

**TITLE:** Voluntary breath-hold technique for reducing heart dose in left breast radiotherapy

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**SHORT ABSTRACT:**

The current priority in breast cancer radiotherapy is to reduce cardiac doses without compromising target tissue coverage. The voluntary breath-hold technique described here is a simple, inexpensive solution to this problem and capable of being instituted widely without the need for specialized equipment.

### **LONG ABSTRACT:**

Breath-holding techniques reduce the amount of radiation received by cardiac structures during tangential-field left breast radiotherapy. With these techniques, patients hold their breath while radiotherapy is delivered, pushing the heart down and away from the radiotherapy field. Despite clear dosimetric benefits, these techniques are not yet in widespread use. One reason for this is that commercially available solutions require specialist equipment, necessitating not only significant capital investment, but often also incurring ongoing costs such as a need for daily disposable mouthpieces. The voluntary breath-hold technique described here does not require any additional specialist equipment. All breath-holding techniques require a surrogate to monitor breath-hold consistency and whether breath-hold is maintained. Voluntary breath-hold uses the distance moved by treatment room lasers from the anterior and lateral reference marks (tattoos) in breath-hold to monitor consistency at CT-planning and treatment setup. Light fields are then used to monitor breath-hold consistency prior to and during radiotherapy delivery.

### **INTRODUCTION:**

Cancer is a leading cause of death worldwide, accounting for 7.6 million deaths in 2008<sup>1</sup>. Of all cancers, breast cancer is the most common with an incidence of over 13.8 million worldwide, and this incidence is increasing<sup>1</sup>. However, improvements in the diagnosis and treatment of breast cancer mean that the number of women surviving their breast cancer is also increasing, and is estimated to treble to 1.7 million by 2040 in the UK alone<sup>2</sup>. Breast radiotherapy forms an important part of many women's breast cancer treatment, halving their risk of breast cancer recurrence and reducing the risk of breast cancer death by 3.8%<sup>3</sup>. With improvements in breast cancer survivorship, any long-term side-effects caused by breast cancer treatments are increasingly important. An innocent bystander in breast radiotherapy is the heart, which is exposed to unwanted radiation as a result of its proximity to radiation fields, especially during left breast irradiation. It is this unwanted dose to the heart that accounts for the 1% increase in non-breast cancer deaths associated with breast radiotherapy<sup>4</sup>. Recent evidence suggests that there is no threshold dose below which the late cardiac effects of breast radiotherapy do not occur<sup>5</sup>, making it critical for the oncology community to establish techniques which minimize cardiac doses without compromising breast tissue coverage. However, since breast radiotherapy accounts for approximately 30% of all radiotherapy treatments<sup>6</sup>, any new technique must be simple and inexpensive in order to be sustainable and avoid an unacceptable burden on healthcare resources.

There are a number of techniques which may be employed to reduce heart doses during breast radiotherapy. Multileaf collimation (MLC) is widely used in the UK [Royal College of Radiologists' (UK) audit 2012] and although effective at sparing heart tissue, it risks simultaneously shielding breast tissue. Inverse-planned intensity modulated radiotherapy (IMRT) improves target tissue conformality<sup>7</sup>, but may also increase low-dose irradiation of the heart, lungs and contralateral breast<sup>7,8</sup>. An increase in low dose irradiation of the heart is undesirable, particularly in light of the data from Darby *et al.*<sup>5</sup>. In addition, inverse-planned

IMRT is more resource-intensive, requiring greater physics and quality assurance (QA) time and expertise. Treating women in the prone (face-down) position may reduce cardiac doses in larger-breasted women<sup>9</sup>, however, questions remain over the positional reproducibility of this technique<sup>10</sup>. Breath-holding techniques, in which patients hold their breath during radiotherapy delivery, result in the heart being pushed down and away from the radiotherapy fields and may minimize the need for a compromise between target tissue coverage and organ-at-risk (OAR) sparing (**Figure 1**)<sup>11</sup>.

There are currently two main breath-holding techniques in clinical use. The first consists of a digital spirometer attached to a balloon valve. Patients breathe through a mouthpiece and a clip is placed on their nose to avoid nasal respiration. The spirometry trace is visualized on a monitor, and inspiration interrupted and held at a predetermined lung volume. The second method was primarily designed for use as a respiratory gating system, although it also has an in-built breath-hold setting. This system uses a video camera to record the motion of an infrared-reflecting marker placed on the chest of the patient. The vertical movement of the marker is displayed in real-time on a monitor, and treatment delivery commences once the marker moves into a pre-specified threshold zone. Both systems markedly reduce cardiac doses in patients receiving left breast radiotherapy. The spirometry-based technique significantly reduces the volume of myocardium irradiated<sup>12-14</sup>, as well as demonstrating comparable intra- and inter-fraction reproducibility compared to standard supine free-breathing breast radiotherapy<sup>15</sup>. Similarly, treatment using the infrared-reflecting markers reduces the mean dose to the heart by over 50%<sup>11,16,17</sup>, whilst maintaining target tissue coverage<sup>11</sup>. Such dosimetric savings are projected to equate to a 10-fold reduction in cardiac deaths<sup>18</sup>.

A drawback of these systems, however, and a barrier to widespread implementation, is their cost. Both systems require investment in the devices themselves, however, in the case of the spirometry system there are also ongoing costs as the mouthpieces are disposable, requiring a new mouthpiece for planning-CT as well as for each fraction of treatment. Cost, coupled with a lack of staff training, explains why only 4% of UK breast treatments were performed using breath-holding techniques in 2012 [Royal College of Radiologists' (UK) audit]. Breath-holding techniques are in more widespread use in the rest of Europe, with 20% of centers using these techniques in 2010<sup>19</sup>. One explanation for this is the development and implementation of a simple, inexpensive and equipment-free breath-holding technique, voluntary breath-hold (VBH). Until recently, however, data was lacking on the reproducibility of the VBH technique. A randomized study conducted at the Royal Marsden Hospital (Sutton, UK), The UK HeartSpare Study, has demonstrated that interfraction reproducibility with the VBH technique is comparable to that with the spirometry-based device. In addition, the VBH technique offers a time advantage at planning-CT and treatment setup and is preferred by patients and radiographers alike<sup>20</sup>. The VBH technique is currently being rolled out to five UK radiotherapy centers to confirm that the technique is feasible in a multicenter setting and that heart-sparing is maintained (HeartSpare II). It is expected that this will pave the way for the UK-wide uptake of heart-sparing breast radiotherapy, and is likely to lead to a significant reduction in heart disease among UK breast cancer survivors.

## **PROTOCOL:**

The study through which this protocol was implemented was approved by the Royal Marsden Committee for Clinical Research (Sutton, UK) and the Research Ethics Committee (London – Riverside, UK) (ISRCTN 53485935).

### **1. Radiotherapy clinic**

- 1.1) Assess patient suitability for the voluntary breath-hold technique in the clinic: left breast or chest wall radiotherapy (without nodal irradiation) recommended by radiation oncologist.
- 1.2) Review the patient's performance status and comorbidities (especially lung-related).
- 1.3) Ask the patient to practice holding their breath at home, while lying down, initially for 5 seconds, and building up in 5 second intervals to 20 seconds.

### **2. Radiotherapy planning-CT session**

- 2.1) Position the patient on the CT couch in the standard treatment position.
- 2.2) Define the position of tattoos and place CT markers (crosses) on the patient midline in free-breathing, approximately half way along the likely field edges. Add lateral markers to each side of the patient in free-breathing, in line with the midline marker.
- 2.3) Ask the patient to practice taking a deep breath in and holding it, initially for 5 seconds, before building up in 5 second intervals to 20 seconds. Instruct the patient to breathe in and breathe out twice before asking them to hold their breath for up to 20 seconds. This relaxes the patient, helps them prepare for the breath-hold and helps breath-hold consistency.
- 2.4) Record the maximum duration for which the patient can comfortably hold their breath.
- 2.5) Repeat the breath-hold and mark the position of the anterior and lateral tattoos in relation to the lasers in breath-hold to help establish reproducibility. Record the height of the lateral tattoo above the couch top during breath-hold before proceeding with the CT scan.
- 2.6) Give the standard breath-hold instructions to the patient and start the scan once satisfied the patient is in breath-hold.
- 2.7) Once the CT scan has been completed, check and record the height of the lateral tattoos on the CT scan to confirm that a consistent breath-hold was performed. If the lateral couch height differs by greater than 3mm from the initial couch height, re-measure the anterior and lateral reference points.

### **3. Radiotherapy treatment planning**

*Note: the radiotherapy treatment planning process is the same as for a standard breast patient.*

- 3.1) Apply tangential radiotherapy fields according to local protocol.
- 3.2) Produce clinical radiotherapy treatment plan which fulfills ICRU criteria.
- 3.3) Record the anterior beam source-to-skin distance (SSD) in addition to recording standard treatment planning data (according to local protocol).

*Note: the anterior beam SSD is used to check the anterior-posterior setup in the treatment room.*

### **4. Radiotherapy treatment setup**

- 4.1) Align the tattoos in free-breathing. Mark the posterior and inferior measurements from the left lateral tattoo and the anterior midline tattoo on the patient's skin (from information recorded at planning-CT session).
- 4.2) Instruct the patient to breathe in and out twice before taking a deep breath in and holding. The reference mark on the patient's skin should rise up to the level of the laser. Ask the patient to repeat the breath-hold procedure a couple of times to confirm reproducibility before proceeding with patient setup.
- 4.3) Ask the patient to perform a breath-hold and align the midline tattoo to the isocenter position superior/inferior and set the field-to-skin distance (FSD) at the midline.
- 4.4) In free-breathing, move the bed laterally to the isocenter.
- 4.5) Measure and mark the medial and lateral field borders in free-breathing.
- 4.6) Set all other machine parameters (eg. field size and gantry, collimator and couch angles) for the first beam (anterior oblique). Ask the patient to perform a breath-hold and check the medial border aligns with mark made in 4.5.
- 4.7) Mark the field edge (as defined by the light field) with a pen at every fraction: this aids visualization of the patient's breath-hold.
- 4.8) Repeat steps 4.6 and 4.7 for the posterior oblique beam, and treat using this beam first.

4.9) If patient setup is out of tolerance (according to local tolerance levels for a standard breast radiotherapy patient), refer to the troubleshooting algorithm (**Figure 2**).

4.10) If there are insufficient cameras to monitor the field edge as well as the position of the gantry relative to the couch from the control room, assess gantry rotation prior to leaving the treatment room in order to avoid collisions.

## **5. Radiotherapy treatment delivery**

5.1) Once in the control room, zoom the treatment room cameras so that the field borders marked on the patient's skin are visible on the control room monitors.

5.2) Once ready to commence treatment, ask the patient to perform a breath-hold (as detailed in 4.2) via the intercom system. Check the light field aligns satisfactorily with the marked field border and then commence treatment (**Figure 3**).

5.3) Monitor the patient's breath-hold during treatment delivery. Treatment should be interrupted if there is concern that there has been a change in breath-hold depth.

## **6. Radiotherapy treatment verification**

6.1) Perform imaging verification of patient position (such as with electronic portal imaging (EPI) or cone-beam CT), following local protocols for type/frequency of imaging and tolerance levels.

6.2) Correct for systematic errors with isocenter moves according to local protocols for standard breast radiotherapy patients. Adjustment of marks on the patient's skin should not be necessary.

### **REPRESENTATIVE RESULTS:**

Real-time electronic portal images (EPI) were matched on-line to digitally reconstructed radiographs (DRRs) for 23 patients (172 treatment fractions). EPI displacements were analyzed for the right anterior and left posterior oblique beams in the (u,v)-plane (v-direction parallel to craniocaudal axis and u-direction perpendicular to this)<sup>21</sup>, and setup errors for the VBH technique estimated. EPI-based population systematic error range (for each beam and in each plane) was 1.5-1.8mm and random error range 1.7-2.5mm.

Tabular dose-volume histogram (DVH) data was used to derive the  $NTD_{mean}$  (a biologically weighted mean of total dose to tissue normalized to 2Gy fractions using a standard linear quadratic model<sup>22</sup>,  $\alpha/\beta=3Gy$ ) for heart, left anterior descending coronary artery (LAD), ipsilateral and whole lungs. In addition, the maximum dose received by the LAD ( $LAD_{max}$ ) was estimated. Normal tissue doses are shown in **Table 1**.

Times for planning-CT session, treatment setup, treatment delivery and total treatment session were recorded, and are shown in **Table 2**. The data demonstrate that planning-CTs can be completed within a standard 30 minute session. Treatment times include CBCT imaging, which was performed for every third fraction. Treatment setup and total session times are, therefore, expected to be shorter than reported here for centers in which CBCT imaging is not part of standard treatment. However, even with CBCT imaging, treatments may be completed within a 20 minute treatment session.

Patients and radiographers were asked to complete validated questionnaires<sup>23</sup> at their planning-CT session as well as twice during their treatment. Sixty-five patient questionnaires and 64 radiographer questionnaires were analyzed. The questionnaires were summarized as patient comfort scores (PCS) and radiographer satisfaction scores (RSS) (out of 9, higher score = more comfortable/satisfactory). Median PCS was 8 (interquartile range 8-9) and median RSS was 7 (interquartile range 6-8).

**Figure 1: The heart-sparing effect of VBH.** Axial and sagittal CT slices from the same patient at the same chest wall level in free-breathing (**Figures 1A and 1C**) and using the VBH technique (**Figures 1B and 1D**). Note that the heart (outlined in yellow) has been pushed down and away from the radiotherapy fields using the VBH technique.

**Figure 2: Troubleshooting algorithm for voluntary breath-hold technique treatment setup.** This algorithm may be used to assist treatment setup where patients are not setting up within tolerance (according to local tolerance levels). As an example, our center uses a 5mm tolerance level. The algorithm should be followed from top to bottom. In the majority of cases, setup can be brought within tolerance by asking the patient to modify their breath-hold depth (deeper or shallower as required).

**Figure 3: Checking breath-hold consistency from the control room.** Control room CCTV stills demonstrating the position of the light field relative to the marked field border for a right anterior oblique beam in free-breathing (**Figure 3A**) and the aligning of the light field and marked field border once the patient is in breath-hold (**Figure 3B**).

**Table 1: Normal tissue doses for the voluntary breath-hold (VBH) technique.** Median, minimum and maximum  $NTD_{mean}$  (Gy) for heart, LAD, ipsilateral and whole lungs are shown, as are median, minimum and maximum  $LAD_{max}$  (Gy). In addition, median, minimum and maximum cardiac doses for standard free-breathing (FB) left breast radiotherapy at our center are shown for comparison.

**Table 2: Planning-CT and treatment session times for the voluntary breath-hold technique.** Median, minimum and maximum planning-CT, treatment setup, treatment delivery and total treatment session times are shown (mins).

## DISCUSSION:



Critical steps in the protocol include: 1) checking for breath-hold consistency at planning-CT and treatment setup; 2) checking the lateral couch height measured on CT is consistent with that measured pre-CT; 3) aligning tattoos in free-breathing but setting FSD in breath-hold; 4) ensuring light field aligns with marked field borders prior to commencing treatment.

The number of breath-holds required during treatment delivery varies from patient to patient, and is primarily dependent on the number of segments being delivered. Suitable interruption points during treatment delivery (to enable the patient to relax before repeating a breath-hold) should be determined on an individual basis depending on the method of delivery. We would strongly suggest that for initial implementation of VBH that a consistent team is used. This enables those involved to become competent more quickly and helps maintain treatment quality. Where problems are encountered during treatment setup, the patient may be asked to modify their breath-hold (deeper or shallower as required). If this fails to improve setup, the patient should be set up again. Vector couch moves should be employed as a last resort. A troubleshooting algorithm is shown in **Figure 2**.

[Place Figure 2 here]

Population systematic and random treatment setup errors are less than those seen in free-breathing tangential field breast radiotherapy<sup>24</sup>, and consistent with other published data on breath-holding techniques<sup>25,26</sup>. VBH reduces median normal tissue doses by 25-58% compared with standard free-breathing breast radiotherapy at our center (**Table 1**). Cardiac doses with VBH are lower than those seen in other published work on breath-holding techniques<sup>11,16,17,26,27</sup>, although methods of recording dose data vary between these studies.

As described in the introduction, all breath-hold techniques use a surrogate to measure inter- and intrafraction reproducibility. The VBH technique uses alignment of the light field with marked field borders to check for consistency before commencing treatment and during treatment delivery. Although not yet formally reported, we have found intrafraction reproducibility (measured using multiple intrafraction EPIs) to be extremely good, with little, if any, intrafraction movement. This is consistent with previously published work<sup>26</sup>. Given the consistent intrafraction reproducibility observed, radiotherapy systems in which light fields do not remain on during treatment delivery need not be a barrier to implementation of VBH. In-room lasers may be used as an alternative to light fields for checking that the breath-hold is maintained during treatment delivery.

VBH offers significant advantages over other heart-sparing techniques, some of which have already been alluded to. It minimizes the trade-off between target and OAR compromise often required when using MLC, it reduces the low-dose irradiation of the heart and is much less resource-intensive than IMRT, and it is more reproducible than prone irradiation whilst benefiting women of all breast sizes. With respect to other breath-holding techniques, VBH gives comparable reproducibility and heart-sparing, while being less expensive to implement as no specialist equipment is required. The low cost of the technique means that there is a very

real opportunity for it to benefit other healthcare systems, especially those with limited resources.

There is already published work demonstrating the feasibility of delivering nodal irradiation in addition to whole breast/chest wall irradiation using the infrared-reflecting markers<sup>17</sup> and spirometry-based<sup>14</sup> systems. Our center is now performing further work to confirm the feasibility of using VBH for nodal irradiation in breast cancer patients. Inverse-planned IMRT is likely to be of benefit in selected patients, especially when delivering a simultaneous integrated boost, and the feasibility of using VBH in these patients needs to be assessed. Finally, breath-holding techniques may be of benefit when treating other tumors, including lung<sup>28</sup>, liver<sup>29</sup> and gastric<sup>30</sup> cancers. Further work is needed to assess the suitability of using the VBH technique for treating sites other than breast.

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#### **DISCLOSURES:**

The authors have nothing to disclose.

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