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Research Article

Impact of DIBH Technique on Dosimetric Parameters of LAD and Its Segments During Left-Sided Breast Cancer Radiotherapy

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Abstract

Deep inspiration breath hold (DIBH) technique plays significant role in reducing the mean heart and LAD doses, however the potential dosimetric impact of DIBH on LAD segments has not been studied in left-sided breast cancer. This study aimed to analyse the potential dosimetric impact of DIBH technique on LAD and its individual segments during breast cancer radiotherapy. This study also investigated the potential correlation of changes in lung volume, changes in heart volume, and patients body mass index with the dose indices of different LAD segments. This study retrospectively included a set of data of thirty female patients who underwent radiation therapy for left breast cancer. Treatment plans were generated on both FB and DIBH CT-dataset for each patient. For comparative analysis, following dosimetric parameters were analysed to evaluate the potential dosimetric impact of DIBH technique; ipsilateral lung [D_{mean}, volume receiving 17Gy, 8Gy, 4Gy]. Heart [D_{mean}, volume receiving V17Gy, 35Gy, V8Gy], LAD and its segments-proximal, middle, and distal [D_{mean}, D_{max}, volume receiving 15Gy]. Analysis revealed that the DIBH technique results in significant reduction in all segmented LAD dose indices. The study evaluated that the DIBH resulted in significant reduction with average value of -31.76%, -16.16% and -24.84% in the D_{mean}, D_{max} and V15Gy of total LAD, respectively. All LAD segments showed variable reduction in dose indices, particularly, the distal LAD segment presented a maximum reduction in D_{mean} and D_{max} dose indices compared to other LAD segments. The analysis demonstrated a negative correlation between changes in lung volume, patient BMI, and all dosimetric indices of the LAD segments. A statistically significant moderate negative correlation was observed between changes in lung volume and the D_{mean} and V15Gy of the proximal LAD segment and V15Gy of distal LAD segments. There is also a positive correlation between change in heart volume and the change in all dose parameters of LAD segments with significant value for D_{mean} of distal LAD segment ($r = 0.462$; $p < 0.05$). The study demonstrated that the DIBH technique resulted in significant reduction in dose parameters for whole LAD as well as its three segments. The study found that the distal LAD segment showed a maximum reduction in D_{mean} and D_{max} dose indices compared to other segments. The study also revealed significant correlations between changes in lung volume, heart volume, and segmented LAD dose parameters.

Keywords

Lad, Dibh, Segmented Lad, Bmi, Heart, Lung

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1. Introduction

Breast cancer is the most frequently diagnosed malignancy among women worldwide. This malignancy poses a major public health challenge in low and middle income countries due to inadequate screening facilities and delayed diagnosis [1]. Adjuvant radiotherapy is considered as standard treatment modality and plays an important role in improving local and regional disease control [2]. However along with the survival benefits, radiotherapy of left-sided breast cancer has shown increased risk of associated radiation toxicities. The resulting mortality and morbidity were mainly due to the higher radiation dose exposure to the lung and heart [3]. There are various techniques available that can be used to reduce the radiation dose exposure to these organs. The deep inspiration breath hold technique (DIBH) such as voluntary DIBH and moderate DIBH using active breathing coordinator (ABC) (Elekta, Stockholm, Sweden) has been proven to decrease the dose to the heart [4]. Prone breast radiotherapy has also been demonstrated to significantly reduce high-dose radiation exposure to the heart [5]. In the past, researchers have evaluated the dose-response relationship between mean heart dose and radiation-induced cardiac event [6, 7]. However, recent studies show that radiation dose to the cardiac substructures especially left ventricle (LV) and left anterior descending coronary artery (LAD) has a greater association with increased risk of cardiac events [8-11]. It is noted that radiation exposure to coronary artery can result in inflammation, which may initiate stenosis in the artery [9, 12]. As per the published data, the LAD coronary artery is one of the common sites for the occurrence of radiation-induced cardiac injury [8-10, 12]. Recent advancements in radiotherapy delivery techniques result in effective sparing of cardiac substructures, especially dose to LAD in patients with left-sided breast cancer [13-19]. As per the published data, DIBH can significantly reduce mean LAD dose compared to free-breathing (FB) radiation therapy [13-15]. Some studies also assessed the feasibility of intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) delivery with the DIBH technique in achieving dose reduction to cardiac substructures, particularly the LAD [15]. Most previous studies have focused on dosimetric comparisons of the mean dose to the whole LAD between DIBH and FB techniques. However, the positions of the proximal, middle, and distal LAD segments relative to the left chest wall vary considerably, which may lead to differential radiation exposure during radiotherapy [13, 20]. Despite this anatomical variability, only one study has comprehensively investigated the dose-sparing effect of DIBH on individual segments of cardiac substructures, particularly the LAD and LV [13]. In previous study, the comparative analysis was performed by retrospectively translating the same treatment plan doses generated on DIBH scan dataset to FB scan dataset by aligning the chest wall. However, lung volume expansion during DIBH results in significant changes in the geometry of the chest wall and the planning target volume (PTV) compared with the FB scan, thereby necessitating different treatment beam geometries for treatment planning on the two scans. The different beam geometries may have variable dosimetric impact on different segments of LAD, therefore further detailed dosimetric comparison is required to accurately evaluate the dose sparing benefits of DIBH for different segments of LAD. In our study we aimed to analyse the segment-specific dosimetric impact of DIBH technique for LAD during left-sided breast cancer radiotherapy. Study also aimed to evaluate the possible correlation between change in lung volume, change in heart volume, patients body mass index (BMI), and dose indices of different LAD segments.

2. Materials and Methods

2.1. Patient Selection

This study retrospectively included a dataset of thirty female patients who had received treatment for left-sided breast cancer. This is a retrospective dosimetric planning study based on comparative analysis of existing patient planning datasets and no investigation were performed with the actual patients. All the patients underwent treatment using the three-dimensional field-in-field technique with DIBH method from 2023 to 2025 with a median age of 55.0 years (range 31-70). Patients were enrolled in the study based on the inclusion and exclusion criteria outlined in Table 1.

Table 1. *Patient Inclusion and Exclusion Criteria for the Study.*

Category	Criteria
Inclusion Criteria	• Patients aged >18 years. • Pathologically confirmed left-sided breast cancer. • Scheduled to receive adjuvant radiotherapy. • Stable DIBH amplitude ≥1 cm above the baseline FB amplitude.

Category	Criteria
	• Ability to maintain breath hold for at least 20 seconds.
Exclusion Criteria	• History of prior thoracic radiotherapy. • Presence of metastatic disease at diagnosis. • Indication for internal mammary node irradiation. • Breath-hold amplitude <1 cm above the baseline FB amplitude.

DIBH-deep inspiration breath hold, FB- free-breathing

2.2. Image Acquisition

The patient computed tomography (CT) simulations were performed by using both the DIBH and FB techniques on the same day. Before DIBH CT-simulation, each patient was underwent 30 min breathing coaching session for three consecutive days to confirm stable and reproducible breathing amplitude for DIBH scan. For each patient, the Respiratory Gating (RGSC) system (Varian Medical Systems, Palo Alto, USA) was used to performed DIBH scan. Patient CT simulation was performed using a Discovery RT CT scanner (GE Medical Systems, USA) with intravenous contrast administration. Patients were positioned supine on a breast board with both arms above their head.

2.3. Structure Delineation

The clinical target volume (CTV) and PTV along with the other critical structure were delineated on both DIBH and FB scan by radiation oncologist according to established contouring guidelines [20]. The critical structure includes ipsilateral lung, contralateral lung, heart, contralateral breast, spinal cord and LAD. The LAD coronary artery was further subdivided into segments and contoured according to the guidelines described by Duane et al [21]. The three LAD segments named as proximal, middle and distal LAD segment.

2.4. Treatment Planning

Eclipse treatment planning system (TPS) (Varian Medical System, Palo Alto, CA, USA) was used to generate treatment plans on both the DIBH and FB scan dataset of each patient. A prescription dose of 40 Gy in 15 fractions using 6-MV photon beams was used for treatment planning in the Eclipse TPS. Dose calculations were performed using the Analytical Anisotropic Algorithm. Three-dimensional field-in-field technique was used to improve dose homogeneity. The treatment plan was performed to achieve adequate isodose coverage of the target volume while minimizing the dose to surrounding normal organs.

2.5. Dosimetric Evaluation and Statistical Analysis

For analysis, the dosimetric parameters of each structure were compared between the DIBH and FB techniques. For comparative analysis, the FB parameters were considered as a reference. To evaluate the average percentage variation between DIBH and FB parameters, the percentage change was first obtained for each individual patient. Finally, the overall average percentage variation was calculated by taking the mean of the individual percentage changes across all patients. Following dosimetric parameters were analysed to evaluate the potential dosimetric impact of DIBH technique; ipsilateral lung [Mean dose (D_{mean}), volume receiving 17Gy (V17Gy), volume receiving 8Gy (V8Gy), volume receiving 4Gy (V4Gy)], Heart [D_{mean}, V17Gy, volume receiving 35Gy (V35Gy), V8Gy], LAD and its segments-proximal, middle, and distal [D_{mean}, Maximum dose (D_{max}), volume receiving 15Gy (V15Gy)].

We performed a Wilcoxon signed-ranks test to determine the statistical significance between all the dosimetric indices obtain through DIBH technique and FB technique. Differences in dose among the segmented LAD regions were assessed using Tukey's HSD post-hoc test following a statistically significant one-way ANOVA. Linear correlation evaluation was performed to analysed the impact of change in lung volume, change in heart volume, and patients BMI on segmented LAD dose indices. A $p < 0.05$ value was considered statistically significant. All statistical tests were performed by using online VassarStats software.

3. Results

All the patients were treated with DIBH technique. The comparative analysis of dose indices between FB plan and DIBH plan were performed after normalising both the plan to deliver 95% of prescription dose to 95% of the target volume. The DIBH technique results in significant reduction in dose indices of both heart and lung except D_{mean}, V8Gy and V4Gy of lung, where the dose reduction was not significant. Figure

1. illustrates the isodose distribution of treatment plans for one of the patients, obtained with FB and DIBH technique. The use of DIBH technique resulted in significant reduction in all dosimetric indices of LAD and its segments (All $p < 0.05$). As tabulated in Table 2, the results indicate that the DIBH mainly resulted in average reduction of -31.76%, -16.16% and -24.84% in the D_{mean}, D_{max} and V15Gy of whole LAD, respectively.

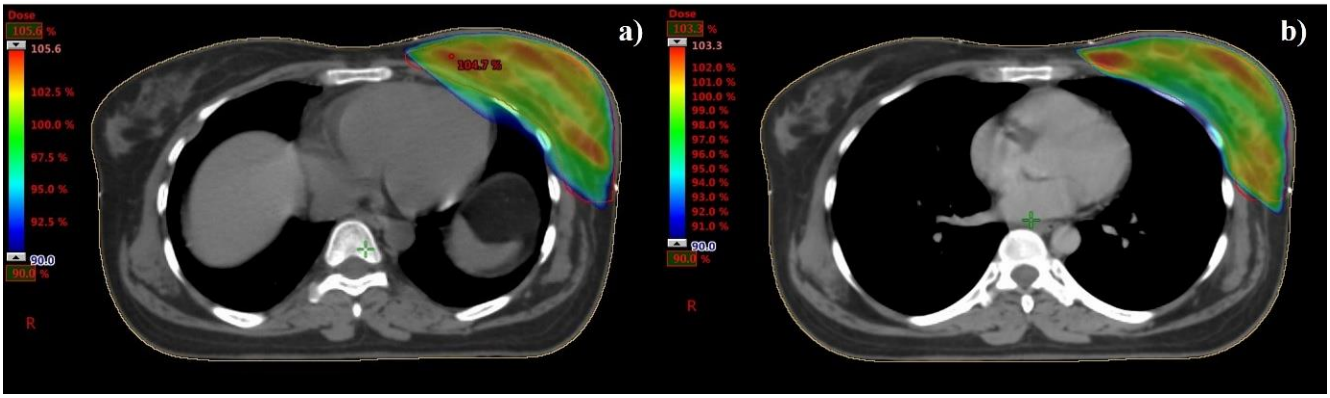

Figure 1. *Representative image showing dose exposure to LAD and heart by a) FB and b) DIBH technique for one of the patients.*

LAD-Left Anterior Descending coronary artery, FB-Free Breathing, DIBH- Deep inspiration breath hold technique

Table 2. *Comparison of organ at risk parameters (mean±sd) between DIBH and FB.*

Structure	Parameters	FB	DIBH	p value
Left Lung	Volume (cc)	824.71±192.76	1518.93±258.83	< 0.05
	D_{mean} (Gy)	9.28±3.51	8.60±2.86	> 0.05
	V17Gy (%)	21.86±9.79	19.60±7.96	< 0.05
	V8Gy (%)	27.04±9.97	25.01±8.26	> 0.05
	V4Gy (%)	36.26±10.05	35.50±8.42	> 0.05
Heart	Volume (cc)	519.48±91.28	465.25±102.16	< 0.05
	D_{mean} (Gy)	5.02±3.54	2.58±1.83	< 0.05
	V35Gy (%)	5.86±6.41	1.81±2.66	< 0.05
	V17Gy (%)	10.76±9.51	4.12±4.63	< 0.05
	V8Gy (%)	13.22±10.74	5.92±6.16	< 0.05
LAD	D_{mean} (Gy)	25.79±13.25	17.17±13.62	< 0.05
	D_{max} (Gy)	33.51±13.32	27.84±15.35	< 0.05
	V15Gy (%)	67.70±37.74	42.87±40.03	< 0.05
Proximal_LAD	D_{mean} (Gy)	18.05±13.44	11.71±11.61	< 0.05
	D_{max} (Gy)	28.82±14.86	21.27±15.48	< 0.05
	V15Gy (%)	45.25±41.24	27.83±37.12	< 0.05
Middle_LAD	D_{mean} (Gy)	29.12±14.83	20.28±16.05	< 0.05
	D_{max} (Gy)	32.81±13.46	26.40±15.56	< 0.05
	V15Gy (%)	75.65±42.71	51.66±48.89	< 0.05
Distal_LAD	D_{mean} (Gy)	29.33±14.63	19.33±16.34	< 0.05
	D_{max} (Gy)	32.77±13.91	24.33±17.11	< 0.05

Structure	Parameters	FB	DIBH	p value
	V15Gy (%)	72.00±44.10	50.85±47.23	< 0.05

DIBH- Deep inspiration breath hold technique, FB-Free Breathing, LAD-Left Anterior Descending coronary artery, D_{mean}-Mean dose, D_{max}-Maximum dose, (V35Gy)-Volume receiving 35Gy, (V17Gy)-Volume receiving 17Gy, (V15Gy)-Volume receiving 15Gy, (V8Gy)-Volume receiving 8Gy, (V4Gy)-Volume receiving 4Gy

Although the three LAD segments have an average reduction in all the dose parameters (D_{mean}, D_{max} and V15Gy) due to DIBH technique, they demonstrated varying dosimetric characteristics, particularly the distal LAD segment showed a maximum reduction in D_{mean} and D_{max} dose indices compared to other two LAD segments, as presented in Figure 2. The proximal, middle, and distal LAD segments demonstrated a mean reduction in D_{mean} of -30.38%, -31.03%, and -36.49%, respectively, and the D_{max} of the proximal, middle, and distal LAD segments demonstrated an average reduction of -22.78%, -21.27%, and -28.85%, respectively, as indicated in Table 2.

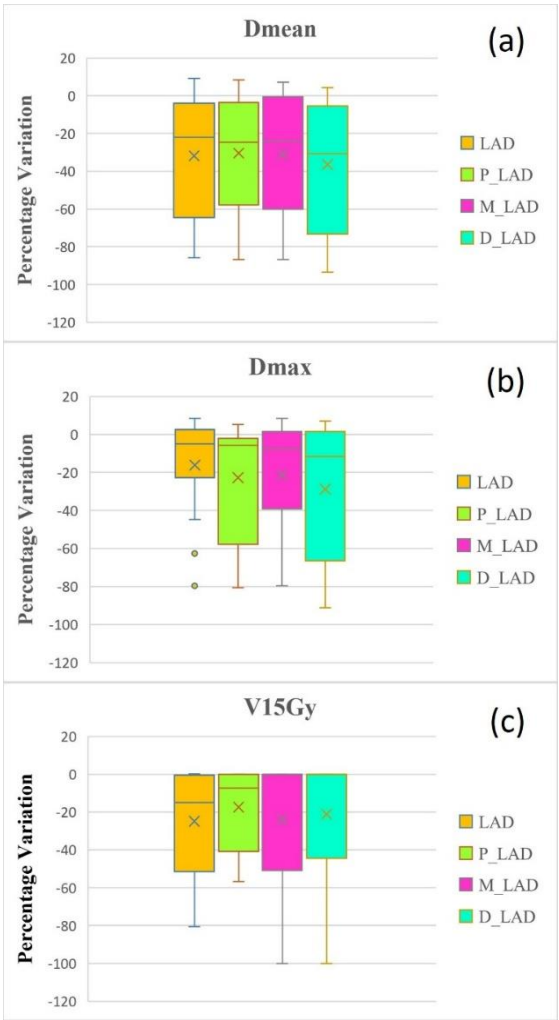

Figure 2. *Box plot showing change in dosimetric parameter a) mean dose (D_{mean}) and b) maximum dose (D_{max}) c) V15Gy for Entire LAD, P_LAD, M_LAD and D_LAD due to DIBH technique over FB.*

DIBH- Deep inspiration breath hold technique, FB-Free Breathing, LAD-Left Anterior Descending coronary artery, P_LAD-Proximal LAD, M_LAD-Middle LAD, D_LAD-Distal LAD, D_{mean}-Mean dose, D_{max}-Maximum dose, V15Gy-Volume receiving 15Gy

The difference in the dose indices of the three LAD segments was further assessed using the Tukey HSD test which demonstrated that, for both the FB and DIBH techniques, statistically significant differences were observed between the proximal and middle LAD segments ($p < 0.05$), as well as between the proximal and distal LAD segments ($p < 0.05$) except in D_{max} with FB plan. The proximal LAD segment exhibited significantly lower dose indices compared to middle as well as distal LAD segments for both the FB and DIBH techniques. However, for both the FB and DIBH technique, the middle and distal LAD segments did not differ significantly in terms of the evaluated dosimetric parameters (all $p > 0.05$). Linear correlation and regression analysis demonstrated a negative correlation between change in lung volume, patients BMI and change in all dose indices to the LAD and its segments. Similarly, analysis revealed a positive correlation between change in heart volume and change in all dose indices to the LAD and its segments as tabulated in Table 3. The correlation analysis revealed a moderate negative correlation between change in lung volume and change in dose parameters to the whole LAD except D_{max}, for which a nonsignificant weak negative correlation was observed ($r = -0.361$; $p > 0.05$). Correlation analysis also demonstrated a weak positive correlation that did not reach statistical significance between change in heart volume and change in dose parameters to the whole LAD except D_{max}, for which significant moderate positive correlation was observed ($r = 0.456$: $p < 0.05$). The analysis showed a weak negative association between patients BMI, and all dosimetric indices of the whole LAD and individual segments, which was not statistically significant (all $p > 0.05$). The evaluation for different LAD segments indicates a significant moderate negative correlation between change in lung volume and change in D_{mean} ($r = -0.446$; $p < 0.05$) and change in V15Gy ($r = -0.471$; $p < 0.05$) for proximal segment of LAD and change in V15Gy ($r = -0.538$; $p < 0.05$) for distal LAD segments. The remaining dosimetric indices of individual segments of LAD demonstrated no statistically significant correlation with the change in lung volume (all $p > 0.05$). Significant moderate positive correlation was observed only between change in heart volume and change in D_{mean} for distal LAD segment (r =

0.462; $p < 0.05$), no statistically significant correlation was observed for rest of the dosimetric parameters of LAD segments and changes in heart volume (all $p > 0.05$).

Table 3. *Correlation Between the relative reduction in Dose to the LAD and Its segments and changes in Lung volume, Heart volume, and Patient BMI.*

Dosimetric Parameter	Structure	Change in LUNG volume		Change in HEART volume		BMI	
		r	p	r	p	r	p
D_{mean} (Gy)	LAD	-0.446	< 0.05	0.358	> 0.05	-0.358	> 0.05
	P_LAD	-0.446	< 0.05	0.045	> 0.05	-0.336	> 0.05
	M_LAD	-0.374	> 0.05	0.279	> 0.05	-0.102	> 0.05
	D_LAD	-0.403	> 0.05	0.462	< 0.05	-0.218	> 0.05
D_{max} (Gy)	LAD	-0.362	> 0.05	0.456	< 0.05	-0.196	> 0.05
	P_LAD	-0.399	> 0.05	0	> 0.05	-0.363	> 0.05
	M_LAD	-0.205	> 0.05	0.341	> 0.05	-0.061	> 0.05
	D_LAD	-0.244	> 0.05	0.425	> 0.05	-0.014	> 0.05
V15Gy (%)	LAD	-0.479	< 0.05	0.247	> 0.05	-0.405	> 0.05
	P_LAD	-0.471	< 0.05	0.215	> 0.05	-0.309	> 0.05
	M_LAD	-0.397	> 0.05	0.201	> 0.05	-0.25	> 0.05
	D_LAD	-0.538	< 0.05	0.279	> 0.05	-0.125	> 0.05

LAD-Left Anterior Descending coronary artery, BMI-Body Mass Index, P_LAD-Proximal LAD, M_LAD-Middle LAD, D_LAD-Distal LAD, D_{mean}-Mean dose, D_{max}-Maximum dose, (V15Gy)-Volume receiving 15Gy

4. Discussion

This comprehensive dosimetric planning study assess the impact of DIBH technique on dose metrics of LAD and its individual LAD segments. This study further evaluated the potential correlation between changes in lung volume, change in heart volume, patient BMI, and the corresponding changes in the dose indices of the LAD and its individual LAD segments. The study demonstrated that the DIBH technique has variable dosimetric impact on three different LAD segments, namely proximal, middle, and distal segments. It was found that the DIBH technique resulted in significant reduction in the D_{mean} of the heart and whole LAD by -42.72% and -31.76%, respectively, which were in line with the previous reported data [13-15]. There are several studies available that showed the dose sparing impact of DIBH technique by analysing the various dose parameters of heart and LAD which include D_{mean}, D_{max}, volume receiving 5Gy (V5Gy), volume receiving 10Gy (V10Gy), V15Gy, volume receiving 20Gy (V20Gy), volume receiving 25Gy (V25Gy) and volume receiving 30Gy (V30Gy) [13-15]. Some studies have also evaluated the use of various planning techniques like field in field conformal and inverse plan optimization in combination with DIBH to protect cardiac substructures, including the LAD [15-18], however there is only one study available that analysed the impact of DIBH technique on dosimetric parameters of individual LAD segments [13]. Previous study revealed that DIBH effectively reduced dose to the different segments of LAD and LV. However, for comparative analysis, the study used the same dose distribution generated on DIBH scan to recalculate the organ dose on FB scan by retrospective translating the dose by using same shift required to align the chest wall on both the scans. We feel that due to lung volume expansion during DIBH scan, it is difficult to align the chest walls of both the scan and may need different beam geometry while calculating the doses on FB scan. In our present study, we comparatively analysed the dose indices by calculating the doses using different beam geometries required for targets in FB scan as well as in DIBH scan and found that DIBH technique has significant variable dose reduction impact across different LAD segments. We found that, DIBH technique results in largest dose reduction in terms of D_{mean} and D_{max} for the distal LAD segment, however, in terms of V15Gy the greatest dose reduction was observed for the middle LAD segment. The study also analysed the difference in the dose indices of the three LAD segments for both the DIBH treatment plan as well as FB treatment plan. Our study indicates that the dose indices

of proximal LAD segments are significantly lower than middle and distal LAD segments in both FB treatment plan as well as DIBH treatment plan which was in line with the previous reported data [9, 13, 22]. This variation may be due to the anatomical position of proximal LAD segment with respect to the target area.

Our study also found a correlation between the change in lung volume, heart volume, patients BMI and a change in dose indices of the LAD and its individual segments. Our finding revealed a negative correlation between change in lung volume and the change in all dose indices of the LAD and its individual segments with significant correlation with D_{mean} and V15Gy of whole LAD and proximal LAD segment and V15Gy of distal LAD segment. No significant correlation was observed with middle LAD segment, however in previous reported study significant correlation was observed between left lung expansion and mean dose reduction to middle and distal LAD segment but not with proximal LAD segment [13]. This difference may be attributed to the use of non-contrast CT simulation in the previous study, which likely reduced the visibility of the LAD and consequently compromised the accuracy of delineating the LAD and its segments. We found a nonsignificant weak negative correlation between patients BMI and the change in all dose indices of the LAD and its individual segments. Our study also demonstrated a positive correlation between the change in heart volume and the change in all dose indices of the LAD and its individual segments with significant correlation with D_{mean} of distal LAD segments and D_{max} of whole LAD, which is in contrast with previous study which reported a stronger positive association with lower doses to LAD and weak correlation with maximum doses to LAD [16]. The possible reason for this may be, in previous reported study, the change in heart volume and change in LAD dose parameters were assessed by using daily cone beam CT (CBCT) scans, however it is observed that the delineation of LAD on CBCT scan introduce high level of uncertainty due to reduced visibility of this cardiac structure on CBCT.

The main limitation of our study is that the comparative analysis of all dose indices of LAD and its segments is solely based on static CT image dataset, the LAD position is highly attributable to intrinsic movement of heart due to cardiac cycle. Although, there is less impact of respiratory motion on LAD position with DIBH technique but it will also contribute some uncertainty in the dose evaluation. Therefore, it is essential to consider these motion-induced dose uncertainties for accurately assessing the dose indices for the LAD and its segments.

5. Conclusion

The DIBH technique resulted in significant reduction in the dose indices for whole LAD as well as its segments. This study demonstrated that the reduction in dose indices for LAD segments is variable, especially the distal LAD segment showing maximum reduction in D_{mean} and D_{max} dose indices compared to other segments. Our study also revealed significant correlation between change in lung volume as well as change in heart volume and dose indices to the LAD segments. There was a nonsignificant correlation between patients BMI and a change in dose indices of the LAD segments. In addition to the reduction of mean heart and LAD doses, DIBH technique can effectively spare all LAD segments which was previously reported as common sites for the occurrence of radiation-induced cardiac injury.

Abbreviations

DIBH	Deep Inspiration Breath Hold
ABC	Active Breathing Coordinator
LV	Left Ventricle
LAD	Left Anterior Descending
FB	Free Breathing
IMRT	Intensity Modulated Radiotherapy
VMAT	Volumetric Modulated Arc Therapy
PTV	Planning Target Volume
BMI	Body Mass Index
CT	Computed Tomography
RGSC	Respiratory Gating for Scanners
CTV	Clinical Target Volume
TPS	Treatment Planning System
D_{mean}	Mean Dose
V17Gy	Volume Receiving 17Gy
V8Gy	Volume Receiving 8Gy
V4Gy	Volume Receiving 4Gy
V35Gy	Volume Receiving 35Gy
V15Gy	Volume Receiving 15Gy
D_{max}	Maximum Dose
P_LAD	Proximal LAD
M_LAD	Middle LAD
D_LAD	Distal LAD
CBCT	Cone Beam Computed Tomography

Author Contributions

Mukesh Meshram: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Resources, Software, Writing – original draft, Writing – review & editing

Sameer Chandorkar: Conceptualization, Data Curation, Formal Analysis, Project administration, Resources, Software, Supervision, Validation, Writing – review & editing

Himanshu Kumbhare: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Software, Writing – review & editing

Arpit Gite: Data Curation, Formal Analysis, Investigation, Methodology, Software, Visualization, Writing – review & editing

Appaso Bandgar: Data Curation, Methodology, Software, Writing – review & editing

Siddesh Kalbut: Data Curation, Methodology, Software, Writing – review & editing

Sabheen Bushra: Data Curation, Methodology, Software,

Writing – review & editing

Jayesh Dherange: Data Curation, Formal Analysis, Methodology, Writing – review & editing

Jayant Nardekar: Data Curation, Formal Analysis, Methodology, Writing – review & editing

Conflicts of Interest

The authors declare no conflicts of interest.

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