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Original Article

Oncology Section

Assessing the Dosimetric Advantage of Deep Inspiration Breath Hold Technique in Left-sided Breast Cancer Radiotherapy: A Prospective Observational Study

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ABSTRACT

Introduction: Addition of RT to breast cancer patients after surgery {Breast Conserving Surgery (BCS) or Modified Radical Mastectomy (MRM)} has clearly demonstrated clinical benefits in many randomised trials and meta-analyses. However, the long-term survival achieved with multi-modality treatment in breast cancer patients may be overshadowed by late toxicities like cardiac morbidity and mortality. Hence, various techniques are used to reduce the cardiac dose, with one crucial measure being the breath hold technique.

Aim: To assess the reduction of cardiac and left anterior descending artery radiation dose using the Deep inspiration breath hold technique during tangential irradiation in left-sided breast carcinoma patients.

Materials and Methods: The present prospective observational study was conducted in the Department of Radiation Oncology in Acharya Harihar Postgraduate Institute of Cancer, Cuttack, Odisha, India, from January 2015 to December 2016. Twelve patients with histopathologically proven left-sided breast cancer who have undergone modified radical mastectomy and have received radiotherapy to the chest wall with or without regional nodal irradiation were included. After adequate training, a planning Computed Tomography (CT) scan was performed at Free Breathing (FB) and another at deep inspiration and Voluntary Breath Hold in Deep Inspiration (VBH-DI). For each patient, target volumes and organs at risk were delineated according to Radiation Therapy Oncology Group (RTOG) guidelines. Further, the following dosimetric parameters were collected for both FB and VBH-DI plan- Heart D_{mean}, Heart D_{max}, the percentage of the organ volume receiving at least 5 Gy (V5),10 Gy (V10), 20 Gy (V20), 30 Gy (V30), 40 Gy(V40), Left Anterior Descending Coronary Artery (LADCA) D_{mean} and LADCA D_{max}. Differences between the two respiratory techniques were analysed using the Shapiro-Wilk test for normality, followed by the independent t-test for normally distributed data and the Mann-Whitney U test for non-normal dosimetric, MHD, and proximal/middle/distal LADCA data, with $p<0.05$ considered statistically significant.

Results: A total of 12 breast cancer patients (each simulated in both FB and vDIBH) were analysed; the mean age was 46.8±9.0 years (31-61), and ECOG performance status was 0 in 41.7% and 1 in 58.3%. The mean heart dose was reduced from 6.49 Gy in FB to 4.96 Gy in VBH-DI, i.e., a 24% reduction, and this difference was statistically significant (p=0.017). Except for V40 of the heart, the mean values of Heart V5, V10, V20, and V30 were reduced in the VBH-DI technique as compared to the FB technique (18.68% vs 13.34%, 15.98% vs 11.03%, 13.74% vs 8.94%, and 11.44% vs 6.85%, respectively), p<0.001. Similarly, the mean dose to the LADCA was reduced from 29.70 Gy in FB to 25.14 Gy in VBH-DI technique (p<0.001).

Conclusion: The present study showed a clear superiority of the VBH-DI technique in cardiac sparing, which will result in a significant reduction in late major coronary events.

Keywords: Cardiac sparing, Coronary events, Left anterior descending coronary artery, Mean heart dose

INTRODUCTION

Breast cancer incidence has increased over the years, with it being the most common cancer in India as well as worldwide, as per GLOBOCAN 2020 data [1]. Advances in treatment, including surgery, systemic therapy, and Radiation Therapy (RT), have significantly improved survival outcomes [2,3]. This has resulted in a higher number of long-term survivors who lived long enough to face the late toxicity of the treatment. Late cardiac toxicity is well known in breast cancer survivors who have received radiotherapy, especially for left-sided breast cancer patients or those requiring internal mammary node irradiation [4]. The study by Darby SC et al., concluded that the rate of major coronary events increases linearly with the mean dose to the heart by 7.4% per Gray with no apparent threshold [5]. Various cardiac-sparing strategies, including prone positioning, IMRT/VMAT, partial-breast irradiation, and breath hold techniques, aim to reduce heart and LAD exposure during left-sided breast irradiation. Among these, voluntary or Deep-inspiration Breath Hold (vDIBH/DIBH) is particularly effective, as deep inspiration displaces the heart posteriorly and inferiorly, increasing heart-chest wall and LAD-chest wall distance, thereby reducing high-dose volumes. Previous studies consistently report significant reductions in MHD, LAD D_{mean}, and heart V5-V30 with DIBH compared to FB [4,6-8]. The present study was designed to evaluate the dosimetric advantage of voluntary breath hold in treatment of left sided breast cancer patients.

MATERIALS AND METHODS

The present prospective, dosimetric, paired comparison study was conducted at Acharya Harihar Postgraduate Institute of Cancer, Cuttack, Odisha, India, from January 2015 to December 2016. A total of 12 left-sided breast cancer patients were included, each undergoing both FB and voluntary vDIBH treatment planning. The study was approved by the Institutional Ethics Committee (005-IEC-AHRCC). The sampling method used was purposive sampling [9].

Inclusion and Exclusion criteria: Histopathologically proven left-sided breast cancer with maximum heart distance ≥10 mm during CT simulation, and only patients who could reproducibly hold their breath for at least 20 seconds with stable chest motion were included in the study. Right-sided breast cancer patients and patients with Chronic Obstructive Pulmonary Disease (COPD), interstitial lung disease, and asthma were excluded from the study.

Study Procedure

After obtaining informed consent, patients were trained to hold their breath for 15 seconds at deep inspiration. After adequate training, a planning CT scan was taken at FB and another at deep inspiration and VBH-DI. For the VBH-DI CT scan, a bell was provided to the patient to signal the technician in the console when they start the breath hold. Both the planning CT scans (FB and VBH-DI) were then transferred to the treatment planning system (Elekta Oncentra), after which target volumes and organs at risk were delineated according to RTOG guidelines [10]. Left anterior descending artery was contoured according to guidelines by Feng M et al., [11]. Treatment planning was then done by tangential fields to the chest wall by Three-dimensional (3D) conformal technique in the Ocentra software. Plans were accepted if ≥ 95% of target volume was covered by 95% isodose curve keeping in mind that there was no hotspot (> 107%) or cold spot (< 95%) and respecting the organs at risk constraints (spinal cord D_{max} < 20 Gy, Heart D_{mean} <8 Gy, lungs V20 < 20%) as per standard guidelines and institutional protocols [12]. The MHD, defined as the maximum distance between the anterior cardiac contour and the posterior tangential field edge as displayed in the beam's eye view, was noted for both FB and VBH-DI plans. We also measured the distance from the LADCA to the posterior chest wall border by drawing a perpendicular line from the LADCA to the posterior chest wall border in the proximal, middle, and distal 1/3 in both plans. Dosimetric parameters, including MHD, heart D_{max} and D_{mean}, heart V5-V40, and LADCA distances (proximal, middle, distal) and doses were extracted from the treatment planning system for analysis. Baseline demographic and clinical characteristics (age, ECOG performance status, T/N stage) were recorded from patient records. To minimise measurement variability, all dosimetric and LADCA distance parameters were contoured and recorded by a single experienced observer. Each parameter was measured twice, and the average value was used for analysis to reduce intra-observer error.

STATISTICAL ANALYSIS

For statistical analysis, data were entered into a Microsoft Excel spreadsheet and then analysed by IBM SPSS 21. First, the basic characteristics—age, age group, ECOG status, T, N, M category, and stage- were analysed in the group of 12 patients using mean, median, and frequency. To analyse the differences between the two respiratory techniques in terms of dosimetric data and MHD and LADCA distances (proximal, middle, distal), a test for normality (Shapiro-Wilk test) was initially performed for each quantitative data set (interval/ratio). Parametric test (Independent t Test) was used for a data set having a normal distribution, and a non-parametric test (Mann-Whitney U Test) was used for a data set having a non-normal distribution. All tests were considered statistically significant if p-value was <0.05.

RESULTS

The mean age in the study participants was 46.83 years, with most of the participants (50%) in the age group of 41 to 50 years. All patients had good performance status (ECOG 0 or 1). There were four patients each in the T2, T3 and T4 categories, while most of the participants (41.2%) were of the N1 disease. As per AJCC TNM staging [13], maximum participants were in stage IIB (41.7%), followed by stage IIIB (33.3%) and IIIA (25.0%) [Table/Fig-1].

Variables	Mean±SD || Median (IQR) || Min-Max || Frequency (%)
Age (years)	46.83±9.01 || 47.00 (40.00 – 53.75) || 31.00 - 61.00
Age group	
31-40 Years	3 (25.0%)
41-50 Years	6 (50.0%)
51-60 Years	2 (16.7%)
61-70 Years	1 (8.3%)
ECOG	
Status 0	5 (41.7%)
Status 1	7 (58.3%)
T Category	
T2	4 (33.3%)
T3	4 (33.3%)
T4	4 (33.3%)
N Category	
N0	4(33.3%)
N1	5 (41.7%)
N2	3 (25.0%)
M Category	0 (0%)
Stage	
II B	5 (41.7%)
III A	3 (25.0%)
III B	4 (33.3%)

[Table/Fig-1]: Demographic and baseline characteristics of the study population.
SD: Standard Deviation, IQR: Inter quartile range, Min: Minimum, Max: Maximum ECOG: Eastern Cooperative Oncology Group Performance Status, T,N,M: AJCC TNM categorization

The mean heart dose was reduced from 6.49 Gy in FB to 4.96 Gy in VBH-DI, i.e., a 24% reduction and this difference was statistically significant (p=0.017). There was also an observed statistically significant difference between the mean MHD between the FB and VBH-DI techniques (2.19 cm vs 1.59cm, p=0.004) [Table/Fig-2].

Parameters	Respiratory technique: Free Breathing (FB) (n = 12)	Respiratory technique: Voluntary breath hold - Deep inspiration (n = 12)	p-value
MHD (cm)***	2.19±0.44	1.59±0.45	0.004[1]
Heart D_{max} (Gy)	40.81±0.89	40.71±0.82	0.787[1]
Heart D_{mean} (Gy)***	6.49±1.38	4.96±1.40	0.017[2]
V5 (%)***	18.68±3.24	13.34±2.01	<0.001[2]
V10 (%)***	15.98±3.12	11.03±2.12	<0.001[2]
V20 (%)***	13.74±3.25	8.94±2.30	<0.001[1]
V30 (%)***	11.44±2.99	6.85±2.17	<0.001[1]
V40 (%)	0.49±0.57	0.19±0.27	0.219[2]
LADCA distance from Chest wall-proximal (cm)***	3.95±0.64	4.57±0.92	0.020[2]
LADCA distance from chestwall-middle (cm)	1.80±0.63	2.47±0.95	0.058[1]
LADCA distance from chestwall-distal (cm)***	0.62±0.19	0.94±0.33	0.006[1]
LADCA D_{max} (Gy)	39.13±3.52	38.82±1.02	0.478[2]
LADCA D_{mean} (Gy)***	29.70±2.38	25.14±2.60	<0.001[2]

[Table/Fig-2]: Comparison between the two respiratory techniques.
MHD: Maximum heart distance; D_{max}: Maximum dose received, Dmin: Minimum dose received, V5: percentage of heart volume receiving ≥ 5 Gy, V10: percentage of heart volume receiving ≥ 10 Gy, V20: percentage of heart volume receiving ≥ 20 Gy, V30: percentage of heart volume receiving ≥ 30 Gy, V40: percentage of heart volume receiving ≥ 40 Gy, LADCA: Left anterior descending coronary artery.
***Significant at p <0.05, 1: Wilcoxon-Mann-Whitney U Test, 2: independent t test

DISCUSSION

Radiotherapy has become an integral part of breast cancer treatment, both in locally advanced and early breast cancer. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis on the role of radiotherapy after mastectomy and axillary surgery showed that radiotherapy reduces both local recurrence and breast cancer mortality [2,3]. The same group also conducted a meta-analysis on early breast cancer and found a significant benefit of adjuvant radiotherapy in terms of local recurrence and breast cancer deaths [2,3]. However, they also suggested an excess of non-breast cancer mortality in patients receiving radiotherapy of which cardiac toxicity was one of the major contributors (rate ratio 1.27, SE 0.07, 2p=0.0001) [3]. The cardiac toxicity due to radiotherapy to the chest wall was then evaluated by Darby SC et al., in 2013, and the authors concluded that the rate of major coronary event increased linearly with the mean dose to the heart by 7.4% per gray (95% CI. 2.9 to 14.5; p<0.0001) with no apparent threshold [5].

A systemic review was done by Smyth LM et al., in 2015 to evaluate the benefit of the DIBH in cardiac dose sparing [14]. Of the ten studies included in this systematic review, all showed a statistically significant reduction in mean heart and LADCA dose in the DIBH plan, ranging from 1 Gy (-43%) to 3.4 Gy (-67%) and 5.9 Gy (-52%) to 14.1 Gy (-71%), respectively [14].

Another review article by Stowe HB et al., showed a significant reduction in mean heart and LADCA dose, ranging from 25 to 67% and 20 to 73%, respectively [4]. The present findings align with the above studies showing significant reductions in mean heart and LADCA doses with breath hold techniques. The meta-analysis by Lu Y et al., also evaluated the heart V5, V10 and V30 which showed a statistically significant reduction in DIBH technique as compared to FB technique (V5 - SMD = -1.58, 95% CI: -2.05 ~ -1.12, p<0.01; V10 - SMD = - 1.40, 95% CI: -1.65 ~ -1.15, p<0.01; V30 - SMD = -1.23, 95% CI: -1.49 ~ 0.97 p<0.01). The present study also showed a statistically significant reduction in heart V5, V10, V20 and V30 in FB vs VBH-DI technique (18.66 vs 13.34, 15.98 vs 11.03, 13.74 vs 8.94 and 11.44 vs 6.85) [6]. In another study by Bartlett FR et al., Mean cardiac doses (Gy) for free-breathing and VBH techniques, respectively, were: heart 1.8 and 1.1, LAD 12.1 and 5.4, maximum LAD 35.4 and 24.1 (all p<0.001) and 88 (95%) patients achieved a reduction in mean heart dose with DIBH [7]. The present study showed similar results as a reduction in D_{mean} for Heart and LADCA with the VBH-DI technique [7].

A study by Ferdinand S et al., in 2021 evaluated the MHD in left-sided breast cancer patients with the DIBH technique. It showed a reduction in the mean MHD of -0.94 cm (-46.7%), which was statistically significant (p<0.001) [8]. This is similar to the finding in the present study where the VBH-DI technique reduces the mean MHC by 0.6 cm (27%) as compared to FB.

Limitation(s)

The study has several limitations. First, the sample size was small (n=12), which may limit the generalisability of the findings. Second, it was conducted at a single centre, which may not fully represent anatomical variability or treatment practices across different institutions. Third, a single observer performed all measurements, so interobserver variability was not assessed, although each parameter was measured twice to reduce intra-observer error. Fourth, the study is dosimetric in nature and does not include long-term clinical follow-up to correlate reductions in heart and LADCA doses with actual cardiac outcomes. Also, this study did not include a priori sample size calculation as it was designed as an exploratory dosimetric evaluation. Therefore, the findings may be underpowered to detect smaller but clinically meaningful differences, and the results should be interpreted with caution pending validation in larger prospective cohorts. Finally, the patient cohort included only left-sided breast cancers, so the findings may not apply to right-sided cases or other tumor sites.

CONCLUSION(S)

The DIBH derives its principle from VBH-DI, and our study showed a clear superiority of the VBH-DI technique in cardiac sparing, which will result in a significant reduction in late major coronary events. With the improvement of treatment strategies and technologies in this era, the survivors of breast cancer who live long enough to experience the late toxicity of cardiac radiation are expected to increase. Hence, newer techniques of cardiac sparing like DIBH should become a necessity rather than a privilege in all cases treated with radiotherapy to the chest wall (especially left side).

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