The UK HeartSpare Study (Stage II): Multicentre evaluation of a voluntary breath-hold technique in patients receiving breast radiotherapy

Frederick R. Bartlett[a,b], Ellen M. Donovan[c], Helen A. McNair[a], Lee A. Corsini[d], Ruth M. Colgan[c], Philip M. Evans[c,e], Lauren Maynard[f], Clare Griffin[f], Joanne S. Haviland[g], John R. Yarnold[h], Anna M. Kirby[a,*]

[a] Department of Radiotherapy, Royal Marsden NHS Foundation Trust, Sutton, UK

[b] Department of Oncology and Haematology, Queen Alexandra Hospital, Portsmouth, UK

[c] Joint Department of Physics, Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Sutton, UK

[d] Department of Radiotherapy, Royal Marsden NHS Foundation Trust, London, UK

[e] Centre for Vision, Speech and Signal Processing, Faculty of Engineering and Physical Sciences, University of Surrey, Guildford, UK

[f] Clinical Trials and Statistics Unit (ICR-CTSU), Institute of Cancer Research, London, UK

[g] Faculty of Health Sciences, University of Southampton, Southampton, UK

[h] Division of Radiotherapy and Imaging, Institute of Cancer Research, Sutton, UK

Running title: HeartSpare multicentre study

[*]**Corresponding author:** Dr Anna Kirby FRCR, Department of Radiotherapy, Royal Marsden NHS Foundation Trust, Sutton, SM2 5PT, United Kingdom. Telephone: +44 20 8661 3169. Fax: +44 20 8661 3127. Email: anna.kirby@rmh.nhs.uk.

Keywords: Radiotherapy; breast cancer; cardiac dose; breath-hold; heart-sparing breast radiotherapy

Number of pages: 15 (including title pages)

Number of tables: 2

Number of figures: 1

Acknowledgements: This article presents independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-1010-23003). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. The work was partly undertaken in The Royal Marsden NHS Foundation Trust which receives a proportion of its funding from the NHS Executive; the views expressed in this publication are those of the authors and not necessarily those of the NHS executive. We acknowledge NHS funding to the NIHR Biomedical Research Centre and the support of the NIHR, through the South London Cancer Research Network. ED is funded by an NIHR Career Development Fellowship CDF-2013-06-005.

Abstract

Background and Purpose: To evaluate the feasibility and heart-sparing ability of the voluntary breath-hold (VBH) technique in a multicentre setting.

Material and Methods: Patients were recruited from 10 UK centres. Following surgery for early left breast cancer, patients with any heart inside the 50% isodose from a standard free-breathing tangential field treatment plan underwent a second planning-CT scan using the VBH technique. A separate treatment plan was prepared on the VBH CT scan and used for treatment. Mean heart, left anterior descending coronary artery (LAD) and lung doses were calculated. Daily electronic portal imaging (EPI) was performed and scanning/treatment times were recorded. The primary endpoint was the percentage of patients achieving a reduction in mean heart dose with VBH. Population systematic (Σ) and random errors (σ) were estimated. Within-patient comparisons between techniques used Wilcoxon signed-rank tests.

Results: 101 patients were recruited during 2014. Primary endpoint data was available for 93 patients, 88 (95%) of whom achieved a reduction in mean heart dose with VBH. Mean cardiac doses (Gy) for free-breathing and VBH techniques respectively were: heart 1.8 and 1.1, LAD 12.1 and 5.4, maximum LAD 35.4 and 24.1 (all $p<0.001$). Population EPI-based displacement data showed Σ of 1.3-1.9mm and σ 1.4-1.8mm. Median CT and treatment session times were 21 and 22 minutes respectively.

Conclusions: The VBH technique is confirmed as effective in sparing heart tissue and feasible in a multicentre setting.

Breast radiotherapy forms an integral part of many women's breast cancer treatment, halving the risk of breast cancer recurrence and reducing breast cancer mortality [1, 2]. Breast radiotherapy is, however, associated with an increase in cardiac mortality [3] and morbidity [4], with patients receiving left breast radiotherapy particularly at risk [5] due to the proximity of the heart to tangential fields. Although mean cardiac doses from breast radiotherapy have reduced substantially since the 1980s [6], the linear relationship between the risk of cardiac events and mean heart dose and absence of a lower dose threshold [7] mean that reducing heart dose in breast radiotherapy remains a priority. Heart-sparing breast radiotherapy techniques, including deep inspiratory breath-hold (DIBH), have been shown to be capable of reducing heart doses by around 50% [8-12].

An audit of UK breast radiotherapy practice by the Royal College of Radiologists in 2012 [Dr Imogen Locke, personal communication] found that, for 49% of patients with 'heart in the field', no cardiac-sparing technique was used. In the majority of the remainder, multileaf collimation was used but, as demonstrated previously [13], this technique risks compromising target tissue coverage. Only 4% of centres used a DIBH technique. This low usage of heart-sparing radiotherapy was thought in part to reflect the fact that commercially-available systems are expensive to purchase and maintain. In order to overcome resource limitations, Stage IA of the UK HeartSpare Study evaluated an equipment-free voluntary breath-hold technique (VBH) using skin surface marks as fiducials, and demonstrated that this technique was comparable to treatment with a commercially-available system in terms of cardiac sparing and reproducibility [14]. Although the results from this single centre study were promising, further evaluation was required to establish the VBH technique as heart-sparing and feasible in other people's hands. This non-randomised study therefore evaluated the heart-sparing ability and feasibility (i.e. reproducibility of set up and scanning/treatment times) of the VBH technique in a national multicentre setting.

Material and Methods

This study was approved by Research and Development and Research Ethics Committees (ISRCTN 62239447). Ten UK centres were selected, all of whom had satisfied the requirements of the UK National Cancer Research Institute (NCRI) FAST-Forward trial quality assurance programme, although participation in FAST-Forward was not a prerequisite to patient participation. Centres were selected on the basis of their FAST-Forward recruitment record and/or active participation in VBH technique development. In order to facilitate implementation at participating centres, all centres were invited to attend a training day. Centres were also provided with a technical video of the VBH technique in order to enhance local training and implementation. Skeleton work instructions were provided and each centre's work instructions were reviewed by the trials team. All centres were required to submit recent electronic portal imaging (EPI) displacement data for ten consecutive left breast radiotherapy patients treated at their centre using standard free-breathing tangential field radiotherapy (minimum of five images per beam). Approval for study participation was granted locally at each centre.

All participants underwent left breast conserving surgery or mastectomy for early stage invasive ductal or lobular carcinoma (pT1-3b N0-1 M0) or ductal carcinoma in situ (DCIS) and were recommended adjuvant radiotherapy to the whole breast or chest wall without nodal irradiation (+/- tumour bed boost). Women whose free-breathing planning-CT scan demonstrated the presence of any heart tissue within tangential radiotherapy fields placed according to standard anatomical borders (i.e. any heart within the 50% isodose) were approached. Patients were treated at 10 UK radiotherapy centres. This prospective study was not randomised.

Patient positioning and image acquisition

Radiotherapy planning-CT scanning was performed in accordance with the FAST-Forward trial protocol [15]. The method for CT scanning using the VBH technique has been described previously [16]. All patients received training in the VBH technique prior to CT scanning [16]. For VBH planning-CT scans, patients were aligned on the CT couch using markers (tattoos) placed during their previous free-breathing planning-CT scan.

The time taken to complete each CT-planning session was recorded. After both scans were completed, patients and radiographers were asked to complete validated questionnaires [17] (see supplementary figures S1 and S2).

Target and organ-at-risk delineation

Target tissue and organs-at-risk (heart, lungs) were delineated in accordance with the FAST-Forward trial protocol on both free-breathing and VBH planning-CT scans. Either volume-based or field-based target outlining was performed, according to centre preference. To ensure consistency, the differences between target tissue PTVs for free breathing and VBH volumes were constrained to be no greater than 10%. The left anterior descending coronary artery (LAD) was also outlined, as described previously [18].

Radiotherapy planning

Computer planning was performed on 3D datasets, and corrections for tissue heterogeneity were applied. Tangential fields were used to encompass the PTV, minimising dose to the ipsilateral lung and heart. Plans were prepared such that ≥90% of whole breast/chest wall PTV was covered by the 95% isodose (V95% ≥90%), V105% ≤7%, V107% ≤2% and maximum point dose (D_{max}) was ≤110%.

Dose constraints were applied for heart and ipsilateral lung. For heart, V25% ≤5% and V5% ≤30% and for ipsilateral lung V30% ≤17%. The prescription dose was 40.05Gy in 15 fractions over 3 weeks, except for patients randomised to a test arm of FAST-Forward for whom the prescribed dose was 26/27Gy in 5 fractions over 1 week. Treatment technique and prescription dose were not specified for boost treatments, and no study data for this portion of a patient's treatment was collected.

Mean heart, LAD, ipsilateral and whole lung and maximum LAD (LAD_{max}) doses were estimated for both free-breathing and VBH treatment plans. Dosimetric data was collected directly from participating centres' computer planning systems.

Radiotherapy delivery

Patients were treated using the VBH technique, although free-breathing treatment (using the free-breathing treatment plan) could be used at the discretion of the attending clinician (for example if a patient was unable to tolerate breath-hold on treatment). The VBH treatment technique for Elekta systems (Elekta, Crawley, UK) has been described previously [16]. For Varian systems, in-room lasers were used instead of light fields, because on Varian systems light fields switch off once the treatment beam is switched on. Treatment verification and corrections were performed according the FAST-Forward trial protocol [15]. For study reporting purposes, megavoltage EPI for both tangential fields was acquired daily and setup errors measured.

Times at which patients mounted/dismounted the couch and at which the radiotherapy beam was switched on and off were recorded for every fraction. Patients and radiographers were asked to complete validated questionnaires recording comfort and satisfaction with the VBH technique on fractions 1 and 4 [17].

Statistical methods

Using the Fleming A'Hern single stage procedure [19], a sample size of 33 patients was estimated to provide 90% power to detect if at least 75% of patients achieve a reduction in mean heart dose (Gy) with VBH compared with free-breathing, and exclude if this is less than 50% of patients (assuming a significance level of 0.05). It was envisaged that there may be a 'learning curve' with implementation of this technique at participating centres. In view of this, the first 5 patients recruited at each centre were included in a sensitivity analysis. Allowing for an additional 10% drop-out rate, the estimated sample size was 90 patients.

Dose-volume histogram (DVH) data was used to determine the percentage of patients in whom a reduction in mean heart dose (Gy) was achieved with VBH and was compared between the two techniques (VBH and free-breathing) within individuals using Wilcoxon signed rank tests as the data was not normally distributed.

EPI displacements were analysed in the (*u,v*)-plane for each patient (v-direction parallel to craniocaudal axis and u-direction perpendicular to this) [20], and population mean displacement (M), systematic (Σ) and random (σ) errors were estimated using the method described by van Herk [21].

Patient comfort and acceptability questionnaires for the VBH technique (see supplementary figures S1 and S2) were summarised as patient comfort scores (PCS) ranging from 0 (least comfortable) to 9 (most comfortable). Radiographer satisfaction questionnaires were summarised as radiographer satisfaction scores (RSS) ranging from 0 (most satisfactory) to 9 (least satisfactory). Scores were calculated at each time-point (CT, first and fourth fractions).

Statistical analyses were performed using SPSS Statistics Version 21 (IBM, Portsmouth, UK).

Results

101 patients were recruited from 10 UK centres between January and October 2014. Primary endpoint data was available for 93 (92%) patients and 88 (87%) patients completed treatment with VBH (see supplementary figure S3). The median age of patients recruited was 56 years (range 27-78). 80 (79%) patients underwent breast conserving surgery, 11 (11%) patients underwent mastectomy (+/- reconstruction) and operation data was missing for 10 (10%) patients.

Initial analysis demonstrated that dosimetric, reproducibility and timing data for the first five 'learning curve' patients treated at each centre were comparable to patients treated subsequently (see supplementary tables S1-3). As such, data for the whole population were analysed together and are presented here.

88/93 (95%) patients achieved a reduction in mean heart dose on their VBH radiotherapy treatment plan compared to their free-breathing treatment plan (mean reduction in dose 41%, $p<0.001$). Two (2%) patients were withdrawn before dosimetric analysis on the basis that no difference in heart position was seen when visually comparing their free-breathing and VBH planning-CT scans. In a further two (2%) patients there was no difference in mean heart dose between the free-breathing and VBH treatment plans, and in one patient mean heart dose was less with free-breathing than VBH. Mean LAD and LAD_{max} doses were reduced with VBH by 55% and 32% respectively (both $p<0.001$). No significant difference in mean lung doses was found between the two techniques. Mean normal tissue doses for free-breathing and VBH techniques are shown in Tables 1 (whole population) and S4 (grouped by centre).

EPI displacement data are given in Tables 2 (whole population) and S5 (grouped by centre). The range of Σ and σ across centres was 0.3-2.6mm and 1.0-3.2mm respectively. One centre detected a systematic error in the superior-inferior direction during the course of the study. This was investigated by the trial management team together with the centre in question, and found to be

due to an incorrect setup procedure. On review, the error was found not to be of clinical significance and the centre's setup procedure was corrected.

Median patient comfort scores (range) [interquartile range] were 8 (2-9) [6-9], 8 (2-9) [6-9] and 9 (0-9) [6-9] at CT-planning, fraction 1 and fraction 4 respectively (where 0 is least comfortable and 9 is most comfortable). Median radiographer satisfaction scores were 2 (0-9) [1-4], 1 (0-9) [0-3] and 1 (0-9) [0-3] at CT-planning, fraction 1 and fraction 4 respectively (where 0 is most satisfactory and 9 is least satisfactory). Supplementary table S6 shows questionnaire results grouped by centre.

The median CT-planning session time was 21 minutes, and was under 30 minutes in 9 out of 10 centres. The median treatment session time over a treatment course was 22 minutes (see Figure 1), with patient setup accounting for 55% and treatment delivery accounting for 36% of this time. Median treatment session times were under 25 minutes for all centres (see supplementary table S7).

Discussion

This non-randomised study demonstrated that implementation of the VBH technique in a multicentre setting was both heart-sparing and feasible. The technique was reproducible across centres, acceptable to patients and radiographers and deliverable in treatment sessions of just over 20 minutes.

Mean heart dose was reduced with VBH in 95% of patients, well in excess of the 75% threshold set. VBH reduced all cardiac dose parameters measured, and the relative reductions seen are consistent with published literature [8-12].

This study detected no significant difference between mean lung doses for free-breathing and VBH techniques. Published data suggest that DIBH techniques, although increasing absolute lung volume irradiated, tend to decrease fractional lung volume irradiated such that mean lung doses are

reported as 4-24% lower than with free-breathing techniques [8, 10-12, 22]. However, the relative reduction in lung dose in the largest of these studies (*n*=53) was also the lowest (4%) and was not statistically significant [11], suggesting that there may in fact be little difference in lung dose between free-breathing and DIBH techniques.

The EPI-based population systematic and random errors in this study were small and consistent across participating centres. The errors were in line with those reported previously using VBH [14, 23] and are well within values recommended for breast radiotherapy [24]. However, one centre did detect a systematic error during the course of study participation. The cause of this error was an incorrect treatment setup procedure, specifically not setting the isocentre to the midline tattoo in breath-hold. This is a vital step in the setup procedure, but easy to overlook if staff are not familiar with DIBH techniques. As a result of this error, all treatment plans of affected patients were reviewed and all were deemed to have received adequate tumour bed and breast coverage. In addition, the work instructions of all participating centres were reviewed for procedural errors. Although no clinical harm resulted, this incident highlights the need for internal auditing of setup procedures and reproducibility data when implementing novel radiotherapy techniques.

This study used validated questionnaires to assess patient comfort and acceptability and radiographer satisfaction with the VBH technique, both important factors in the implementation of new radiotherapy techniques. VBH was viewed favourably by patients and radiographers alike in previous studies [14, 23]. However, in those studies it was compared to techniques which were viewed less favourably, and it is possible that this may have artificially enhanced the profile of VBH. However, the median questionnaire scores, narrow interquartile ranges and consistency in scores across participating centres suggest that VBH is acceptable to both patients and radiographers in a multicentre setting.

Breast radiotherapy accounts for approximately 30% of all radiotherapy treatments within the UK National Health Service (NHS) [25] such that new breast radiotherapy techniques need to be time-efficient in order to be sustainable and avoid an unacceptable burden on healthcare resources. Data from this study suggest that VBH radiotherapy CT-planning sessions should fit comfortably into a 30-minute slot. The majority (60%) of CT-planning session time was devoted to patient setup, which included patient training in the VBH technique. Although the median reported CT session time was 20 minutes, these times did not include the application of tattoos, as this had already been performed at patients' free-breathing planning-CT session. However, these pre-existing tattoos may have actually increased setup time as it was necessary to align tattoos with lasers prior to scanning in VBH. Overall, it is anticipated that VBH CT-planning sessions, including the marking of tattoos, will be achievable within a standard 30-minute slot.

Median treatment session times show that just over 20 minutes is required for treatment. Around half of this time is taken up with patient setup, with about a third of the total time required for treatment delivery. Treatment delivery using VBH does take longer than a standard free-breathing technique because several (usually 4-6) breath-holds are required to deliver the treatment. Treatment session times are likely to reduce once centres feel comfortable enough with the technique not to perform daily online imaging. In addition, treatment session times can be expected to reduce with increasing experience at delivering VBH, as has been observed at our centre, where treatment times now average around 11 minutes [Steven Landeg, personal correspondence].

In addition to failing to meet eligibility criteria (*n*=1) and not reducing heart dose with VBH (*n*=5, discussed above), reasons for study withdrawal can be split into two subgroups: i) patient difficulty with breath-holding (*n*=6) and ii) technique limitations (*n*=2). Five patients were unable to maintain their breath-hold (one patient developed a chest infection during treatment) and one patient's breath-holds were inconsistent. This represents a low failure rate (approximately 1 in 17 patients) and, although higher than seen at our centre, is likely to reduce further as centres become more

experienced at patient training. With regard to technique limitations, one patient required bolus for treatment. Bolus covering the whole chest wall is currently incompatible with VBH as it obscures the skin marks during treatment. Solutions to this problem are being explored and include using thinner bolus (such that skin marks are visible through the bolus) and customised bolus (cutting the bolus such that the skin marks remain visible). One patient required a customised shell to support breast tissue, precluding the use of DIBH.

The data presented here suggest that VBH is both heart-sparing and feasible to implement in a multicentre setting. In line with other breath-holding techniques, VBH effectively halves the mean heart dose during left breast radiotherapy; reducing mean heart dose from 2Gy to 1Gy in a 50 year old woman with ≥1 cardiac risk factor can be expected to more than halve the absolute risk of a radiotherapy-induced acute coronary event by 80 years, from 1.1% to 0.5% [7]. This study has demonstrated in a multicentre setting that VBH is reproducible and acceptable to patients and radiographers, although some additional treatment time is likely to be required. It is anticipated that the results of this study will lead to VBH becoming a standard of care in the NHS for patients requiring heart-sparing breast radiotherapy. It is recommended, however, that centres implementing VBH audit their setup data at an early stage in order that systematic errors caused by inadequate/incorrect setup procedures may be identified and rectified.

Conclusions

The VBH technique is confirmed as effective in sparing heart tissue and feasible in a multicentre setting.

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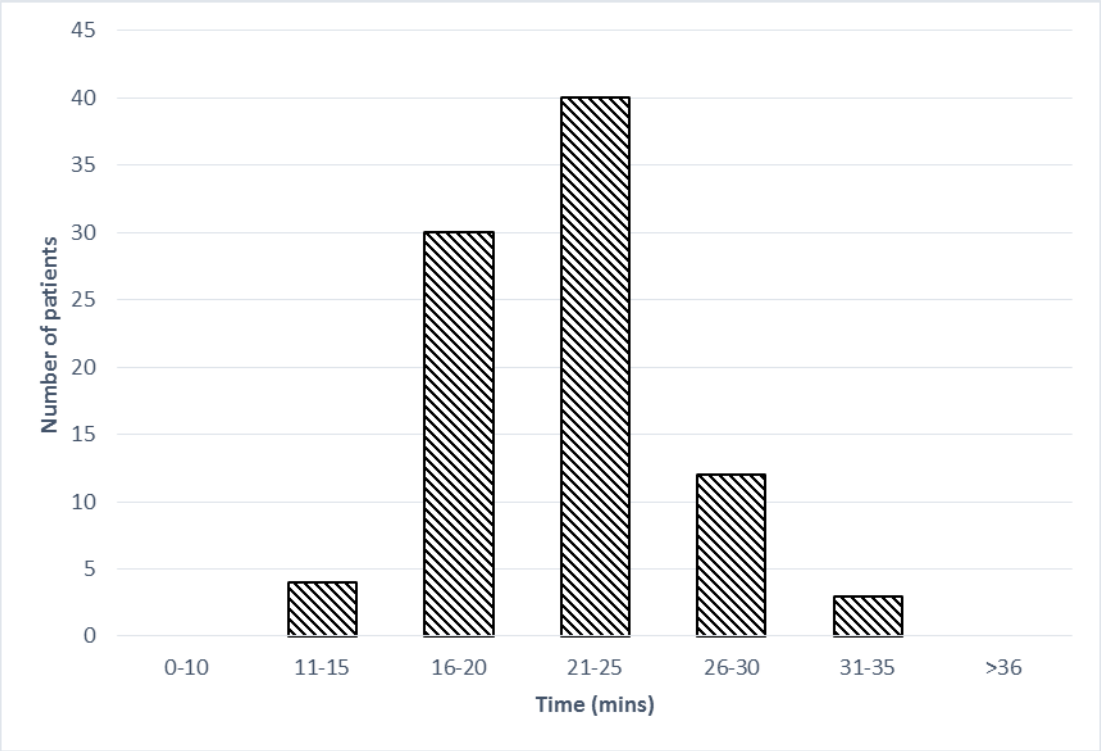
Figures

Figure 1 Histogram showing mean treatment session times for a course of treatment



Tables

Table 1

Mean normal tissue doses (Gy) for free-breathing and voluntary breath-hold (VBH) techniques with 95% confidence intervals in brackets.

	Free-breathing	VBH	*p*
Heart	1.79 (1.66-1.91)	1.04 (0.97-1.12)	<0.001
LAD	11.9 (10.8-13.1)	5.3 (4.5-6.1)	<0.001
LAD_{max}	35.2 (33.4-37.1)	24.0 (20.8-27.1)	<0.001
Ipsilateral lung	3.9 (3.6-4.2)	4.0 (3.7-4.2)	0.762
Whole lung	1.9 (1.8-2.1)	2.0 (1.9-2.1)	0.374

Table 2

Population mean displacement (M), systematic (Σ) and random (σ) translational errors (mm) for the voluntary breath-hold (VBH) technique measured by electronic portal imaging (EPI) and in the (*u,v*)-plane.

		Right anterior oblique beam (RAO)	Left posterior oblique beam (LPO)
u-plane	M	0.4	-0.2
	Σ	1.9	1.7
	σ	2.0	1.9
v-plane	M	0.3	0.1
	Σ	1.3	1.4
	σ	1.7	1.8