

Received: 16 June 2016
Revised: 19 August 2016
Accepted: 30 August 2016

© 2016 The Authors. Published by the British Institute of Radiology under the terms of the Creative Commons Attribution-NonCommercial 4.0 Unported License <http://creativecommons.org/licenses/by-nc/4.0/>, which permits unrestricted non-commercial reuse, provided the original author and source are credited.

Cite this article as:

Dunkerley N, Bartlett FR, Kirby AM, Evans PM, Donovan EM. Mean heart dose variation over a course of breath-holding breast cancer radiotherapy. *Br J Radiol* 2016; **89**: 20160536.

SHORT COMMUNICATION

Mean heart dose variation over a course of breath-holding breast cancer radiotherapy

¹NICOLLE DUNKERLEY, MSc, ²FREDERICK R BARTLETT, MD, ³ANNA M KIRBY, MD, ⁴PHILIP M EVANS, DPhil and ⁵ELLEN M DONOVAN, PhD

¹Medical Physics Department Royal Surrey County Hospital, Guildford, UK

²Oncology Department Portsmouth Hospitals NHS Trust, Portsmouth, UK

³Radiotherapy Department The Royal Marsden NHS Foundation Trust, London, UK

⁴Centre for Vision, Speech and Signal Processing, University of Surrey, Guildford, UK

⁵Physics Department, The Royal Marsden NHS Foundation Trust, London, UK

Address correspondence to: Dr Ellen M Donovan

E-mail: Ellen.Donovan@rmh.nhs.uk

Objective: The purpose of the work was to estimate the dose received by the heart throughout a course of breath-holding breast radiotherapy.

Methods: 113 cone-beam CT (CBCT) scans were acquired for 20 patients treated within the HeartSpare 1A study, in which both an active breathing control (ABC) device and a voluntary breath-hold (VBH) method were used. Predicted mean heart doses were obtained from treatment plans. CBCT scans were imported into a treatment planning system, heart outlines defined, images registered to the CT planning scan and mean heart dose recorded. Two observers outlined two cases three times each to assess interobserver and intraobserver variation.

Results: There were no statistically significant differences between ABC and VBH heart dose data from CT planning

scans, or in the CBCT-based estimates of heart dose, and no effect from the order of the breath-hold method. Variation in mean heart dose per fraction over the three imaged fractions was <6 cGy without setup correction, decreasing to 3.3 cGy with setup correction. If scaled to 15 fractions, all differences between predicted and estimated mean heart doses were <0.5 Gy and in 80% of cases, they were <0.25 Gy.

Conclusion: Variation in mean heart dose was at an acceptable level over the duration of breath-holding radiotherapy and was well predicted by the planning system.

Advances in knowledge: Mean heart dose was not adversely affected by fraction-to-fraction variations throughout a course of heart-sparing radiotherapy using two well-established breath-holding methods.

INTRODUCTION

A reduction in local recurrence and a decrease in mortality result from the use of radiotherapy as a therapeutic agent for breast cancer.¹ Whilst this is a positive effect of radiotherapy, the Early Breast Cancer Trialists' Collaborative Group meta-analysis of 2005 suggests an increase in late non-breast cancer-related mortality associated with radiotherapy, a large component of which is due to cardiovascular disease.² More recent evidence suggests that there is no mean heart dose threshold for radiation-related cardiac effects.³ This evidence has driven efforts to investigate and implement techniques to reduce cardiac radiation exposure whilst maintaining target coverage in breast cancer radiotherapy including intensity-modulated radiotherapy, prone positioning and breathing manoeuvres.⁴⁻⁶

Breath-holding is effective in reducing the cardiac radiation dose.⁶⁻⁸ The setup reproducibility of breathing control methods is shown to be of the order of 3 mm for both

systematic and random error.^{8,9} Electronic portal imaging (EPI) movie loops and EPI dosimetry confirm consistency and stability during radiation delivery.^{10,11} These imply that radiation dose received by the heart is maintained close to the level predicted in the radiotherapy treatment plan. There will be differences in received dose from that predicted as setup and breath-hold variations, although small, do occur fraction to fraction, and often thresholds are used in breast cancer radiotherapy so that setup error is not corrected below an action level. Confirming the impact of these variations on mean heart dose is not trivial, as volumetric imaging information is not available during radiation delivery for most breast radiotherapy treatments. Borst et al⁹ and McIntosh et al¹² focused on a detailed comparison of a breathing control method with free breathing, covering aspects such as patient position reproducibility and organ-at-risk doses from treatment plans. Alderliesten et al¹³ used heart outline information to derive planning organ-at-risk margins for the heart in cases

where surface imaging was used to monitor a breath-hold treatment. In none of these studies were heart dose data estimated throughout the treatment duration or for both equipment-assisted and voluntary breath-hold (VBH) techniques.

This study reports a retrospective analysis of mean heart dose using cone-beam CT (CBCT) images acquired immediately prior to breath-holding breast cancer radiotherapy. The study purpose was to estimate received mean heart dose, to determine any differences between two breath-hold methods and evaluate any variation over the treatment course.

METHODS AND MATERIALS

Patient cohort and imaging data

The data used in this study were obtained from the HeartSpare 1A clinical trial comparing active breathing control (ABC) with VBH. Treatment verification was carried out using megavoltage EPI. In addition, kilovoltage CBCT images were acquired on an Elekta AB (Publ), Stockholm, Sweden X-ray volumetric imaging system¹⁴ on first, third and fifth fractions per breath-hold technique. Data retrieval issues meant 20/23 cases were available with 113 associated CBCT data sets. These were exported to a Philips Radiation Oncology Systems, Madison, Wisconsin, US Pinnacle treatment planning system for rigid registration with the planning CT scan for heart delineation and dose calculation.

Organ delineation

A CBCT image acquisition time of 30 s required two breath-holds, which introduced blurring artefacts to the images (the acquisition could not be interrupted during the exposure). The adequacy of the image information for outlining was assessed by visual inspection by two experienced practitioners (a therapeutic radiographer and a clinical oncologist) working with the cardiac outlining guidance of a clinical trial protocol. Both practitioners outlined the heart on one ABC and one VBH scan from the same case three times at 2-week intervals. One practitioner (Observer 1) repeated the sequence of outlining on a second case. All other cases were outlined by Observer 1.

Data and analysis

The heart outlines from the imported CBCT images appeared as structures on the plans used for treatment. Mean heart dose data were collected. The gold standard data were the predicted mean heart dose from the treatment plans using CT planning scans. Estimated doses were expressed as mean heart dose per fraction (in centigray), as only five or six fractions were imaged and this avoided assumptions about the missing data. Heart volumes were recorded for the observer variation study.

Two conditions were considered: the first where it was assumed that no setup correction was made and the second, post-image registration, where all setup errors were assumed to be corrected, *i.e.* online daily correction. This was achieved by exporting the X-ray volumetric CBCT images so that they were in the same frame of reference as the CT planning scan but without registration data, *i.e.* in a non-setup correction state. The heart was outlined and dose data were acquired for this

condition. Then, rigid registration to the planning CT image was carried out and heart dose data acquired in the corrected position.

Data sets were compared (i) between ABC and VBH at pre-treatment CT; (ii) between CBCT data for each breath-hold method and the corresponding pre-treatment CT data; (iii) between ABC and VBH CBCT-based data; and (iv) over the treatment duration for each breath-hold technique.

The data were tested for normality using the Shapiro–Wilk test and differences in the means or distributions were tested for statistical significance using an independent-samples two-sided Student's *t*-test or non-parametric Mann–Whitney *U*-test as appropriate. The null hypothesis was no statistically significant difference between the means, or the distributions, and a *p*-value of 0.05 was used as the threshold for statistical significance. Statistical analyses were carried out using IBM SPSS® Statistics v. 22 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL).

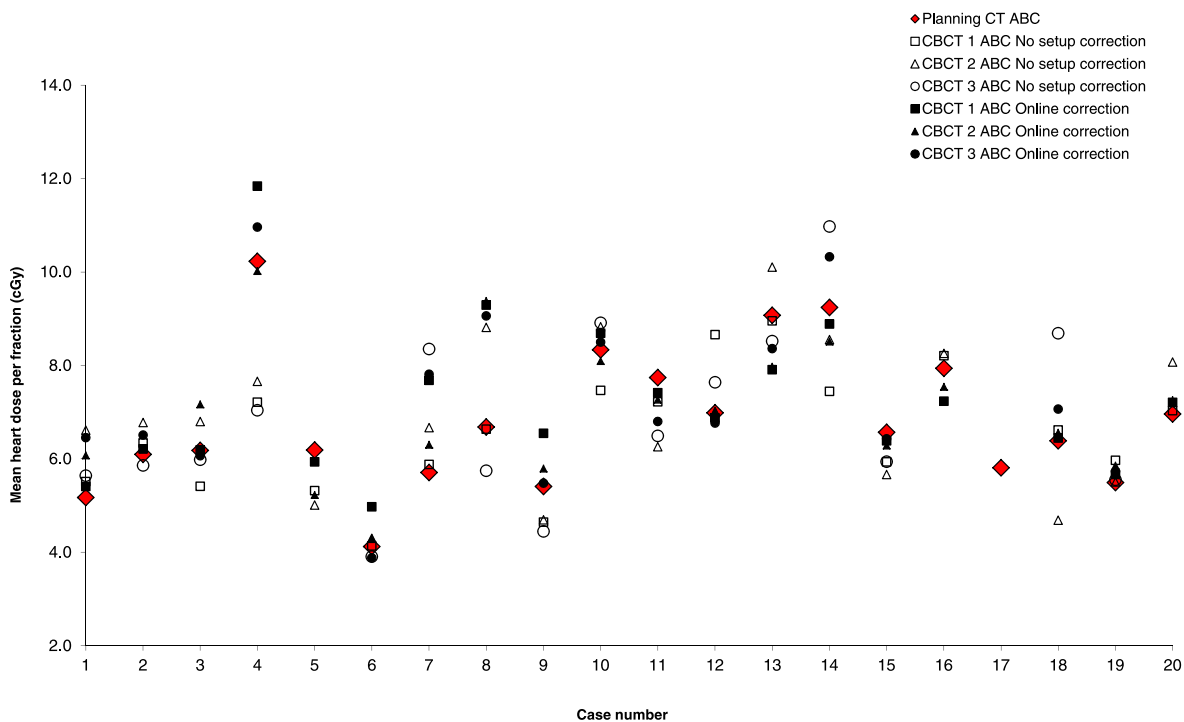
RESULTS

Whilst blurring occurred on the CBCT images, both observers were able to outline the heart on the CBCT images. The standard deviation of volumes and mean heart doses from the repeat outlining on the images was taken as a measure of the observer variation: 77 cm³ (ABC images) and 87 cm³ (VBH images) for the heart volumes and 2 cGy (both ABC and VBH images) for the corresponding mean heart dose. Absolute volumes were 547 cm³ (ABC) and 543 cm³ (VBH) and absolute mean heart doses were 99 cGy (ABC) and 95 cGy (VBH), assuming a 15-fraction treatment.

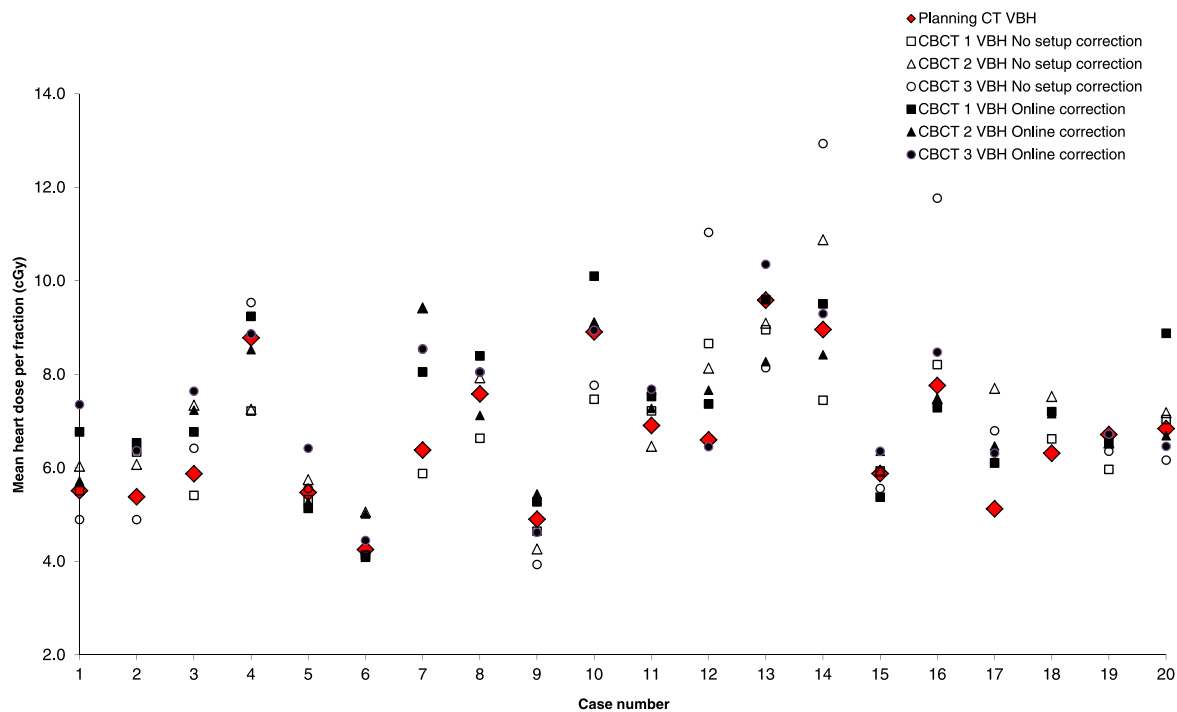
Figure 1 shows mean heart dose per fraction (in centigray) for each case for the ABC (upper panel) and VBH (lower panel) methods, respectively, with and without setup error correction. Correcting the setup error resulted in improvements in the agreement with the gold standard data from the treatment plan and/or reduction in the variation of the mean heart dose values.

As expected, there were no statistically significant differences between ABC and VBH techniques in the mean heart dose data prediction based on CT planning scans. There were no statistically significant differences in the estimated mean heart dose per fraction between the outlines based on the CBCT scans and those predicted for the corresponding CT-based treatment plans for either breath-hold technique. Neither was there a statistically significant difference in estimated heart doses received between the two breath-hold methods. There appeared no effect from the order of breath-hold method (whether the patient started with ABC or VBH). Variations from the expected mean heart dose per fraction from the imaged fraction data were <6 cGy, with 16/20 of cases showing changes of 2 cGy or less when online correction of setup error was applied. Tables 1 and 2 summarize the data from the acquired imaging for both ABC and VBH. In addition, data are scaled to 15 fractions assuming the variation from the 3 imaged fractions represents the variation over all fractions. These data are provided to give context to the results with respect to the heart dose expected from completed treatments in breath-hold.

Figure 1. Mean heart dose per fraction for (a) active breathing control (ABC) and (b) voluntary breath-hold (VBH) techniques. Mean heart dose per fraction is estimated from pre-treatment CT scan data and cone-beam CT (CBCT) images. Data are given both where no setup error was corrected and where all error was corrected. It can be noted that data retrieval issues means there are no data CBCT for Case 17.



(a)



(b)

Table 1. Predicted and estimated mean heart dose—active breathing control breath-hold

Case number	CT planning scan prediction 15 fractions (Gy)	Without setup correction			Setup correction applied		
		Predicted dose 3 fractions (cGy)	Estimated dose 3 fractions from imaging data (cGy)	Estimated dose 15 fractions from imaging data (Gy)	Predicted dose 3 fractions (cGy)	Estimated dose 3 fractions from imaging data (cGy)	Estimated dose 15 fractions from imaging data (Gy)
1	0.78	15.5	17.8	0.89	15.5	17.9	0.90
2	0.91	18.3	19.0	0.95	18.3	18.9	0.95
3	0.93	18.5	18.2	0.91	18.5	19.4	0.97
4	1.53	30.7	21.9	1.09	30.7	32.8	1.64
5	0.92	18.6	10.3	0.52	18.6	11.2	0.56
6	0.62	12.4	12.3	0.62	12.4	13.2	0.66
7	0.86	17.1	20.9	1.04	17.1	21.8	1.09
8	1.00	20.0	21.2	1.06	20.0	27.7	1.38
9	0.81	16.2	13.8	0.69	16.2	17.8	0.89
10	1.25	25.0	25.2	1.26	25.0	25.3	1.26
11	1.16	23.2	20.0	1.00	23.2	21.5	1.08
12	1.05	21.0	23.3	1.16	21.0	20.7	1.03
13	1.36	27.2	27.6	1.37	27.2	24.2	1.21
14	1.39	27.7	27.0	1.34	27.7	27.7	1.39
15	0.99	19.7	17.5	0.87	19.7	19.1	0.96
16	1.19	23.8	16.5	0.82	23.8	14.8	0.73
17 ^a	0.87						
18	0.96	19.2	20.0	1.00	19.2	20.1	1.01
19	0.82	16.5	17.0	0.85	16.5	17.2	0.87
20	1.04	20.9	15.1	0.75	20.9	14.5	0.72

Bold values indicate a change >0.25 Gy.

^aNot possible to retrieve cone-beam CT images.

DISCUSSION

This work has shown that the radiation dose to the heart received by patients throughout a course of breath-holding radiotherapy for breast cancer is not statistically significantly different from that predicted, is not affected by the breath-holding techniques investigated and varies by <0.25 Gy over the whole treatment for the majority of cases.

Neither this work nor that of Borst et al⁹ and McIntosh et al¹² was able to obtain volumetric data during each fraction of treatment directly, which would enable a more accurate determination of received heart dose. However, all three studies show a similar pattern—estimates of cardiac dose with breath-holding during treatment agree well with those predicted. The reproducibility of breath-hold methods is similar, or better, than generally reported values for free breathing.^{8,9} EPI dosimetry and cine, or movie loop, data have been reported and demonstrated good consistency and stability within fractions and

throughout the radiotherapy episode.^{10,11} It was thus likely that doses received by the heart during treatment would be close to those predicted from the CT planning study. This work has enabled quantification of that agreement and in 80% of cases, the differences were no >0.25 Gy with none >0.5 Gy. A decrease in heart dose up to 50% (1.0–2.0 Gy typically) is achieved when using a breath-hold technique compared with free breathing.^{9,12} The fraction-to-fraction variations found in this study do not negate this improvement from the use of breath-holding radiotherapy. In addition, our study showed that good agreement was observed for both the ABC method and the VBH technique and was maintained throughout the course of 15 fractions of treatment. This is reassuring for those already offering breath-holding treatments to patients and those intending to do so.

Borst et al⁹ and McIntosh et al¹² evaluated metrics such as maximum dose to the heart and data for the left descending coronary artery. We selected mean heart dose, as the Darby et al³

Table 2. Predicted and estimated mean heart dose—voluntary breath-hold

Case number	CT planning scan 15 fractions (Gy)	Without setup correction			Setup correction applied		
		Predicted dose 3 fractions (cGy)	Estimated dose 3 fractions from imaging data (cGy)	Estimated dose 15 fractions from imaging data (Gy)	Predicted dose 3 fractions (cGy)	Estimated dose 3 fractions from imaging data (cGy)	Estimated dose 15 fractions From imaging data (Gy)
1	0.83	16.5	16.5	0.82	16.5	19.8	0.99
2	0.81	16.1	16.7	0.83	16.1	19.3	0.97
3	0.88	17.6	20.3	1.01	17.6	21.6	1.08
4	1.32	26.3	26.1	1.31	26.3	26.6	1.33
5	0.82	16.4	16.9	0.84	16.4	16.8	0.84
6	0.64	12.8	13.4	0.67	12.8	13.6	0.68
7	0.96	19.1	26.1	1.30	19.1	26.0	1.30
8	1.14	22.7	25.0	1.25	22.7	23.6	1.18
9	0.74	14.7	12.6	0.63	14.7	15.3	0.77
10	1.34	26.7	26.1	1.30	26.7	28.2	1.41
11	1.04	20.7	20.5	1.03	20.7	22.5	1.12
12	0.99	19.8	26.9	1.35	19.8	21.5	1.07
13	1.44	28.8	25.9	1.29	28.8	28.2	1.41
14	1.34	26.9	32.0	1.60	26.9	27.2	1.36
15	0.88	17.6	16.6	0.83	17.6	18.1	0.90
16	1.16	23.3	25.3	1.27	23.3	23.2	1.16
17	0.77	15.4	21.0	1.05	15.4	18.9	0.94
18	0.95	18.9	15.9	0.79	18.9	14.4	0.72
19	1.01	20.1	19.0	0.95	20.1	19.8	0.99
20	1.03	20.5	24.0	1.20	20.5	22.0	1.10

Bold values indicate a change >0.25 Gy.

work demonstrated this to be a meaningful metric to enable an individualized cardiac risk for a female requiring breast radiotherapy. The quality of the CBCT images meant that whilst it was possible to contour the heart, outlining small-scale structures such as the left descending coronary artery was not possible. Hardware improvements to the CBCT system, which allow gating, will improve image quality which will assist image registration and outlining. Our work, and that of Lorenzen et al,¹⁵ show that mean heart dose is not sensitive to large changes in heart volume. If we were to repeat this study with a gated CBCT, it is unlikely that different results and conclusions would be obtained even with changed heart outlines.

CONCLUSION

Estimates of the mean heart dose received by patients undergoing a course of breast cancer radiotherapy varied little over the treatment duration for two validated, consistent and stable breath-holding techniques.

ACKNOWLEDGMENTS

The authors are grateful for the help of Dr Alison Ranger.

FUNDING

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). Ellen Donovan is funded by an NIHR Career Development Fellowship (CDF-2013-06-005). The work was partly undertaken in The Royal Marsden National Health Service (NHS) Foundation Trust, which receives a proportion of its funding from the NHS Executive. We acknowledge NHS funding to the NIHR Biomedical Research Centre at The Royal Marsden/Institute of Cancer Research. The views expressed in this publication are those of the authors and not necessarily, those of the NHS, the National Institute for Health Research or the Department of Health.

REFERENCES

- Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, et al; Early Breast Cancer Trialists' Collaborative Group. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011; **378**: 1707–16. doi: [http://dx.doi.org/10.1016/S0140-6736\(11\)61629-2](http://dx.doi.org/10.1016/S0140-6736(11)61629-2)
- Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al; Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; **366**: 2087–106. doi: [http://dx.doi.org/10.1016/S0140-6736\(05\)67887-7](http://dx.doi.org/10.1016/S0140-6736(05)67887-7)
- Darby SC, Ewertz M, McGale P, Bennett AM, Blom-Goldman U, Brønnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013; **368**: 987–98. doi: <http://dx.doi.org/10.1056/NEJMoa1209825>
- Schubert LK, Gondi V, Sengbusch E, Westerly DC, Soisson ET, Paliwal BR, et al. Dosimetric comparison of left-sided whole breast irradiation with 3DCRT, forward-planned IMRT, inverse-planned IMRT, helical tomotherapy and topotherapy. *Radiother Oncol* 2011; **100**: 241–6. doi: <http://dx.doi.org/10.1016/j.radonc.2011.01.004>
- Kirby AM, Evans PM, Donovan EM, Convery HM, Haviland JS, Yarnold JR. Prone versus supine positioning for whole and partial breast radiotherapy: a comparison of non-target tissue dosimetry. *Radiother Oncol* 2010; **96**: 178–84. doi: <http://dx.doi.org/10.1016/j.radonc.2010.05.014>
- Lu HM, Cash E, Chen MH, Chin L, Manning WJ, Harris J, et al. Reduction of cardiac volume in left-breast treatment fields by respiratory maneuvers: a CT study. *Int J Radiat Oncol Biol Phys* 2000; **47**: 895–904. doi: [http://dx.doi.org/10.1016/S0360-3016\(00\)00512-5](http://dx.doi.org/10.1016/S0360-3016(00)00512-5)
- Pedersen AN, Korreman S, Nyström H, Specht L. Breathing adapted radiotherapy of breast cancer: reduction of cardiac and pulmonary doses using voluntary inspiration breath-hold. *Radiother Oncol* 2004; **72**: 53–60. doi: <http://dx.doi.org/10.1016/j.radonc.2004.03.012>
- Bartlett FR, Colgan RM, Carr K, Donovan EM, McNair HA, Locke I, et al. The UK HeartSpare Study: randomised evaluation of voluntary deep-inspiratory breath-hold in women undergoing breast radiotherapy. *Radiother Oncol* 2013; **108**: 242–7. doi: <http://dx.doi.org/10.1016/j.radonc.2013.04.021>
- Borst GR, Sonke JJ, den Hollander S, Betgen A, Remeijer P, van Giersbergen A, et al. Clinical results of image-guided deep inspiration breath hold breast irradiation. *Int J Radiat Oncol Biol Phys* 2010; **78**: 1345–51. doi: <http://dx.doi.org/10.1016/j.ijrobp.2009.10.006>
- Brouwers PJ, Lustberg T, Borger JH, van Baardwijk AA, Jager JJ, Murrer LH, et al. Set-up verification and 2-dimensional electronic portal imaging device dosimetry during breath hold compared with free breathing in breast cancer radiation therapy. *Pract Radiat Oncol* 2015; **5**: e135–41. doi: <http://dx.doi.org/10.1016/j.prro.2014.10.005>
- Colgan R, James M, Bartlett FR, Kirby AM, Donovan EM. Voluntary breath-holding for breast cancer radiotherapy is consistent and stable. *Br J Radiol* 2015; **88**: 20150309. doi: <http://dx.doi.org/10.1259/bjr.20150309>
- McIntosh A, Shoushtair AN, Benedict SH, Read PW, Wijesooriya K. Quantifying the reproducibility of heart position during treatment and corresponding delivered heart dose in voluntary deep inhalation breath hold for left breast cancer patients treated with external beam radiotherapy. *Int J Radiat Oncol Biol Phys* 2011; **81**: e569–76. doi: <http://dx.doi.org/10.1016/j.ijrobp.2011.01.044>
- Alderliesten T, Betgen A, Elkhuizen PH, van Vliet-Vroegindeweij C, Remeijer P. Estimation of heart-position variability in 3D-surface-image-guided deep-inspiration breath-hold radiation therapy for left-sided breast cancer. *Radiother Oncol* 2013; **109**: 442–7. doi: <http://dx.doi.org/10.1016/j.radonc.2013.09.017>
- Donovan EM, Castellano IA, Eagle S, Harris E. Clinical implementation of kilovoltage cone beam CT for the verification of sequential and integrated photon boost treatments for breast cancer patients. *Br J Radiol* 2012; **85**: E1051–7. doi: <http://dx.doi.org/10.1259/bjr/28845176>
- Lorenzen EL, Taylor CW, Maraldo M, Neilson MH, Offersen BV, Andersen MR, et al. Inter-observer variation in delineation of the heart and left anterior descending coronary artery in radiotherapy for breast cancer: a multi-centre study from Denmark and the UK. *Radiother Oncol* 2013; **108**: 254–8. doi: <http://dx.doi.org/10.1016/j.radonc.2013.06.025>