

## The cardiac dose-sparing benefits of deep inspiration breath-hold in left breast irradiation: a systematic review

Lloyd M. Smyth, MMedRad (RT), BBiomed,<sup>1,2</sup> Kellie A. Knight, HScD, MHLthSc (RT), BAppSc (RT),<sup>2</sup> Yolanda K. Aarons, BAppSc (MedRad),<sup>1</sup> & Jason Wasiak, MPH<sup>1</sup>

<sup>1</sup>Epworth Radiation Oncology, Level 4, The Epworth Centre, Richmond, Victoria

<sup>2</sup>Department of Medical Imaging & Radiation Sciences, Faculty of Medicine, School of Biomedical Sciences, Nursing & Health Sciences, Monash University, Clayton, Victoria

### Keywords

Adverse effects, breast neoplasms, heart, radiotherapy, review

### Correspondence

Lloyd M. Smyth, Epworth Radiation Oncology, Level 4, The Epworth Centre, 32 Erin Street, Richmond VIC 3121, Australia.  
Tel: +61 3 99368277; Fax: +61 3 94833332;  
E-mail: lloyd.smyth@epworth.org.au

### Funding Information

No funding information provided.

Received: 18 September 2014; Revised: 18 November 2014; Accepted: 22 November 2014

*J Med Radiat Sci* **62** (2015) 66–73

doi: 10.1002/jrms.89

### Abstract

**Introduction:** Despite technical advancements in breast radiation therapy, cardiac structures are still subject to significant levels of irradiation. As the use of adjuvant radiation therapy after breast-conserving surgery continues to improve survival for early breast cancer patients, the associated radiation-induced cardiac toxicities become increasingly relevant. Our primary aim was to evaluate the cardiac-sparing benefits of the deep inspiration breath-hold (DIBH) technique. **Methods:** An electronic literature search of the PubMed database from 1966 to July 2014 was used to identify articles published in English relating to the dosimetric benefits of DIBH. Studies comparing the mean heart dose of DIBH and free breathing treatment plans for left breast cancer patients were eligible to be included in the review. Studies evaluating the reproducibility and stability of the DIBH technique were also reviewed. **Results:** Ten studies provided data on the benefits of DIBH during left breast irradiation. From these studies, DIBH reduced the mean heart dose by up to 3.4 Gy when compared to a free breathing approach. Four studies reported that the DIBH technique was stable and reproducible on a daily basis. According to current estimates of the excess cardiac toxicity associated with radiation therapy, a 3.4 Gy reduction in mean heart dose is equivalent to a 13.6% reduction in the projected increase in risk of heart disease. **Conclusion:** DIBH is a reproducible and stable technique for left breast irradiation showing significant promise in reducing the late cardiac toxicities associated with radiation therapy.

### Introduction

Adjuvant radiation therapy is the standard of care for women after breast-conserving surgery for low-risk breast cancer. According to the most recent Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis, adjuvant radiation therapy after breast-conserving surgery better than halves the risk of local recurrence and reduces the rate of breast cancer mortality compared to surgery alone.<sup>1</sup> However, as survival improves for breast cancer patients, the long-term effects of radiation therapy become increasingly relevant. The EBCTCG reports an increased rate of mortality from heart disease in the group of women treated with radiation therapy (risk ratio = 1.27).<sup>2</sup>

### Quantifying the risk of radiation-induced cardiac morbidity and mortality

Even with modern radiotherapy techniques, portions of the heart may still receive doses greater than 20 Gy when the left breast is irradiated depending on tumour location, the position of shielding and the use of respiratory manoeuvres.<sup>3,4</sup> Tumour laterality is an important predictor of cardiac doses. Mean heart and left anterior descending coronary artery (LADCA) doses are greatest when the left breast is treated, and this is reflected in an increased risk of cardiac mortality in patients receiving left breast irradiation compared to right breast irradiation.<sup>5</sup>

The increased risk of cardiac mortality and morbidity due to radiation exposure is reported to be small and dose dependent.<sup>6,7</sup> Based on a large study of breast cancer patients treated with radiation therapy in Denmark and Sweden,<sup>8</sup> Sardaro *et al.* estimated a 4% increase in the risk of heart disease for each 1 Gy increase in mean heart dose.<sup>6</sup> With regard to coronary heart disease, Darby *et al.* calculated that the rate of major coronary events after breast radiotherapy increases by 7.4% for each 1 Gy increase in mean heart dose; this increase is with no minimum dose threshold and is independent of the presence of pre-existing cardiac risk factors.<sup>7</sup> Major coronary events were defined as myocardial infarction (heart attack), coronary revascularisation or death from ischemic heart disease.<sup>7</sup>

### **Deep inspiration breath-hold and cardiac sparing**

Despite reducing the dose to cardiac structures during left breast irradiation, modern tangential techniques are not able to completely spare the heart and LADCA.<sup>3</sup> Techniques that involve respiratory motion management may further decrease the exposure of cardiac structures to radiation. Inspiration breath-hold strategies, including deep inspiration breath-hold (DIBH), have shown the greatest promise in reducing heart doses without compromising target coverage or increasing contralateral breast dose.<sup>9</sup> DIBH causes favourable changes to the internal thoracic anatomy such that there is increased spatial separation between the heart and the target volume, which results in a decreased volume of the heart within the tangential fields.<sup>10,11</sup>

The aim of this paper was to review the available literature concerning DIBH. The primary aim of was to assess the dosimetric benefits of DIBH compared to standard free breathing approaches for left breast cancer patients and the estimated potential to subsequently reduce long-term cardiac morbidity and mortality. The secondary aim of this paper was to assess the reproducibility and stability of DIBH. Conclusions about the impact of DIBH on observable clinical outcomes related to tumour control and long-term toxicities were beyond the scope of this review.

## **Method and Materials**

### **Data sources and search strategy**

A structured search was performed in PubMed from 1966 to April 2014 using the following combination of key terms; 'breath hold' or 'breathing control' or gating and breast and 'radiation therapy'. The literature search was

limited to articles published in English and no attempt was made to locate unpublished material or to contact authors of unpublished studies. Articles retrieved by the initial search were independently scanned by two authors to exclude irrelevant studies. The title and abstract of the remaining articles were assessed against the inclusion criteria.

### **Study selection criteria and procedure**

All published studies involving the use of DIBH for the irradiation of the left breast or left chest wall, with or without treating the axillary, supra-clavicular or internal mammary chain lymph nodes were considered for inclusion in this review.

We included studies that reported the mean heart dose of a DIBH treatment plan and a free-breathing treatment plan for each subject. A comparison between DIBH and free breathing was required for each study due to the heterogeneity of radiation therapy techniques used between different studies at different time-points. Furthermore, only studies which adopted a tangential field approach were reviewed, regardless of whether three-dimensional conformal radiation therapy (3DCRT) or intensity intensity modulated radiation therapy (IMRT) was used.

Studies ineligible for the primary aim of this review were considered for the secondary aim. With regard to the secondary aim of this review, studies were included if they quantitatively investigated the reproducibility or stability of DIBH techniques.

## **Results**

The search strategy identified 139 studies for potential inclusion in the review. Independent screening of these articles based on title and abstract identified 45 relevant articles. Of these articles, we excluded 14 studies that did not report the mean heart dose of DIBH and free breathing approaches. Other studies were excluded for not comparing DIBH and free breathing plans for individual subjects, reporting volumetric rather than dosimetric endpoints, or having less than ten subjects. The remaining ten studies were included for the primary aim of the review.

### **Dosimetric benefits of DIBH**

Ten studies (total of 268 patients) were included to evaluate the dosimetric benefits of DIBH for cardiac structures. Details regarding these studies and the reported dosimetric endpoints for cardiac structures are summarised in Table 1. Each of these studies was a case

**Table 1.** Summary of the studies included for dosimetric analysis.

Study	Size	Treatment site	Modality	Prescribed dose (Gy)
Lee et al. <sup>12</sup>	<i>n</i> = 25	Left breast	3DCRT	50.4 Gy
Mast et al. <sup>13</sup>	<i>n</i> = 20	Left breast	3DCRT	42.45 Gy
			IMRT	
Swanson et al. <sup>14</sup>	<i>n</i> = 87	Left breast and LCW ± SCF	IMRT	45 Gy
Hayden et al. <sup>15</sup>	<i>n</i> = 30	Left breast	IMRT (SIB)	50 Gy (60 Gy)
Hjelstuen et al. <sup>16</sup>	<i>n</i> = 17	Left Breast + SCF + AX + IMC	3DCRT	50 Gy
Wang et al. <sup>17</sup>	<i>n</i> = 20	Left breast	IMRT	42.4 Gy
				50 Gy
Vikström et al. <sup>18</sup>	<i>n</i> = 17	Left breast	3DCRT	50 Gy
Borst et al. <sup>19</sup>	<i>n</i> = 19	Left breast	IMRT	50 Gy
			IMRT (SIB)	50.7 Gy (64.4 Gy)
Stranzl et al. <sup>20</sup>	<i>n</i> = 11	Left breast + IMC	3DCRT	Not reported
Stranzl et al. <sup>21</sup>	<i>n</i> = 22	Left breast	3DCRT	50 Gy

3DCRT, three-dimensional conformal radiation therapy; IMRT, intensity modulated radiation therapy; SIB, simultaneous integrated boost; LCW, left chest wall; AX, axilla; SCF, supra clavicular fossa; IMC, internal mammary chain.

series where patients were simulated once in a free breathing state and once during DIBH to produce two different treatment plans for dosimetric comparison. Nine studies had a cohort size of 30 or fewer patients. The largest study (*n* = 87) was conducted by Swanson et al.<sup>14</sup> and by virtue of cohort size had the greatest relative power of the ten reviewed studies. Four studies<sup>14,15,17,19</sup> used static sequence IMRT to irradiate the target whilst five studies<sup>12,16,18,20,21</sup> employed a 3DCRT approach. One study<sup>13</sup> produced DIBH and free breathing plans using both IMRT and 3DCRT.

As highlighted in Table 2, there was a statistically significant reduction (with a significance level of *P* = 0.05) in mean heart and LADCA dose in the DIBH plans of all studies when compared with free breathing

plans. This finding was independent of the specific radiation therapy technique used. Borst et al. reported the greatest absolute reduction in mean heart dose (3.4 Gy).<sup>19</sup> Stranzl et al. reported the smallest absolute reduction in mean heart dose (1.0 Gy),<sup>21</sup> however, free breathing plans in their study also had the lowest mean heart dose of all studies (2.3 Gy) especially when compared to Borst et al. where free breathing plans had a mean heart dose of 5.1 Gy.<sup>19</sup> In the largest study reviewed, Swanson et al.<sup>14</sup> reported an absolute reduction in mean heart dose of 1.7 Gy between DIBH and free breathing plans.

Mean heart dose reductions were similar when comparing IMRT and 3DRCT, with these techniques achieving average reductions of 2.2 Gy and 1.9 Gy

**Table 2.** Studies reporting mean heart dose and mean LADCA dose for free breathing versus DIBH plans for left breast irradiation.

Study	Mean heart dose (Gy)			Mean LADCA dose (Gy)		
	FB	DIBH	Reduction Gy (%)	FB	DIBH	Reduction Gy (%)
Lee et al. <sup>12†</sup>	4.5	2.5	2.0 (44%***)	26.3	16.0	10.3 (39%***)
Mast et al. <sup>13</sup>	3.3 <sup>‡</sup>	1.8 <sup>‡</sup>	1.5 (45%**)	18.6 <sup>‡</sup>	9.6 <sup>‡</sup>	9.0 (48%**)
	2.7 <sup>‡</sup>	1.5 <sup>‡</sup>	1.2 (44%**)	14.9 <sup>‡</sup>	6.7 <sup>‡</sup>	8.2 (55%**)
Swanson et al. <sup>14‡</sup>	4.2	2.5	1.7 (40%****)	–	–	–
Hayden et al. <sup>15‡</sup>	6.9	3.9	3.0 (43%****)	31.7	21.9	9.8 (31%****)
Hjelstuen et al. <sup>16†</sup>	6.3	3.1	3.2 (51%***)	23.0	10.9	12.1 (53%***)
Wang et al. <sup>17‡</sup>	3.2	1.3	1.9 (59%***)	20.0	5.9	14.1 (71%***)
Vikström et al. <sup>18†</sup>	3.7	1.7	2.0 (54%*)	18.1	6.4	11.7 (65%*)
Borst et al. <sup>19‡</sup>	5.1	1.7	3.4 (67%***)	11.4	5.5	5.9 (52%***)
Stranzl et al. <sup>20†</sup>	4.0	2.5	1.5 (38%**)	–	–	–
Stranzl et al. <sup>21†</sup>	2.3	1.3	1.0 (43%***)	–	–	–

DIBH, deep inspiration breath-hold; LADCA, left anterior descending coronary artery; FB, free breathing.

†3DCRT.

‡IMRT.

\**P* < 0.05; \*\**P* < 0.01; \*\*\**P* < 0.001; \*\*\*\**P* < 0.0001.

**Table 3.** The stability and reproducibility of performing DIBH.

Author	Size	Imaging modality	Anatomy assessed	Inter-fraction variation						Intra-fraction variation					
				Magnitude of translation (mm)			Magnitude of rotation (°)			Magnitude of translation (mm)			Magnitude of rotation (°)		
				AP	SI	LR	AP	SI	LR	AP	SI	LR	AP	SI	LR
Betgen <i>et al.</i> <sup>22†</sup>	<i>n</i> = 19	3DSI CBCT	Breast Surface	1.2	3.1	1.0	1.42	0.48	0.09	0	0.5	0.2	0.07	0.03	0.03
Gierga <i>et al.</i> <sup>23†</sup>	<i>n</i> = 20	3DSI	Breast Surface	2.0	1.2	0.3	–	–	–	–	–	–	–	–	–
McIntosh <i>et al.</i> <sup>24†</sup>	<i>n</i> = 10	kV	Heart Position	2.0	1.0	1.0	–	–	–	–	–	–	–	–	–
Cerviño <i>et al.</i> <sup>25</sup>	<i>n</i> = 20	3DSI	Breast surface	Variation in chest wall excursion (mm)						Variation in chest wall excursion (mm)					
				2.1 <sup>†</sup> , 0.5 <sup>‡</sup>						1.5 <sup>†</sup> , 0.7 <sup>‡</sup>					

DIBH, deep inspiration breath-hold; CBCT, cone beam computed tomography; 3DSI, three-dimensional surface imaging; kV portal, kilo-voltage portal imaging; AP, anterior–posterior; SI, superior–inferior; LR, left–right.

<sup>†</sup>Without visual feedback.

<sup>‡</sup>With visual feedback.

respectively. In the only study comparing the use of DIBH in the context of both IMRT and 3DCRT, the dose reduction conferred by DIBH was 0.3 Gy greater in the 3DCRT arm compared to the IMRT arm.<sup>13</sup>

In addition to reporting on mean heart dose, seven studies<sup>12,13,15–19</sup> (total of 148 patients) reported the mean LADCA dose. There was considerable variability in the LADCA doses reported by these studies, ranging from 11.4 to 31.7 Gy in free breathing plans and 5.5–21.9 Gy in DIBH plans. As expected, the mean LADCA doses were much greater than for the heart, which is reflective of the geometric relationship between the heart, LADCA and target tissues during left breast irradiation. As with the mean heart dose, the mean LADCA dose was smaller in DIBH plans compared to free breathing plans in all of the seven studies,<sup>12,13,15–19</sup> with the greatest absolute reduction reported by Wang *et al.*<sup>17</sup> (14.1 Gy). The smallest reduction in mean LADCA dose was 5.9 Gy, as reported by Borst *et al.*<sup>19</sup>

Similar to the mean heart dose, the benefit of using DIBH was slightly greater for patients treated with IMRT compared to 3DCRT, with average LADCA dose reductions of 9.5 Gy and 8.8 Gy respectively. Conversely, however, Mast *et al.*<sup>13</sup> demonstrated that the reduction in mean LADCA dose using DIBH was marginally greater in 3DCRT compared with IMRT. Overall, there was little difference between 3DCRT and IMRT in terms of the dosimetric advantages conferred by DIBH in reducing mean heart and LADCA dose.

### Reproducibility and stability of DIBH

A total of four studies (total of 69 subjects) investigated the reproducibility or stability of DIBH

techniques (see Table 3). All studies assessed the reproducibility of DIBH, whilst Betgen *et al.*<sup>22</sup> and Cerviño *et al.*<sup>25</sup> additionally assessed the stability of DIBH. The largest inter-fraction translational variation in any plane was 3.1 mm in the superior–inferior plane.<sup>22</sup> However, Gierga *et al.*<sup>23</sup> and McIntosh *et al.*<sup>24</sup> reported that inter-fraction variations in DIBH set up were most prominent in the anterior–posterior plane. In the studies reporting both inter-fraction and intra-fraction variations,<sup>22,25</sup> the magnitude of intra-fraction variations (representing the stability of DIBH) as assessed by external surface anatomy, was smaller than the inter-fraction variations (representing the reproducibility of DIBH).

Overall, inter-fraction and intra-fraction variations were modest regardless of the image matching protocol used, with intra-fraction variations notably smaller compared to inter-fraction variations.

### Discussion

There are no studies to date investigating the clinical outcomes of using DIBH for left breast irradiation. Therefore, there are no data available to assess the impact of DIBH on the rate of late cardiac toxicities. With the long period of latency associated with late cardiac morbidity and mortality, the relative infancy of DIBH and the limited number of published clinical series regarding its use, it may be many years before data are available to assess the impact of DIBH on cardiac toxicity. As such, a theoretical and dosimetric approach to estimating the benefits of DIBH is necessary in the interim to determine whether the clinical implementation of DIBH is worthwhile.

### Potential impact of DIBH on the risk of cardiac morbidity

Sardaro *et al.*<sup>6</sup> estimate that a 1 Gy increase in mean heart dose equates to a 4% increase in the risk of late heart disease and Darby *et al.*<sup>7</sup> estimate that a 1 Gy increase in mean heart dose equates to a 7.4% increase in the rate of major coronary events, such as myocardial infarction or death from ischemic heart disease. In the ten studies reviewed, free breathing treatment plans were associated with mean heart doses ranging from 2.3 Gy<sup>21</sup> to 6.9 Gy,<sup>15</sup> depending on the specific radiotherapy technique used and whether additional lymph node groups were included in the target volume. Based on the estimate made by Sardaro *et al.*<sup>6</sup> and Darby *et al.*,<sup>7</sup> this represents a 9.2% to 27.6% increase in long-term heart disease risk from baseline risk levels and a 17–51% increase in the rate of major coronary events.

In all ten studies, DIBH produced a statistically significant reduction in the mean heart dose from free breathing plans, which would lead to a notably smaller increase in the risk of late cardiac morbidity for these women. The mean heart dose in the DIBH plans ranged from 1.3 Gy<sup>21</sup> to 3.9 Gy,<sup>15</sup> which may equate to an increased heart disease risk of only 5.2–15.6% and an increased rate of major coronary events of only 9.6–28.9%. The exact mean heart dose reduction is dependent on the specific radiation therapy technique used, whether the internal mammary chain lymph nodes are irradiated and the prescribed dose to the target volume. Data from the available studies are not sufficient to conclude whether DIBH is more beneficial for IMRT or 3DCRT.

There are no studies to date that assess the relationship between LADCA dosimetric endpoints and late coronary events. As such, an estimate of the reduction in late coronary morbidity as a result of using DIBH to spare the LADCA cannot be made. Nevertheless, the literature recognises the importance of considering the LADCA in left breast radiation due to its anatomic location and spatial relationship to the target tissue.<sup>4,26</sup> Given the physiological significance of this structure and the mean LADCA doses in both free breathing and DIBH plans reported in this review, clinicians would be well advised to consider the LADCA as an organ at risk. Future studies are necessary to evaluate normal tissue complication probabilities for the LADCA.<sup>27</sup>

### Impact of the reproducibility and stability of DIBH

The benefits of DIBH for the heart compared to free breathing seem clear, however, these estimates regarding the increase in cardiac morbidity risk are based on

dosimetric studies. The dosimetry of these plans must be accurately translated to the delivered dosimetry during treatment in order for these benefits to be realised. This requires that DIBH is reproducible and stable on a daily basis. A limited number of studies reporting on small cohorts have investigated the reproducibility and stability of DIBH. These studies agree that the inter-fraction and intra-fraction variability in set up position when using DIBH is small.

Betgen *et al.*<sup>22</sup> investigated the role of online image guidance to correct for inter-fraction variations. Using a pre-treatment online correction protocol, they found that inter-fraction variability prior to set up could be markedly reduced from 1.2, 3.1 and 1 mm to 0.3, 0.4 and 0.1 mm in anterior–posterior, superior–inferior and left–right planes respectively. Therefore, online image guidance may play an important role in ensuring that DIBH is reproducible on a daily basis. Combined with sub-millimetre intra-fraction variability, Betgen *et al.*<sup>22</sup> showed that the set up for DIBH is both reproducible and stable.

Additionally, Cerviño *et al.*<sup>25</sup> explore the role of a visual feedback system to supplement audio-based coaching of patients. Their findings suggest that the stability and reproducibility of DIBH can be further increased with real-time visual feedback, which together confer sub-millimetre inter-fraction and intra-fraction variations in chest-wall excursion.

In terms of the dosimetric impact of DIBH reproducibility on cardiac sparing, McIntosh *et al.*<sup>24</sup> found that in 10 patients the difference between the planned and treated mean heart dose was insignificant when compared to the mean heart dose in free breathing plans. This study found that the average difference in mean heart dose and mean LADCA dose between planning and treatment was 8% and 9% of the same dosimetric endpoints in the free breathing plan.

Thus, the available data from the four studies assessed in this review demonstrate that DIBH is reproducible and stable and that the dosimetric impact of inter-fraction variations is insignificant. However, from these studies it is not possible to directly draw a comparison with the stability and reproducibility of left breast irradiation during free breathing. The available data suggest that imaging technology may play an important role in the clinical implementation of DIBH, however, further studies will be required to determine the optimal imaging protocol to reproduce and monitor DIBH treatments.

### Alternatives to DIBH: cardiac shielding

Multi-leaf collimation is an obvious alternative to DIBH when it comes to protecting the heart during left breast

irradiation. In a study of 67 left breast patients, Bartlett *et al.*<sup>28</sup> investigated the impact of shielding the heart with multi-leaf collimation on target tissue coverage. They found that the average mean heart dose across 67 subjects was 0.8 Gy when using multi-leaf collimation to shield the heart, which is less than the smallest reported average mean heart dose achieved using DIBH (1.3 Gy).<sup>21</sup>

However, completely shielding the heart from irradiation in tangential fields will simultaneously shield a portion of the medial and inferior part of the breast tissue, depending on the exact positioning of the collimator leaves. In the study conducted by Bartlett *et al.*,<sup>28</sup> 35% of patients had less than 90% of the whole breast target volume covered by 95% of the prescription dose.

Of the ten studies primarily assessed in this review, two reported on coverage of the planning target volume (PTV) coverage.<sup>16,18</sup> In both of these studies, 99% of the PTV received 95% isodose coverage when DIBH was used to spare the heart and there was no significant difference between DIBH and free breathing plans.<sup>16,18</sup> Therefore, although multi-leaf collimation provides slightly better sparing of the heart, the available data suggest that the cardiac sparing conferred by DIBH does not come at the expense of PTV coverage. Because local recurrence is most likely to occur in the region close to the original tumour, the location of the original tumour should be considered when deciding which cardiac sparing strategy is most appropriate.

## Limitations

The main limitation of this review is that it is based on dosimetric rather than clinical studies. As such, the reported reduction in the risk of late cardiac morbidity and mortality is an estimate rather than an observation. As discussed previously, the aim of this review was to provide an estimate to inform decisions regarding the implementation of DIBH in future clinical practice. Future research will be necessary to confirm the estimated benefits of DIBH. However, this will require randomised studies with long-term follow-up to observe the late cardiac effects related to left breast irradiation.

One limitation of basing estimates on dosimetric studies is that the planned dosimetry does not always accurately represent the delivered dosimetry. For this reason, the reproducibility and stability of DIBH was secondarily assessed in this review. However, the impact of respiratory motion on the free breathing plans could not be assessed. Dose plans created from free breathing scans do not account for respiratory motion, and therefore, there is uncertainty about how accurately these free breathing plans were delivered. As such, the mean

heart dose delivered to the patient may be greater or lesser than planned. This will depend on the respiratory phase of the patient at the moment that the free breathing planning scan was taken. However, a study conducted by Frazier *et al.*<sup>29</sup> suggests that this uncertainty due to normal respiratory motion is minimal. They super-imposed free breathing-based dose plans for breast irradiation onto scans taken at the end of normal expiration and inspiration to assess the difference in dosimetry for the breast target volume and lung due to normal respiratory motion. These differences were insignificant for the ipsilateral lung and target breast tissue.<sup>29</sup>

Finally, it must be stressed that the majority of studies included in this review had small sample sizes. Thus, their results are subject to either the low probability of finding a true effect, a low positive predicative value when an effect was claimed or even the potential to exaggerate the estimate of the magnitude of the effect.<sup>30</sup> Furthermore, this review was limited by the non-randomised nature of the included studies and the variable methods of patient selection. This made a number of the reviewed studies susceptible to selection bias,<sup>31</sup> leading to a possible overestimation of the reduction in mean heart dose conferred by DIBH. Wang *et al.*<sup>17</sup> only produced DIBH dose plans for patients with unfavourable cardiac anatomy on the original free breathing plan, where greater than 10 cm<sup>3</sup> of the heart would have received greater than 50% of the prescription dose. Only these patients (20 of 53) were included for analysis in their study, and as such, the reduction in heart dose reported by this study may be exaggerated as it only applies to this subset of patients with unfavourable cardiac anatomy. In the study conducted by Swanson *et al.*,<sup>14</sup> only DIBH plans that showed improvements in cardiac dose relative to free breathing plans were included for analysis. As a result, 12 DIBH dose plans that failed to improve the cardiac dose were excluded from further analysis.

## Conclusion

The current evidence base regarding the benefits of DIBH for left breast cancer patients is exclusively limited to dosimetric studies. Based on a review of these studies, using DIBH rather than free breathing plans for left breast radiation therapy may reduce the mean heart dose by up to 3.4 Gy and mean LADCA dose by up to 14.1 Gy. In light of the reported reproducibility and stability of DIBH, these dosimetric benefits should be preserved when the treatment is delivered. According to current estimates of the excess cardiac toxicity associated with radiation therapy, DIBH can reduce the projected

increased risk of heart disease by 13.6% and reduce the projected percentage increase in the rate of major coronary events by 25.2%. The reduction in mean heart and LADCA dose for a given patient is dependent on the specific radiation therapy technique used, the prescription dose and whether the internal mammary chain lymph nodes require irradiation. The limitations inherent to this systematic review indicate the need for future studies with long-term follow up so that the estimated benefits of DIBH for cardiac toxicity can be confirmed.

## Acknowledgements

None.

## Conflict of Interest

The authors declare no conflict of interest.

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