



Phase III randomised trial

The UK HeartSpare Study (Stage IB): Randomised comparison of a voluntary breath-hold technique and prone radiotherapy after breast conserving surgery



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ABSTRACT

Purpose: To compare mean heart and left anterior descending coronary artery (LAD) doses (NTD_{mean}) and positional reproducibility in larger-breasted women receiving left breast radiotherapy using supine voluntary deep-inspiratory breath-hold (VBH) and free-breathing prone techniques.

Materials and methods: Following surgery for early breast cancer, patients with estimated breast volumes >750 cm³ underwent planning-CT scans in supine VBH and free-breathing prone positions. Radiotherapy treatment plans were prepared, and mean heart and LAD doses were calculated. Patients were randomised to receive one technique for fractions 1–7, before switching techniques for fractions 8–15 (40 Gy/15 fractions total). Daily electronic portal imaging and alternate-day cone-beam CT (CBCT) imaging were performed. The primary endpoint was the difference in mean LAD NTD_{mean} between techniques. Population systematic (Σ) and random errors (σ) were estimated. Within-patient comparisons between techniques used Wilcoxon signed-rank tests.

Results: 34 patients were recruited, with complete dosimetric data available for 28. Mean heart and LAD NTD_{mean} doses for VBH and prone treatments respectively were 0.4 and 0.7 ($p < 0.001$) and 2.9 and 7.8 ($p < 0.001$). Clip-based CBCT errors for VBH and prone respectively were ≤ 3.0 mm and ≤ 6.5 mm (Σ) and ≤ 3.5 mm and ≤ 5.4 mm (σ).

Conclusions: In larger-breasted women, supine VBH provided superior cardiac sparing and reproducibility than a free-breathing prone position.

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The number of breast cancer (BC) survivors is increasing due to improvements in detection and more effective treatments [1]. However, improvements in survival mean more women will live to see the late effects of their cancer treatments. Breast radiotherapy is associated with a 1–2% excess of non-BC mortality at 15 years, the majority of which is attributable to cardiac disease [2], and recent work has demonstrated a linear, no-threshold relationship between mean heart dose and the risk of subsequent major coronary events (MCE) [3]. It remains unclear which cardiac substructures contribute to the development of MCE, although evidence from myocardial perfusion [4] and coronary angiography [5,6] studies implicates the left anterior descending coronary artery (LAD).

The development and implementation of heart-sparing breast radiotherapy techniques remains an international priority. Breath-holding techniques reduce heart doses [7–10] but have not yet been widely implemented in the UK [2012 Royal College of Radiologists audit] due to resource costs and staff training. A recent UK study (HeartSpare IA) demonstrated a voluntary breath-hold technique to be as effective at heart-sparing and as reproducible as breath-holding treatment with the active breathing coordinator™ (ABC) (Elekta, Crawley, UK) [11]. Additional benefits, including shorter treatment setup times and lower implementation costs, are likely to establish this technique as the standard of care for many left-sided women in the UK. However, there remains a group of larger-breasted women in whom the relative benefits of breath-hold vs. prone positioning are unknown. Previous work has shown that, although the prone position moves the heart closer to the chest wall under gravity, larger breasts fall further forward, allowing for shallower tangential radiotherapy

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beam placement [12,13] and reduced cardiac doses in larger-breasted women [14].

This single centre randomised non-blinded crossover study compares cardiac dosimetry for the supine voluntary breath-hold (VBH) technique with free-breathing prone positioning in larger-breasted women using a within-patient comparison.

Materials and methods

This study was approved by the Research and Development and Research Ethics Committees (ISRCTN 53485935). Women with left BC who had undergone breast-conserving surgery for invasive ductal or lobular carcinoma (pT1-3b,N0-1,M0), who required radiotherapy to the breast alone (\pm tumour bed boost) without nodal irradiation, and who had an estimated breast volume of $>750\text{ cm}^3$ were approached. All patients were treated at one institution. Randomisation procedures followed those reported previously [11].

Patient positioning and image acquisition

Before CT-planning, radio-opaque wire was used to delineate clinically palpable breast tissue with the patient in a supine position. The supine VBH CT-planning procedure has been described previously [15]. For free-breathing prone CT-planning, patients were positioned on an Orfit AIO Solution[®] prone breast board (ORFIT Industries, Wijnegem, Belgium) (see Fig. 1). A marker (tattoo) was placed ipsilaterally in the posterior axillary line and aligned axially with a posterior midline marker using lateral lasers. A second posterior marker was placed 15 cm inferiorly to the primary posterior marker, in line with sagittal lasers. CT data (Philips Medical Systems, UK) were acquired without contrast for both scans (2 mm slices, C6 to below diaphragm). Both scans were performed in one CT-planning session, with patients dismounting the couch between scans. Photographs of patient positioning were taken for both techniques to aid treatment setup. The time taken to complete each CT was recorded, from the time the patient mounted the CT couch to the time at which they dismounted the couch. After completing both scans, patients and radiographers completed validated questionnaires to assess comfort and satisfaction respectively (see Figs. S1 and S2) [16].

Target and organ-at-risk delineation

Target and organ-at-risk (OAR) volumes were delineated on both CT scans. The whole breast clinical target volume (WBCTV) was defined using the radio-opaque wire and any additional breast

tissue visualised on CT (limited by pectoral fascia and 5 mm from skin). The tumour bed was defined using tumour bed clips (inserted at surgery), and included any associated seroma or distortion of breast architecture. A 15 mm margin was added (limited by WBCTV) to form the partial breast CTV (PBCTV). The method for outlining the heart, LAD and lungs has been described previously [11]. The contralateral breast (CB) was also outlined, encompassing CB tissue visualised on CT.

Radiotherapy planning

Tangential fields were applied to encompass WBCTV. Philips Pinnacle 9.2 (Philips Medical Systems, Palo Alto, US) and the collapsed-cone algorithm ($0.25 \times 0.25 \times 0.25\text{ cm}$ resolution) were used to produce plans such that the 95% isodose covered $\geq 90\%$ of the WBCTV and $\geq 95\%$ of the PBCTV [14]. Where required, multileaf collimation (MLC) was used to shield cardiac tissue. Segments were used to improve dose homogeneity and all plans fulfilled ICRU 62 criteria (dose variation $\leq +7\%$ and -5% , hot-spots $\leq 107\%$) [17]. Patients were prescribed 40 Gy in 15 fractions over 3 weeks using 6 and/or 10 MV photons.

Dose-volume histogram (DVH) data were used to derive NTD_{mean} (a biologically weighted mean of total dose to tissue normalised to 2 Gy fractions using a standard linear quadratic model [18], $\alpha/\beta = 3\text{ Gy}$) for LAD, heart, ipsilateral and whole lungs and CB. In addition, the maximum LAD dose (LAD_{max}) was calculated. Conformity and homogeneity indices were calculated for both techniques using established formulae [17,19].

Radiotherapy delivery

Patients were randomised to receive one or other technique for fractions 1–7, before switching techniques for fractions 8–15. Patient setup for VBH has been described previously [15]. Prone positioning was reproduced at treatment by aligning tattoos to lasers and using CT-planning photographs to check consistency. The left posterior oblique (LPO) field borders were checked using treatment plan measurements and CT skin-rendered views. Visualisation of the right anterior oblique (RAO) field borders was impeded by the prone board structure. Electronic portal images (EPI) were acquired daily and matched on-line to digitally reconstructed radio-graphs on fractions 1–3 and 8–10 using iView software (Elekta, Crawley, UK). Systematic shifts were applied if errors were $>5\text{ mm}$ in the (u,v)-plane on at least three consecutive days. For study purposes setup errors were measured off-line for every fraction. The LPO was treated first and the RAO treated second.



Fig. 1. Patient positioned on Orfit AIO Solution[®] prone breast board (ORFIT Industries, Wijnegem, Belgium).

On-board kV-CT (CBCT) images of the chest were acquired immediately after setup on alternate days using the Elekta Synergy X-ray Volume Imaging System (Elekta, Crawley, UK). CBCT procedures for supine [20] and prone [14] techniques have been described previously. CBCT data were acquired primarily for study purposes, although were used to make systematic shifts where errors were >10 mm in any plane or >5 mm on three consecutive days and/or insufficient chest wall was visible on EPI to make such shifts. Daily CBCT imaging for prone treatment was used where errors were >5 mm in opposite directions. Clip-based matches were performed by manually registering CBCT volumes to the reference planning-CT.

Times at which patients mounted and dismounted the couch and the 'beam on' time were recorded for every fraction. Patients and radiographers completed questionnaires on fractions 1, 7, 8 and 15.

Statistical methods

The primary endpoint was the difference in mean LAD NTD_{mean} between VBH and prone techniques. Assuming a 2-sided significance level of 0.05 and standard deviation (SD) of the difference in measurements of 6.7%, a sample size of 50 patients (allowing for a 10% drop-out rate) was estimated to provide 83% power to detect an absolute difference of 3 Gy between mean LAD NTD_{mean} using the two techniques (assuming 0.1 correlation between techniques and SD of 5 Gy for each). During the study clinicians noted VBH was consistently better than prone at sparing heart tissue. An unplanned interim analysis was conducted and reviewed by an independent group (two clinicians and a statistician) after primary endpoint data was available for 27 patients. Following this review, the decision was made to close trial recruitment early following randomisation of 34 patients. The observed SD for the two techniques were lower than had been estimated in the original sample size calculation. Therefore, the power of the study remained 83% to detect a 3 Gy difference in mean LAD NTD_{mean} despite stopping recruitment early (assuming 4 Gy SD for each technique and a 0.1 correlation gave a SD of differences of 5.37).

Since Q-Q plots and Kolmogorov-Smirnov tests demonstrated that normal tissue dose data were not normally distributed, Wilcoxon signed-rank tests were used to compare doses between VBH and prone treatments, using each patient as their own control. Wilcoxon signed-rank tests were also used to compare timing data, target tissue and OAR volumes and numbers of segments used for each technique. McNemar's test was used to compare frequency of MLC use for cardiac shielding, beam energies and frequency of systematic moves. Translational and rotational CBCT registration results were analysed in 3-dimensions for each patient. Population mean displacement (M), systematic (Σ) and random (σ) errors were estimated [21]. EPI displacements were analysed for each beam in the (u,v)-plane for every patient [22]; population M , Σ and σ were estimated. Paired t -tests were used to compare M between VBH and prone techniques. Patient comfort and radiographer satisfaction questionnaires were scored 0–9 (0 least comfortable, 9 most comfortable and 0 most satisfactory, 9 least satisfactory). Median comfort and satisfaction scores were calculated for each technique at each timepoint (CT, first and last fractions) and Wilcoxon signed-rank tests used to compare scores. Statistical analyses were performed using SPSS Statistics Version 21 (IBM, Portsmouth, UK).

Results

Thirty-four patients were randomised between January 2013 and April 2014. Twenty-two (65%) patients completed the study as per protocol, and complete dosimetric data was available for

28 (82%) (see Fig. 2 and Supplementary material). 170/229 (74%) planned prone fractions and 221/221 (100%) of planned VBH fractions were completed. The median age of patients recruited was 57 years (range 25–79) and median BMI was 31.2 (range 24.5–38.3). Table S1 shows median target and OAR volumes and radiotherapy treatment plan characteristics for both techniques. Median WBCTV was similar for both techniques: 1064 cm³ (prone) vs. 1029 cm³ (VBH) and the difference between WBCTV for prone and VBH radiotherapy plans in all patients was <10%. Median target tissue coverage was $\geq 95\%$ for both techniques. Ipsilateral and whole lung volumes were significantly smaller in the prone position (all $p < 0.001$), but there was no significant difference between techniques for other OAR volumes.

All cardiac dose parameters (Gy) were statistically significantly lower with VBH than prone treatment [95% confidence intervals]: heart NTD_{mean} 0.44 [0.38–0.51] vs. 0.66 [0.61–0.71] ($p < 0.001$), LAD NTD_{mean} 2.9 [1.8–3.9] vs. 7.8 [6.4–9.2] ($p < 0.001$), and LAD_{max} 21.0 [15.8–26.2] vs. 36.8 [35.2–38.4] ($p < 0.001$). Heart NTD_{mean} was lower using VBH than prone treatment in 26/28 (93%) patients, as was LAD NTD_{mean} (27/28, 96%) and LAD_{max} (24/28, 86%). Within-patient comparisons of heart NTD_{mean} and an example of the relationship between breast and cardiac tissue dosimetry for VBH and prone treatments are shown in Figs. 3 and 4 respectively. Ipsilateral and whole lung NTD_{mean} were significantly lower using the prone technique than using VBH: 3.73 [3.42–4.04] vs. 0.34 [0.27–0.42] ($p < 0.001$) and 1.81 [1.65–1.97] vs. 0.20 [0.16–0.24] ($p < 0.001$) respectively. Mean CB dose was significantly lower with VBH than prone treatment: 0.10 [0.08–0.11] vs. 0.33 [0.23–0.43] ($p < 0.001$).

Population M , Σ and σ for CBCT clip-based matches and EPI-based matches are shown in Tables 1 and S2 respectively. Displacement errors for prone treatment were consistently greater than for VBH irrespective of imaging technique. Systematic moves were performed in 11/23 prone treatments and 2/23 VBH treatments ($p = 0.01$).

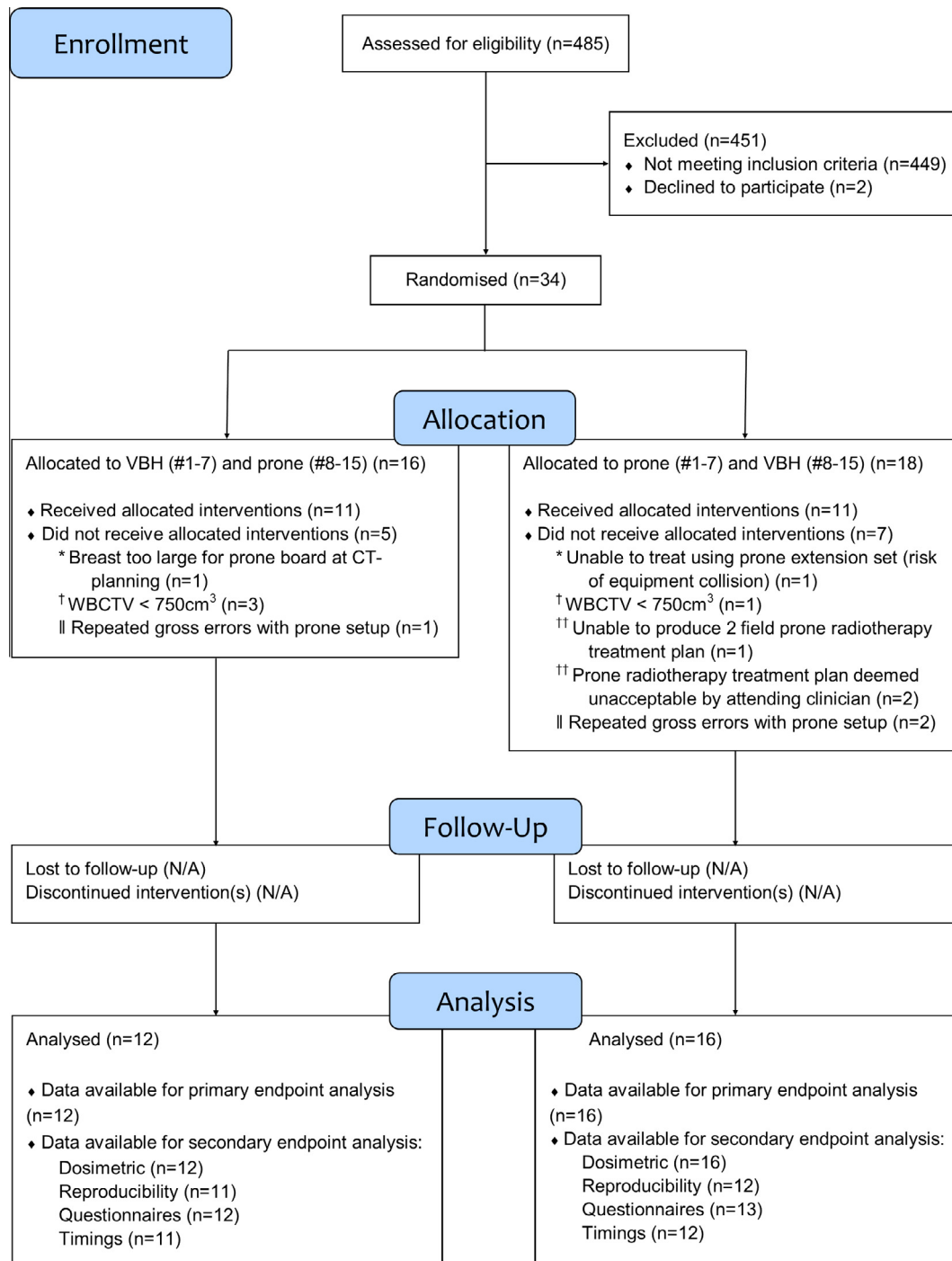
Patients found VBH more comfortable than prone treatment at all timepoints (all $p \leq 0.013$). No significant difference in radiographer satisfaction was found at CT ($p = 0.06$) or last fraction ($p = 0.05$), although for the first fraction VBH was more satisfactory ($p = 0.01$) (see Table S3).

Median radiotherapy CT-planning and treatment times are shown in Table 2. There was no significant difference between techniques for planning-CT session times ($p = 0.24$). Treatment setup and total treatment session times were significantly less with VBH ($p = 0.01$, $p = 0.002$ respectively), although 'beam on' time was less with prone treatment ($p = 0.004$).

Discussion

This randomised crossover study compared supine VBH with free-breathing prone treatment in terms of cardiac doses and setup reproducibility. Our results demonstrate that, for the majority of patients, VBH offers better cardiac sparing and a more favourable reproducibility profile than treatment in the prone position.

There was a highly statistically significant difference between techniques in favour of VBH for all cardiac dose parameters measured, in keeping with published non-randomised data [23]. However, cardiac doses for both techniques were low. Prone mean heart dose was lower than seen in standard free-breathing left breast radiotherapy [24] and lower than reported in other studies comparing prone and supine treatments [14,25,26]. Cardiac doses for VBH were lower than previously reported [11], perhaps because MLC use and/or beam angle alterations to avoid cardiac tissue are likely to result in relatively less WBCTV coverage compromise in larger- vs. smaller-breasted women. Contrary to published reports



Further information on protocol breaches labelled *, †, ‡ and ‡‡ can be found in the supplementary material.

Fig. 2. CONSORT 2010 flow diagram for The HeartSpare Study (Stage IB). More detail on patient protocol breaches is given in the Supplementary material.

[25,27,28], this study demonstrates that comparable dose homogeneity for prone and supine plans is achievable by the use of additional segments.

Consistent with previous work [29] our results showed positional reproducibility for prone treatment to be inferior to supine treatment. Reproducibility for supine VBH [11] and prone [29–31] treatments in this study was consistent with published reports. Reproducing the prone treatment position is difficult for several reasons, including the instability of breast and subcutaneous tissue, and the fact that target and OAR dosimetry is optimised by rotation of the patient towards the treated side. Reproducibility

in this study was hindered by an inability to site a contralateral posterior axillary line tattoo due to excess soft tissue, something noted in previous work [29]. In line with recommendations from that study, a second midline posterior tattoo was introduced in order to improve reproducibility. However, rotational errors were greatest around the anterior-posterior axis, something which might be improved by increasing the distance between posterior tattoos. Additionally, we used a commercially available prone platform selected for its comfortable head position and improved arm positioning (no ‘T-bar’ [29]). However, radiographers found arm position difficult to reproduce since, without a T-bar, patients were

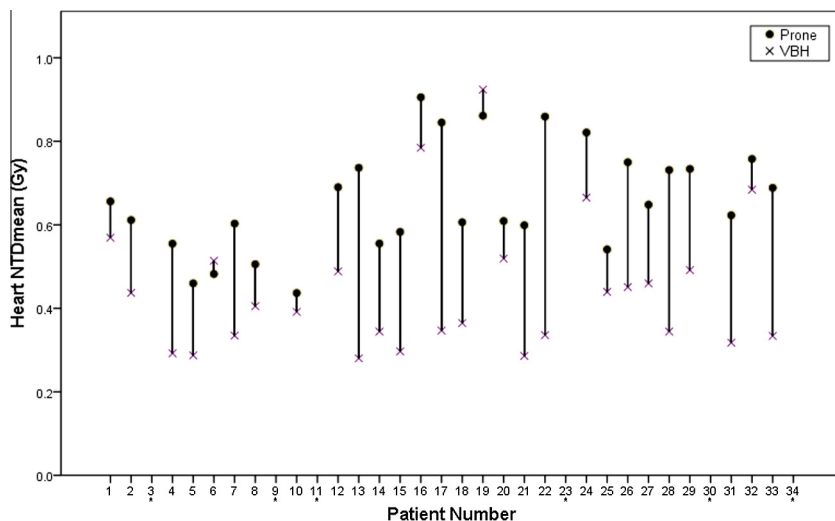


Fig. 3. Hi-Lo chart showing within-patient comparisons of heart NTD_{mean} (Gy) for voluntary breath-hold (VBH) and prone techniques (* indicates no data available).

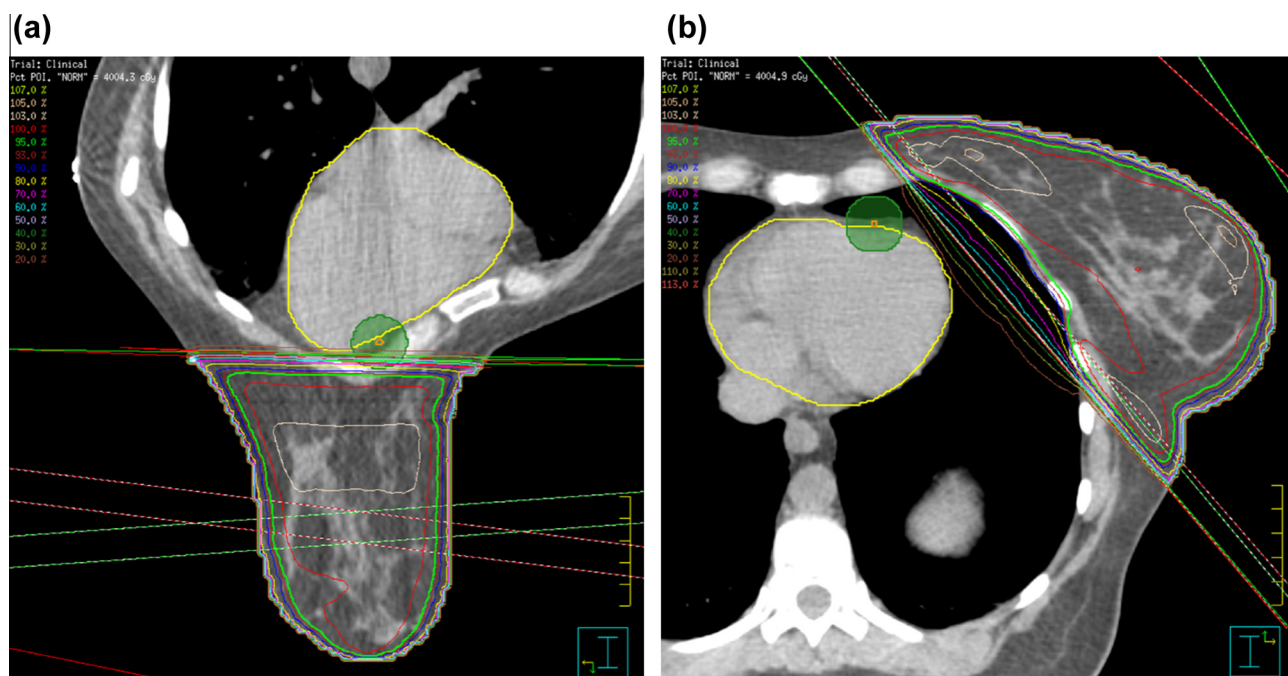


Fig. 4. Axial CT slices of (a) prone and (b) supine voluntary breath-hold (VBH) treatment plan from the same patient, demonstrating the anatomical and dosimetric relationship between breast tissue, heart (yellow outline), and LAD (green colour wash with orange bullseye).

able to use their elbows to support themselves. For prone treatment, systematic errors were consistently greater than random errors, suggesting that reproducibility could be improved by implementation of a CBCT-based correction protocol.

Patients generally found prone treatment less comfortable than VBH, describing the headrest as uncomfortable, rib discomfort around the treated breast aperture and feeling unstable due to tilting. Radiographers found prone treatments less satisfactory at the first fraction, reflecting difficulties with prone setup and reproducibility.

It was anticipated that CT session times would be shorter for prone CT-planning than VBH, given that VBH sessions included breath-hold training. The opposite was found, however, reflecting the additional care required to optimise prone position reproducibility at CT-planning (head comfort, patient rotation, CB position, avoiding elbow support). Reproducing these positions on treatment

accounts for the difference in treatment setup and total treatment session times between the two techniques. Two to three breath-holds were required per treatment beam for VBH, meaning that VBH treatment delivery was longer than for prone treatment.

The study was stopped early due to a significant difference in cardiac dosimetry between prone and VBH techniques. Although only 65% of patients completed the study as per protocol, primary endpoint data was available for 82% and the original power of the study remained despite stopping recruitment early. Reasons for failure to complete the study included failure to meet inclusion criteria, prone treatment plan issues, prone equipment shortcomings and prone setup difficulties (see [Supplementary material](#)). In addition, the crossover design of the study allowed clinicians to compare VBH and prone treatment plans prior to treatment. This study may be criticised for using mean LAD dose as its primary endpoint, as a recent study demonstrated considerable

Table 1

Population mean displacement (M), systematic (Σ) and random (σ) translational (mm) and rotational ($^{\circ}$) errors in 3-dimensions for clip-based cone-beam CT versus planning CT matches for voluntary breath-hold (VBH) and prone techniques.

		Translational			Rotational		
		VBH	Prone	p	VBH	Prone	p
Right–left (R–L)	M	−0.1	1.5	0.48	1.3	0.0	0.06
	Σ	1.8	5.9		1.2	1.9	
	σ	1.9	5.4		1.5	1.5	
Superior–inferior (S–I)	M	2.0	5.2	0.10	−0.5	−1.0	0.15
	Σ	3.0	6.5		1.4	2.7	
	σ	2.6	4.5		1.1	2.1	
Anterior–posterior (A–P)	M	0.0	−3.1	0.04	−0.2	−1.4	0.02
	Σ	1.8	5.2		1.7	3.5	
	σ	3.5	4.6		1.3	2.3	

Total number of CBCTs: 174 (88 VBH, 86 prone).

Table 2

Median of mean radiotherapy CT-planning session and treatment times for voluntary breath-hold (VBH) and prone techniques with ranges in brackets (min).

	VBH	Prone	p
CT-planning session	23 (15–62)	22 (14–48)	0.240
Treatment setup	8 (4–12)	9 (6–20)	0.010
'Beam on' time	5 (4–7)	3 (2–13)	0.004
Leaving treatment room	2 (1–3)	2 (1–4)	0.689
Total treatment time	17 (13–22)	20 (13–49)	0.002

Data for 61 CTs (31 VBH, 30 prone) and 188 treatment fractions (138 VBH, 150 prone).

inter-observer variability in LAD outlining [32]. However, this effect was minimised in our study by the same clinician outlining the LAD for all treatment plans. This was a single centre study at a centre where prone treatment is not in routine use, and this may affect the generalisability of our results, especially with regard to positional reproducibility.

Despite demonstrating a statistically significant superiority for supine VBH over free-breathing prone treatment in terms of cardiac sparing and positional reproducibility, there is much to satisfy proponents of either technique in this study; cardiac doses were low for both techniques and reproducibility was, for the majority of women, within tolerance levels used for standard tangential field breast radiotherapy. In addition, continued improvements in prone breast board technology are likely to enhance both patient comfort and reproducibility. However, given the inferior reproducibility and paucity of visible chest wall on EPI, a CBCT-based correction protocol is indicated for prone treatment. It is hoped that the results of this study will inform the decisions of centres considering implementation of either of these heart-sparing techniques. However, it is expected that in the UK the focus of work will shift to developing the VBH technique further, especially as we anticipate it to be more compatible with complex breast radiotherapy techniques, such as simultaneous integrated boost, arc therapies, and regional nodal treatments.

Conclusion

Our data suggest that, in larger-breasted women, supine VBH treatment is better at sparing cardiac tissues and more reproducible than treatment using a free-breathing prone technique. Patients find VBH more comfortable than the prone position. Treatment setup and total treatment session times are shorter with VBH.

Conflict of interest

Orfit Industries (Wijnegem, Belgium) loaned the prone breast platforms used in this study.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.radonc.2014.11.018>.

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