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Deep inspiration breath hold: dosimetric benefits to decrease cardiac dose during postoperative radiation therapy for breast cancer patients

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Abstract

Background: Postoperative radiation therapy (RT) is the standard treatment for almost all patients diagnosed with breast cancer. Even with modern RT techniques, parts of the heart may still receive higher doses than those recommended by clinically validated dose limit restrictions, especially when the left breast is irradiated. Deep inspiration breath hold (DIBH) may reduce irradiated cardiac volume compared to free breathing (FB) treatment. This study aimed to evaluate the dosimetric impact on the heart and left anterior descending coronary artery (LAD) in FB and DIBH RT planning in patients with left breast cancer.

Materials and methods: A retrospective cohort study of women diagnosed with left-sided breast cancer submitted to breast surgery followed by postoperative RT from 2015 to 2019. All patients were planned with FB and DIBH and hypofractionated dose prescription (40.05 Gy in 15 fractions).

Results: 68 patients were included in the study. For the coverage of the planned target volume evaluation [planning target volume (PTV) eval] there was no significant difference between the DIBH versus FB planning. For the heart and LAD parameters, all constraints evaluated favored DIBH planning, with statistical significance. Regarding the heart, median V16.8 Gy was 2.56% in FB *vs.* 0% in DIBH ($p < 0.001$); median V8.8 Gy was 3.47% in FB *vs.* 0% in DIBH ($p < 0.001$) and the median of mean heart dose was 1.97 Gy in FB *vs.* 0.92 Gy in DIBH ($p < 0.001$). For the LAD constraints D2% $<$ 42 Gy, the median dose was 34.87 Gy in FB versus 5.8 Gy in DIBH ($p < 0.001$); V16.8 Gy $<$ 10%, the median was 15.87% in FB versus 0% in DIBH ($p < 0.001$) and the median of mean LAD dose was 8.13Gy in FB versus 2.92Gy in DIBH ($p < 0.001$).

Conclusions: The DIBH technique has consistently demonstrated a significant dose reduction in the heart and LAD in all evaluated constraints, while keeping the same dose coverage in the PTV eval.

Key words: breast cancer; radiation therapy; cardiotoxicity; coronary disease

Introduction

Breast cancer (BC) is the most frequently diagnosed and most frequent cause of cancer death in women worldwide [1]. Postoperative radiation therapy (RT) is part of the standard treatment for most patients diagnosed with BC with increase in local control, disease-free survival, and overall survival [2–8]. As patient survival increases, the long-term effects of RT become increasingly relevant. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reported an increase in the mortality rate from heart disease in the group of women treated with RT (hazard ratio = 1.27), especially when the conventional RT techniques were used [2]. New technologies increase the precision of radiation to the target and help reduce the dose in normal tissues, thus minimizing the risk of toxicity and morbidity [9]. However, even with modern RT techniques, portions of the heart can still receive doses greater than those recommended by the constraints, especially when the left breast is irradiated. With the movement of the chest wall and internal organs, there is a spatial variation of these organs being more or less irradiated [10–12]. To reduce the cardiac volume irradiated, some techniques using RT adapted to breathing are being used. Deep inspiration breath hold (DIBH) is premised on reducing the cardiac volume irradiated compared to free breathing (FB) treatment. After lung expansion, there is a posterior and inferior displacement of the heart, momentarily moving it away from the chest wall, and, consequently, from the irradiated region. This dynamic becomes especially interesting in patients who have a greater contact surface between the heart and the chest wall [13, 14].

Studies demonstrating the dosimetric superiority of DIBH in the left breast, as well as its technical feasibility, have never been formally performed in Brazil and Latin America. This study aimed to evaluate the reduction of radiation dose in the heart and LAD and to compare the planning related to the doses received by the other organs at risk (lungs and right breast) in FB and in DIBH RT planning in patients with BC.

Materials and methods

This is a retrospective cohort study. From 2015 to 2019, women diagnosed with cancer of the left breast submitted to surgical treatment followed by postoperative RT were included. The medical records of patients planned with the FB and DIBH techniques were evaluated.

All patients with left breast cancer were selected for the technique as long as they were clinically able to maintain a predictable breathing pattern and withstand short periods of apnea of approximately 15 seconds. For DIBH, patients must breathe voluntarily to reach a predefined threshold or breathing interval window. All patients were planned with a hypofractionated regimen (40.05 Gy dose in 15 fractions) with a 3D conformal field-in-field technique [15].

Contouring was based on the European Society for Radiotherapy and Oncology (ESTRO) consensus guidelines [16, 17]. The planning target volume (PTV) was defined as 5 mm margin around the breast clinical target volume (CTV). For dose evaluation, the PTV was cropped 5 mm from the skin (PTV eval).

Organs at risk dose constraints, regarding both the volume that received xxGy (VxxGy) and the dose received by yy% of the volume (Dyy%) were obtained using the dose volume histogram (DVH) tool of the planning system. For the purpose of this study, the following parameters were collected: mean dose, V16.8 Gy, and V8.8 Gy of the heart and for LAD: D2% < 42 Gy, and V16.8 Gy < 10%. All evaluated dose parameters are summarized in supplement A.1 [18].

The constraints used for this study were those defined in the RTOG 1005 trial [18] for conventional fractionation. They were extrapolated using the radiation biologically effective dose formula for hypofractionation (40.05 Gy in 15 fractions), considering the heart α/β ratio equal to 1.5. The parameters used for the LAD, such as D2% < 50 Gy, volume that receives 20 Gy (V20 Gy) < 10% and mean dose, were also recalculated [19].

Before treatment, a cone beam computed tomography and fluoroscopy imaging were performed to ensure that the patient was breathing in the required range.

Radiation was delivered when the patient was breathing according to the plan within a range that was considered acceptable. Fluoroscopy reduced errors and allowed the deep inspiration level to be accurately reproduced since it indicated the stability of the chest wall and the displacement of the heart away from the radiation field during treatment.

Statistical analysis

The data from the RT planning in FB and DIBH were compared through the constraints used to approve the planning. In the intragroup comparison (paired analysis), the Wilcoxon test was used. For each parameter, the hypothesis test was performed considering the null hypothesis as the median of the differences between the evaluated constraints. If $p < 0.05$, the null hypothesis is rejected (in other words, there is a difference for the variable), when comparing the DIBH versus FB planning.

Results

Patient characteristics, surgical treatment, and diagnosis

A total of 68 patients were included in the study. The median age was 50.5 years (ranging from 34 to 78 years). Most patients underwent conservative surgery (n = 49; 72.1%); 27.9%, mastectomy with preservation of the skin or the nipple-areolar complex. 14 women underwent immediate breast reconstruction.

Regarding the characteristics of the tumor, 52.9% of the patients were located in the upper outer quadrant. 76.5% had invasive carcinoma without other specifications, 17.6% had ductal carcinoma in situ, and 5.9% had invasive lobular carcinoma. On immunohistochemical analyses, 50% were luminal A-like, 33.8% luminal B-like, 11.8% triple negative, 2.9% triple positive and 1.5% HER2 positive.

As for post-surgical staging, 48.5% were classified as IA; 19.2% IIA; 17.6% 0; 13.2% IIB and 1.5% IB.

Radiation treatment outcomes

The variables D95% (Gy) and D90% (Gy) of the PTV eval, right breast Dmax (Gy), and left lung V4.5 Gy (%) showed no significant difference between FB and DIBH planning. The median for D95% for the PTV eval was 38.02Gy in the DIBH versus 38.01 Gy in the FB ($p = 0.94$). The median for the D90% in the PTV eval was 38.73 Gy in DIBH versus 38.7 Gy in FB ($p = 0.966$) — Table 1.

Regarding the constraints of the left lung, all parameters analyzed had a statistically significant difference in favor of planning in DIBH: V16.8 Gy (%) ($p < 0.001$); V8.8 Gy (%) ($p < 0.001$); V4.5 Gy (%) ($p = 0.003$); mean dose (Gy) ($p < 0.001$) — Table 1.

The same was observed for the parameters of the heart and LAD. All the evaluated constraints had a significant difference in favor of DIBH planning. For the heart, median V16.8 Gy was 2.56% in FB *vs.* 0% in DIBH ($p < 0.001$); median V8.8 Gy was 3.47% in FB *vs.* 0% in DIBH ($p < 0.001$) and the median of mean heart dose was 1.97 Gy in FB *vs.* 0.92 Gy in DIBH ($p < 0.001$). For the LAD, median D2% was 34.87 Gy in FB *vs.* 5.8 Gy in DIBH ($p < 0.001$); median V16.8 Gy was 15.87% in FB versus 0% in DIBH ($p < 0.001$) and the median of mean LAD dose was 8.13 Gy in FB versus 2.92 Gy in DIBH ($p < 0.001$) — Table 1.

Figure 1 illustrates that heart and LAD parameters had a difference with statistical significance in favor of DIBH planning. In Figure 2, we demonstrated the mean heart dose of all the patients in FB and DIBH. Figure 3 shows RT planning with FB versus DIBH of the same patient, demonstrating the importance of the distance between the chest wall and the heart. Figure 4 shows a dose-volume histogram demonstrating the reduction of doses to the heart and LAD in DIBH.

Discussion

In the first epidemiological studies that included breast RT, higher mortality from cardiac causes was later observed for patients who received RT of the left breast compared to the right side. In addition, cardiac dose reduction has been shown to decrease ischemic heart disease [20].

The mean heart dose is the only parameter reported in older studies and does not appear to reliably reflect cardiac risk. Furthermore, currently, it continues to be the constraint most evaluated in left breast RT planning by radiation oncologists [21].

Although the pathophysiological mechanisms of RT-induced cardiac damage are not fully understood, it is known to be a combination of multiple effects. In vitro studies show radiation effects (which include oxidative effects, cytokine activity, and endothelial damage) on micro and macrovascular systems, which may accelerate the atherosclerosis process [22].

Patients with BC who receive doses ≥ 2 Gy in the cardiac volume are more likely to experience inflammatory effects caused by radiation. Endothelial cells are sensitive to RT and atherosclerotic changes can result in radiation-induced cardiovascular disease which includes coronary stenosis, leading to the process of myocardial perfusion deficiency, ischemia, and fibrosis [23]. In the present study, the median of mean heart dose was 1.97 Gy in FB versus 0.92 Gy in DIBH ($p < 0.001$).

Darby et al. reported in a case-control study that the rates of coronary events (acute myocardial infarction, coronary revascularization, or death by ischemic heart disease) increased linearly with the mean heart dose with a relative risk of 7.4% per Gy ($p < 0.001$) after breast RT. This study was based on the population of 2.168 women undergoing RT in Sweden and Denmark between 1958 and 2001. The median of mean heart dose was 4.9Gy (6.6 Gy for the left side, 2.9 Gy for the right side). The increase in risk started after 5 years of RT and continued for another 20 years [24].

Darby's important findings have been validated by van den Bogaard et al. The authors evaluated the dose distributions in the cardiac structures of the tomographic planning exams and performed a multivariate analysis using Cox regression. Pre-treatment risk factors, such as age, previous heart disease, diabetes, chronic obstructive pulmonary disease, smoking, and body mass index were considered. The result of the study revealed a cumulative increase in the incidence of acute coronary events of 16.5% per Gy ($p = 0.042$) at 9 years after RT [25].

In a series in which conventional RT techniques were used, patients with BC on the left side had a higher risk of cardiac mortality [26]. Among the various techniques that are available to decrease the cardiac dose, DIBH contributes to displacing the heart away from the chest wall, thus reducing the dose to the heart and substructures such as LAD, without compromising target dose coverage. When using this method, the patient inspires up to a specified limit, maintaining this level of inspiration during the delivery of the entire dose, in each of the irradiation fields [27].

It is estimated that at least 75% of patients with left BC can benefit from this technique which should be established in clinical practice as a routine for these patients. Individual anatomical data can also predict the benefit of DIBH, such as measuring the maximum distance between the anterior contour of the heart and the posterior edges of the tangential fields, which are strongly correlated with cardiac dose. These findings were found in the study by Rochet et al. and can be used for patient selection [28].

Several studies have demonstrated a reduction in the mean heart dose with the DIBH technique [29–32]. Figure 3 compares RT planning with FB versus DIBH of the same patient, thus demonstrating the importance of the distance between the chest wall and the heart. The dosimetric benefits of the dose-volume histogram with the reduction of doses to the heart and LAD in DIBH can be observed in Figure 4. The data demonstrate that DIBH is the key to achieve the best result in cardiac volume constraints.

Due to the long latency period of RT-induced cardiac morbidity and mortality, there are currently almost no prospective data demonstrating that DIBH definitively reduces the incidence of heart disease. However, the dosimetric advantages of the use of this technique are considerable, with reductions in mean heart dose from 25 to 67% and LAD from 20 to 71%, as observed in several studies [33–36].

In the present study, the heart and LAD dose reductions were very considerable with DIBH. For the parameters of the heart and LAD, all the evaluated constraints had a significant difference in favor of DIBH planning, reflecting the benefits of this approach.

One of the largest published series also confirmed the favorable results in heart dose reduction. The study involved 319 patients with BC, with 144 patients on the left side treated with DIBH and 175 patients treated in FB (83 on the left side and 92 on the right side). When the outcome was compared between the groups, the DIBH schedules showed larger reductions in heart doses compared to the left side FB designs; V20Gy was reduced from 7.8% to 2.3% ($p < 0.0001$), V40Gy from 3.4% to 0.3% ($p < 0.0001$)

and the mean heart dose from 5.2 to 2.7Gy ($p < 0.0001$). The lung dose was also slightly reduced. These data reinforce the advantages of DIBH with lower heart and lung irradiation, without compromising target coverage [37].

In the current study, a dosimetric benefit was also found in DIBH with a statistically significant difference in favor of planning in DIBH for all left lung constraints analyzed (V16.8Gy, V8.8Gy, V4.5Gy, and mean dose).

This study is limited by its retrospective design. Moreover, a limited number of patients were included. As our study focused on dosimetric issues only, clinical results including patient-reported side effects were not demonstrated. However, our study can contribute to providing more evidence in support of using DIBH technique more extensively in clinical practice, especially in Brazil and Latin America.

It is known that specialized centers are needed to apply this effective technique and such tools are not available in most Brazilian RT services [38, 39]. However, overcoming barriers to reducing mortality from BC in Brazil still involves access to screening mammography and, above all, the structuring of the care network for a quick and timely diagnostic investigation and access to quality treatment. Efforts in this direction must be made to guarantee access to quality public healthcare for the Brazilian population. Ideally, the DIBH technique should be offered to all patients with left BC who are treated in the public or private sector [40].

Conclusion

DIBH can reduce the dose to the heart. We confirmed that the DIBH technique is feasible and has consistently demonstrated significant dose reduction in heart and LAD under all evaluated constraints while maintaining effective dose coverage in the PTV. In addition, DIBH allowed an additional dose reduction in the left lung.

Author contributions

FAMD and SAH conceived the project; all authors performed the literature search and contributed to the literature analysis and synthesis of data; FAMD created the figures and tables; FAMD wrote the article; and all authors were involved in further editing and finalising the manuscript.

Conflict of interest

None declared.

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Data availability statement for this work

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Ethics committee approval

This manuscript has ethics committee approval.

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Figure 1. Heart and left anterior descending coronary artery (LAD) parameters had a difference with statistical significance in favor of deep inspiration breath hold (DIBH) planning

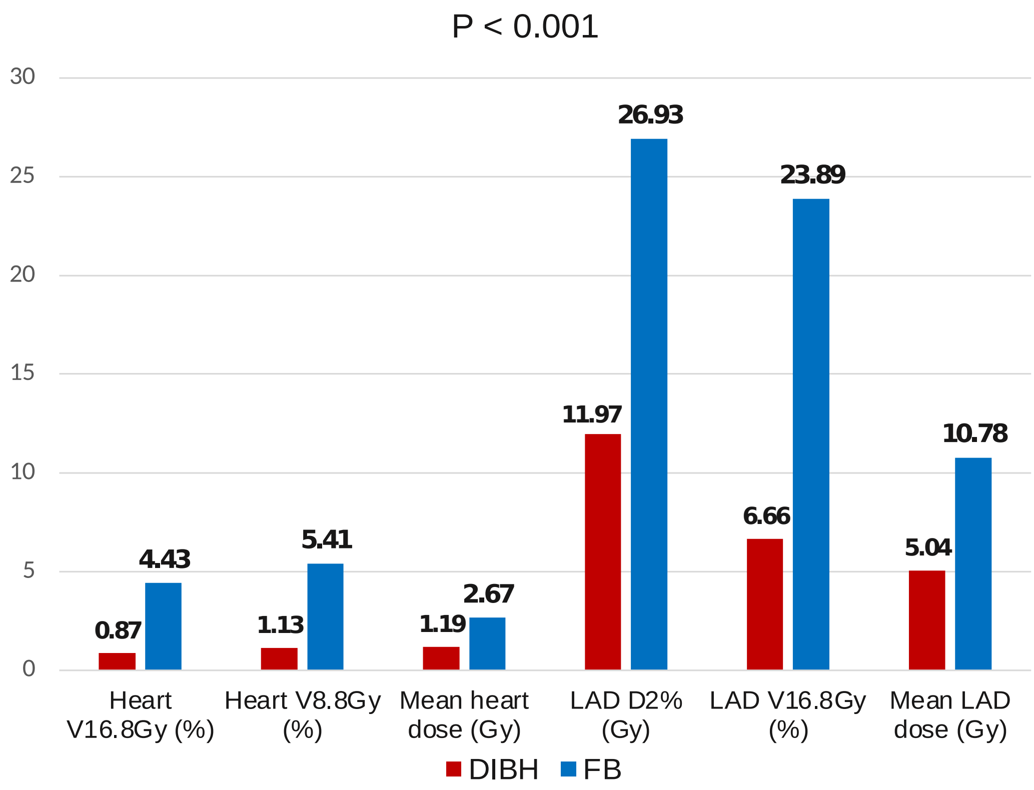

Figure 2. Mean heart dose of the 68 patients in free breathing (FB) and deep inspiration breath hold (DIBH)

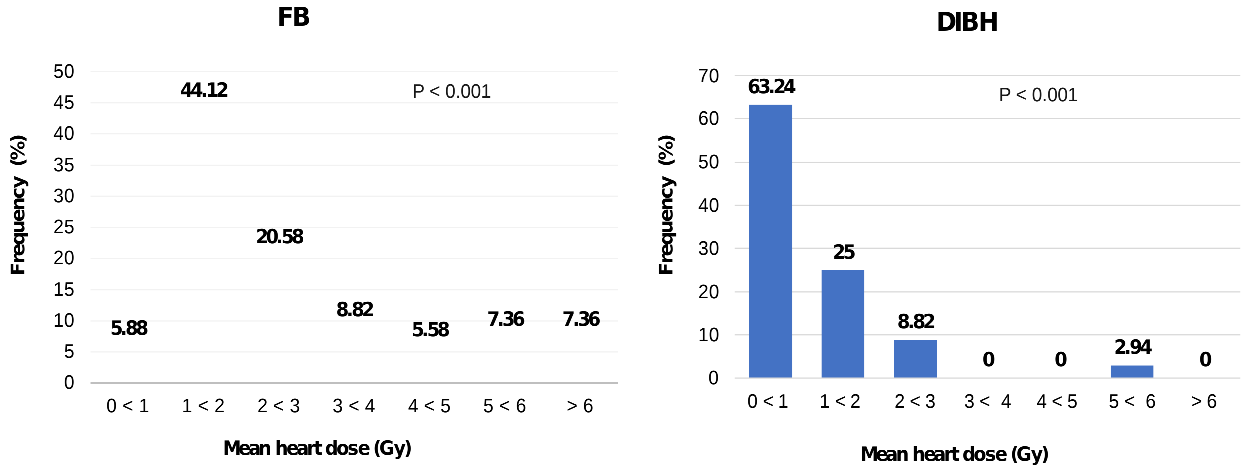

Figure 3. Radiotherapy (RT) planning with free breathing (FB) versus deep inspiration breath hold (DIBH) ofthe same patient, demonstrating the importance of the distance between the chest wall and the heart

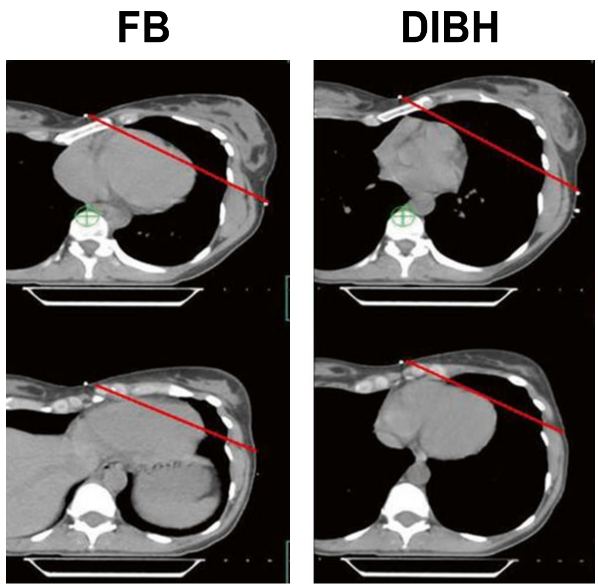

Figure 4. Dose-volume histogram demonstrates the reduction of doses to the heart and left anterior descending coronary artery (LAD) in deep inspiration breath hold (DIBH)

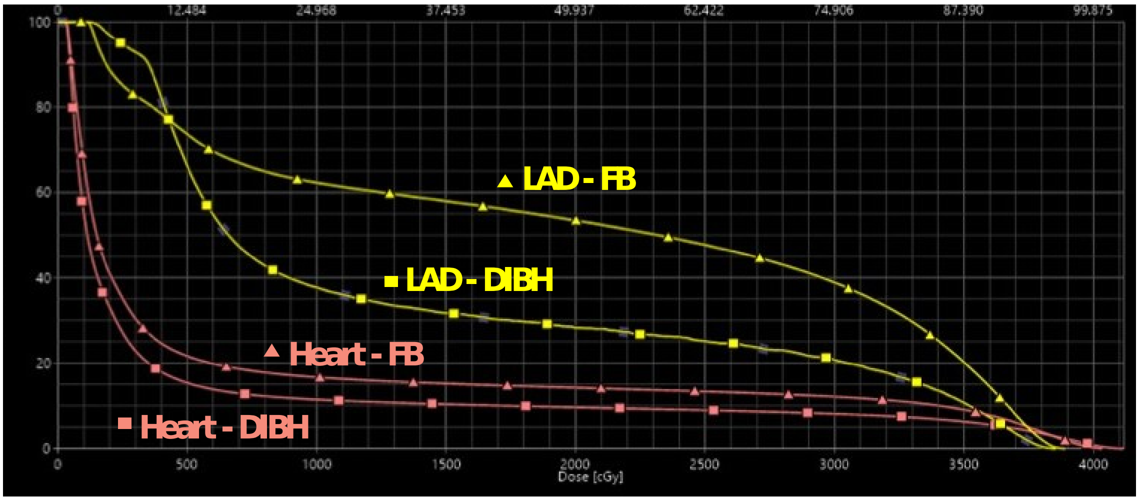

Table 1. Radiation treatment outcomes

Variables		Mean	Median	Interquartile range	p-value
PTV eval D95% [Gy]	FB	36.45	38.02	0.41	0.940
	DIBH	36.48	38.01	1.09	
PTV eval D90% [Gy]	FB	38.27	38.73	0.4	0.966
	DIBH	38.30	38.70	0.392	
Left lung V16.8 Gy (%)	FB	12.91	12.97	6.965	< 0.001
	DIBH	15.61	14.58	6.837	
Left lung V8.8 Gy (%)	FB	16.58	16.28	7.252	< 0.001
	DIBH	19.03	18.02	7.185	
Left lung V4.5 Gy (%)	FB	24.07	23.71	7.79	0.003
	DIBH	25.71	24.80	7.32	
Left lung Mean dose [Gy]	FB	6.56	6.03	2.452	< 0.001
	DIBH	8.23	6.67	3.13	

Right lung V4.5Gy (%)	FB	0.00	0.00	0	1
	DIBH	0.00	0.00	0	
Heart V16.8 Gy (%)	FB	0.87	0.00	0.67	< 0.001
	DIBH	4.43	2.56	6.285	
Heart V8.8 Gy (%)	FB	1.13	0.00	1.207	< 0.001
	DIBH	5.41	3.47	7.322	
Heart Mean dose [Gy]	FB	1.19	0.92	0.502	< 0.001
	DIBH	2.67	1.97	2.27	
Right breast Dmáx [Gy]	FB	3.41	3.09	0.82	0.606
	DIBH	4.26	2.98	0.902	
LAD D2% < 42 Gy [Gy]	FB	11.97	5.80	6.927	< 0.001
	DIBH	26.93	34.87	25.722	
LAD V16.8 Gy < 10% (%)	FB	6.66	0.00	0.727	< 0.001
	DIBH	23.89	15.87	41.977	
LAD mean dose [Gy]	FB	5.04	2.92	2.382	< 0.001
	DIBH	10.78	8.13	12.522	

PTV — planning target volume; LAD — left anterior descending coronary artery; FB — free breathing; DIBH — deep inspiration breath hold

Supplementary File

Table S1. Dose parameters of left breast treatment with a hypofractionated regimen (40.5 Gy in 15 fractions)

PTV eval	**D95% > 36Gy** **D90% > 38Gy**		
Left lung		Ideal	Acceptable
	V16.8Gy	< 12%	< 15%
	V8.8Gy	< 16%	< 35%
	V4.5Gy	< 23%	< 50%
	Mean	< 6Gy	< 10.4Gy
Right lung	V4.5Gy < 1%		
Lungs	V16.8Gy < 6%		
LAD	V16.8Gy < 10% D2% < 42Gy Mean		
Heart		Ideal	Acceptable
	V16.8Gy	< 2 %	< 5 %
	V8.8Gy	< 3 %	< 30 %
	Mean < 3.6Gy		
Right breast		Ideal	Acceptable
	Dmax	< 2.8Gy	< 7.5Gy

Note: D%: represents the irradiation dose received by x% of the volume. Dmax: maximum dose. VGy: percentage of the volume that received a dose in Gy. Mean: mean dose. PTV eval: PTV evaluation.