-sided breast cancer proceeding to adjuvant left breast only radiation therapy were invited to participate in the BRAVEHeart clinical trial (NCT02881203),[27] approved by the Northern Sydney Local Health District Human Research Ethics Committee. Patients were randomized prior to computed tomography (CT) simulation to manage DIBH with visual feedback from either the Breathe Well system (Opus Medical) monitoring the chest surface or the RPM/Respiratory Gating for Scanners system (Varian) monitoring an infrared reflector block placed on the abdomen.

Twenty-six patients were available for analysis with mean age 59 (range, 34-82) years. Of 32 recruited, 2 were unable to maintain breath hold, 1 presented a rib fracture, 2 did not achieve acceptable heart dose with intensity modulated radiation therapy so were treated with a Volumetric Modulated Arc Therapy (VMAT) approach, and for 1 patient the arm of the Breathe Well device could not be positioned as a prior shoulder injury required placement superiorly on the couch.

All patients were contoured according to European Society for Radiotherapy and Oncology guidelines for clinical treatment volume (CTV) breast[28] with a 5 mm planning treatment volume (PTV) margin. Both volumes were cropped 5 mm from skin edge. The standard dose was 40.05 Gy to the PTV in 15 fractions with opposed tangential intensity modulated radiation therapy planning. One patient randomized to the chest surface arm received 50 Gy in 25 fractions. Patients were positioned supine with both arms

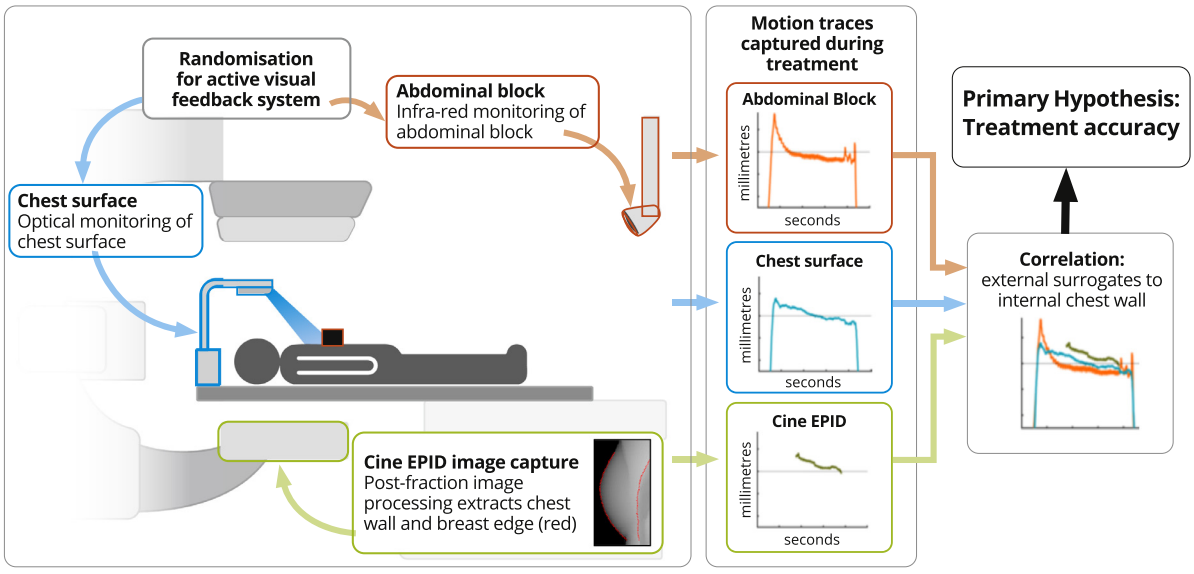

Figure 1 The BRAVEHeart study. Motion during treatment was captured for the chest surface, a reflector block on the patient abdomen near the xiphoid process, and the internal chest wall through cine images captured from the electronic portal imaging device (EPID). Treatment accuracy was assessed using the deviation of the internal chest wall position from the planned position.

raised above their head. Daily cone beam CT images were used for patient positioning using the chest wall as the primary match structure and applying couch shifts in 3 translational dimensions with rotation up to 3°.

The Breathe Well device held a visual feedback screen in the patient's eyeline on a centrally positioned arm, the mounting point for the optical depth camera (Fig. 1). Anterior-posterior motion was captured for a region of interest between the breasts and centered on the patients' sternal tattoo. A dedicated screen on the console desk signaled to radiation therapists when to manually gate treatment. The default gating window was ±2 mm. For patients with a breath hold depth of <8 mm, the gating window is reduced by 0.25 mm/mm, for example, a breath hold depth of 6 mm had a gating window of ±1.5 mm. To maintain tracking accuracy within 2 mm, sensor to chest distance was adjusted to between 20 and 30 cm with sternal angle <25° from the horizontal. Daily quality assurance took 15 minutes.

The RPM system (including later versions termed Respiratory Gating for Scanners) used an infrared camera to track reflective dots on a block placed on the patient. RPM was fully integrated with the linac control system, automatically gating the treatment beam when the anterior-posterior breathing trace was outside the ±2.5-mm gating window. Visual feedback was provided with an in-house screen attached to the head of the couch at the patient's right by a flexible arm.

Visual feedback was only enabled for the device the patient was randomized to, the active system. However both systems recorded the motion of their respective external surrogate, with the nonrandomized device passively monitored without influencing the patient.

At CT simulation, patients received training on DIBH on the randomly assigned device and patient ability to maintain a breath hold for 20 seconds was assessed. The Breathe Well system recorded the target breath hold depth during a training breath hold prior to the actual CT scan, whereas for RPM the position of the gating window was manually adjusted to be centered around the breath hold depth actually achieved during the CT scan.

Chest wall extraction

Cine EPID image frames captured with a framegrabber were analyzed offline to extract the chest wall position. An in-house Matlab script extracted both chest wall and breast edge. Horizontal intensity profiles were taken every 2 mm across the full vertical range of the chest wall and the intensity changes at the air/breast and lung/chest wall interfaces fitted, following previous publications.[14,25,29] The multileaf collimator may obscure the chest wall for part of the treatment so where the breast edge is still visible this was used to infer chest wall position by assuming a fixed distance between chest wall and breast edge for the duration of the breath hold. This approach is based on the reported strong correlation between chest wall and breast surface intrafraction motion.[17]

The chest wall position error per frame reported in the beams-eye view (Fig. 2) is the mean difference of all points along the chest wall from the planned position

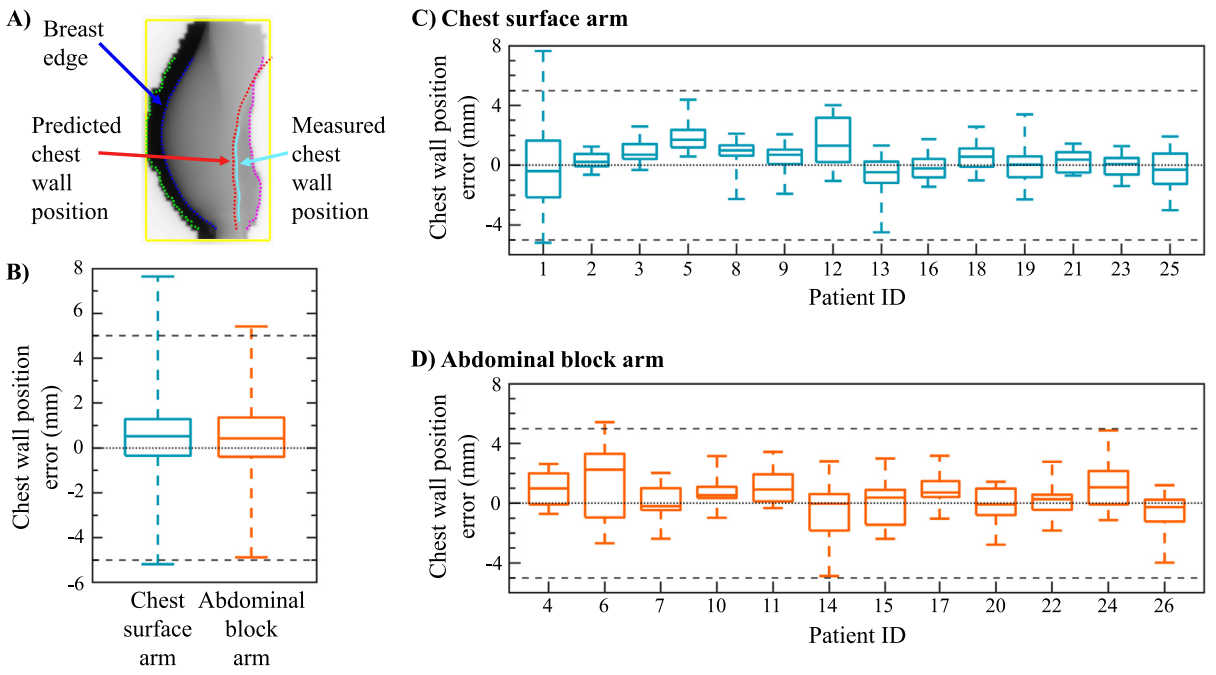

Figure 2 (A) Chest wall position error is the difference between measured and predicted position. Mean per-fraction chest wall position error for (B) all fractions by trial arm; (C) chest surface arm patients; (D) abdominal block arm patients. Lines at ±5 mm represent treatment tolerance.

given by the digitally reconstructed radiograph. Uncertainty in the chest wall position is estimated to be ± 1 mm due to the 1 mm pixel resolution of the cine EPID images. The digitally reconstructed radiograph was generated using a custom Hounsfield Unit range of −600 to −300 to minimize differences in the chest wall intensity profile between the digitally reconstructed radiograph and cine EPID images.

Data analysis

Treatment accuracy was assessed by comparing the per-fraction mean chest wall position error between the 2 arms of the trial. A generalized estimating equation model which adjusts for repeated measurements within individuals and can be used when data is not normally distributed was used to test the trial primary hypothesis.

Following van Herk,[30] the group systematic error (M), SD of the systematic error (Σ) and SD of the random error (σ) for the chest wall position error are reported. Breath hold depths for each arm were compared using an unpaired t test with Welch correction after a Shapiro-Wilk test confirmed normality.

Correlation between internal chest wall motion and external surrogate motion was calculated intrafraction, for the set of timepoints comprising each field, where the chest wall position could be extracted. Spearman correlation was used as the data was not distributed normally for all fields. The relationship between internal and external motions during treatment delivery within a single breath hold can be estimated by $y \approx ax + b$ where y is the true internal chest wall position, x the external surrogate position, a the scaling factor dependent on patient anatomy and monitoring angle differences between beams-eye view and anterior-posterior direction, b the offset factor representing setup and baseline error with respect to the patient positioning at CT simulation.

Reproducibility and stability of individual breath holds were assessed following the definitions by Cerviño et al[22] (Fig. 3A) where the chest wall position could be extracted. Where beam-on time is interrupted within delivery of a field—for example where a patient needs multiple breath holds to complete the delivery—breath holds lasting ≥5 seconds were used for the analysis.

System usability assessment

Usability of the novel Breathe Well system was compared with RPM by administering questionnaires to patients and staff (Appendix E1).[27] Patients were asked to respond after CT simulation and at the end of the first and last weeks of treatment; 1 end-of-treatment questionnaire was not completed. Radiation therapists were asked to respond when they had used the device for 5 CT simulation sessions or after 5 and after 20 treatment fractions. Statistical significance was tested with Wilcoxon matched-pairs signed rank test.

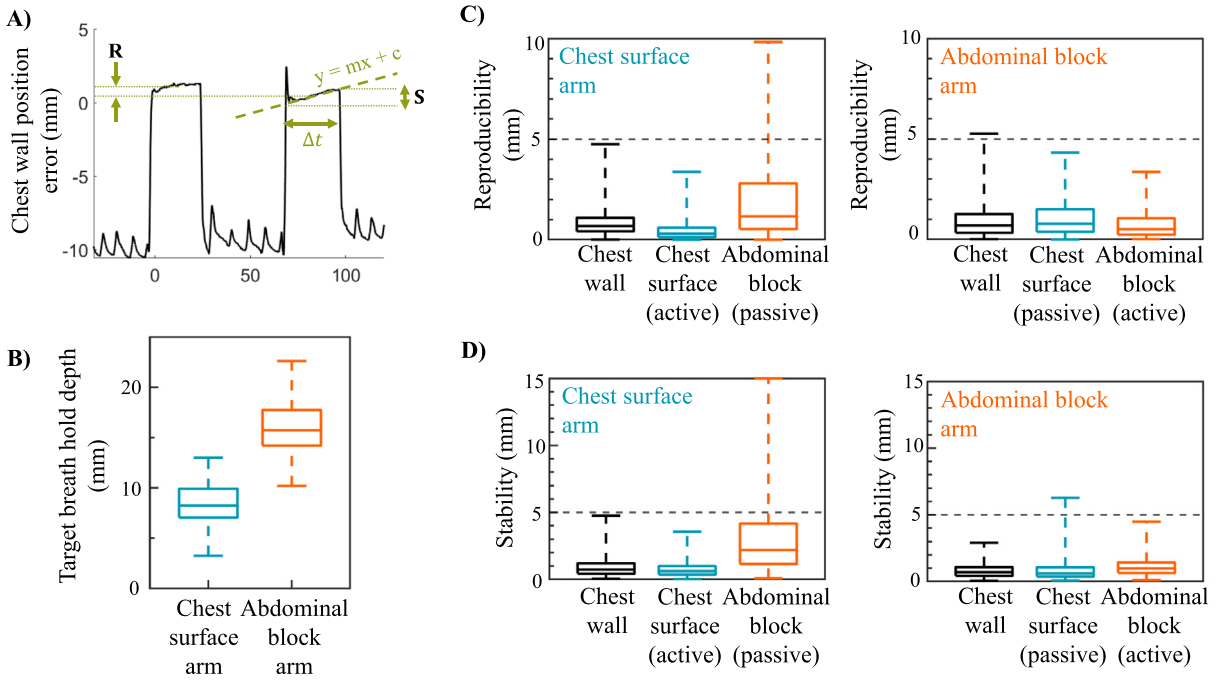

Figure 3 (A) Representative trace illustrating reproducibility and stability. (B) Target breath hold depths on each trial arm. (C) Reproducibility and (D) stability on each trial arm. Lines at 5 mm represent treatment tolerance.

The appointment length for each treatment fraction was estimated by extracting the time between the patient appointment start when the patient is brought to the treatment room and the end of treatment, as recorded in the ARIA patient management system (Varian).

Results

Treatment fraction data could be analyzed for 26 patients consisting of external chest surface motion traces, abdominal block motion traces, and cine EPID imaging for 388 fractions out of 400 delivered. Incomplete data for the remaining fractions due to technical or human error was not included in analysis. The chest wall position was extracted from 73% of the 239,296 cine EPID frames processed. In total, 68% of fields are delivered in a single breath hold averaging 21.3 seconds beam-on time.

Figure 2 shows the distribution of the mean chest wall position error per fraction for each trial arm as a whole and for individual patients. No statistical evidence could be found for superior treatment accuracy defined as a smaller absolute chest wall position error on the chest surface arm (generalized estimating equation model, $P = .77$). The population mean error (M), systematic (Σ), and random (σ) errors were M= 0.4 mm, Σ = 0.7 mm, and σ = 1.4 mm for the chest surface arm and M= 0.4 mm, Σ = 0.7 mm, and σ = 1.5 mm for the abdominal block arm. Chest wall position error is within ±5 mm for 98% of frames on the chest surface arm, 99% of frames on the abdominal block arm. However, there is patient-specific variation in the range of mean chest wall position error per fraction (Fig. 2C, D). For patient 1 on the chest surface arm 1292 out of 7630 frames, 17%, where chest wall could be extracted had position error >5 mm. For patient 6 on the abdominal block arm this was 333 out of 6211 frames, 5%.

Figure 3B shows the target breath hold depths recorded at CT simulation for patients on each arm. The breath hold depth measured at the sternum on the chest surface arm had a median (interquartile range [IQR]) of 8.2 (2.9) mm, whereas that measured at the xiphoid process on the abdominal block arm was found to be significantly larger at 15.7 (3.5) mm (unpaired t test, $P = <.0001$). Seven patients on the chest surface arm had breath hold depths of >8 mm leading to a reduced Breathe Well gating window width. There was a correlation between appointment time and breath hold depth on the chest surface arm $r = -0.63$ ($P = .02$), whereas no significant correlation was observed on the abdominal block arm.

Figure 3C, D shows the breath hold reproducibility and stability of the internal chest wall and external surrogates. The external surrogate used for visual feedback to the patient exhibits better reproducibility and stability than the passively monitored site. On the chest surface arm, reproducibility of the internal chest wall position had a median (IQR) of 0.7 (0.7) mm, whereas the chest surface (active feedback system) showed 0.3 (0.5) mm and the abdominal block (passively monitoring) showed 1.2 (2.3) mm. On the abdominal block arm, chest wall showed 0.7 (0.9) mm, whereas abdominal block (active) showed 0.5

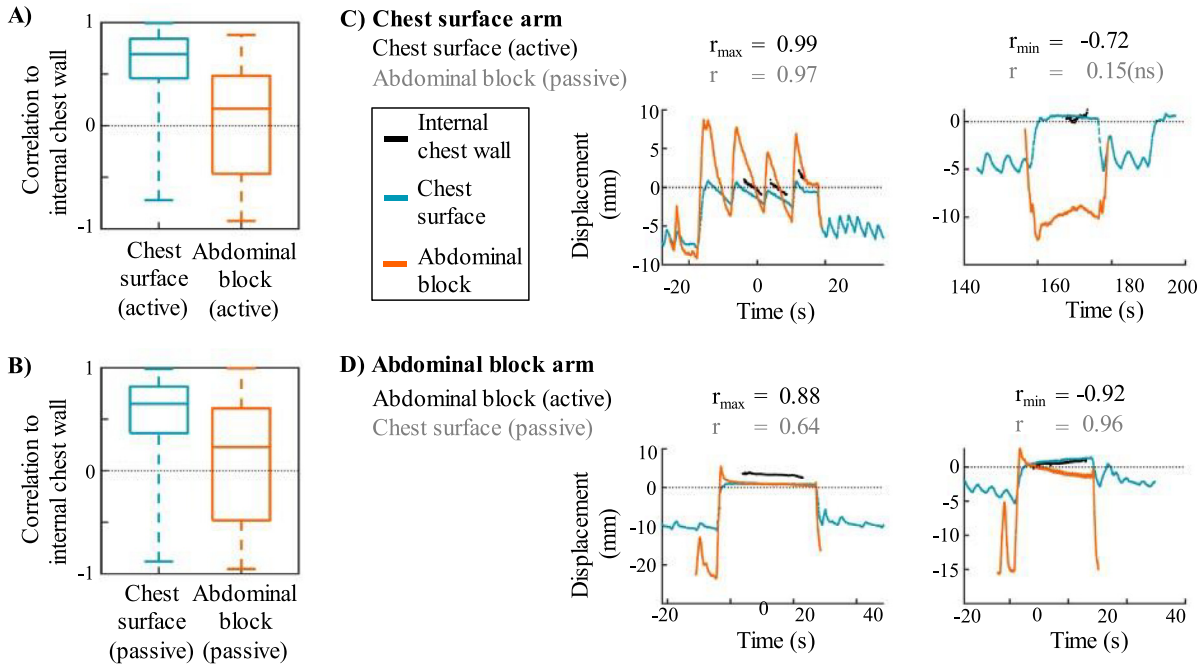

Figure 4 Per-field correlation between motion of the external surrogate and internal chest wall. (A) As the actively monitored point; (B) as the passively monitored point. Motion traces for fields with the highest (r_{max}) and lowest (r_{min}) correlation between actively monitored external surrogate and internal chest wall for (C) chest surface arm and (D) abdominal block arm. (ns) signifies there was no significant correlation i the passively monitoring system (P > 0.05).

(0.8) mm and chest surface (passive) showed 0.8 (1.1) mm.

Stability showed a similar trend with median (IQR) stability on the chest surface arm of the internal chest wall 0.7 (0.8) mm, of the chest surface 0.6 (0.6) mm, and the passive abdominal block 2.1 (3.0) mm. On the abdominal block arm, the respective results were internal chest wall 0.7 (0.7) mm, chest surface (passive) 0.6 (0.7) mm, and abdominal block (active) 0.9 (0.8) mm.

Figure 4 shows the per-field mean correlations between the external surrogate motion and internal chest wall position error. Correlations are shown for the external surrogate both as the active (Fig. 4A), and passive (Fig. 4B) monitoring point. On the chest surface arm data for 476 fields was collected and correlations were significant ($P < .05$) for 431 fields measured with Breathe Well (active) and 402 fields measured with RPM (passive). On the abdominal block arm, data was collected for 346 fields with significant correlations ($P < .05$) for 321 fields measured with Breathe Well (passive) and 284 measured with RPM (active). Median (IQR) correlations for chest surface were r =0.69 (0.38) (active) and 0.65 (0.45) (passive) and for abdominal block 0.17 (0.95) (active) and 0.23 (1.08) (passive). Figure 4C, D shows motion traces where the active system recorded the highest and lowest correlations to the internal chest wall motion (with $P < .05$).

Patient appointment length was collected for 220 treatment fractions on the chest surface arm and 178 on the abdominal block arm. Median (range) appointment length on the chest surface arm was 15 (10-32) minutes and on the abdominal block arm was 15 (9-31) minutes.

Patient experience was investigated by use of a questionnaire (n = 14 chest surface arm, n = 12 abdominal block arm). The majority of patients had no difficulties seeing the screen or holding their breath for the required time, no difficulties hearing breath hold instructions from the staff and found audio instructions helpful, and used a computer either every day or most days (see Appendix E1 for detailed results). Figure 5A shows responses to the question "How comfortable did you feel with the breath hold screen? (Position of screen, distance to screen, etc)." There is a statistically significant improvement in comfort with the breath hold screen from the CT timepoint to the end of treatment for the Breathe Well system ($P = .03$), whereas RPM showed a median within 2 points of the maximum score of 10 at all timepoints (Fig. 5A). Figure 5B shows responses to the question "How easy was it for you to follow the visual information on the screen to reach your breath hold level and hold your breath at the correct level?" indicating patients found the visual feedback from both systems easy to use. There is a visually identifiable trend for increasing ease of use across the timepoints with the Breathe Well system but this did not reach statistical significance. Figure 5C showing responses to the question "How does the breath hold experience make you feel?" identified a trend toward improvement in patient anxiety across the course of treatment with the chest surface system but this was not statistically

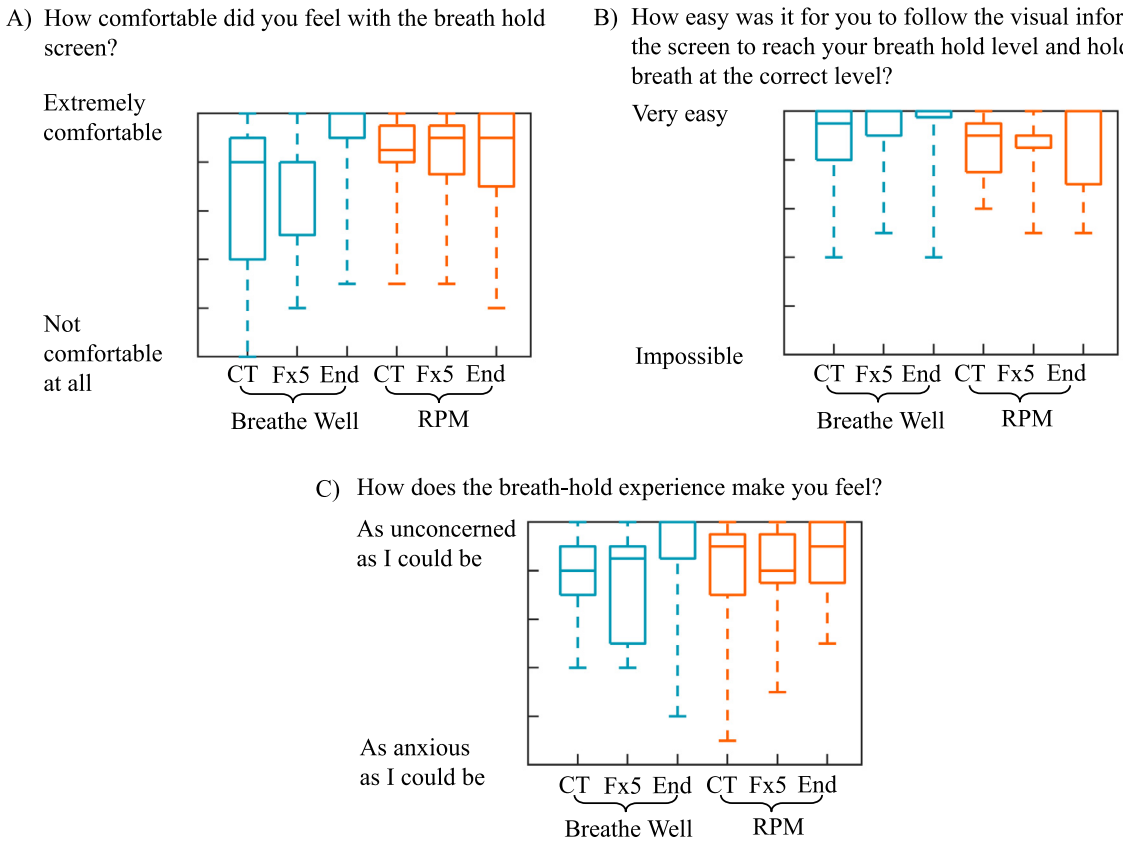

Figure 5 Patient responses to three questions (A, B and C) focusing on patient experience. Questionnaires were collected at 3 timepoints: computed tomography (CT) simulation, after 5 treatment fractions (Fx5), and end of treatment.
Abbreviation: RPM = Real-time Position Management.

significant (between CT simulation and end of treatment, $P = .16$).

Nineteen questionnaires were collected from 11 radiation therapists (see Appendix E1 for complete results). Therapists were familiar with the RPM device in standard use at the site, but were only introduced to the Breathe Well device for this trial. These consisted of 4 after therapists had completed 5 CT simulation sessions with the Breathe Well device, 9 after therapists had completed 5 linac sessions with the device and a further 6 for therapists who completed 20 linac sessions. Therapists had a range of experience with between 1 and 30 years since qualification.

Figure 6A shows therapists' opinion on ease of setup, with no significant differences between the 2 devices detected at each timepoint (at timepoints CT; after 5 and after 20 treatments $P = .5$; .06; .25). Figure 6B show therapists' opinion on ease of operating each system. Respiratory Gating for Scanners scored significantly easier for both linac treatment points ($P < .01$ after 5 treatments; $P = .03$ after 20), but no significant difference was recorded after 5 CT simulations ($P = .5$). Asked which system they would prefer to operate, 18 out of 19 questionnaires across 11 therapists recorded RPM. Eleven of these responses noted integration with the linac and no need for manual gating as a reason. Other themes included uncertainty on whether to re-baseline a patient during treatment and familiarity with RPM.

Discussion

This study allocated patients performing DIBH to a visual feedback system monitoring either the chest surface at the sternum or an abdominal block near the xiphoid process. The internal chest wall position error was measured from cine EPID imaging captured during treatment. To our knowledge, this study is the first prospective randomized study of 2 DIBH devices where both devices monitor all patients, and provides a template for future device comparisons that include treatment accuracy and the patient and radiation therapist experience.

The study showed (Fig. 2) that for some patients in isolated fractions the mean internal chest wall position fell outside the 5 mm tolerance. This could not be ascertained from the external surrogate position. Over 15 or 25 fractions this has limited impact on the mean chest wall position error with the mean error across the population close to 0, but with 5-fraction hypo-fractionated treatment coming into clinical use position errors will have a more

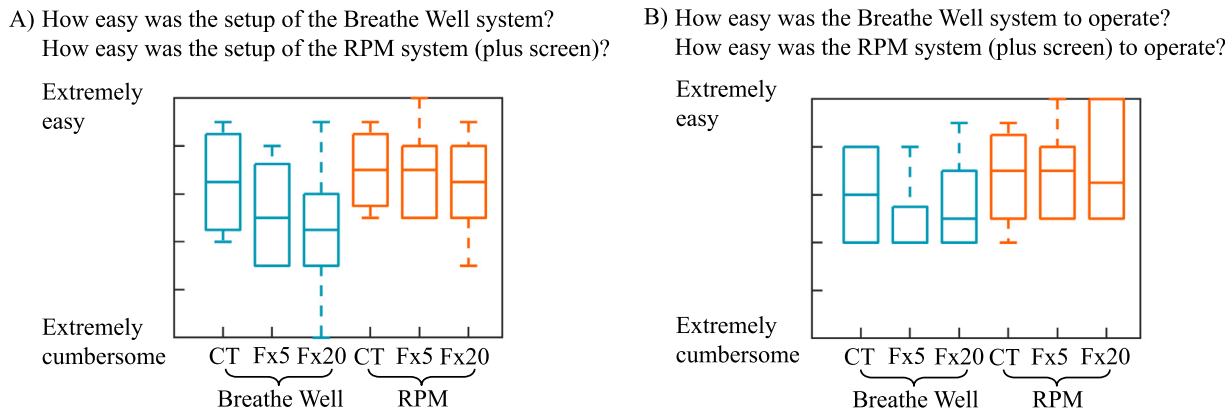

Figure 6 Radiation therapist responses to the two questions focusing on device usability (A and B). Questionnaires were collected at 3 timepoints: after 5 sessions of computed tomography (CT) simulation (n = 4), after treating 5 fractions (Fx5) (n = 9), and after treating 20 fractions (Fx20) (n = 6).
Abbreviation: RPM = Real-time Position Management.

significant impact which can be missed by current external surrogate monitoring.[31] Real-time monitoring of internal chest wall position using a modification of the cine EPID chest wall extraction in this study such as that by Carr et al[29] could provide extra quality assurance at time of treatment to catch these outlier cases.

Skyttä et al[32] compared placement of the RPM marker block on the abdomen and sternum and reported lateral random errors of 1.3 and 1.5 mm for those patient groups after breath hold level correction. This compares to the 1.4 and 1.5 mm random errors in this study. Skyttä et al[32] however found a similar magnitude of systematic error, whereas in this study the systematic error for both arms was only 0.4 mm. This could be due to the use of daily image guidance throughout treatment in this work, whereas Skyttä et al[32] used image guidance for the first 3 fractions only.

The Breathe Well device sets breath hold depth in a practice breath hold before the actual CT scan. If the patient did not center their breath hold depth in the gating window when the actual scan was taken (eg, if their breath hold position was near the edge of the gating window), this will introduce a systematic error throughout treatment. Configuring the ability to allow this correction could lead to reduced systematic errors in this system.

Median reproducibility and stability of the internal chest wall position during DIBH was submillimeter on both trial arms (Fig. 3C, D). On the chest surface arm reproducibility and stability of the abdominal block position is degraded compared with the abdominal block arm, however the internal chest wall position still shows good reproducibility and stability, implying stronger correlation of chest wall to external chest surface than to abdomen.

In this trial, internal and external motions were simultaneously acquired allowing direct comparison. On both arms the chest surface correlates significantly better to the internal chest wall movement than the abdominal block does. However, treatment delivery is equally accurate in both arms. Daily errors in patient positioning and baselining are likely to have a much larger effect on treatment accuracy than motion within breath hold, but the random nature of these minimizes impact when taken across the course of treatment.

Further efforts to reduce treatment error would seem to be best focused on controlling sources of random error between CT simulation and each treatment fraction such as breathing baseline variations and more subtle setup errors such as patient rotation that may not be compensated for by limited angle couch shifts.

Limitations to this study include that the chest wall internal surrogate may not accurately reflect motion of the dosimetrically important organs at risk, in particular the heart. Although DIBH is intended to reduce heart dose, chest wall and heart motion may not be well correlated. A dosimetric analysis is planned to assess the impact of the recorded chest wall motion on the dose delivered to these structures. In addition, motion in the superior-inferior direction was not considered and may contribute to a larger systematic and random error as shown by Delombaerde et al.[25]

Conclusions

The novel Breathe Well device was compared with standard of care RPM for managing DIBH treatment for breast cancer with visual feedback. Treatment accuracy was assessed through position error of the internal chest wall identified on cine EPID image capture. No evidence of superiority of treatment accuracy was found with the novel device compared with standard of care. The population mean error (M), systematic (Σ), and random (σ) errors were M= 0.4 mm, Σ = 0.7 mm, and σ = 1.4 mm for the chest surface arm and M= 0.4 mm, Σ = 0.7 mm, and σ = 1.5 mm for the abdominal block arm. Patient satisfaction questionnaire scores were

similar for the 2 systems and median length of appointment was 15 minutes for both systems. The median correlation coefficient between internal and external movements was higher for chest surface than abdominal block but this is not interpreted as statistically significant.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2024.101572.

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