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Does the deep-inspiration breath-hold technique effectively protect cardiac substructures in radiotherapy for left-sided breast cancer patients?

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HIGHLIGHTS

- We assessed the doses received by cardiac substructures during breast radiotherapy.
- The study involved 25 left-sided breast cancer patients in both DIBH and FB conditions.
- Our findings emphasize the importance of accurately contouring left ventricle and the left anterior descending artery.
- The current planning protocols are insufficient to protect the heart and prevent cardiotoxicity.

ABSTRACT

For radiotherapy in patients with left-sided breast cancer, the deep inspiration breath-hold (DIBH) technique has been introduced to reduce cardiac toxicity and lower the risk of mortality due to cardiovascular complications. This technique was studied in 25 patients who had two sets of image data for DIBH and free-breathing (FB) treatments. The dose data from the FB and DIBH plans were then analyzed and compared. Additionally, the mean dose and dose-volume parameters for the heart, left ventricle (LV), and left anterior descending (LAD) artery were calculated and analyzed. Stricter criteria have been applied to these values, and the current treatment plans have been reviewed. Our results show that radiation doses to cardiac substructures, such as the LV and LAD artery, do not meet the stricter criteria in nearly all cases. Since radiation dose to these substructures is crucial in preventing late cardiac complications, relying solely on the DIBH technique is not enough for protecting the heart. It is essential to consider these substructures during the treatment planning phase for patients with left-sided breast cancer. Additionally, there should be an exploration of newer techniques that can help achieve the stricter criteria for protecting heart substructures.

KEYWORDS

Deep inspiration breath hold
Free breathing
Breast cancer
Radiation therapy

HISTORY

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1 Introduction

External beam radiation therapy (EBRT) has proven to be an effective treatment for breast cancer, significantly reducing the possibility of local recurrence by 70-80% and thereby increasing the chances of long-term survival (Fisher et al., 1995; Clark et al., 1996). Adjuvant breast radiotherapy following partial mastectomy has been shown to enhance local control and decrease the risk of breast cancer mortality by 5% after 15 years (Group et al., 2005). However, there are always concerns about potential damage to healthy tissues, especially when radiation targets the left side of the chest wall or the left breast. Such treatments often expose the myocardium and coronary arteries to radiation, potentially increasing the risk of cardiac complications and mortality due to cardiovascular damage. Numerous studies have indicated that a thorough evaluation of the potential risks and benefits associated with breast cancer treatment is essential (Fisher et al., 1995; Veronesi et al., 2002; Van Dongen et al., 2000). Radiation-induced ischemic heart disease continues to be a leading cause of death among long-term survivors (Darby et al., 2013; Prosnitz et al., 2005; Group et al., 2011; Borger et al., 2007). Recent studies indicate that deaths from heart complications in breast cancer patients who received radiation therapy are 30% higher than in those who did not undergo radiation therapy (Taylor et al., 2017). Furthermore, patients with left-sided breast cancer are at a higher risk of cardiac death compared to those with right-sided breast cancer (Roychoudhuri et al., 2007; van den Bogaard et al., 2017; Darby et al., 2005). A significant

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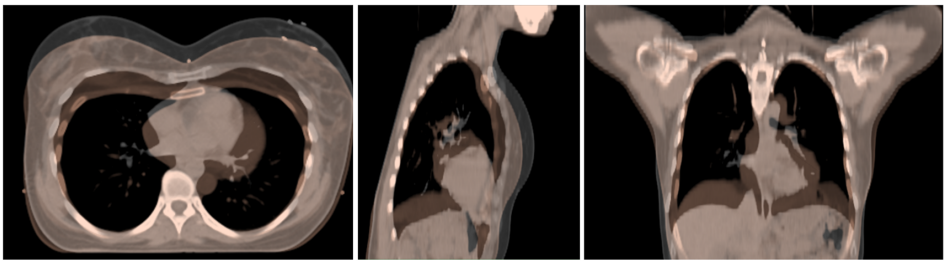

Figure 1: CT images of a patient are shown as examples in DIBH (gray) and FB (pale orange) conditions, presented in three axial (left), sagittal (middle), and coronal (right) views.

study evaluated patients who had been previously treated with radiation for breast cancer. The findings revealed that the risk of experiencing a major coronary event increased in a linear relationship with the mean dose of radiation received by the heart (Darby et al., 2013). Specifically, the relative risk rose by 7% per Gray of radiation dose.

The risk of cardiotoxicity is believed to be higher with radiation therapy to the left breast, as the tangential fields often encompass parts of the left ventricle (LV) and left anterior descending artery (LAD) (Schultz-Hector and Trott, 2007; Taylor et al., 2008; Gyenes et al., 1997). Over the past decade, several cardioprotective strategies have significantly reduced the heart dose caused by radiation therapy. These methods include the use of Intensity-Modulated Radiation Therapy (IMRT) (Hurkmans et al., 2002; Schubert et al., 2011; Mast et al., 2013), helical tomotherapy (Schubert et al., 2011; Hui et al., 2004), Deep Inspiration Breath Hold (DIBH) techniques (Group et al., 2005; Jagsi et al., 2007; Korreman et al., 2006; Hayden et al., 2012; Vikström et al., 2011), proton therapy (Bradley et al., 2016; Orecchia et al., 2015), and treatment in the prone position (Mast et al., 2013; Kirby et al., 2011, 2010). Quantitative assessments of normal tissue toxicity indicate that there is no significant relationship between dose or volumetric parameters and the occurrence of cardiotoxicity. Current dose criteria primarily consider the whole heart (WH) as the organ at risk (OAR); however, studies indicate that the radiation sensitivity of the LAD differs from that of the myocardium (Nieder et al., 2007; Nilsson et al., 2012).

In radiation therapy of the left breast, LAD stenosis frequently occurs in the distal and middle sections, particularly in areas close to the tangential fields (Nilsson et al., 2012; Correa et al., 2007). Furthermore, dosimetric studies indicate that meeting the WH dose criteria does not eliminate the presence of hot areas with doses exceeding 50 Gy in the middle and distal LAD (Nilsson et al., 2016). Consequently, there is an urgent need to better understand the impact of radiation doses on the LAD. Furthermore, many experts agree that the LAD should be regarded as a separate OAR, distinct from the WH. Recent studies emphasize the importance of enhancing the LAD contour to achieve better contouring similarity and consistency in dose reporting (Lee et al., 2017; Aznar et al., 2011). However, accurately assessing the LAD dose remains challenging due to cardiac and respiratory motion artefacts, which can hinder the proper determination of the LAD contour (Aznar et al., 2011; Ding and Friedman, 2000).

Minimizing the radiation dose to the critical substructures of the heart is crucial during breast radiation therapy to reduce long-term side effects. Regardless of the technique employed, the lower anatomical regions of the heart should be regarded as critical OARs (Feng et al., 2011). Specifically, it is important to consider the dose parameters for the left ventricle (LV) and the left anterior descending (LAD) artery, as well as the mean heart dose (Piroth et al., 2019).

The aim of this study is to retrospectively assess the dose parameters for various heart substructures that are not typically considered during the treatment planning phase. Additionally, we compared our results to two sets of criteria: the standard QUANTEC criteria and a recently proposed set of more stringent guidelines. We also investigated the impact of heart movement, specifically the displacement of LAD and LV, by analyzing the variations in the main contours and considering Planning Risk Volumes (PRVs) for both substructures.

2 Material and Methods

The treatment plans for 25 patients with left-sided breast cancer (LSBC) with both CT simulation image datasets with DIBH and FB condition were examined. The data were acquired from in Reza Radiotherapy and Oncology Center (RROC). For patients who underwent mastectomy, a prescription dose of 50 Gy was administered. For those who had breast-conserving surgery, the prescribed dose was 50 Gy, with an additional boost of 10 Gy to the tumor bed. Each treatment session for all 25 patients was planned to deliver a dose of 2 Gy. Figure 1 displays a single patient's FB and DIBH conditions, captured in three views: axial, sagittal, and coronal. The images associated with the FB condition are in pale orange, while those related to the DIBH condition are in gray.

All treatment plans were produced using Prowess Panther 5.50 treatment planning software. Limbus AI software was also used to generate the automatic contours of the heart, LV and LAD in CT simulation image dataset. The Limbus AI software exports an RT Structure file, which is imported into Prowess Panther 5.50. After adjusting the patient origin in Prowess Panther, the Limbus-generated contours are properly positioned. The contours generated by Limbus have been reviewed and approved

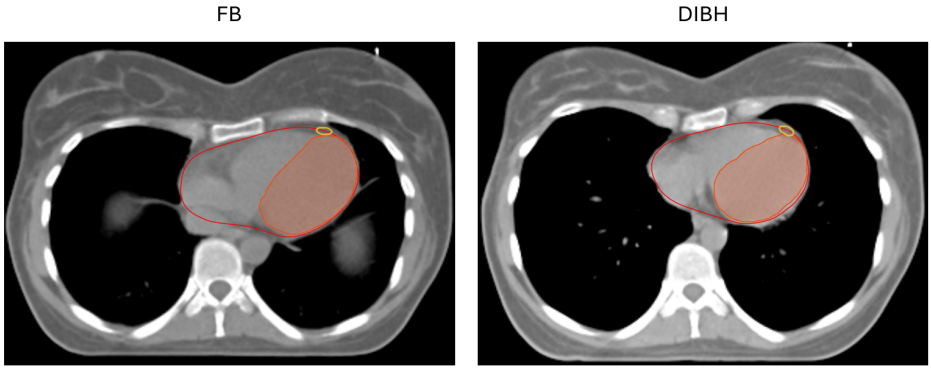

Figure 2: CT images with contours generated by Limbus AI software for the heart (red contour), LV (orange contour), and LAD (yellow contour) of a patient in both DIBH and FB conditions.

by a qualified radiation oncologist. Dose calculations have been conducted for all contours created by the Limbus AI software. Figure 2 displays CT images with contours created by Limbus AI software for the heart (red contour), LV (orange contour), and LAD (yellow contour) of a patient in both DIBH and FB conditions.

Table 1: Summary of patient characteristics. The last column shows the number of patients.

Characteristic	Value	No.
Age (year)	23-33	6
	33-43	5
	43-53	8
	53-63	6
BMI	20-25	9
	25-30	5
	30-35	8
	< 35	1
	Unspecified	2
Grade	Well-differentiated	1
	Moderately-differentiated	15
	Poorly- or Undifferentiated	9
Hormone receptors	HR+/HER2-	5
	HR+/HER2+	14
	HR-/HER2+	2
	HR-/HER2-	2
	PR-	6
	PR+	17
Radiotherapy	Breast and boost	20
	Postmastectomy chest wall	5
Number of fractions	25	10
	30	14
	33	1
Dose per fraction (Gy)	2	25
	2	25
Surgery	Breast-conservative	15
	Mastectomy	10
Chemotherapy	Adjuvant	13
	Neoadjuvant	10
	Both adjuvant and neoadjuvant	1
	No chemotherapy	1
CT-simulation image thickness (mm) - DIBH	5	24
	3	1
CT-simulation image thickness (mm) - FB	5	22
	3	3

Table 2: The QUANTEC criteria for the heart.

Volume	Modality	Endpoint	Criteria	Values
Whole heart	3D-CRT	Late cardiac mortality	V25	< 10%

Table 3: Dose criteria for the heart and its substructures in breast radiation therapy.

Volume	Criteria	Values
Whole heart	Mean dose	< 2.5 Gy
LV	Mean dose	< 3 Gy
	V5	< 17%
	V23	< 5%
LAD	Mean dose	< 10 Gy
	V30	< 2%
	V40	< 1%

Table 1 summarizes patient characteristics extracted from patient documents, including age, BMI, grade, hormone receptor status, and treatment plan. Table 2 presents the QUANTEC criteria values applicable to the heart, specifically the V25 parameter, utilized at the RROC. There are currently no established criteria for LAD or LV in radiotherapy centers and hospitals in Iran.

Based on studies regarding cardiac toxicity, the DEGRO panel of breast cancer experts has recommended criteria for a safe treatment plan that minimizes damage to the heart and its substructures. These criteria are detailed in Table 3 (Piroth et al., 2019) and include stricter guidelines for evaluating treatment plans. Dose calculations and data analysis have been conducted using both sets of criteria. Dose parameters were calculated and compared for all patients for DIBH and FB treatment plans. In five FB treatment plans, electron beams are employed to effectively target the internal mammary glands.

The displaced contours and PRVs were defined based on the main contours of the heart's substructures, specifically the LV and LAD, under both FB and DIBH conditions. For the LV, a symmetric margin of 4 mm was used, while for the LAD, a 5 mm margin was applied. These margins were considered in the anterior, posterior, left, and right directions to establish the PRVs. Additionally, the main contours of these substructures were displaced in the anterior and posterior directions within the PRV

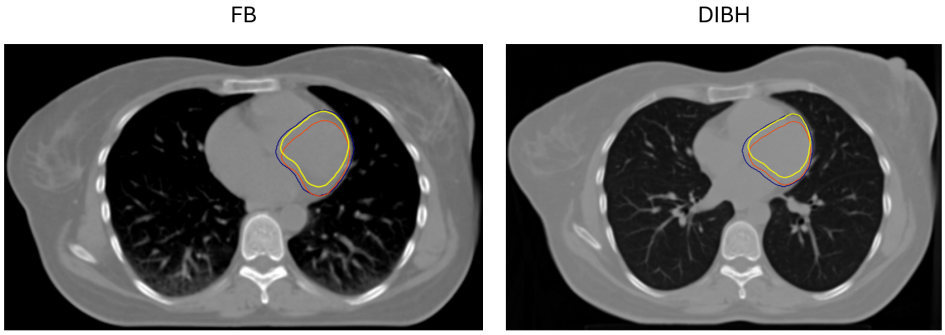

Figure 3: CT images display PRV contours associated with the LV in dark blue, alongside contours displaced towards the anterior (yellow) and posterior (orange).

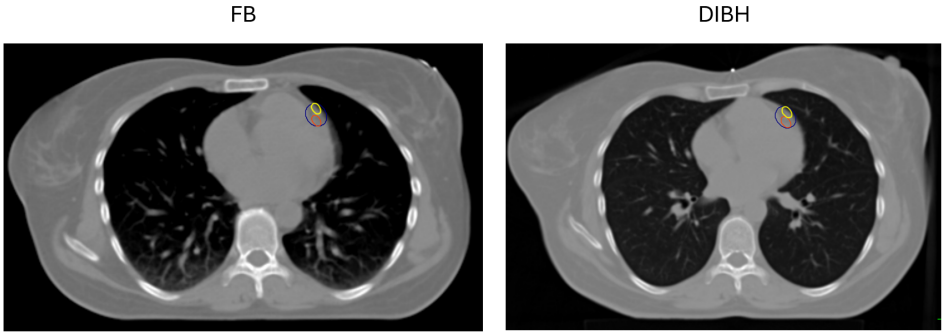

Figure 4: CT images display PRV contours associated with the LAD in dark blue, alongside contours displaced towards the anterior (yellow) and posterior (orange).

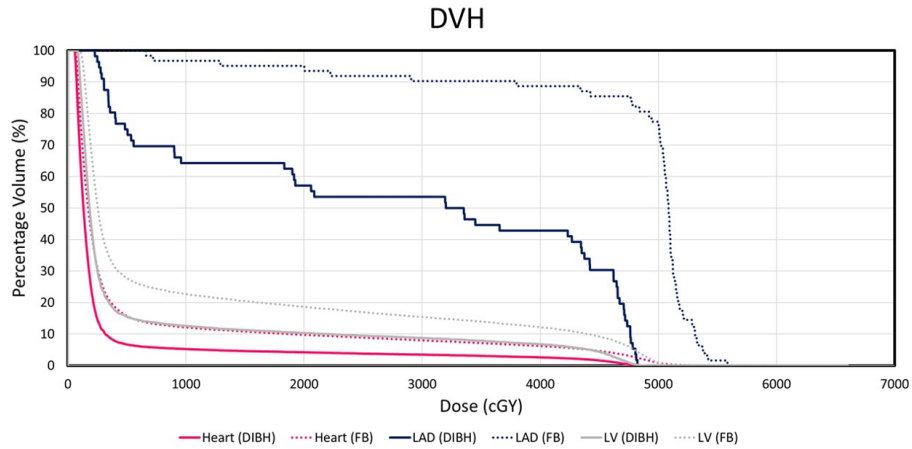

Figure 5: DVH plot of heart (pink), LAD (navy blue), and LV (gray) for a patient as an example to compare FB (dotted-line) and DIBH (solid-line) conditions.

range. Figures 3 and 4 illustrate the PRVs and their respective displacements for the LV and LAD in the anterior and posterior directions. All dose parameters for these PRVs and displaced contours were recalculated. Box plots of the dose volume parameters were created using Origin software version 2019 for all the data.

3 Results

The DVH plot for both the FB and DIBH conditions for one patient is shown in Fig. 5. It is evident that the DVH curves for all three OARs -the heart, LAD, and LV- are significantly higher in the FB condition compared to the DIBH condition. This difference is particularly pronounced for the LAD.

Dose parameters for the heart, LV, and LAD were assessed for 25 patients, adhering to the QUANTEC and a more stringent criteria as detailed in Tables 2 and 3. The analysis was conducted for both FB and DIBH conditions. Results are illustrated in column plots in Figs. 6 to 10. In Fig. 6, it is evident that the mean doses received by the heart, LAD, and LV ranged from 160.9 to 1339.8 cGy, 460.3 to 4854.7 cGy, and 201.0 to 1936.7 cGy, respectively. The V25 of the heart was calculated to be between 0.55% and 25.16% (Fig. 7). Additionally, V30LAD and V40LAD ranged from 0.0% to 100.0% (Fig. 8). For the LV, V5 and

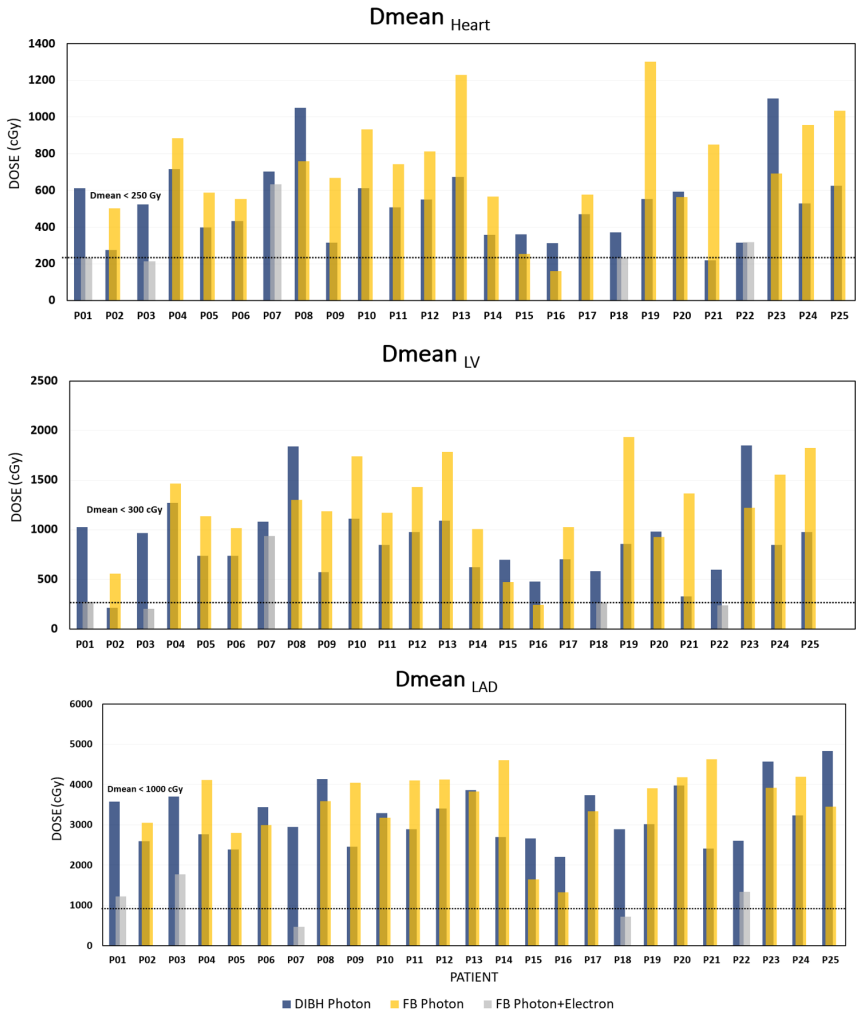

Figure 6: Mean doses for the heart, left ventricle (LV), and left anterior descending artery (LAD) for those contours delineated by Limbus AI software under both FB and DIBH conditions. The black dashed line indicates the value of the strict criteria.

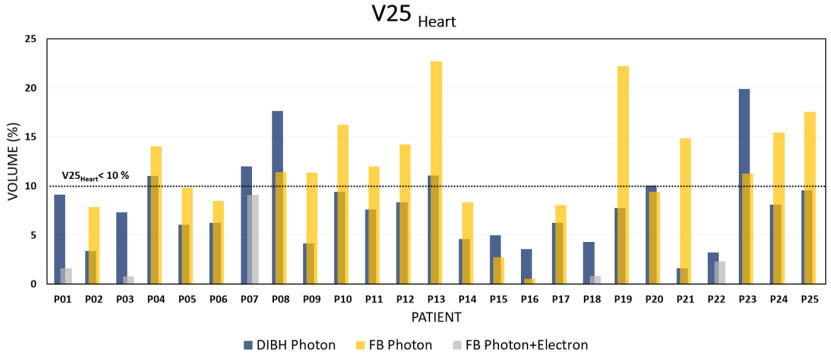

Figure 7: The heart V25 for those contours delineated by Limbus AI software under both FB and DIBH conditions. The black dashed line indicates the value of the strict criteria.

V23 values were between 4.2% and 61.4%, and 0.3% and 0.36%, respectively (Fig. 9).

In the analysis of 25 treatment plans, a general trend showed that the doses received by the heart and LV were lower with DIBH technique compared to FB. However, there was no significant statistical trend observed for the dose parameters of the LAD. In Fig. 10, the mean heart doses for two treatment strategies are shown: whole breast (WB) and WB with an additional local boost, examined during both FB and DIBH methods. It is noted that adding a local boost does not alter the trend in the data concerning the advantages of either the DIBH or FB technique for a patient.

Boxplots for all PRVs, as well as for the posterior and anterior displaced contours, are displayed in Figs. 11 to 13. The box plots clearly indicate that the radiation dose

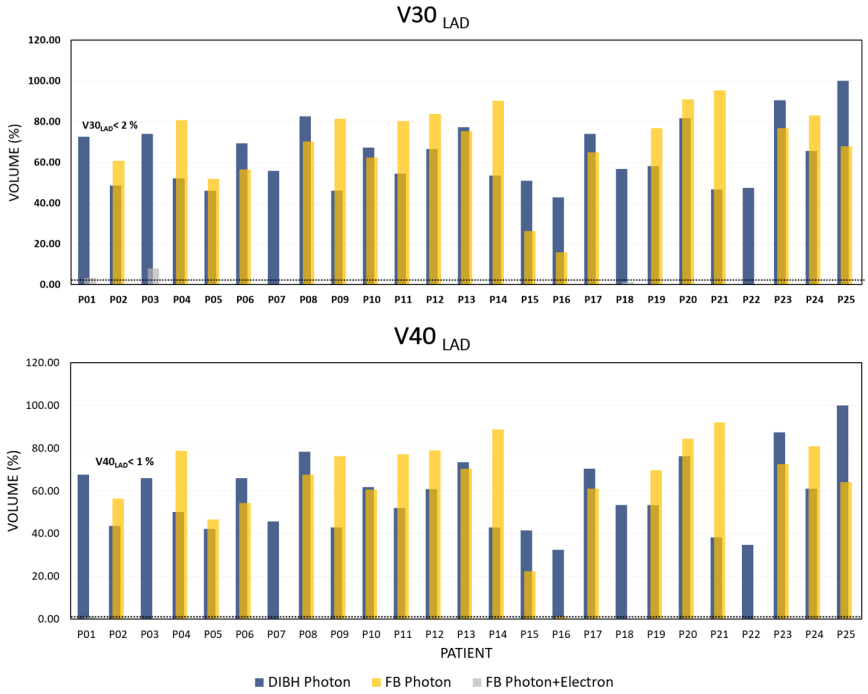

Figure 8: The LAD V30 and V40 for those contours delineated by Limbus AI software under both FB and DIBH conditions. The black dashed line indicates the value of the strict criteria.

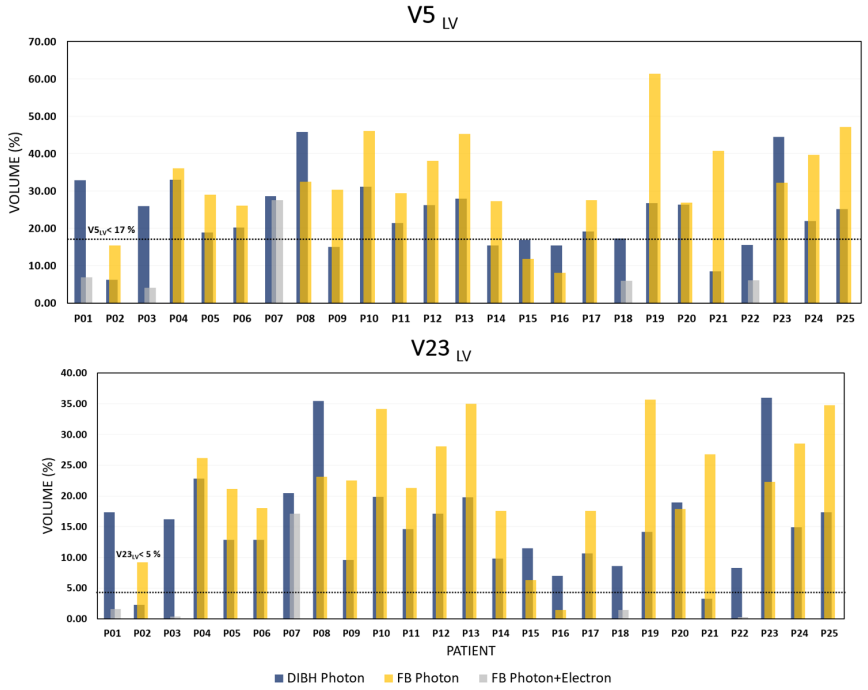

Figure 9: The LV V5 and V23 for those contours delineated by Limbus AI software under both FB and DIBH conditions. The black dashed line indicates the value of the strict criteria.

to cardiac substructures is lower when using the DIBH technique compared to the FB technique. However, it is evident that most treatment plans still fail to meet the established criteria. Additionally, displacements that are representative of cardiac motion have not improved this situation. Notably, a significant decreasing trend in posterior displacement is observed for both the LV and the LAD contours.

4 Discussion

As known, various technical options are available to reduce the mean heart dose. Conventional methods such as t-IMRT or field-in-field techniques do not effectively reduce the dose to the heart and lungs. However, DIBH-based multi-angle or rotational IMRT techniques, Prone condition, and using thermoplastics have shown promising

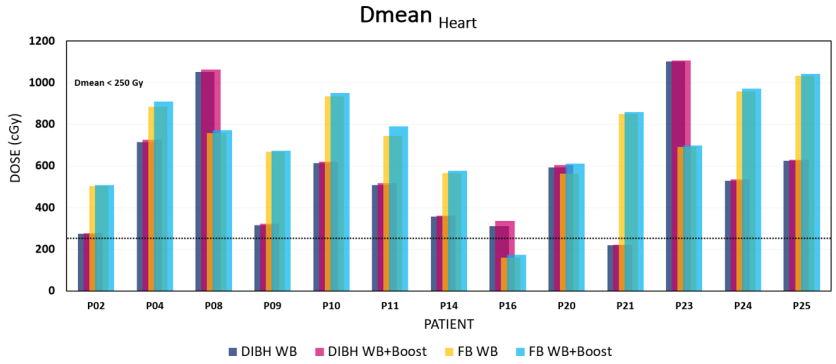

Figure 10: Mean heart doses for two treatment plans: whole breast (WB) and WB plus a local boost, under FB and DIBH technique. The black dashed line indicates the strict criteria.

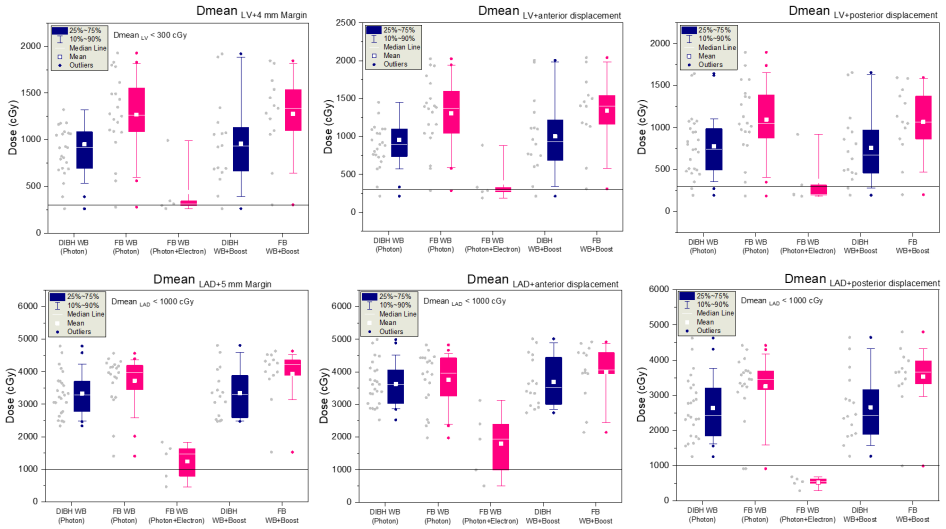

Figure 11: Box plot of mean dose for PRV contours and antero-posteriorly shifted contours for LV and LAD.

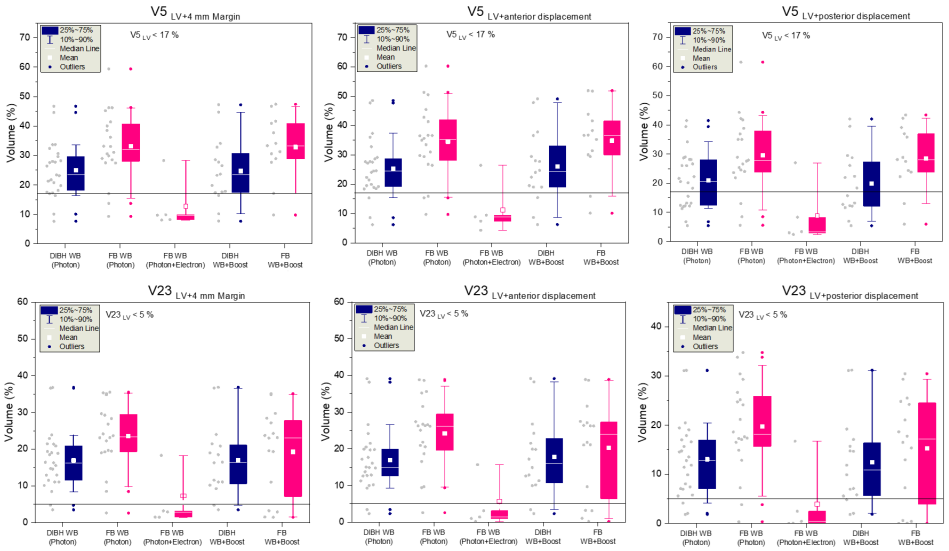

Figure 12: Box plot of V5 and V23 for PRV contours and antero-posteriorly shifted contours for LV.

results in reducing heart and its substructure doses. Partial breast radiotherapy can also be considered for elderly patients with low-risk cancer (Piroth et al., 2019; Boda-Heggemann et al., 2016; Coles et al., 2017; Corradini et al., 2018; Lohr et al., 2009; Pignol et al., 2008).

The treatment plans of 25 patients were evaluated in this study, with our main focus on V25 parameter, which should be less than 10%. This criterion has been met

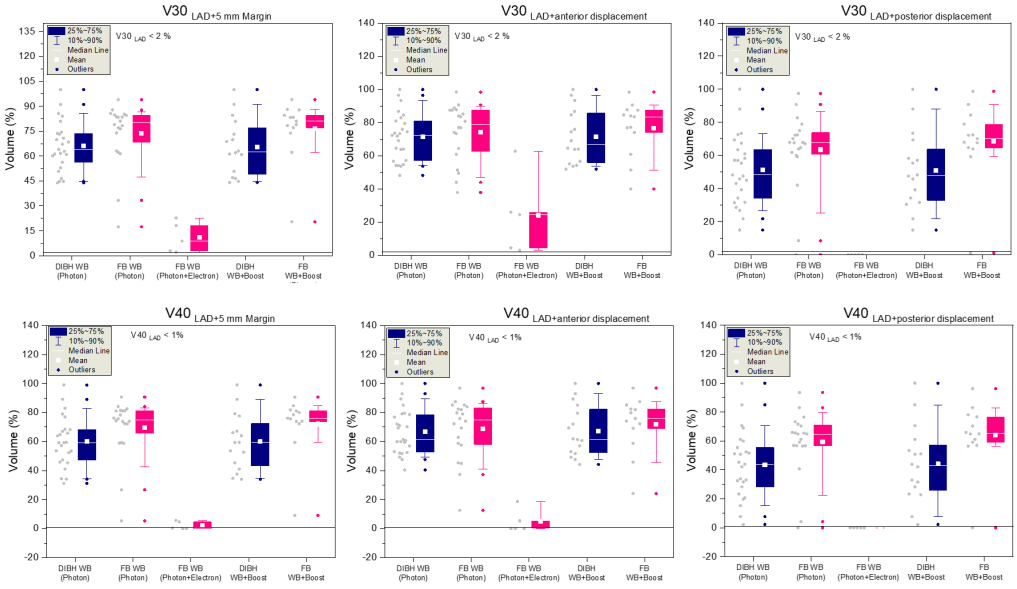

Figure 13: Box plot of V30 and V40 for PRV contours and antero-posteriorly shifted contours for LAD.

Table 4: A summary of the characteristics of the treatment plans, the ratio of the volume of the lungs and the heart V15.

Patient	Volume ratio (DIBH:FB)			Beams		Plan characteristic	
	Left Lung	Right Lung	Heart V15	DIBH	FB	Number of fractions	Prescribed dose (cGy)
1	2.02	1.84	2.59	Photon	Photon+Electron	25	5000
2	2.13	2.03	0.51	Photon	Photon	30	6000
3	1.75	1.65	3.16	Photon	Photon+Electron	30	6000
4	2.31	1.36	0.69	Photon	Photon	30	6000
5	1.54	1.79	0.78	Photon	Photon	25	5000
6	1.69	1.59	0.80	Photon	Photon	25	5000
7	1.75	1.90	1.04	Photon	Photon+Electron	25	5000
8	1.19	1.13	1.68	Photon	Photon	30	6000
9	1.93	1.63	0.43	Photon	Photon	30	6000
10	1.73	1.70	0.61	Photon	Photon	30	6000
11	1.83	1.94	0.63	Photon	Photon	30	6000
12	1.88	1.86	0.56	Photon	Photon	25	5000
13	2.04	1.97	0.71	Photon	Photon	25	5000
14	1.89	1.80	0.36	Photon	Photon	30	6000
15	1.09	1.13	2.05	Photon	Photon	25	5000
16	0.90	0.91	2.81	Photon	Photon	25	5000
17	2.15	1.94	0.76	Photon	Photon	25	5000
18	1.98	1.92	1.60	Photon	Photon+Electron	30	6000
19	1.90	1.76	0.36	Photon	Photon	25	5000
20	1.59	1.60	1.11	Photon	Photon	30	6000
21	1.86	1.62	0.12	Photon	Photon	30	6000
22	1.76	1.73	1.20	Photon	Photon+Electron	30	6000
23	1.56	1.47	1.93	Photon	Photon	30	6000
24	1.70	1.55	0.66	Photon	Photon	30	6000
25	1.89	1.62	0.65	Photon	Photon	33	6600

for 18 treatment plans in DIBH conditions. 5 out of 7 treatment plans in which the criteria were not met, DIBH were more appropriate than FB. Recent studies have recommended that the heart mean dose should not exceed 2.5 Gy (Piroth et al., 2019) and only one out of 25 investigated plans in DIBH conditions and two out of 25 treatment plans in FB conditions met this criterion (Fig. 6).

As the primary treatment plans did not consider any criteria for LAD and LV substructures, none of them in DIBH conditions met the criteria of mean dose, V30 and V40 for LAD. However, without prior determination, In DIBH conditions, one, two, and seven treatment plans and, In FB conditions, five, five, and seven treatment plans had met the mean dose, V23, and V5 criteria for LAD, respectively.

The DIBH:FB volume ratio of lungs is reported in Table 4, which is less than one only for one patient (i.e., patient no. 16). Also, the heart V15 was obtained for all patients and the subsequent DIBH:FB ratio. This value is smaller than one for all patients treated with photon beam in DIBH condition (except patients no. 16 and 20), indicating that a smaller volume of heart was exposed with > 15 Gy dose in DIBH condition than FB.

For the patient no. 16, the volume of the lungs in the FB condition was greater than in the DIBH condition; for this reason, the FB treatment plan had better results than the DIBH. It is likely that the patient was in a deep inhalation phase during the imaging.

When choosing a photon and electron beam for treatment planning under FB condition, it's important to note that electrons penetrate to a lesser depth. As a result, the volume of the heart exposed to the radiation field is significantly reduced. In these cases, the DIBH:FB ratio of heart V15 is greater than one, and the mean dose and dose volume parameters are very low. The electron beam can lead to serious skin reactions in patients and often fails to provide a uniform dose distribution within the target area. As a result, its inclusion in most treatment plans is often considered an undesirable option. However, if a center does not offer the DIBH option, the use of electron beams becomes unavoidable in certain cases.

Considering the PRVs and the displaced contours of the LV and LAD (i.e., the box plots in Figs. 11 to 13), it is evident that favourable conditions for these substructures were not achieved. While shifting the contour posteriorly slightly decreased the total delivered dose, this change did not significantly affect our ability to meet the proposed criteria.

The data clearly indicates that the treatment plan for the heart and its substructures has not met the necessary stringent criteria, which raises concerns for breast cancer patients, particularly those with left-sided breast cancer. Although the DIBH technique was planned for the selected patients, the plan ultimately failed to meet the proposed criteria.

Our recommendation, based on the results of this study, is to develop a new protocol for planning the treatment of breast cancer patients. This protocol should include the stricter criteria used in our study during the treatment planning phase by medical physicists, even when considering the DIBH technique. The treatment plan must be designed according to these updated and more stringent criteria. Currently, it is often not feasible to meet these stricter criteria with existing modalities for most breast cancer cases. Therefore, there is an opportunity to explore more advanced radiation therapy techniques, such as volumetric modulated arc therapy (VMAT).

Given the significance of breast cancer patients - who make up nearly a quarter of all patients undergoing radiation therapy at RROC- it is essential to implement these advanced radiation therapy methods. In the near future, we plan to introduce this advanced modality alongside the DIBH technique for breast cancer patients at RROC.

5 Conclusions

Breast radiation therapy can result in non-negligible cardiac toxicity, particularly for patients with left-sided breast cancer. Fortunately, modern techniques allow for effective sparing of the heart during treatment planning. Although the mean dose to the heart may be minimized, certain cardiac structures, such as the LV or LAD, might still receive high levels of radiation. The DIBH and FB treatments were planned for 25 patients in this study. We found that only 18 out of the 25 plans met the cardiac V25 criteria using the DIBH technique. Furthermore, only one plan achieved a stricter mean cardiac dose of 2.5 Gy, and just one plan met the proposed criteria for the LV. This highlights the importance of considering the LV and LAD as critical OARs during the treatment planning phase. We strongly recommend adopting stricter criteria for the heart and its substructures, even when using the DIBH technique, particularly with advanced radiation therapy techniques like Volumetric Modulated Arc Therapy (VMAT).

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Conflict of Interest

The authors declare no potential conflict of interest regarding the publication of this work.

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