VIA MEDICA

ORIGINAL ARTICLE

Oncology in Clinical Practice
DOI: 10.5603/ocp.97982

ISSN 2450-1654
eISSN 2450-6478

Impact of deep inspiration breath hold irradiation on dose reduction to the heart and left coronary artery in breast cancer

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Abstract

Objectives. Deep inspiration breath-hold (DIBH) is an effective and feasible approach to reducing the radiation dose to the heart in left-sided breast cancer radiotherapy (RT). This study aimed to assess the impact of DIBH on dose reduction to the heart and the left anterior descending coronary artery (LAD) in left-sided early breast cancer patients with intact breasts.

Material and methods. We compared RT plans of 42 patients from computed tomography datasets acquired for free breathing (FB) and DIBH techniques with 6 MeV photon tangential fields. The prescribed dose was 50 Gy in 25 fractions.

Results. DIBH enabled significant dose reduction to the heart and the LAD. A significantly lower mean heart dose (MHD) was observed in DIBH compared to FB planning (2.9 *vs.* 6.0 Gy, respectively; $p < 0.0001$). The considered LAD parameters, namely D_{max} 0.2 cm^3, mean dose, and V45Gy, were all significantly reduced in DIBH compared to FB planning (33.3 *vs.* 47 Gy; $p < 0.0001$, 16.7 *vs.* 30.1 Gy; $p < 0.0001$ and 0.5 vs 1.7 cm^3; $p < 0.0001$, respectively). Reduction in any of the LAD dose parameters was not correlated with MHD reduction. The LAD parameters were found to be significantly reduced in the group of patients with modest MHD reduction defined as < 2.8 Gy (31.2 *vs.* 46.9 Gy; $p = 0.0001$, 15 *vs.* 26.9 Gy; $p < 0.00001$, and 0.5 *vs.* 1.6 Gy; $p = 0.0005$, respectively).

Conclusions. DIBH has a pronounced impact on dose reduction to the LAD. This influence is not correlated with the MHD and is present even in patients with modest MHD reduction with DIBH.

Keywords: DIBH, breast cancer, radiotherapy

Introduction

Adjuvant radiotherapy (RT) after breast-conserving surgery in breast cancer patients improves local control and overall survival. However, in patients with left-sided tumors, radiation increases cardiac toxicity. In a classic study, Darby et al. [1] demonstrated

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Received: 2 December 2023; Accepted: 5 March 2024; Early publication: 29 May 2024

that rates of major coronary events (myocardial infarction, necessity for coronary revascularization, and death from ischemic heart disease) increase linearly with the mean heart dose (MHD) by 7.4% per Gray (Gy) after left-sided breast cancer RT. These results have been independently validated by van den Boogard et al. [2]. Their study showed that for the first 9 years after radiation exposure, the risk of major coronary events increases by 16.5% per Gy [2]. Several techniques to optimize heart dose exist, namely deep inspiration breath-hold (DIBH), prone position, intensity-modulated RT, partial breast irradiation, and proton beam therapy [3–5]. Specifically, the DIBH procedure, which requires careful positioning and monitoring during treatment, is an effective and feasible technique that reduces the MHD by moving the heart away from the thoracic wall. Studies showed that DIBH irradiation decreases heart volume in the treatment field [5–9], MHD [5, 7, 10–17], and the radiation dose to the left anterior descending coronary artery (LAD) [5, 10, 12–18]. As radiation-induced heart injury leads to a higher risk of coronary events, we assumed that the dose to coronary vessels may be an important factor. In this study, we present an analysis of the MHD and different measures of radiation exposure of the LAD in patients treated with DIBH. We also present the development and prospective evaluation of DIBH in our Institution.

Material and methods

Forty-two consecutive female left-sided early breast cancer patients planned for DIBH radiotherapy at the Radiotherapy Center NU-MED between 2016 and 2017 were analyzed retrospectively. All patients underwent breast-conserving surgery procedures and were referred for adjuvant RT. Patients after mastectomy or scheduled for adjuvant lymph node irradiation were excluded from the study. We also excluded all patients with invasive breast cancer who received external beam boost [either free breathing (FB) or DIBH] after whole breast irradiation due to heterogeneity of the boost. At the first visit, each patient had a consultation with the treating physician who explained the nature and rationale of the DIBH procedure. Good compliance is crucial in the DIBH procedure, so patients with poor lung function and unable to sustain breath were not considered optimal candidates. At the time of the study, no established criteria for DIBH irradiation in terms of MHD reduction were available at our Institution. Consequently, the treatment modality was chosen individually for each patient by the staff. Before the planned computed tomography (CT) simulation, patients were trained on the treatment machine and were considered eligible if they were able to hold their breath for at least 30 seconds. Surface monitoring system Align RT™ (VisionRT Ltd, London, UK) was used to check if the patient's chest wall was stable during the procedure.

The CT simulation was performed on the wing board in both FB and DIBH positions. Scans without intravenous contrast medium were acquired with a 3 mm slice width.

Target structures and organs at risk (OAR) were contoured both on FB and DIBH scans. Clinical target volume (CTV) included glandular tissue of the left breast down to the deep fascia, without the underlying muscle and rib cage. Planning target volume (PTV) was created by expanding the CTV by 5 mm isotropic margins. OAR were defined as the heart, LAD, and ipsilateral lung. The heart and the LAD were contoured manually by two independent radiation oncologists according to previously published guidelines [19]. The heart was contoured together with the pericardium starting superiorly and just inferiorly to the left pulmonary artery. When the LAD was not visible on CT scans, the interventricular groove was used as its surrogate. Lungs we contoured using an automatic segmentation tool.

Treatment planning

Free breathing and DIBH CT data sets were transferred to the Eclipse™ planning system (Varian Medical Systems Palo Alto, CA, USA), and treatment plans with static 6 MV photon opposite conformal tangential fields with multileaf collimators (MLC) were created. The comparison of FB and DIBH plans is presented in Figure 1. An additional field-in-field approach was allowed to provide optimal dose distribution and PTV coverage. The total dose was 50 Gy in 25 fractions prescribed to the isocenter. In DIBH plans, virtual wedges were not allowed, as their exact position could not be exactly reproduced in case of automatic beam off. Some examples of beam's eye views for DIBH and FB plans are shown in Figure 2.

The following optimal dose constraints for OAR were used: V20Gy < 35% and a mean lung dose (MLD) < 20 Gy for the ipsilateral lung. The MHD was kept as low as possible, preferably lower than 4 Gy [20], but without penalizing PTV coverage [21].

In daily practice in our institution, the LAD is not considered an OAR, as no recommended dose constraints are available in the literature. For the study, we used three dosimetric parameters from the literature to describe dose distribution in the LAD. The first one was the mean LAD dose, which is the most commonly used parameter in studies assessing the influence of DIBH on coronary vessels [5, 8, 10, 12–14]. The second one was the maximum dose, which is very important as the LAD is a serial structure. Because of uncertainties about the exact position of the LAD due to its movements associated with heartbeat, we considered the maximum dose to the 0.2 cm^3 of the

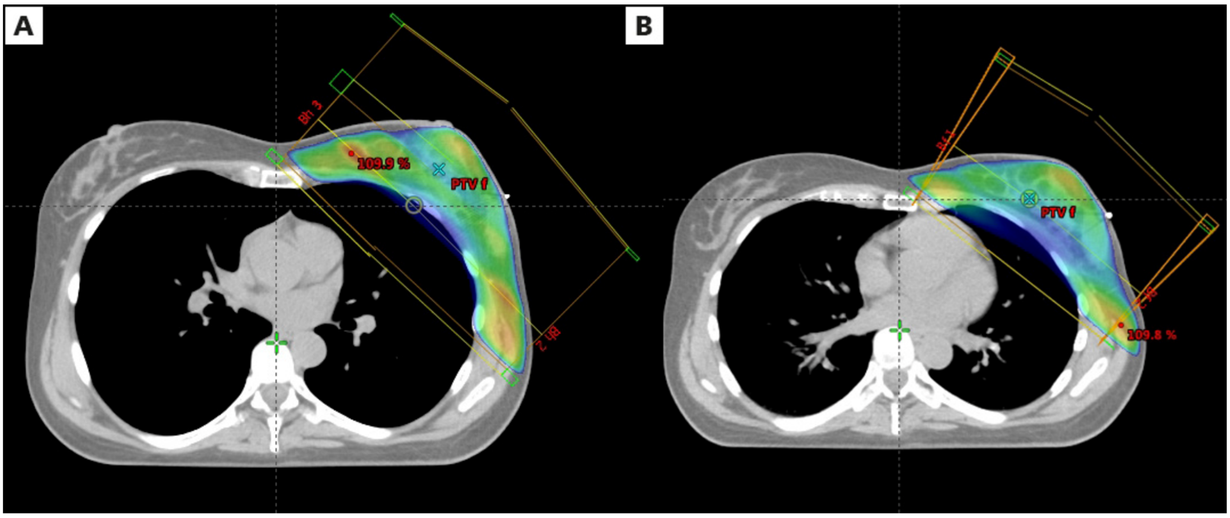

Figure 1. Axial views of computed tomography (CT) based radiation free breathing (FB) (**A**) and deep inspiration breath-hold (DIBH) (**B**) plans. The area in colour-wash represents volume covered by 95% isodose

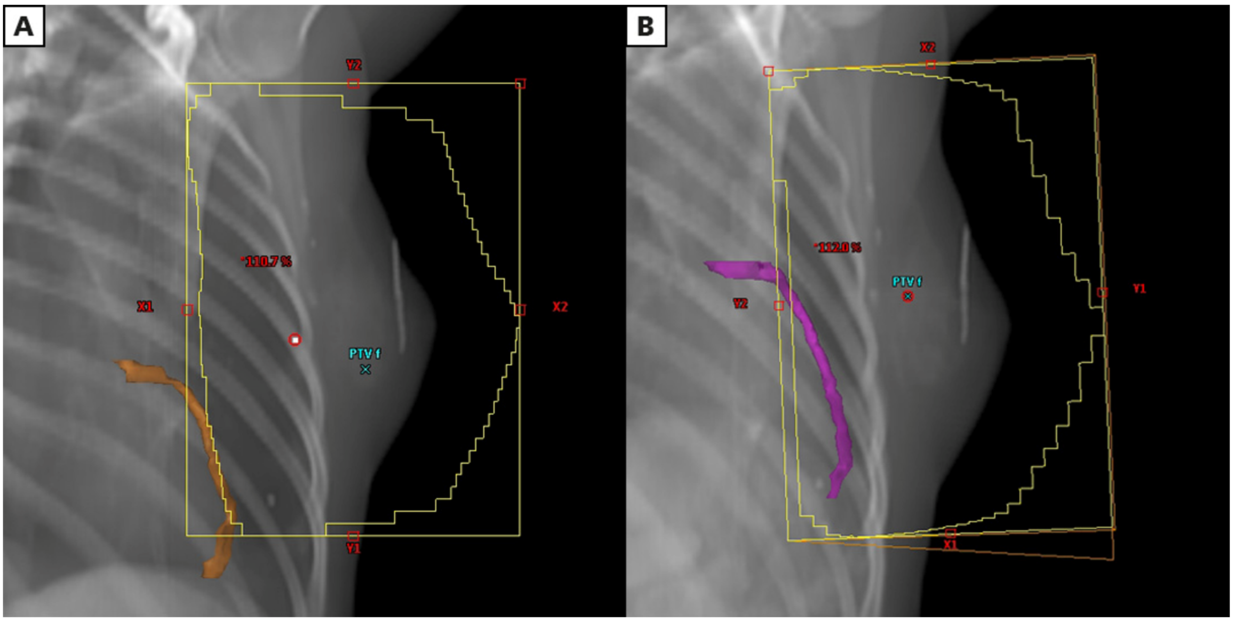

Figure 2. Beam's eye view (BEV) of the tangential radiation fields of the same patient planned for deep inspiration breath-hold (DIBH) (**A**) and free breathing (FB) (**B**). Note that in (**A**) the left anterior descending coronary artery (LAD) is situated at the edge of radiation field, while in (**B**) it is almost completely included inside

LAD instead of point maximum as a second constraint [9]. The third and last analyzed parameter was V45Gy as it is postulated that doses $\geq$ 45 Gy are associated with a higher risk of ischemic myocardial perfusion defects [22].

Treatment verification and monitoring

Treatment was delivered with a Siemens Artiste linear accelerator. We used a voluntary technique for DIBH [23]. During the whole RT session, radiographers had direct audio-visual contact with the patient to give commands and instructions on breathing when needed. Before each fraction, the patient was asked to breathe in the same way as during the simulation. Two orthogonal 1 MV films were taken during the first 3 fractions to verify positioning and make changes if necessary. Surface monitoring system Align RT was used to achieve stable and reproducible patient position using a 3-mm tolerance limit. The beam was automatically turned off during treatment if the patient's surface was out of the limit.

Electronic portal images (EPI) were obtained daily from each treatment field and compared online with digitally reconstructed radiographs (DRR) before treatment delivery.

In the case of Align RT failure or poor compliance, patients were treated with FB plans prepared beforehand and could return to the DIBH procedure as soon as it was possible.

Statistical methods

STATA 8.0 software was used for statistical analyses. Categorical variables were compared using a two-sided Pearson chi-square test. A dosimetric comparison was carried out by using a paired Student's t-test and Wilcoxon signed rank test. Statistical significance was considered at $p < 0.05$.

Results

The characteristics of patients are presented in Table 1. In 32 patients (76%), MHD dose reduction with DIBH planning was considered clinically relevant, and they were treated with this technique. Only in one patient, the MHD was higher in DIBH than in FB, but this difference was 0.2 Gy and was considered clinically insignificant. The remaining 10 patients (24%) received the FB treatment.

Table 1. Patient characteristics

Age, mean (range)	**53 (33–68)**
Systemic treatment, no. (%)	
Hormonal therapy	36 (86%)
Chemotherapy	16 (38%)
Trastuzumab	8 (19%)
Histology, no. (%)	
Ductal invasive carcinoma	33 (78%)
Lobular	3 (8%)
Other	6 (14%)
T stage, no. (%)	
T_{is}	1 (2%)
T_1	31 (74%)
T_2	9 (22%)
T_3	1 (2%)
N stage, no. (%)	
N_0	41 (98%)
$N_{1\ (mi)}$	1 (2%)
CTV FB mean/median/range [cm^3]	904/778/344–2751
CTV DIBH mean/median/range [cm^3]	897/785/341–2630
CTV volume FB/DIBH	p = 0.23*
PTV FB mean/median/range [cm^3]	1279/1155/589–3511
PTV DIBH mean/median/range [cm^3]	1277/1151/591–3394
PTV volume FB/DIBH	p = 0.82*

*Student's t-test; CTV — clinical target volume; DIBH — deep inspiration breath hold; FB — free breathing; PTV — planning target volume

Significantly, a lower MHD was observed in DIBH compared to FB planning (2.9 *vs.* 6.0 Gy, respectively; $p < 0.0001$), and the average MHD reduction between DIBH and FB was 3.1 Gy. MHD < 4 Gy was achieved in 33 (78.6%) DIBH plans compared to 11 (26.2%) FB plans.

The analyzed LAD parameters, namely D_{max} 0.2 cm^3, mean dose, and V45Gy, were all also significantly reduced in DIBH compared to FB planning (33.3 *vs.* 47 Gy; $p < 0.0001$, 16.7 *vs.* 30.1 Gy; $p < 0.0001$ and 0.5 vs 1.7 cm^3; $p < 0.0001$, respectively). The mean reduction of the above-mentioned parameters achieved with DIBH planning was 13.7 Gy, 13.4 Gy, and 1.2 cm^3, respectively.

Such a reduction in any of the LAD dose parameters turned out not to be correlated with an MHD decrease. Therefore, we subsequently analyzed the impact of DIBH on the LAD parameters in patients with a modest MHD reduction, defined as < 2.8 Gy (n = 20). We found that these parameters were all significantly reduced in DIBH compared to FB plans (31.2 *vs.* 46.9 Gy; $p = 0.0001$, 15 *vs.* 26.6.9 Gy; $p < 0.00001$, and 0.5 *vs.* 1.6 Gy; $p = 0.0005$, respectively) (Tab. 2).

Deep inspiration breath-hold had a significant but not pronounced impact on ipsilateral lung irradiation. The MLD to the left lung was significantly lower in DIBH than in FB (9.8 *vs.* 11.1 Gy; $p < 0.00001$) as was V20Gy (18.6 *vs.* 20.9%; $p < 0.0001$). In 6 patients (14.3%), DIBH resulted in higher V20Gy and in 9 patients (21.4%) in a higher MLD.

Discussion

Deep inspiration breath-hold in our Institution was proven to be a feasible and effective procedure for sparing heart in patients with left-sided early breast cancer treated with RT after breast-conserving surgery.

Table 2. Comparison of heart and left anterior descending coronary artery (LAD) doses between free breathing (FB) and deep inspiration breath-hold (DIBH) planning

	FB [Gy]	**DIBH [Gy]**	**Reduction [%]**	**p value**
Whole group (42 patients)				
MHD	6.0	2.9	51.7	< 0.00001
D_{max} 0.2 cm^3	47	33.3	21.5	< 0.0001
V45Gy	1.7	0.5	70.6	< 0.0001
Mean LAD dose	30.1	16.7	44.5	< 0.0001
Modest MHD reduction group (20 patients)				
D_{max} 0.2 cm^3	46.9	31.2	33.5	0.0001
V45Gy	1.6	0.5	68.7	< 0.00001
Mean LAD dose	26.9	15	44,2	0.0005

MHD — mean heart dose

The benefits of DIBH in terms of MHD reduction in our cohort was 3.1 Gy and was consistent with other reported studies where it ranged from 1 to 3.4 Gy [5, 7, 12, 23]. It should also be mentioned that DIBH enabled achieving the optimal (< 4 Gy) MHD in more than 75% of patients while this constraint was fulfilled only in about one-quarter of FB subjects.

The study revealed a pronounced impact of DIBH on the LAD dose. To date, there are no established dose constraints to the coronary vessels as there are no prospective studies assessing the impact of absorbed doses on clinically relevant endpoints such as coronary events. Based on available clinical data, Piroth et al. [24] proposed constraints for left-sided breast-only RT. These include the MHD, mean LAD dose, and LAD V30 and V40 [24]. Dose to the left ventricle was also included as clinically relevant [22]. It is postulated that left ventricle V5 could be a predictor of acute coronary events after breast RT [2]. Nevertheless, the left coronary artery seems to be an important OAR in RT of left-sided breast cancers due to its anatomical location and importance, as it supplies blood to the left ventricle. This hypothesis is supported by large well-conducted studies showing that long-term cardiac mortality after breast cancer RT is associated mostly with coronary disease resulting in ischemic heart disease and myocardial infarction [23, 25]. According to these data, further studies on heart toxicity in breast cancer RT patients should take LAD, as an OAR, into consideration. In the era of conformal RT, this structure can be successfully identified and spared without compromising target coverage.

The most widely studied dosimetric parameter for the LAD is the mean dose [8, 11–13, 23]. In all published studies, mean doses to the LAD were significantly smaller in DIBH than in FB RT plans. However, there was considerable variability in the doses reported by the authors, which ranged from 5.5 to 21.9 Gy in DIBH and 11.4 to 31.7 Gy in FB. Dose reduction ranged from 5.9 to 10.3 Gy. These differences can be partially explained by different planning techniques and intra-observer variability in the contouring of coronary vessels, due to the scarcity of contouring guidelines at the time of the treatments and difficulties in delineation of small structures [19, 21, 23]. It should also be mentioned that, both in research and clinical settings, planning CT in breast cancer patients is performed without contrast media, which makes contouring less accurate. Some authors proposed adding an isotropic margin to the coronary artery to account for uncertainties of internal organ motion and intra-observer variability [13]. In our cohort, mean doses to the LAD in DIBH and FB were 16.7 and 30.1 Gy, respectively, with a resulting dose reduction of 13.4 Gy, in line with other mentioned studies.

No correlation between the reduction in the MHD and significant gain in the LAD dosimetric parameters was found. This can be explained by the anatomic location of the coronary vessel, which in DIBH is often situated at the edge of the radiation field (Fig. 1). As a result, even minor changes in thoracic geometry between DIBH and FB can cause substantial differences in dose distribution within this structure, while heart volume included in the radiation field would not change much. We also showed that, even in the group of patients with a modest reduction in the MHD in DIBH plans, there was still a significant improvement in all analyzed dose distribution parameters within the LAD. This finding suggests that the MHD may not be the most relevant parameter when assessing the risk of cardiac toxicity in breast cancer RT. It seems reasonable to assess the MHD in conjunction with the dose to the coronary artery, especially in patients with a low MHD. This hypothesis, however, requires further studies and correlation with clinical data.

The study demonstrated that DIBH yields lung dosimetric advantages both in terms of MLD and V20Gy. However, this effect was not as unequivocal as with the heart and the LAD, and it should be kept in mind that in a significant group of patients, DIBH plans were inferior to the FB technique in terms of the MLD and V20Gy. Some recent studies with significant groups of patients show similar results [5, 26–28]. In some patients with special concerns about lung toxicity, when DIBH is not sufficient to reduce the dose to the heart and the ipsilateral lung, radiotherapy in the prone position is a promising option [5]. Data on the influence of DIBH on the lung dose are limited, and this issue needs further research.

Conclusions

Our study showed that the DIBH technique results in significant sparing of the coronary vessels in early left-sided breast cancer patients treated with postoperative RT. DIBH has a pronounced impact on dose reduction to the LAD. This influence is not correlated with the mean heart dose and is present even in patients with a modest mean heart dose reduction with DIBH.

Article Information and Declarations

Data availability statement

The data that support the findings of this study are available on request from the corresponding author.

Ethics statement

The study is analysis based od the retrospective data (CT) that were completely anonymyzed. All medical procedures i.e. CT scans were performed as a part of routine radiotherapy planning. Taking these to account patients were not asked to provide consent as well as ethical approval was not required.

Author contributions

P.W.: conception and design, collection and assembly of data, data analysis and interpretation, manuscript writing; J.W.-M.: conception and design, collection and assembly of data, data analysis and interpretation; A.Blukis: conception and design, collection and assembly of data; M.A.-S., P.U., A.R. M.U.: collection and assembly of data; M.P., S.D.: data analysis and interpretation, manuscript writing; B.A.J.-F., A.Badzio: conception and design, data analysis and interpretation, manuscript writing.

All authors approved the final manuscript.

Funding

The study was not financed/supported by any institution/company

Acknowledgements

None.

Conflict of interest

All authors declare no conflict of interest.

Supplementary material

None.

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