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Phase III randomised trial

The UK HeartSpare Study: Randomised evaluation of voluntary deep-inspiratory breath-hold in women undergoing breast radiotherapy

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ABSTRACT

Purpose: To determine whether voluntary deep-inspiratory breath-hold (v_DIBH) and deep-inspiratory breath-hold with the active breathing coordinator™ (ABC_DIBH) in patients undergoing left breast radiotherapy are comparable in terms of normal-tissue sparing, positional reproducibility and feasibility of delivery.

Methods: Following surgery for early breast cancer, patients underwent planning-CT scans in v_DIBH and ABC_DIBH. Patients were randomised to receive one technique for fractions 1–7 and the second technique for fractions 8–15 (40 Gy/15 fractions total). Daily electronic portal imaging (EPI) was performed and matched to digitally-reconstructed radiographs. Cone-beam CT (CBCT) images were acquired for 6/15 fractions and matched to planning-CT data. Population systematic (Σ) and random errors (σ) were estimated. Heart, left-anterior-descending coronary artery, and lung doses were calculated. Patient comfort, radiographer satisfaction and scanning/treatment times were recorded. Within-patient comparisons between the two techniques used the paired *t*-test or Wilcoxon signed-rank test.

Results: Twenty-three patients were recruited. All completed treatment with both techniques. EPI-derived Σ were $\leqslant$1.8 mm (v_DIBH) and $\leqslant$2.0 mm (ABC_DIBH) and σ $\leqslant$2.5 mm (v_DIBH) and $\leqslant$2.2 mm (ABC_DIBH) (all p non-significant). CBCT-derived Σ were $\leqslant$3.9 mm (v_DIBH) and $\leqslant$4.9 mm (ABC_DIBH) and $\sigma \leqslant$ 4.1 mm (v_DIBH) and $\leqslant$ 3.8 mm (ABC_DIBH). There was no significant difference between techniques in terms of normal-tissue doses (all p non-significant). Patients and radiographers preferred v_DIBH ($p = 0.007$, $p = 0.03$, respectively). Scanning/treatment setup times were shorter for v_DIBH ($p = 0.02$, $p = 0.04$, respectively).

Conclusions: v_DIBH and ABC_DIBH are comparable in terms of positional reproducibility and normal tissue sparing. v_DIBH is preferred by patients and radiographers, takes less time to deliver, and is cheaper than ABC_DIBH.

Breast cancer is the most common cancer in women, with a current estimated worldwide incidence of 1.38 million [1]. With improved treatments, the number of breast cancer (BC) survivors is increasing, and in the UK alone is expected to treble to 1.7 million by 2040 [2]. This surge in survivor numbers makes the late effects of BC treatment, including those related to radiotherapy, of increasing concern to patients and healthcare providers alike. Breast radiotherapy reduces the risk of recurrence and improves survival after surgical excision of early BC [3]. However, the benefits derived from breast radiotherapy are compromised by an increase in non-BC deaths, the majority of which are cardiovascular in origin [4]. Although it is not yet clear which cardiac structure(s) is most important in the pathogenesis of radiation related heart disease (RRHD), the anatomical position of the left anterior descending artery (LAD) makes it particularly susceptible to high doses of radiation. There is now mounting evidence that irradiation of the LAD is a key factor in the development of RRHD [5–7]. Irradiation of other tissues, including lung and chest wall, also contributes to late morbidity and mortality from breast radiotherapy [4,8–10].

The current priority in breast radiotherapy is to develop and validate techniques which enable clinicians to maintain coverage of target tissues (breast/chest wall) whilst reducing radiation to adjacent organs-at-risk (OAR), especially the heart and LAD. Breath-holding techniques, in which the heart is pushed down and away from the radiotherapy field, are a solution to this problem. Compared to free-breathing radiotherapy, deep-inspiratory breath-hold with the active breathing coordinator™ (ABC_DIBH)

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(Elekta, Crawley, UK) significantly reduces the volume of heart irradiated [11–13], whilst voluntary deep-inspiratory breath-hold (v_DIBH) using the Varian RPM system has been shown to significantly reduce median heart and LAD volumes receiving >50% of the prescription dose [14–16]. Such dosimetric savings are projected to equate to a 10-fold reduction in cardiac deaths [16]. Nonetheless, despite convincing evidence that DIBH reduces the dose delivered to cardiac tissues, it was used in only 19% of EORTC centres 3 years ago [17] and just 4% of UK centres in 2012 [Royal College of Radiologists audit]. ABC_DIBH has been shown to be reproducible [18] but is expensive to implement due to costs of equipment including daily disposable mouthpieces. v_DIBH, in particular the technique described in this study, would be a low-cost alternative but data on its reproducibility are lacking. This randomised crossover study was designed to answer whether or not the treatment of breast radiotherapy patients in v_DIBH is at least as good as ABC_DIBH in terms of positional reproducibility, normal tissue sparing and feasibility of delivery.

Methods and materials

This study was approved by the Royal Marsden Committee for Clinical Research and the Research Ethics Committee (ISRCTN 53485935). All women underwent left breast conserving surgery or mastectomy for early stage invasive ductal or lobular carcinoma (pT1-3b N0-1 M0) and were recommended adjuvant radiotherapy to the whole breast or chest wall without nodal irradiation (+/− tumour bed boost). Women with left breast cancer requiring radiotherapy to the breast or chest wall alone were approached. All patients were treated at the Royal Marsden Hospital, Sutton, UK. Randomisation was arranged via telephone at the Clinical Trials and Statistics Unit at the Institute of Cancer Research (ICR-CTSU), Sutton, UK, where patient details were recorded and order of breath-holding techniques was allocated. Randomisation was not blinded. Computer-generated random permuted blocks of size 4 were used for allocation, with no stratification.

v_DIBH technique

The v_DIBH technique used in this study required no additional equipment. Patients were asked to breathe in and out twice before being asked to take a deep breath and hold. Breath-hold consistency was checked at CT and treatment by the distance moved by the laser from the anterior and lateral tattoos in breath-hold. All breath-hold techniques require a method of monitoring intra-fraction breath-hold reproducibility. In this study the borders of the light field were marked with ink with the patient in breath-hold. Treatment room cameras were zoomed so that the pen marks and light field were visible on the control room monitors. Visualising these enabled radiographers to check breath-hold consistency prior to and during treatment. A more detailed account of the v_DIBH technique is given in the supplementary material.

Patient positioning and image acquisition

Training was given to patients for both techniques immediately prior to scanning. ABC_DIBH training followed the method described by Remouchamps et al. [18] and for v_DIBH is described in the supplementary material. Both CT scans were performed in one CT-planning session and patients remained on the CT couch between scans. All patients were scanned on a supine breast board, with arms extended above the head in supports (Med-Tec, Iowa, USA). Markers were placed bilaterally 1–2 cm posterior to the mid-axillary line and aligned axially with a midline marker using lateral lasers. CT data (Philips Medical Systems, UK) were acquired without contrast in both ABC_DIBH and v_DIBH using 3 mm slices from C6 to below the diaphragm. The time taken to complete each planning session was recorded, from the time the patients mounted the CT couch to the time at which they dismounted the couch. After both scans were completed patients were asked to complete validated comfort and acceptability questionnaires and radiographers were asked to complete radiographer satisfaction questionnaires [19].

Target and organ-at-risk delineation

Target and OARs were delineated on both CT scans. The whole breast clinical target volume (WCBTV) encompassed the 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 uniform margin of 15 mm was added (limited by WBCTV) to form the partial breast CTV (PBCTV). For mastectomy patients, the chest wall CTV (CWCTV) was defined using anatomical landmarks (inferior border of clavicle (superior), 1 cm below inframammary fold (inferior), midline (medial) and anterior border of serratus anterior (lateral)), taking into account the position of the contralateral breast tissue and limited by pectoral fascia and 5 mm from skin. The heart was outlined in accordance with the UK National Cancer Research Institute Intensity Modulated and Partial Organ RadioTherapy (IMPORT) study criteria [20]. The LAD was outlined according to the method described by Taylor et al. [21,22]. The lungs were outlined by adapting a pre-installed lung template and edited to exclude major airways.

Radiotherapy planning

Tangential fields were applied to encompass WBCTV/CWCTV. The depth of lung tissue included in tangential fields was $\leqslant$2.5 cm. Philips Pinnacle 9.2 (Philips Medical Systems, Palo Alto, USA) and the collapsed-cone algorithm ($0.25 \times 0.25 \times 0.25$ cm resolution) were used to produce plans such that $\geqslant$90% of the WBCTV/CWCTV and $\geqslant$95% of the PBCTV were covered by the 95% isodose [23]. Where required, MLC leaves were used to shield cardiac tissue whilst maintaining target tissue constraints. Segments (field-in-field technique) were used, where necessary, to improve dose homogeneity and all plans fulfilled ICRU 62 criteria (dose variation $\leqslant$ +7% and −5%, hotspots $\leqslant$ 107%) [24]. Patients were prescribed 40 Gy in 15 fractions over 3 weeks using 6 or 10 MV photons.

Tabular DVH data (dose (Gy) per voxel) were used to derive the NTD_{mean} (a biologically weighted mean of total dose to tissue normalised to 2 Gy fractions using a standard linear quadratic model [25], α/β = 3 Gy) for heart, LAD, ipsilateral and whole lungs. In addition, the maximum dose received by the LAD (LAD_{max}) was estimated.

Radiotherapy delivery

Patients were randomised to receive one treatment technique for fractions 1–7 and the second technique for fractions 8–15. Patient setup is described in the supplementary material. Real-time electronic portal images (EPI) were acquired daily and matched on-line to DRRs on fractions 1–3 and 8–10 using iView software (Elekta, Crawley, UK). Shifts were applied if errors were >5 mm in the (u,v)-plane on at least two consecutive days. For study purposes setup errors were measured off-line for every fraction. The left posterior oblique beam (LPO) was treated first and the right anterior oblique beam (RAO) treated second.

On-board kV-CT (CBCT) images of the chest were acquired immediately after setup on fractions 1, 4, 7, 8, 11 and 14 using the Elekta Synergy X-ray Volume Imaging System (Elekta, Crawley,

UK). CBCT procedures have been described previously [26]. CBCT data were acquired for study purposes only and were not used to make isocentre shifts. For technical reasons it was not possible to interrupt CBCTs, meaning that patients could only be in breath-hold for about two-thirds of the time taken to complete the CBCT. The CBCT volume was manually registered to the reference planning-CT, and both chest wall and clip-based matches were performed. For chest wall matches, a best-fit match was made for the area of chest wall directly posterior to the target tissue. The correction reference point was set to the isocentre.

On average, four to six breath-holds were required per treatment, with two extra for CBCT imaging.

Times at which patients mounted the couch, the radiotherapy beam was switched on and off and at which patients dismounted the couch, were recorded for every fraction. Patients and radiographers were asked to complete questionnaires on fractions 1, 7, 8 and 15.

Statistical methods

A sample size of 23 patients was estimated to provide 95% power in order to rule out an excess of 2 mm in mean displacement (primary outcome) for v_DIBH versus ABC_DIBH, assuming a significance level of 0.05 (1-sided as testing for non-inferiority). EPI displacements were analysed for each beam in the (u,v)-plane for every patient (v-direction parallel to craniocaudal axis and u-direction perpendicular to this) [27]. Mean displacements and standard deviations were compared for ABC_DIBH and v_DIBH treatments for each patient. Using the method described by van Herk [28], population mean displacement (MD), systematic (Σ) and random (σ) errors were estimated. CBCT registration results were analysed in 3-dimensions for each patient and for both chest wall and clip-based matches; population MD, Σ and σ were calculated. Paired t-tests were used to compare the parameters listed above (population MD, Σ and σ), normal tissue doses and timing data (CT and treatment session times) between ABC_DIBH and v_DIBH, using each patient as their own control. Data normality was confirmed using Q–Q plots and Kolmogorov–Smirnov tests (all p non-significant). Patient comfort and acceptability questionnaires were summarised as patient comfort scores ranging from 0 (least comfortable) to 9 (most comfortable). Radiographer satisfaction questionnaires were summarised as radiographer satisfaction scores ranging from 0 (most satisfactory) to 9 (least satisfactory). Scores were calculated for each technique and at each timepoint (CT, first and last fractions). In order to eliminate any time effect, the difference in questionnaire scores between the two techniques at each timepoint was calculated for each patient. Single sample Wilcoxon signed-rank tests were then used to test whether the median of the differences was significantly different from zero.

Statistical analyses were performed using SPSS Statistics Version 19 (IBM, Portsmouth, UK).

Results

Twenty-three patients were randomised between February and August 2012. The study ended when the final patient completed their radiotherapy course, and there was no long-term trial-related follow-up. All patients completed treatment with both techniques. The median age of patients recruited was 61 years (range 36–82). Nineteen patients (83%) underwent BCS and four (17%) underwent mastectomy. Table S1 (supplementary material) shows mean target and OAR volumes for both techniques. Mean WBCTV was similar for both techniques: 677 cm^3 (ABC_DIBH) vs 676 cm^3 (v_DIBH), as was mean target tissue coverage. There was no significant difference in lung volumes between the two techniques. However, heart volumes were significantly smaller with v_DIBH: 577 cm^3 vs 544 cm^3 ($p < 0.001$).

Table 1 shows population MD, Σ and σ estimated using EPI. There was no significant difference between the two techniques in MD, Σ or σ.

Table 2 shows population MD, Σ and σ for CBCT chest wall and clip-based matches. Twenty-two patients underwent CBCTs and clip-based matches were possible in 18 (4 patients underwent mastectomy). There was no significant difference between the two techniques in Σ or σ for either chest wall or clip-based matches. MD was less with v_DIBH in the anterior–posterior (AP) direction. Errors were generally greater for chest wall matches than for clip-based matches.

There was no significant difference between mean normal tissue doses (Gy) for ABC_DIBH and v_DIBH (standard deviation in brackets): heart NTD_{mean} 0.6 (0.2) vs 0.6 (0.1) ($p = 0.41$), LAD NTD_{mean} 3.8 (2.9) vs 3.5 (2.3) ($p = 0.18$), LAD_{max} 32.6 (11.5) vs 30.6 (12.4) ($p = 0.18$), ipsilateral lung NTD_{mean} 4.2 (0.7) vs 4.2 (0.7) ($p = 0.53$), whole lung NTD_{mean} 2.0 (0.3) vs 2.0 (0.3) ($p = 0.22$). Fig. 1 demonstrates the heart-sparing effect of DIBH.

The number of patients in whom the median of the differences in patient comfort scores at each timepoint (CT, first and last fractions) was <0 (1), 0 (9) or >0 (12), $p = 0.007$ (i.e. patients found v_DIBH more comfortable) and for radiographer satisfaction scores <0 (9), 0 (11) or >0 (3), $p = 0.03$ (i.e. radiographers found v_DIBH more satisfactory).

Mean planning-CT session times (minutes) were 27 (ABC_DIBH) and 24 (v_DIBH) ($p = 0.02$). Mean treatment setup times were 11 (ABC_DIBH) and 9 (v_DIBH) ($p = 0.04$), mean treatment times (first beam onto last beam off) were 7 min for both techniques ($p = 0.08$), mean dismount time 2 min for both ($p = 0.97$). Mean total treatment time per session was 19 min for both techniques ($p = 0.62$).

Discussion

This randomised crossover study compared ABC_DIBH and v_DIBH in terms of setup reproducibility, normal tissue sparing and feasibility of delivery. Our results demonstrate that the two techniques are similar in terms of these parameters. Consistent with other published data, both techniques were well tolerated [15,18]. Baseline data (Table S1, supplementary material) suggest that target volume outlining was consistent. Lung volumes were similar for both techniques, minimising any effect on calculated cardiac doses. Heart volumes were significantly smaller with v_DIBH, suggesting a different physiological response between a machine-initiated breath-hold (ABC_DIBH) and a voluntarily-initiated breath-hold (v_DIBH).

Treatment setup errors were consistent with other studies of DIBH which have used EPI for verification [18,29], but smaller than many free-breathing studies [30], suggesting that DIBH is at least as reproducible as standard free-breathing breast radiotherapy. In this study, errors were greatest in the u-direction, which is subject to the most change with variations in depth of DIBH or breathing pattern (e.g. chest vs abdominal breathing).

Population MD, Σ and σ derived from CBCT data were greater than errors derived from EPI. EPI is known to underestimate setup errors in breast cancer patients due to differences in visibility of anatomical landmarks between the two imaging techniques, time taken to acquire images and the fact that CBCT provides 3D anatomical information [31]. The inability to interrupt CBCT acquisition resulted in some image blurring and compromised matching. Chest wall deformation during respiration meant that chest wall matches were subject to greater errors than clip-based matches. In view of this, it is likely that CBCT-derived setup errors in this study are an overestimate of the true setup errors associated

Table 1
Population mean displacement (MD), systematic (Σ) and random (σ) setup errors for ABC_DIBH and v_DIBH techniques measured by electronic portal imaging (EPI) for each beam and in the (u,v)-plane (mm).

		Right anterior oblique beam (RAO)			Left posterior oblique beam (LPO)		
		ABC_DIBH	v_DIBH	p	ABC_DIBH	v_DIBH	p
u-direction	MD	−0.5	−0.2	0.52	0.5	0.1	0.49
	Σ	1.9	1.8		2.0	1.5	
	σ	2.2	2.1	0.74	2.4	2.5	0.24
v-direction	MD	0.7	0.5	0.63	0.9	0.8	0.79
	Σ	2.0	1.7		1.9	1.5	
	σ	2.0	1.7	0.46	2.0	2.0	0.83

Total number of EPIs: 665.

Table 2
Population mean displacement (MD), systematic (Σ) and random (σ) errors in 3-dimensions for chest wall and clip-based cone-beam CT versus planning CT matches for ABC_DIBH and v_DIBH techniques (mm).

		Chest wall match			Clip-based match		
		ABC_DIBH	v_DIBH	p	ABC_DIBH	v_DIBH	p
Right–left (R–L)	MD	0.3	0.5	0.78	0.4	0.4	0.93
	Σ	4.4	2.5		3.2	2.4	
	σ	3.8	2.4	0.07	2.3	2.3	0.99
Superior–inferior (S–I)	MD	2.3	3.4	0.32	−0.1	1.7	0.10
	Σ	4.9	3.9		2.9	3.6	
	σ	3.3	4.1	0.62	3.4	2.7	0.42
Anterior–posterior (A–P)	MD	−1.7	0.3	0.03	−1.8	0.6	0.01
	Σ	3.3	2.8		2.7	3.0	
	σ	2.6	2.7	0.76	3.5	2.7	0.53

Total number of CBCTs: 126.

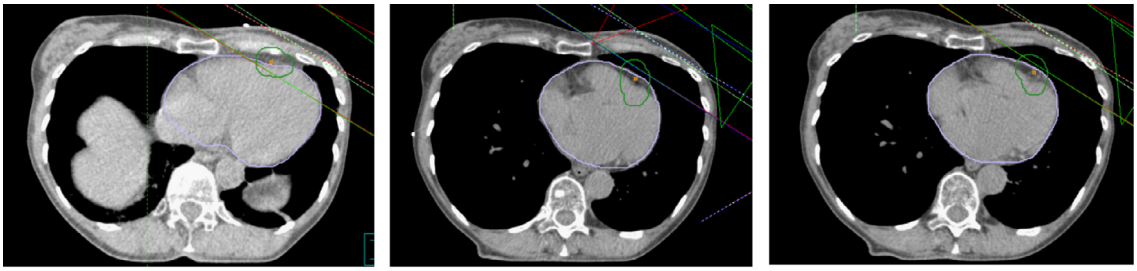

Fig. 1. Axial CT slices of one patient taken during free breathing, v_DIBH and ABC_DIBH. Heart, left anterior descending coronary artery (LAD) and LAD with 1 cm margin have been outlined. Key: magenta – heart, orange – LAD, dark green – LAD plus 1 cm margin.

with these techniques. Clip-based match errors were better than DIBH setup data reported by another centre [29]; in relation to free-breathing data, σ were similar but Σ greater than previously reported [32]. The difference in MD in the AP direction suggests imprecision of the ABC equipment and/or procedure. Possible explanations for this include inaccurate spirometry or balloon valve cut-off and the inability of the ABC device to control breathing pattern or chest wall shape.

Our results suggest that there is no significant difference between ABC_DIBH and v_DIBH in terms of normal tissue sparing. Cardiac doses reported in this study were lower than in other published data [29,33–36], although comparison is not straightforward due to differences in target volumes and LAD margins. Ipsilateral lung doses were consistent with other published works [29,34], although whole lung doses are not widely reported.

By freeing patients of equipment, v_DIBH was seen as more comfortable than ABC_DIBH. Patients found the mouthpiece and nose-clip used in ABC_DIBH claustrophobic. One patient with dentures found the ABC mouthpiece difficult to grip. Given that v_DIBH was a new technique to our department (unlike ABC_DIBH) it was encouraging that radiographers found v_DIBH more satisfactory than ABC_DIBH.

The timing data demonstrate small but significant advantages with v_DIBH at planning-CT and treatment setup. The difference at CT can be accounted for by the need to set an inspiratory threshold for ABC_DIBH at this session (not required for v_DIBH), and at treatment setup by the fact that a radiographer must leave the room to operate the ABC device. Treatment times for both techniques are likely to be shorter than suggested as CBCTs are not part of standard treatment.

ABC_DIBH is expensive due to capital investment in the device itself and the ongoing costs of single-use mouthpieces. The v_DIBH technique described here is a less costly alternative as no specialised equipment is required. v_DIBH currently takes longer to deliver than our centre's free-breathing technique although treatment times are expected to fall with increasing experience. This is the subject of an ongoing service evaluation within our institution. Whilst the capital costs associated with ABC_DIBH are a major

factor in preventing its widespread uptake across the UK National Health Service (NHS), the results presented here should reassure centres with ABC about the reproducibility and normal tissue sparing of ABC_DIBH in left breast radiotherapy. Otherwise, v_DIBH appears to be an effective, reproducible, comfortable and less costly alternative. The feasibility of rolling out v_DIBH to other UK centres will now be assessed in the context of the UK NCRI FAST-Forward trial (HeartSpare II), with the ultimate aim of increasing availability of heart-sparing breast radiotherapy in the UK. Further work is needed to evaluate the role of v_DIBH in breast radiotherapy for nodal irradiation and partial breast treatment.

Conclusion

Our data suggest that ABC_DIBH and v_DIBH are comparable in terms of positional reproducibility and normal tissue sparing. Patients find v_DIBH more comfortable than ABC_DIBH, and radiographers find v_DIBH more satisfactory. v_DIBH offers a time advantage at planning-CT sessions and treatment setup, and is cheaper as no specialised equipment is required.

Conflict of interest

None declared.

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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.2013.04.021.

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