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Can we predict who will benefit from the deep inspiration breath hold (DIBH) technique for breast cancer irradiation?

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Abstract

Background: The objective was to explore the clinical use of an “in-house” prototype developed to monitor respiratory motion to implement the deep inspiration breath hold technique (DIBH), compare dosimetric differences, and assess whether simple anatomic metrics measured on free breathing (FB) computed tomography scan (CT) can help in selecting patients that would benefit the most from the technique.

Materials and methods: A prospective study was conducted on patients with left breast cancer with an indication of adjuvant radiotherapy for breast only. Treatment simulation consisted of four series of CTs: the first during FB and three in DIBH to assess the reproducibility and stability of apnea. Contouring was based on the RTOG atlas, and planning was done in both FB and DIBH. Dosimetric and geometric parameters were assessed and compared between FB and DIBH.

Results: From June 2020 to December 2021, 30 patients with left breast cancer were recruited. Overall, the DIBH technique presented a mean dose reduction of 24% in the heart and 30% in the left anterior descendent coronary artery (LAD) ($p < 0.05$). The only geometric parameter correlated to a 30% dose reduction in the mean heart dose and LAD doses was the anterolateral distance from the heart to the chest wall of at least 1.5 cm measured on FB ($p < 0.0001$).

Conclusion: The prototype enabled the use of the DIBH technique with dose reductions in the heart and LAD. The benefit of the DIBH technique can be predicted on FB CT by measuring the distance between the heart and chest wall at the treatment isocenter.

Key words: breast cancer; radiotherapy; deep inspiration breath-hold (DIBH); free breathing (FB)

Introduction

Breast cancer is the first non-cutaneous cancer pathology in terms of incidence among women in Brazil and the world [1]. Despite having the highest mortality rate, it has high cure rates, especially in the early stages.

Radiation therapy (RT) has demonstrated clear clinical benefits for all patients treated with breast-conserving therapy (BCT) and patients after radical mastectomy with risk factors for relapses.

RT is one of the cornerstones of breast cancer treatment, reducing the risk of recurrence by half and providing an absolute reduction of 3 to 8.5% in cancer-specific mortality [2, 3]. Despite some controversy, part of this benefit may be counterbalanced by the non-cancer-related mortality and morbidity from late cardiovascular injury by up to 27% and an increase in the risk of ischemic coronary heart disease by 7.4% per Gray (Gy) in the mean dose on the heart [3–5].

Breast cancer accounts for approximately 20% or more of all treatments in a radiotherapy department [6]. Any new technique must be simple and low-cost to be sustainable and avoid an unacceptable burden on health resources.

Several studies have confirmed the effectiveness of breath-hold strategies in lowering the cardiac dose for left-sided breast cancer (with and without internal mammary nodes)

treated with RT. Different methods are used to monitor and control respiratory motion [e.g., real-time position management (RPM) system [7], respiratory gating for scanners (RGSC), active breathing control (ABC) [8], and voluntary moderate deep inspiration breath-hold (vmDIBH)] were found to deliver comparable dosimetric benefits [9]. It is estimated that this strategy can lead to a 10-fold reduction in cardiac mortality [10]. However, these systems are expensive [11] and, therefore, difficult to access, especially in the public health system of low-middle-income countries. Furthermore, they are compatible only with equipment from the respective manufacturers.

In our institution's radiation oncology department, we developed a respiratory movement detection system equipped with an optical camera and an infrared emitter aiming patients with an indication for thoracic Radiotherapy, such as breast cancer, lymphomas, and lung neoplasms. The device generates a user-friendly interface that displays respiratory movement and its inaccuracies. Based on this individualized data generated by the system, patients can be safely treated using the DIBH technique.

Therefore, this study was conducted to clinically evaluate the benefit of the developed monitoring system and analyze the dosimetric differences with and without the DIBH technique in the target, heart, and left anterior descending coronary artery (LAD). In addition, to search for geometric parameters that can identify which patients would benefit most from the technique.

Materials and methods

The institution's research ethics committee approved this prospective study to assess the clinical benefit of the in-house developed prototype by number (x.xxx.xxx).

The prototype

The prototype has an optical camera, an infrared source, and a reflective fiducial. It also has a mechanical stabilization system, which controls the vibrations caused by the movement of the CT scanner and the linear accelerator couch (Fig. 1).

The prototype was designed to be versatile, providing sub-millimeter accuracy and processing 30 frames per second in real-time. The developed software can modulate the infrared sensitivity and optically increase the noise/signal ratio.

Furthermore, it allows movement in two axes to focus on the target fiducial. Accuracy was certified using solid water phantoms of different thicknesses at varying distances

from the camera measured by the lap laser of the CT scanner, a certified ruler, and by checking the reproducibility during CT simulation in 3 series of DIBH. The system would be considered safe if the value indicated by the equipment and the physical measures presented a Pearson's correlation coefficient ('r') ≥ 0.9 . After several iterations, the system proved robust and safe for clinical use with $r = 1$ (100% correlation).

Clinical study

A prospective non-randomized study was designed for patients diagnosed with breast cancer and indication for RT. Inclusion criteria were age equal to or greater than 18 years, any gender, radiotherapy only to the left breast or left chest wall, without elective lymph node irradiation, cognitive ability to understand the training for the procedure and agreement and signature of the informed consent form.

Exclusion criteria were patients with difficulty maintaining deep inspiration for at least 15 seconds (time required to perform planning computed tomography - CT in DIBH), with another simultaneous neoplasm, body weight equal to or greater than 100 kg, and pregnancy.

At the first visit, the patient was instructed to practice the breath-hold technique after inclusion in the study.

Subsequently, for both free breathing (FB) and DIBH, the CT simulation was performed with the patient in the supine position, one arm up, in a standard breast board. The planning consisted of four CT series performed without contrast: one in FB and three in DIBH to assess the stability and reproducibility of inspiration. After the FB scan, patients were asked to hold successive breaths for 15 to 20 seconds to determine their comfortable inspiration level, which should be within a 6 mm range. The inspiration amplitude was defined individually.

The volumes of interest: clinical target volume (CTV) of breast/chest wall, heart, and anterior descending coronary artery (LAD) were contoured according to Radiation Therapy Oncology Group (RTOG) guidelines (www.rtog.org). For the planning target volume (PTV), an isometric margin of 5 mm was added to the CTV, cropped by 5 mm from the skin surface for dose evaluation. RT planning was performed on FB and DIBH CTs.

Planning was done using the standard opposing tangents technique with “field-in-field” forward modulation to improve dose homogeneity. The prescribed dose was 40 Gy in 15 fractions, with or without boost. FB plans met the same criteria as DIBH plans to achieve comparable target coverage. Dosimetric constraints described in the RTOG 1005 study protocol (May 2011 version; www.rtog.org) were followed. Every effort was made to achieve the lowest possible cardiac dose in the DIBH and FB plans without compromising target coverage. Since the constraints for the LAD are defined only for conventional fractionation [12], equivalent doses were calculated by the biologically effective dose (BED) formula, considering an alpha/beta ratio of 1.5 [13]. Thus, for the LAD, $D2\% < 50\text{Gy}$ and $V20\text{ Gy} < 10\%$ were translated into $D2\% < 42\text{ Gy}$ and $V16.8\text{ Gy} < 10\%$, respectively. The Eclipse treatment planning system version 13.7 (Varian Medical Systems, Inc.) was used for all the delineation and calculation processes. Geometric references in the skin were defined during CT simulation: displacement of the skin marks from FB to DIBH was measured. In the CT scan images, the distance from the anterior and anterolateral wall of the chest to the heart, towards the treatment isocenter in FB and DIBH, and the caudal displacement of the heart from FB to DIBH were also measured (Fig. 2). All measures were then correlated with the obtained dosimetric parameters in FB and DIBH.

Statistics

The sample size to access the differences in mean heart doses (primary objective) was calculated considering a Wilcoxon signed-rank test (matched pairs), one-sided tailor's test, 5% as α error, 80% as power ($1 - \beta$ error), and a 0.5 Gy reduction in mean heart dose. As a result, at least 28 patients should be recruited.

The Wilcoxon test (one-sided analysis) was also used for all the other matched dosimetric variables comparisons.

A Pearson's correlation Matrix Heatmap was used to highlight possible interactions between dosimetric and geometric variables visually. Those variables with more probability of statistical significance were assessed with the Spearman test.

The significance level was set at 5% ($p \leq 0.05$). Calculations were performed using the packages Python version 3.7.15, Panda version 1.3.5, SciPy version 1.7.3, and G*Power version 3.1.9.7.

Results

Between June 2020 and December 2021, 30 patients were recruited after the prototype validation and commissioning. Adequate target coverage and dose constraints were achieved in almost all patients (Figure 3). All dose parameters evaluated for the heart and LAD showed a significant reduction in DIBH compared to FB. A mean dose reduction of 24% in the heart and 30% in the LAD was achieved. The volume that received 16.8 Gy (V16.8) and the volume that received 8.8 Gy (V8.8), both in the heart and in the LAD, was reduced with the DIBH (Figures 4 and 5, and Table 1). From all the geometric parameters highlighted in the heatmap, selected and then analyzed, only the anterolateral distance from the heart to the chest wall towards the treatment isocenter in both FB and DIBH (CT_ALD_FB and CT_ALD_DIBH), respectively, presented a statistically significant correlation with the dose reduction (Fig. 6). The threshold value for this specific variable was defined by a scatter plot (Fig. 7): a distance of at least 1.5 cm in the CT FB was related to a 30% reduction in mean doses to the heart and LAD ($p < 0.0001$), when compared to those with smaller distance. Analyzing the 26 patients with a distance CT_ALD_FB equal to or greater than 1.5 cm, the heart mean dose in FB was 2.21 Gy versus 1.58 Gy in DIBH, with an absolute dose reduction of 0.6 Gy (32% benefit). Nevertheless, six (23%) out of these 26 patients, presented only a 2% dose reduction from 1.48 Gy in FB to 1.45 Gy in DIBH, and in these cases, we considered that DIBH would be unnecessary.

Discussion

Prior to evaluation for radiotherapy, patients with breast cancer may be exposed to cardiotoxicity when drugs, such as anthracyclines and trastuzumab, are used as part of the treatment regimen [15, 16]. Thus, as exposure of the heart to ionizing radiation during radiotherapy for breast cancer may increase the subsequent rate of ischemic heart disease, reducing treatment morbidity is crucial, especially in older women and those with pre-existing heart disease that may be at increased risk following radiation exposure [14].

The increase is proportional to the mean dose in the heart, and deleterious effects are more likely if the tumor is in the left breast, starting a few years after exposure and continuing for at least 20 years. Recent evidence suggests that there is no limit below which late effects of breast radiotherapy do not occur [3, 4], making it essential for the

oncology community to establish procedures that minimize cardiac exposure without compromising adequate coverage of breast tissue.

To achieve consistent dosimetric results, contouring is a crucial point in the radiotherapy planning process. We recognize that the lack of contrasted CT scans for contouring in our study may represent a limitation. However, even in this situation, the LAD contouring is not always precise [17], which reflects a general difficulty concerning this matter. Nevertheless, all the contours were performed by the same operator (SRS), strictly following the referred guidelines, and checked by another one (HAC). Furthermore, the doses were compared individually between the techniques for each patient. So, we considered the dosimetric results reliable.

There are also some remarks regarding the DIBH technique. The main disadvantage is the patient's limitation in maintaining the DIBH for the necessary time during the treatment simulation, without which it is not possible to carry out adequate radiotherapy planning. However, the radiation beam can be turned off for the treatment itself when the patient leaves the pre-defined range of its inspiratory amplitude and rests for another period of adequate DIBH, turning the treatment safe.

Another limitation of implementing this technique is the high cost of the technology provided by the manufacturers. This is reflected in environments where resources are limited, such as low-middle-income countries, mainly in the public health system. One of the alternatives is developing a respiratory monitoring device, as others have already done [18].

After validating and commissioning the prototype, we could implement the DIBH technique in our service and make it available to patients. The dosimetric analysis was consistent with the findings of different studies already published [19–26], demonstrating a significant reduction in the doses received by the heart and LAD while maintaining adequate target coverage, sometimes even better, demonstrating clinically that the developed system is reliable. It is noteworthy that, even in FB, all organ dose constraints were met in this population. Thus, patients could be safely treated in FB according to the dosimetric recommendations followed. However, the ALARA (As Low as Reasonably Achievable) concept should be considered whenever possible as, to our knowledge, there are no reported results on the impact of this strategy on late cardiac toxicities.

However, the use of the DIBH technique requires a longer stay in the treatment room. Therefore, determining which patients will benefit most from this strategy is crucial in

hospitals with a high workload. In our study, it was possible to establish an easy and consistent geometric parameter (at least 1.5 cm anterolateral distance from the heart to the chest wall - Figure 2b) to select the patients who would most benefit from this technique and allows the institution to optimize schedules and save available resources. We consider this finding original and the most significant contribution of our study. In addition, in our series, among the patients with greater distance ($> 1.5\text{cm}$), 23% had little or no dosimetric benefit at all with DIBH (only a 2% reduction in mean heart dose).

Other studies also established predictive parameters for patient selection, but different from those described in this study [27, 28]. We defined a simple and easy-to-evaluate measure, contributing as one more factor in the selection of patients for the DIBH technique. Interestingly, with all the technological developments and efforts to obtain better quality and safety of treatments, the old concept or recommendation of the lung volume visualized in the simulation and portal films from the “2D era” ended up being our most important factor related to better cardiac protection. Indeed, if these structures are outside the field boundaries, the radiation dose is expected to be minimal. Here, we have just demonstrated that this measurement can still be used as a surrogate for evaluating the heart and LAD doses.

Conclusion

We developed a simple, versatile, affordable, universal prototype and validated it for clinical use. It was possible to contribute with reductions in heart and LAD doses and, at the same time, identify a geometric parameter that can be previously evaluated for the selection of patients for the DIBH technique: the anterolateral distance from the heart to the chest wall of at least 1.5 cm, simple and easy to measure, could predict a 30% reduction in cardiac doses. The DIBH technique is already in use in our department and will benefit many patients. We hope that this prototype may in the near future be available to other institutions with the same limited resources.

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Figure 1. Prototype for the deep inspiration breath hold (DIBH) technique implementation. The system is fixed to the computed tomography (CT) simulator couch. A reflective fiducial is placed in the xiphoid appendix of the patient to reflect the respiratory motion. The optic camera and infrared detector detect the fiducial. The signal is transmitted to the monitor that displays the movement of the respiratory cycle and a band that turns green when the patient reaches a certain amplitude of inspiration that is individualized for each patient. This amplitude, with a maximum range of 6 mm, is recorded and should be reproduced throughout the treatment. The therapist and patient can view the monitor to control the process

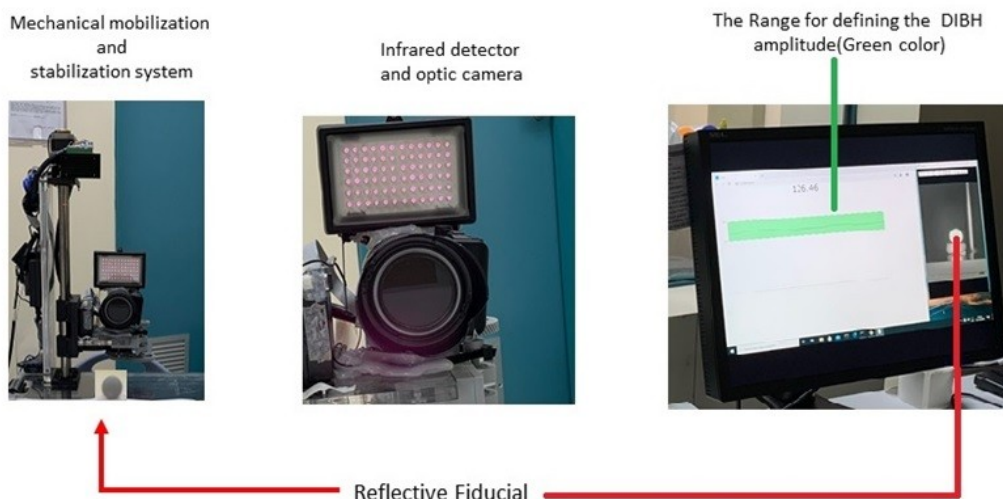


Figure 2. Geometric parameters measured in the skin (schema in the left): caudal displacement of skin marks from free breathing (FB) to deep inspiration breath hold (DIBH) during the computed tomography (CT) simulation; and in the CT scan images:

the distance from the anterior and anterolateral wall of the chest to the heart, towards the treatment isocenter in FB and DIBH (axial view), and the caudal displacement of the heart from FB to DIBH in the isocenter projection (coronal view)

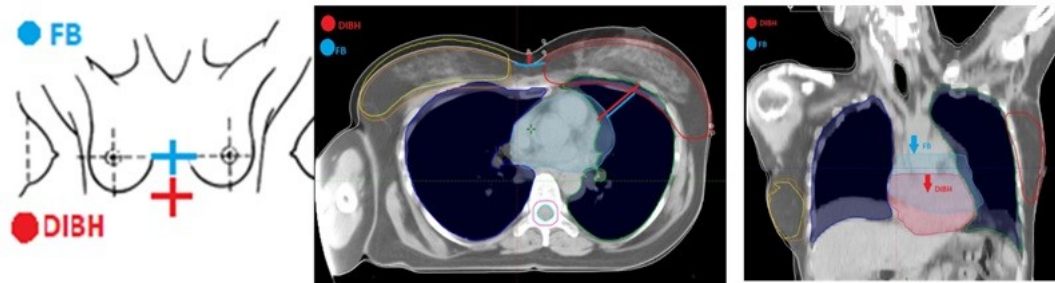


Figure 3. Target coverage in the 30 patients in free breathing (FB) and deep inspiration breath hold (DIBH), respectively. PTV95% — volume of the planning target volume that receives at least 95% of the dose; PTV90% — volume of the planning target volume that receives at least 90% of the dose

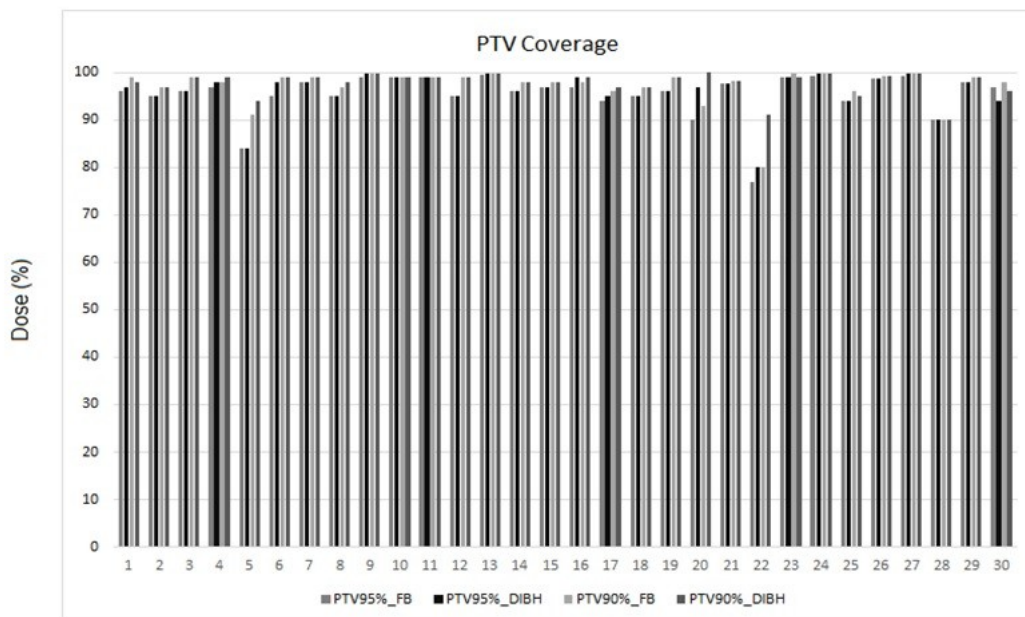


Figure 4. Boxplots of the heart doses in free breathing (FB) and deep inspiration breath hold (DIBH), respectively. Heart_21.4Gy — volume of the heart that receives 21.4 Gy; Heart_8.8Gy — volume of the heart that receives 8.8 Gy; Heart Dm — heart mean dose

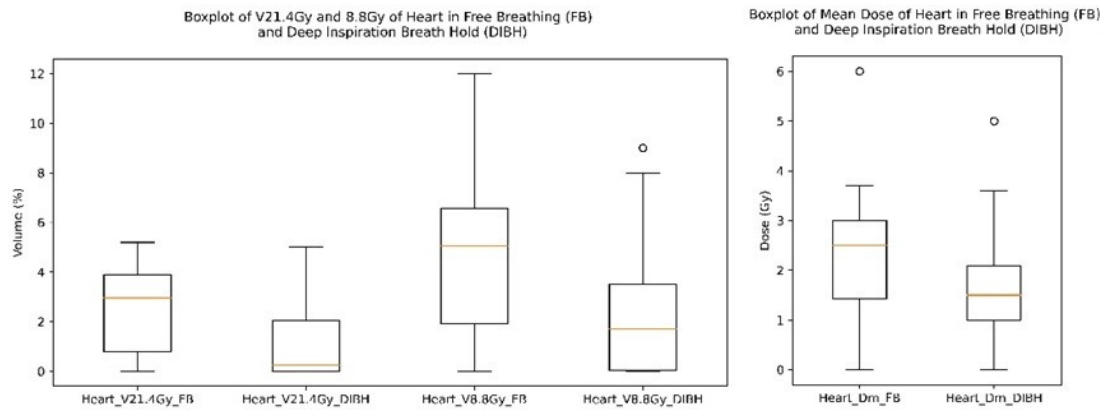


Figure 5. Boxplots of the left anterior descending coronary artery (LAD) doses in free breathing (FB) and deep inspiration breath hold (DIBH), respectively. LAD16.8 — volume of the LAD that receives 16.8 Gy; LAD2% — dose in 2% of the LAD; LAD mean — LAD mean dose

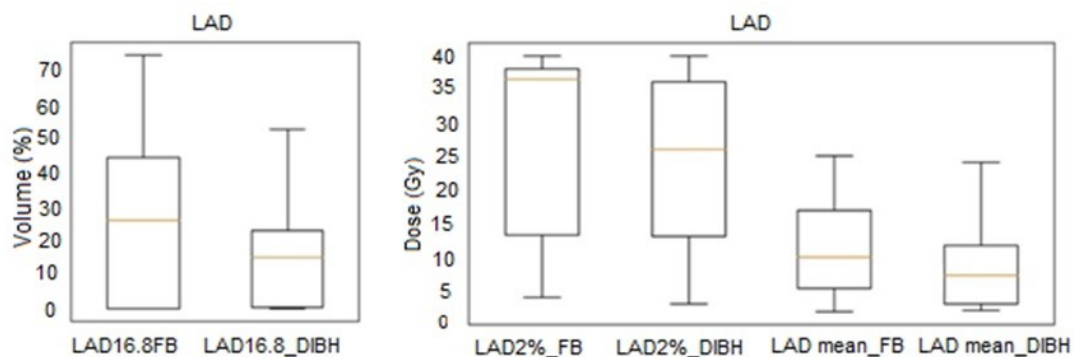


Figure 6. Heat map with the correlation of the studied variables measured in free breathing (FB) and deep inspiration breath hold (DIBH), respectively. The darker blue color indicates a higher correlation. The only variable significantly correlated to the dose reduction was the anterolateral distance between the chest wall and the heart ($p < 0.0001$). Legend (starting from top to bottom on the "Y" axis and on the "X" from left to right): PTV_V95% — volume of the planning target volume that receives 95% of the

dose; PTV_V90% — volume of the planning target volume that receives 90% of the dose; _FB, PTV_D50% — dose in 50% of the planning target volume; PTV_V107% — volume of the planning target volume that receives 107% of the dose; Heart_V21.4 Gy — Volume of the heart that receives 21.4 Gy; Heart_V8.8 Gy — Volume of the heart that receives 8.8 Gy; Heart_Dm — heart mean dose; Heart_Dmax — heart maximum dose; LungIpsi_V16.8 Gy — volume of the ipsilateral lung that receives 16.8 Gy; LungIpsi_V8.8Gy — volume of the ipsilateral lung that receives 8.8 Gy; LungIpsi_V4.5Gy — volume of the ipsilateral lung that receives 4.5 Gy; LungIpsi_Dm — ipsilateral lung mean dose; BreastCL_V3Gy — volume of the contralateral breast that receives 3 Gy; SkinMarks — displacement of the skin marks; CT_ANT FB-DIBH — displacement of anterior distance of the heart to the chest wall from FB to DIBH; CT_ALD — antero-lateral distance from the heart to the chest wall; CT_Heart_Caudal_FB-DIBH — caudal displacement of the heart from FB to DIBH; LAD_DmGy — left anterior descending coronary artery mean dose; LAD_D2% — dose received by 2% of the left anterior descending coronary artery, LAD_V16.8 Gy — volume of the left anterior descending coronary artery that receives 16.8 Gy.

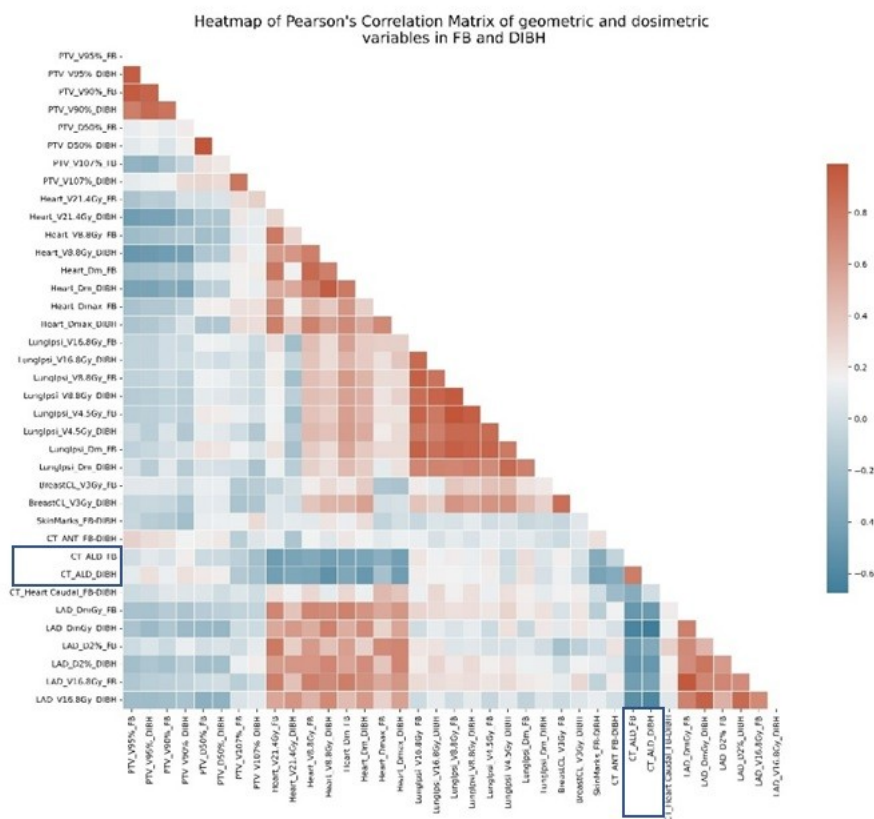


Figure 7. Scatter plot of the ratio between heart mean dose (D_m) in free breathing (FB) and in deep inspiration breath hold (DIBH) versus the anterolateral distance (ALD) from the heart to the chest wall towards the isocenter in FB to define the threshold value of this variable

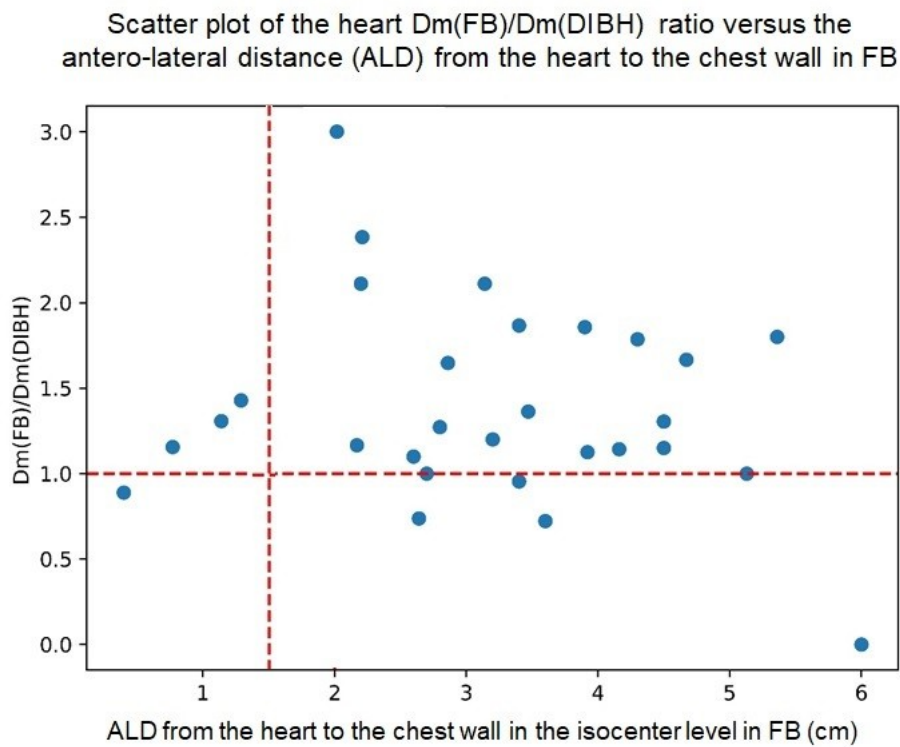


Table1. Mean values of the dosimetric parameters obtained in free breathing (FB) and deep inspiration breath hold (DIBH) in the 30 analyzed patients

Parameter	FB (Min–Max)	DIBH (Min–Max)	DIBH variation	p*
PTV				
V95%	95.4% (77.0–99.4)	96.0% (80–99.8)	0.01%	0.022
V90%	97.2% (80.0–99.9)	97.8% (90.0–100.0)	0.01	0.175
Heart				
V21.4 Gy	2.5% (0–5.2)	1.2% (0–5)	–50.0%	0.0015
V8.8 Gy	4.5%(0–12)	2.5% (0–9)	–44.5%	<0.001

Dm	2.3 Gy (0–6)	1.7 Gy (0–5)	–24.0%	< 0.001
LAD				
V16.8 Gy	25.9% (0–75)	16.3% (0–53%)	–47.1%	0.004
D2%	27.7 Gy (4–40)	23.7 Gy (3–40)	–14.5%	0.039
Dm	11.8 Gy (2–24)	8.3 Gy (2–24)	–29.6%	0.003

FB — free breathing; DIBH — deep inspiration breath hold; PTV — planning target volume; LAD — left anterior descending coronary artery; Vxx% — volume that receives xx% of the dose; VyyGy — volume that receives yyGy; Dm — mean dose; D2% — dose in 2% of the volume; *Wilcoxon test