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REVIEW ARTICLE

Review of deep inspiration breath-hold techniques for the treatment of breast cancer

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Abstract

Radiation treatment to the left breast is associated with increased cardiac morbidity and mortality. The deep inspiration breath-hold technique (DIBH) can decrease radiation dose delivered to the heart and this may facilitate the treatment of the internal mammary chain nodes. The aim of this review is to critically analyse the literature available in relation to breath-hold methods, implementation, utilisation, patient compliance, planning methods and treatment verification of the DIBH technique. Despite variation in the literature regarding the DIBH delivery method, patient coaching, visual feedback mechanisms and treatment verification, all methods of DIBH delivery reduce radiation dose to the heart. Further research is required to determine optimum protocols for patient training and treatment verification to ensure the technique is delivered successfully.

Introduction

Breast cancer is the most common cancer to affect women in Australia.[1] A recent review of optimal radiation therapy utilisation rates suggested the proportion of breast cancer patients in whom radiation therapy should be recommended is 87%.[2] A large meta-analysis by the Early Breast Cancer Trialists' Group[3] found that patients treated with radiation therapy after breast-conserving surgery (BCS) had a 7% chance of local recurrence at 5 years follow-up compared to 26% in patients who were not given radiation therapy. In addition, at 15 years after diagnosis the analysis showed an absolute risk reduction of 5.4% in breast cancer-related mortality with radiation therapy after BCS compared to BCS alone.

Despite its benefits, radiation therapy to the breast can result in complications. Multiple epidemiological studies have shown cardiac mortality and morbidity to be a long-term complication of left breast irradiation.[4,5] Long-term data from these studies are derived from patients treated prior to 1985. Since then, advancements in breast radiation therapy have limited dose delivered to the heart, presumably resulting in fewer cardiac deaths. A large retrospective study by Darby et al.[6] compared the ratio of patients who had received radiation therapy to the left breast and died of heart disease to that of the right breast. The cardiac mortality ratio decreased in successive patient cohorts from 1.21 for patients diagnosed in 1973–1982 to 1.08 in patients diagnosed in 1983–1992 and then finally to 0.99 in patients diagnosed in 1993–2001 at 5–9 years after diagnosis. A confounding factor was that this decrease was partially attributed to internal mammary chain (IMC) irradiation omission in most patients in the more recent era.

Another large retrospective study by Rutter et al.[7] analysed the data of 344,831 patients diagnosed with breast cancer between 1998 and 2006. No significant difference in overall survival based on tumour laterality was found. This remained true even when restricted to the 27,725 patients with a minimum of 10 years follow-up. These are compelling data as 44% of major coronary events are expected to have occurred within 10 years of diagnosis.[8]

Evidence exists that any reduction in radiation exposure to the heart will lower the incidence of ischaemic heart disease in breast cancer patients. A retrospective population based study by Darby et al.[8] analysed 2168 patients from Nordic cancer registries. They found the relative risk for ischaemic heart disease increased by 7.4% for every 1 Gray (Gy) increase in mean heart dose. However, as the study includes patients from as early as 1958, patients planned without modern CT planning had their radiation treatment plans reconstructed 'on the CT scan of a woman with typical anatomy' to estimate the radiation exposure to the heart. Even with this weakness, the article highlights that it is likely that any reduction in exposure to the heart is beneficial to the patient.

IMC lymph node irradiation is associated with greater radiation exposure to the heart.[9] IMC treatment is controversial in itself; several studies have shown it to provide a significant increase in disease-free survival,[10,11] while other studies have found it to provide no significant advantage[12] or have not recommended its inclusion unless pathologically proven.[13] The recently presented results from the MA.20[14] and EORTC 22922[15] trials have demonstrated the benefit of loco-regional radiation therapy, including treatment of the internal mammary nodes, for node-positive breast cancer. With the likely increased uptake of IMC irradiation, it is vital to adopt treatment techniques that minimise dose to the heart such as the deep inspiration breath-hold (DIBH) technique.

The DIBH technique involves the patient inspiring to a specified threshold and then holding that level of inspiration during every radiation therapy field delivered. The use of this technique can be associated with lower radiation exposure to the heart without compromising coverage of the breast or chestwall.[16–24] A number of studies have shown a reduction in the mean heart dose[25–42] (Table 1).

Table 1. Overview of DIBH studies that include mean heart dose in their analysis.

Publications	BH method	Patients	Treatment site(s)	Mean FB heart [mean, Gy]	Mean BH heart [mean, Gy]	Reduction in mean heart dose (FB vs. BH)
Stranzl and Zurl[25]	vDIBH (RPM)	22	Breast/CW+/−Boost	2.3 (0.6–6.5)	1.3 (0.5–2.4)	43.5%
Stranzl et al.[26]	vDIBH (RPM)	11	Breast/CW + IMC	4.0 (1.2–8.5)	2.5 (0.7–6.4)	37.5%
Borst et al.[27]	vDIBH (Other)	19	Breast/CW+/−Boost	5.1 (1.2–10.8)	1.7 (1.1–2.5)	66.7%
Vikstrom et al.[28]	vDIBH (RPM)	17	Breast	3.7 (3.2–20.1)	1.7 (2.2–10.1)	54.1%
Johansen S et al.[29]	vDIBH (RPM)	16	Breast	6.5 (2.2–19.1)	2.5 (1.4–9.4)	61.6%
McIntosh et al.[30]	vDIBH (RPM)	10	Breast	NR	NR	48.0%
Hjelstuen et al.[31]	vDIBH (RPM)	17	Breast + SCF + Ax + IMC	6.2 (2.5–14.4)	3.1 (1.8–9.7)	50.0%
Wang et al.[32]	ABC	20	Breast	3.2 (1.5–7.4)	1.3 (0.7–2.2)	58.4%
Hayden et al.[33]	vDIBH (RPM)	30	Breast + Boost	6.9	4.0	42.4%
Nissen et al.[34]	ABC	227*	Breast	5.2 (1.6–6.6)	2.7 (0.8–6.2)	48.1%
Reardon et al.[35†]	vDIBH (RPM)	10	Breast	1.6	0.9	45.2%
Swanson et al.[36]	ABC	87	Breast +/− SCF + Ax	4.2	2.5	40.5%
Bruzzaniti et al.[37]	vDIBH (RPM)	8	Breast	1.7 (1.3–2.5)	1.2 (1.0–1.4)	26.2%
Mast et al.[38‡]	ABC	20	Breast	3.3	1.8	45.5%
Comsa et al.[39]	ABC	20	Breast +/− Boost	3.1	1.2	75.0%
Bolukbasi et al.[40§]	vDIBH (RPM)	10	Breast	1.7 (1.2–2.5)	0.7 (0.4–1.0)	62.0%
Osman et al.[41‡]	vDIBH (RPM)	13	Breast + SCF + Ax + IMC	9.0 (4.1–12.8)	5.0 (2.0–8.9)	44.4%
Rochet et al.[42]	vDIBH (Other)	35	Breast/CW +/− SCF + Ax	2.5	0.9	64.0%

Table includes studies with both conventional and/or hypofractionated dose prescriptions. DIBH, deep inspiration breath-hold, BH, breath-hold; FB, free breathing; Gy, Gray; vDIBH, voluntary deep inspiration breath-hold; RPM, real-time position management; CW, chest wall; IMC, internal mammary chain; SCF, supra-clavicular fossa; Ax, axilla; ABC, active breathing control/coordinator.

*144 left-sided patients treated with DIBH compared to 83 left-sided patients treated while free breathing. Data for 92 right-sided patients are not included in this table.

†Comparison of DIBH 3D conformal radiation therapy plans to free-breathing intensity modulated radiation therapy (IMRT) plans.

‡3D conformal radiation therapy values shown.

§Forward planned IMRT radiation therapy values shown.

The DIBH technique was clinically implemented at Nepean Cancer Care Centre in 2009[33] and Crown Princess Mary Cancer Centre Westmead in 2011. Nationally, many centres have now adopted the technique, making the critical evaluation of the current literature on DIBH imperative for identifying gaps in the evidence. The aim of this review is to provide a broad overview of the literature in regard to implementation, utilisation, patient compliance, planning methods and treatment verification of the DIBH technique.

Methods

Relevant journal articles were searched using the MEDLINE Database. Searches were restricted to English-language full-text articles published between 2000 and 2014, and were conducted using combinations of a Medical Subject Heading (MeSH) and multi-purpose keywords (n = 48). MeSH of the articles from this initial search were analysed and another search was performed using only MeSH (n = 117) (Table 2).

A total of 118 articles were identified, including duplicate search entries. Using the inclusion criteria (Table 3), articles were excluded based on review of the abstract and title, resulting in 34 evaluable articles. Relevant journal articles were hand searched from reference lists (n = 1), as was the last year (January–December 2014) of the *International Journal of Radiation Biology Physics, Radiotherapy & Oncology* and *Practical Radiation Oncology* (n = 3). Information pertaining to the general topics of breath-hold method, utilisation/patient selection, patient compliance/training, planning and treatment verification were gathered from the resulting 38 journal articles.

Table 2. MEDLINE search terms used.

Serial number	Search term	Number of articles
1	Breast Neoplasms/rt [Radiotherapy]	6392
2	deep inspiration breath hold.mp.	91
3	deep inhalation breath hold.mp.	1
4	DIBH.mp.	57
5	mDIBH.mp.	12
6	2 OR 3 OR 4 OR 5	98
7	1 AND 6	48
8	Inhalation/	4997
9	Respiration/	69703
10	Respiratory-Gated Imaging Techniques/	440
11	Respiratory Mechanics/	13136
12	Breath Holding	195
13	8 OR 9 OR 10 OR 11 OR 12	22013
14	1 AND 13	117
15	7 OR 14	118

Table 3. Inclusion criteria for review of DIBH techniques.

Site	Whole breast or chestwall irradiation
Laterality	Left breast (or planned as left breast)
Technique	Deep inspiration breath-hold
Outcomes	Heart/dose parameter free-breathing vs. breath hold Inter-/intra-fraction motion during breath-hold

Breath-Hold Methods

Different breath-hold methods have been utilised. The two dominant methods are the spirometry-based active breathing coordinator (ABC) system (Elekta, Stockholm, Sweden) and the video-based real-time position management (RPM) system (Varian Medical Systems, Palo Alto, CA).

The ABC device was developed at the William Beaumont Hospital, Michigan.[43] The device is essentially a mouth piece attached to a spirometer and the patient's nose is pegged to ensure they are breathing only through the device (Fig. 1). As the spirometer is connected to a computer, the radiation therapists are able to visualise the patient's level of inspiration. Once the patient has reached the required threshold, pinch valves in the spirometer remotely close, preventing the patient from exhaling or inhaling outside the required threshold.

Some ABC devices may not be interlocked with the linear accelerator and may require the treating radiation therapist to manually turn on the beam when the patient is at the required level of inspiration. Current iterations of the ABC device are interlocked with the linear accelerator. ABC has shown to provide very reproducible

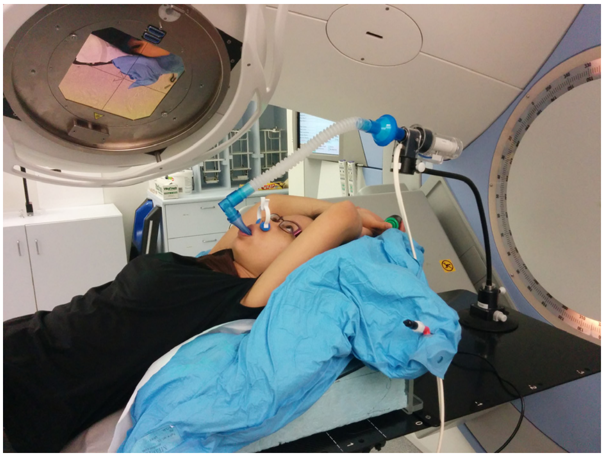

Figure 1. Demonstration of an active breathing coordinator (ABC) set up. The green thumb switch held in the right hand must be pressed during the breath hold manoeuvre; the release of the button signals interruption of breath-hold. Photo courtesy of Nepean Cancer Care Centre.

levels of inspiration[44] and is a viable option for delivery of a DIBH technique.[17,32,34,36]

The Varian RPM system was jointly developed by the University of California Davis Cancer Center and Varian Associates.[45] The system incorporates an infrared camera mounted on the wall of the treatment unit. The camera is surrounded by infrared lights aimed in the same direction as the camera. A marker box with reflective dots is placed on the patient and used as a surrogate to measure the expansion of the patient's thorax during breathing. The camera detects the marker box and calculates the position and movement of the thorax. The reflective marker box is most commonly placed near or on the xiphoid process[20,22,23,25,26,28–30,33,35] but has also been placed between the xiphoid process and umbilicus,[37] on the umbilicus,[40] and on the right chest.[24]

During the DIBH manoeuvre, the patient must voluntarily breathe to the required threshold. In some cases, the patient is able to see this threshold using a visualisation method such as a computer monitor or display goggles (Fig. 2). The size of this threshold, or gating window, varies from 2 mm[28] up to a maximum of 5 mm.[30,33] The system is linked to the linear accelerator and will automatically trigger beam-hold if the patient's breathing falls outside of the acceptable threshold; this ensures the patient will only receive radiation at deep inspiration. Like ABC, RPM is able to reproduce the level of inspiration required[45] and is a viable method of delivering DIBH treatment.[30]

The methods other than RPM have been used to verify the patient has reached, and voluntarily held, deep inspiration. These methods are sometimes described in the literature using the umbrella term 'voluntary deep inspiration breath hold' (vDIBH), which includes the RPM method.

A novel image-guided radiation therapy (IGRT)-based method of vDIBH was described by Borst et al.[27] This method used fluoroscopy to ensure the patient is breathing to the required threshold. At treatment, cone beam computed tomography (CBCT) scans were used to correct for any set up error. The beam was delivered manually when the patient was breathing to an acceptable level as verified by fluoroscopy. This technique produced pre-correction setup errors of <2 mm and was able to accurately reproduce the level of deep inspiration.

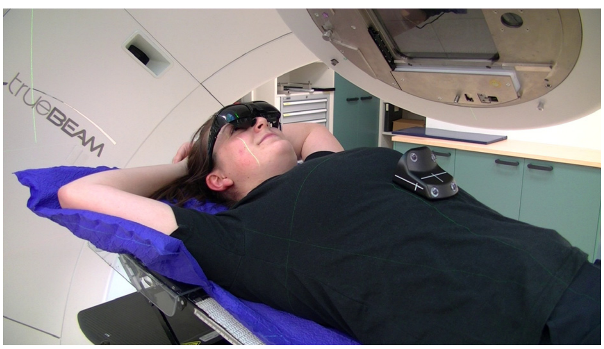

Figure 2. Demonstration of a real-time position (RPM) set up with the marker box (block) positioned on the xiphoid process. Visual feedback is provided using modified video goggles. Photo courtesy of Crown Princess Mary Cancer Centre.

Alderliesten et al.[46] outlined the additional use of 3D surface imaging to complement and possibly replace the IGRT method used in the previous study. 3D surface imaging is a non-ionising form of treatment verification that uses optical tracking to ensure the patient has not moved from a set position. Good correlation was found with the 3D surface imaging and concurrently taken CBCT scans, but the study ultimately did not recommend using 3D surface imaging as the sole method of set up verification and monitoring.

Bartlett et al.[47] compared ABC DIBH to vDIBH in a randomised crossover study. The vDIBH technique was performed by first checking the displacement of lateral tattoos at deep inspiration. For each treatment beam, the patient was asked to perform a breath-hold and radiation was only administered when the light field and previously marked field borders correlated. Set up reproducibility and normal tissue sparing were found to be comparable between ABC and vDIBH. However, it was noted patients found the vDIBH technique more comfortable and less claustrophobic.

Other vDIBH methods utilised in the literature include: monitoring of the lateral tattoo position,[48] the use of a real-time skin-surface-distance device to monitor the position of the patient's anterior surface,[48] and magnetic sensors attached to the patient's thorax.[49]

DIBH techniques utilising both RPM and ABC reduced dose to the heart. Because of this, and the lack of data comparing the two main techniques used, the choice of DIBH method is largely up to the institution and will most likely be based on existing equipment within the centre.

Utilisation/Patient Selection

Beyond left-laterality, patient selection for DIBH varied within the literature. The requirement to breath-hold for a specific duration of time,[28,33,36] presence of heart in-field,[17,49] evaluation of heart in free-breathing dose volume histogram,[32,36] cardiac contact distance,[50] patients <60 years[34] and an adequate understanding of the procedure,[27] were all used as selection criteria.

Difficulties arise in the use of heart measurements taken from conventional simulation images. Although evidence does exist showing good correlation with the measurement of the maximum heart distance (MHD) and the resultant mean heart dose in one planning study,[51] a study by Borger et al.[52] could not establish a dose–volume relationship for heart disease based on the MHD measurement. This was largely attributed to organ motion and the apparent overestimation of heart volume in simulator films.

Rochet et al.[42] found that parasagittal cardiac contact distance correlated well with mean heart dose and may potentially be used for patient selection. This study also suggested at least 75% of patients with left-sided breast cancer may benefit from the DIBH technique in terms of potentially clinically relevant dose reduction to cardiac structures and, therefore, DIBH should be instituted as routine clinical practice for left-sided patients.

Wang et al.[32] used a rapid planning method to select patients with unfavourable cardiac anatomy based on dosimetry. Patients underwent a free-breathing CT scan. A plan was produced within 9 min using an automated script in the Pinnacle3 (Philips Healthcare, Best, The Netherlands) planning system. If the plan resulted in a heart V50% >10 cm^3, the patient was deemed to have unfavourable cardiac anatomy and underwent an ABC-based DIBH procedure. Although this method is unique in its ability to select patients likely to benefit the most from DIBH, it is limited by its reliance on the rapid production of a plan from a breathing CT scan.

Patient Compliance/Training

Patient education regarding the DIBH technique is important as it requires the patient to actively breathe in before every treatment field to ensure successful delivery. High levels of compliance have been shown.

Variation existed regarding real-time feedback available to the patient. A study by Cervino et al.[53] compared stability and reproducibility of a vDIBH technique utilising 3D surface imaging. The study found visual feedback given to the patient increased the reproducibility of the DIBH manoeuvre from 2.1 mm without feedback to 0.5 mm with visual feedback. The study involved patients wearing video goggles connected to the computer system to provide this feedback in the least obstructive way possible.

The degree of patient training and coaching varied across the literature. A session or allocated time before CT scanning in which the patient is trained to perform the DIBH manoeuvre is common;[17,19,20,22–25,28,30,33,34,37,39,40,44,48,54] however only a few explicably indicated this was a separate session to the CT simulation procedure.[17,19,22,37,39,44,54] When stated, the typical training session took 15–30 min.

One study indicated the patient was given written instructions prior to their simulation session, and also described a mock-up fraction (fraction zero) scheduled the day before the first treatment to ensure the patient was able to perform the procedure correctly.[27] There are few reports on the value of different coaching methods for the patient or training requirements for the radiation therapists performing the technique. This is an area for future research, especially considering the importance of patient compliance in this technique.

Planning

A wide array of planning techniques has been reported in the DIBH literature, but generally RT was planned as either 3D-conformal RT[25,28] or intensity modulated radiation therapy (IMRT).[27,32,40] One planning study compared volumetric modulated arc therapy (VMAT) to 3D-conformal RT.[41]

A study by Stanzl et al.[26] evaluated the value of DIBH when wide tangents are used to treat the IMC and found considerably lower cardiac exposure was possible when DIBH was used compared to free breathing. This is important as multiple planning studies have indicated superior dose coverage of the partially wide tangent technique compared to the traditional photon–electron technique.[55,56] However, in a planning study by van der Laan et al,[57] the wide tangent technique resulted in higher doses to the heart and lungs. DIBH allows this potentially superior planning technique to be used while minimising cardiac dose.

Treatment Verification

There is some concern regarding the verification of the heart position and set up reproducibility with the DIBH technique. Using the left anterior descending coronary artery (LADCA) as the key indicator for heart toxicity, a CT-based study by Jagsi et al.[58] found inter-fractional reproducibility of this vessel at DIBH was similar to free-breathing scans.

Wang et al.[59] assessed the clinical implications of the displacement of this vessel and the heart periphery. They reported displacement of the heart periphery due to cardiac motion varied in the posterior aspect of the heart, which is not included in conventional treatment fields; the displacement of the LADCA varied considerably between patients. Due to this finding, the study recommended maintaining a 5 mm margin around the LADCA.

McIntosh et al.[30] quantified the reproducibility of the heart position using weekly orthogonal kV images on 10 patients. The images were registered according to bony anatomy and then again according to heart shadow; the difference between the two registrations was calculated as the displacement of the heart if a bony anatomy registration was used for isocentre correction. The study found that the ‘heart shifts’ on average were <3 mm in all three axes.

The optimal treatment verification image (TVI) protocol for the DIBH technique is an area for future research to ensure both the reproducibility of the patient position and the displacement of the heart or LADCA.

Recommended Future Research

There are two key aspects of DIBH that require further investigation. Firstly, there are no clear selection criteria to predict which patients will benefit most from the DIBH technique other than left breast laterality. There is evidence to suggest parasagittal cardiac contact distance is a promising metric for selection and this should be assessed in all future DIBH planning studies.

Secondly, patient compliance and treatment verification are additional areas for further research. Optimum visual feedback methods and coaching strategies have not yet been explored.

Conclusion

As local control and survival for patients with early breast cancer are now excellent, the minimisation of treatment-related toxicity and, in particular, the minimisation of cardiac toxicity associated with breast RT, is now a priority. Radiation treatment techniques and technologies that minimise dose to the heart are essential. The DIBH technique has consistently shown to lower the dose received to the heart.

Of interest is the value the DIBH technique has for patients indicated to receive IMC irradiation. The DIBH technique facilitates the use of planning techniques such as wide-angled tangents that provide superior dose coverage of the IMC volume.

Multiple methods exist to achieve the DIBH technique, with the two most widely used being ABC and RPM. As there is little data comparing the two methods, and because both methods have shown to be effective in facilitating the DIBH technique, the choice of method is up to the cancer centre and will be largely based on the pre-existing equipment in the department.

Further research should be aimed at clarifying optimum staff training, patient-selection criteria, patient coaching and treatment verification protocols to ensure the technique is delivered successfully and efficiently uses resources of the health care system.

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Conflict of Interest

The authors declare no conflict of interest.

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