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DOSIMETRIC EVALUATION OF CARDIAC AND LEFT ANTERIOR DESCENDING ARTERY DOSE IN PATIENTS WITH LEFT-SIDED BREAST CANCER TREATED BY DIFFERENT TECHNIQUES OF HYPOFRACTIONATED ADJUVANT RADIOTHERAPY AFTER BREAST CONSERVATIVE SURGERY

Nindra Armugam, Zoha Mohd Saleem, Chandipriya Veluru, Erukula Ramanjaneyulu

The aims: *to dosimetrically evaluate the dose to the heart and left anterior descending artery in left-sided early breast cases using different techniques.*
Materials and methods: *Prospective observational/analytical study done in cases of left-sided BCS referred for adjuvant RT in 54 patients. Patients who underwent left-sided BCS (breast conservative surgery), patients aged between 18- and 75 years performance status ECOG 0-2, histological confirmed DCIS, Invasive Breast Cancer-Stage 1, 2, 3, patients without any evidence of metastatic disease Irrespective of hormonal receptor and HER-2 neu status are included in the study.*
Results*: All the 3 parameters for LAD showed the highest doses with 3DCRT and lowest with VMAT. Thus our study favoured VMAT (p<0.01) as the planning technique to achieve the least doses of LAD. However, for the heart, there was no statistically significant difference between 3DCRT and IMRT (p=0.349) for the average mean dose (Gy). On the other hand, there was a statistically significant difference between 3DCRT Vs VMAT and IMRT Vs VMAT (95 % CI, p<0.01), again favouring VMAT as the choice of planning technique. The average heart max dose(Gy) and average heart V20(%) showed statistically significant benefits with VMAT (p<0.01). There was a statistically significant benefit (p<0.000) with VMAT for both LV parameters. At the same time, there was a statistically significant benefit in terms of ipsilateral lung dose with VMAT (p<0.000), the dose to the right lung, right breast and favoured 3DCRT (p<0.01). PTV95 % (Gy) by 3DCRT, IMRT, and VMAT in our study is 41.01, 41.96, and 41.76, respectively. Though the difference between the 3 techniques seems meagre, there was a statistically significant difference (p<0.012) favouring IMRT.*
Conclusion*: We conclude that using the VMAT technique in radiotherapy for left-sided breast cancer can significantly reduce radiation doses to the heart and LAD, potentially reducing cardiac risk. For all patients, the cardiac doses are considerably decreased for all dose levels without compromising the dose coverage to PTV, which is an advantage over IMRT and 3DCRT*
Keywords*: Volumetric Modulated Arc Therapy (VMAT), Three-Dimensional Conformal Radiation Therapy (DCRT), Intensity-modulated radiation therapy (IMR*T)

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1. Introduction

Breast cancer (BC) is the most frequently diagnosed cancer in women. This can be attributed to the increasing use of screening mammography and better awareness among women. Breast cancer is thought to be caused by a combination of our genes, lifestyle choices, and environment. There are many things or factors that can increase or decrease the risk of developing breast cancer. One of the biggest risk factors is increasing age. With increasing age, patients are also prone to hypertensive, hyperlipidemic, and diabetic conditions. Well, all of this constitutes metabolic X syndrome, which is, in turn, a risk factor for breast cancer. The increasing incidence of breast cancer can understand this in the developed world where obesity prevails, or it can be re-framed as morbid obesity. Any cancer per se is the interplay of genetic factors with or without family history along with environmental and socioeconomic factors.

The known risk factors of breast cancer are female gender, early menarche, late menopause, nulliparity, older age at first childbirth(>30yrs), Breast Cancer genes (BRCA1 and BRCA2) genetic mutations, personal history of prior breast diseases like Ductal Carcinoma In Situ (DCIS), Lobular Carcinoma In Situ(LCIS), Atypical Ductal hyperplasia.

Radiation therapy (RT) is essential and critical in managing breast cancer. In radiation Oncology practice, breast cancer typically constitutes approximately 25 % of the total patient caseload. The approach and treatment of breast cancer are multimodal, comprising surgery, chemotherapy (adjuvant, neoadjuvant, palliative) and radiotherapy.

None is superior to the other, and all work hand in hand synergistically. Radiotherapy is a modality for both adjuvant and palliative care. While adjuvant treatment aims to decrease local recurrence, palliative treatment controls symptoms in locally advanced cases, which may present with bleeding, skin ulceration and necrosis.

With recent developments in radiotherapy techniques, postoperative adjuvant therapy for breast cancer has evolved from merely pursuing improved local control and survival to reducing late complications and improving quality of life while maintaining the same local control. An important late complication afflict patients in adjuvant radiotherapy is cardiovascular injuries, requiring critical treatment decisions to balance the therapeutic effect and injury to normal tissues.

Radiation takes its toll on the heart's vascular supply by two most important pathway-synergistic effects on age-related coronary artery disease (CAD), resulting in increased frequency of infarctions or persistent progressive rarefaction of microvasculature leading to increased lethality of infarctions. Simultaneous use of anthracycline, trastuzumab-based chemotherapy, and even taxanes have an additive effect on this cardiac toxicity. Conspicuous evidence shows that for every Gray (Gy) increase in cardiac dose, mortality is increased by 3 % at 20 years. In the recent update of the European Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis, radiotherapy compared with no radiotherapy was associated with excess mortality (rate ratio 1.3) from heart disease though substantial heterogeneity exists among the trials included in this overview in terms of the target volume, fraction size, and radiotherapy techniques. Most patients in these trials received conventionally fractionated radiotherapy typically consisting of 25 fractions of 2 Gy administered over 5 consecutive weeks.

Hypo fractionation, or delivery of greater than standard 1.8–2 Gy fraction sizes per day, is a method of shortening overall treatment time in breast cancer. There are many potential benefits in delivering postoperative Whole Breast Irradiation (WBI) in a shorter period. The advantages include improved convenience for the patients due to the lower number of radiotherapy sessions, less acute skin toxicity as a result of lower total doses, and lower costs for the healthcare system, but reported a high rate of quite devastating late radiation morbidity including severe fibrosis, plexopathy, and rib fractures.

In addition, experimental data indicated that most tumours, including breast cancer, exhibit a low fractionation sensitivity (high alpha/beta value). In contrast, radiation-induced late normal

Tissue damage exhibits a high fractionation sensitivity (low alpha/beta value). Consequently, hypofractionated radiotherapy was thought to be harmful to patients and conventionally fractionated radiotherapy is considered the standard of care in most countries [1, 2].

However, retrospective data indicated that the use of hypofractionated radiotherapy in 13–16 fractions using 2.5–3.3 Gy per fraction to decreased total doses of 39–43 Gy is not associated with high radiation-induced acute and late toxicity and seemed to result in local recurrence rates as low as those achieved with conventionally fractionated radiotherapy in the adjuvant setting. These observations prompted research groups, first from Ontario and later from the United Kingdom, to compare hypofractionated adjuvant radiotherapy to adjuvant conventionally fractionated radiotherapy in preferentially early breast cancer [3].

Traditionally, breast radiotherapy used a fluoroscopic technique with two-dimensional planning. This was followed by 3-Dimensional Conformal RT (3D-CRT) with two conventional tangential radiotherapy fields. Intensity Modulated RT (IMRT) has been widely used for the past decade, permitting fluence variation across the radiotherapy fields and allowing optimal dose distribution according to an individual's anatomy. It has been suggested that IMRT results in improved dose homogeneity within the irradiated breast with added sparing of the heart and lung when compared with 3-D CRT. Breast IMRT ranges from photon-only IMRT to mixed electron and photon IMRT with 2 to 16 fields of various photon and electron beam energies. [4] Adjustments in RT treatment parameters can alter the amount of radiation delivered to cardiac structures. Therefore, we are conducting this study to determine the dosimetric evaluation of cardiac and left anterior descending artery dose in patients with left-sided breast cancer treated with hypofractionated adjuvant radiotherapy after conservative breast surgery by different techniques.

2. Materials and methods

Prospective observational/analytical study done at Radiation Oncology department, Omega hospitals, Hyderabad Enrolled cases of left-sided BCS referred for adjuvant RT by keeping a two-sided confidence interval of 95 %, with binominal distribution Margin of error – 0.1

Proportion – 0.058

The sample size has come to – 54 patients.

Study Period-August 2018 to August 2019 6.

Bioethics: 141-46121-171-213567 dated as - 12/6/2018.

Inclusion criteria: Patients who underwent left-sided BCS (breast conservative surgery), patients between 18 and 75 years performance status ECOG 0-2i histological confirmed DCIS, Invasive Breast Cancer-Stage 1, 2, 3, patients without any evidence of metastatic disease Irrespective of hormonal receptor and HER-2 neu status.

Exclusion Criteria- Presence of multicentric or multifocal disease. Patients with recurrences (IBTR)**,** pregnancy, margin positive disease, patients with prior history of thoracic irradiation (lymphoma), with H/O any dermatological disorders or allergic skin conditions.

Procedure

Strict institutional protocols were followed for breast cancer patients. A 2-clamp chest cast made of thermoplastic material was individually prepared for each patient in a supine position with hands over the head. The patient's position was reproduced on CT Simulator, three radio-opaque fiducial markers were placed on the mask, and the CT scan reference points were defined (GE Medical systems). A planning CT scan with minimum available slice thickness (1.25-2.5mm) with contrast was obtained. The volumetric image data was then transferred to the treatment planning system, i.e., Monaco Planning System and PTV and OARs were delineated in CMS MONACO Version 5.11 with Monte Carlo algorithm for IMRT, VMAT and collapsed cone algorithm

for 3DCRT. An Elekta linear accelerator with triple photon energy and a multi-leaf collimator in our institution was utilized for the study, and dose calculation was done.

CTV, PTV and required OARs were delineated on individual axial CT slices for all patients, namely the contralateral breast, right lung, left lung, spinal cord, heart, left ventricle and left anterior descending artery (Fig. 1).

DOSE PRESCRIPTION-4256cGy in 16 fractions at 266cGy per fraction (Table 1).

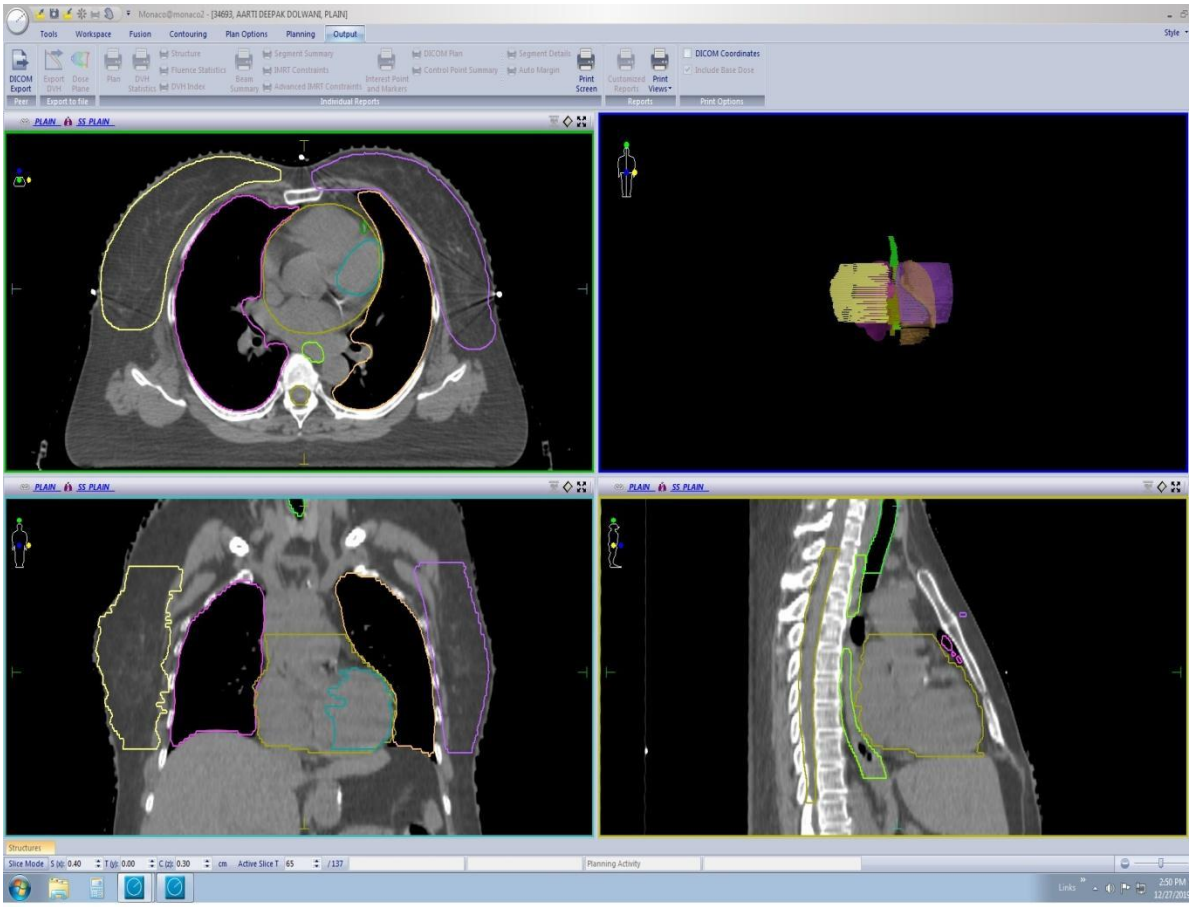

Fig. 1. Contouring of PTV and OARs

Table 1

Dose constraints to OARs (according to RTOG 1005) [5]

OAR	Ideal DVH Limits	Acceptable DVH Limits
Contralateral breast	Dmax≤240cGy	Dmax≤384cGy
	V1.44<5 %	V2.4≤5 %
Ipsilateral Lung	V16<15 %	V16<20 %
	V8≤35 %	V8≤40 %
	V4≤50 %	V4≤55 %
Contralateral Lung	V4≤10 %	V4≤15 %
Heart (Ca.Left Breast)	V16<5 %	V20<5 %
	V8<30 %	V8<35 %
	Mean<320cGy	Mean<400cGy

A dosimetric comparison of the plans was made based on the following outcome measures or parameters extracted from Dose-volume Histograms (DVH), i.e. HI (Homogeneity index), CI (Conformity index). In addition, mean dose (Dmean), Maximum dose (D max) and Minimum dose (D min) were calculated for both the heart and LAD after giving dose constraints for the 3 techniques.

V20 % for the LAD, Heart and Left Lung was estimated for the 3 techniques. It is defined as volume (in %) receiving 20Gy of dose. Similarly, V5 % and V3 % were calculated for the right lung and contralateral breast, respectively.

3DCRT-Conventional 3D CRT treatment planning is manually optimized.141 This means that the treatment planner chooses all beam parameters, such as the number of beams, beam directions, shapes, weights etc., and the computer calculates the resulting dose distribution.95 % of the prescribed dose should be received by 95 % of the tumour volume (Fig. 2).

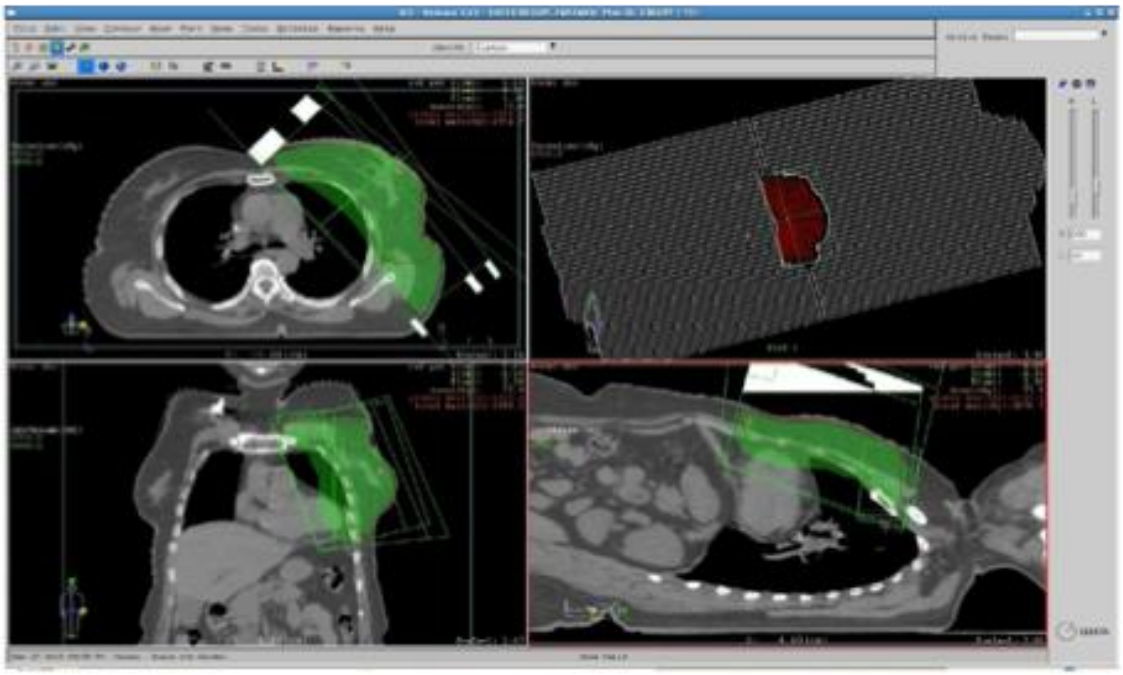

Fig. 2. Dose distribution of 3DCRT

Dose-volume histograms of the PTV and OAR of the 3D-CRT plans were generated using mean doses received by heart, LAD, LV and V20 % of LAD, heart, left lung .V5 % for Right lung and V3 % for contralateral breast.

The heterogeneity index (HI) and the conformity index (CI) are defined as follows: The Heterogeneity index (HI) is defined as the fraction of the PTV with a dose between 95 % and 107 % of the prescribed dose (V95 % -V107 %). HI = (D2-D98) ÷ Dpres x100 %, where D98 is the dose received by 98 % of the target volume on the c- DVH; D2 is the dose received by 2 % of the target volume on the c-DVH; Dpres is the prescribed dose. The HI should be less than 15 for an acceptable plan, and lower DHI values indicate a more homogeneous dose distribution. However, CI is defined as the fraction of the PTV surrounded by the reference dose (V95 %) multiplied by the fraction of the total body volume covered by the reference PTV dose [(PTV95 % ÷ PTV) × (PTV95 % ÷ V95 %)]. A higher CI value indicates higher dose conformity to the target.[6] CI and HI were measured for IMRT and VMAT.

In the case of IMRT, the dose distribution is inversely determined, i.e. treatment planner will decide before the dose distribution he wants, and the computer then calculates a group of beam intensities that will be produced, as nearly as possible, the desired dose distribution144.7 field IMRT and VMAT was used for planning (Fig. 3).

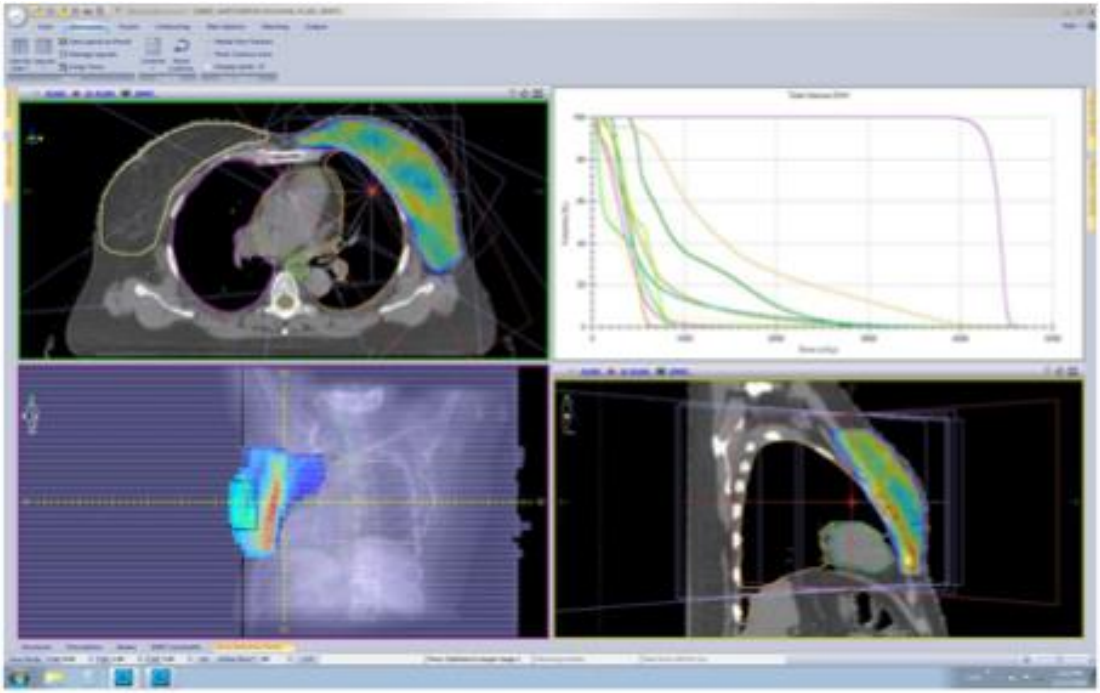

Fig. 3. Dose distribution of IMRT

The dose to the heart and left anterior descending artery by different techniques. Mean and maximum dose to the heart and left anterior descending artery with 3DCRT, IMRT, IMRT-VMA.

Statistical Analysis Plan

Qualitative factors like Stage, Age Distribution, and Volume of the left breast have been represented with frequencies and percentages. To Compare the quantitative parameters like LAD V20(%), LAD Mean (Gy), LAD Max (Gy), LV V5(%), LV Mean (Gy), etc., between 3 procedure groups, we have used ANOVA with Post-Hoc Tests. To compare Conformity Index(CI) and Heterogeneity Index(HI) between IMRT and VMAT, we have used an unpaired t-test.

All the data will be entered and maintained in MS. Excel and analyzed using SPSS19.0v. p value less than 0.05 will be considered significant.

3. Results

The study population consisted of 54 left-sided breast cancer patients who underwent breast-conservative surgery and received radiation as adjuvant therapy. All the cases were planned for the same dose of 42.56 Gy in 16 fractions to the left breast(PTV). The patient characteristics. The study population was 31-75 yrs, and stages ranged from stage 0 to IIIC. Though the tumour size in a few patients was smaller, they were upstaged to stage III based on the hormonal status according to the 8th edition of AJCC prognostic stage grouping.7.4 % patients (4) belonged to stage 0 , 31.5 % (17) to stage I , 38.9 % (21) to stage II and 22.2 % (12) to stage III (Table 2).

The primary objective of our study was to estimate the mean and maximum dose to the left anterior descending artery and heart in left-sided BCS cases while planning with 3DCRT, IMRT, and VMAT in an adjuvant setting (Table 3).

Our study's average mean and maximum LAD doses (Gy) for 3DCRT, IMRT, and VMAT are 16.6, 10.35, 7.54 and 41.27, 29.53, and 17.17, respectively. Our study's average mean and maximum heart doses (Gy) for 3DCRT, IMRT, and VMAT were 6.89, 6.59, 5.46 and 42.98, 38.81, and 36.2, respectively. Apart from the mean and maximum doses, a V20(%) parameter. All the 3 parameters for LAD showed the highest doses with 3DCRT and lowest with VMAT. Thus our study favoured VMAT ($p < 0.01$) as the planning technique to achieve the least doses of LAD (Table 4).

Table 2

Percentage distribution according to demographic distribution

Age (Yrs)	Frequency	Per cent
≤45	18	33.3
46-60	30	55.6
61 &	6	11.1
Above		
Total	54	100
Stage		
0	4	7.4
IA	4	7.4
IB	13	24.1
IIA	13	24.1
IIB	8	14.8
IIIA	9	16.7
IIIB	2	3.7
IIIC	1	1.9
Stage category		
0	4	7.4
I	17	31.5
II	21	38.9
III	12	22.2

Table 3

Percentage distribution according to the volume of breast

The volume of the left breast(cc)	Frequency	Per cent
Valid ≤500	2	3.7
500	32	59.3
1000		
1000&	20	37
Above		

Table 4

Average dose parameters in our study

Dose Parameter	Technique		
	3DCRT	IMRT	VMAT
LAD mean (Gy)	16.6	10.35	7.54
LAD Mmax(Gy)	41.25	29.53	17.7
LAD V20 %	37.56	14.52	6.73
Heart mean(Gy)	6.89	6.59	5.46
Heart max(Gy)	42.98	38.81	36.2
Heart V20 %	11.88	5.87	3.66
Left lung V20 %	23.67	226.2	21.7
Right lung V5 %	0	21.08	14.58
Contralateral breast V3 %	0.33	41.01	36.51
PTV 95 %	41.01	41.96	41.76
CI		0.88	0.86
HI		1.073	1.077

However, for the heart, there was no statistically significant difference between 3DCRT and IMRT (p=0.349) for the average mean dose (Gy). On the contrary, there was a statistically significant difference between 3DCRT Vs VMAT and IMRT Vs VMAT (95 % CI, p<0.01), again favouring VMAT as the choice of planning technique. Furthermore, the average heart max dose(Gy) and average heart V20(%) showed statistically significant benefits with VMAT (p<0.01).

LV mean LV V5 and doses amongst the 3 groups. There was a statistically significant benefit (p<0.000) with VMAT for both LV parameters. While there was a statistically significant benefit in terms of ipsilateral lung dose with VMAT(p<0.000), the dose to the right lung, right breast, and favoured 3DCRT(p<0.01)

PTV95 % (Gy) by 3DCRT, IMRT, and VMAT in our study is 41.01, 41.96, and 41.76, respectively. Though the difference between the 3 techniques seems meagre, there was a statistically significant difference (p<0.012) favouring IMRT. Yet the dose received by PTV is >95 % and <110 % (ICRU-83 recommendations) of the prescribed 42.56Gy in all the 3 techniques, which is also acceptable, meaning the PTV coverage was not compromised in any of the arms.

4. Discussion

Breast cancer radiotherapy inevitably involves radiation exposure to the normal tissues, which can result in adverse effects such as heart disease. Balancing dose constraints between the high dose region of cardiac substructures and mean heart dose is still the most direct and best strategy to reduce radiation-induced cardiac injury. In the landmark study by Sarah Darby et al. [7], the mean dose for the whole heart (Gy) was 5.4, Mean dose for the left anterior descending coronary artery (Gy) was 9.9. The Danish Breast Cancer Cooperative Group (111) recommends that the heart volume receiving more than 20 Gy be kept under 10 %.In this group, the mean doses to cardiac structures are 2.9±2.2 Gy for the heart and 17.8±14 Gy for the whole LAD. Mirjam E Mast et al. [8] compared 3D-Conformal (3D-CRT) to Intensity Modulated Radiotherapy (IMRT) treatment plans based on free-breathing (FB). The heart means (Gy), maximum(Gy), and V20(%) for 3D-CRT Vs IMRT were 3.3 Vs 2.7, 29.9 Vs 24.7, and 5 Vs 3.5, respectively. The LAD mean(Gy) maximum(Gy), V20(%) for 3D-CRT Vs IMRT in free- breathing were 18.6 Vs 14.9, 35.5 Vs 31.4, 42.5(±25.6) Vs 32.8(±27.1) respectively. Reshma Jagsi et al. [9] reported the comparative mean doses for free-breathing 3DCRT Vs IMRT with DIBH for LAD - 8.95 (±3.19) Vs 5.29 (±2.32) (p<0.001).

According to Maslyukova E et al. [10], the V25(volume of heart receiving 25Gy), mean dose to the heart(D mean) and mean dose to the LAD (D mean LAD) for free breathing patients were 9.49 %, 4.97 Gy and 19.5 Gy respectively. Badakhshi et al. [11] compared VMAT, IMRT and 3D-CRT in 12 breast cancer patients, both right and left-sided, planned for 50Gy. In left-sided cases, the mean dose to the entire heart was 12.41, 8.78 and 6.55Gy. No difference was seen for V20 between all techniques. Carolyn W. Taylor et al. [12] reviewed the mean heart doses in left-sided breast cancer, and it was 5.4 Gy (range, <0.1-28.6 Gy). Nicolini et al. [13] reported a mean dose to the heart of 6.0 and 7.4Gy with VMAT and IMRT, respectively.

Our study's average mean heart dose (Gy) for 3DCRT, IMRT, and VMAT was 6.88, 6.59, and 5.45, respectively. However, there was no statistically significant difference between 3DCRT and IMRT (95 % CI, p=0.349). There was a statistically significant difference between 3DCRT Vs VMAT and IMRT Vs VMAT (95 % CI, p<0.01). In our study, the average heart max dose(Gy) for 3DCRT, IMRT, and VMAT was 42.98, 38.81, and 36.20, respectively(95 % CI, p<0.000). The average heart V20(%) for 3DCRT, IMRT, and VMAT was 11.87, 5.86, 3.66, respectively (95 % CI, p<0.01)

The LAD mean(Gy) for 3DCRT, IMRT, and VMAT in our study was 16.59, 10.35 and 7.54, respectively (95 % CI, p<0.000). The average LAD max (Gy) for 3DCRT, IMRT, and VMAT was 41.26, 29.53 and 17.17respectively (95 % CI, p<0.01). However, the average LAD V20 (%) for 3DCRT, IMRT, and VMAT was 37.55, 14.51 and 6.73, respectively (95 % CI, p<0.000).

Veerle AB van den Bogaard et al. [14] stated that LV-V5 was significantly associated with the cumulative incidence of ACEs, with a hazard ratio of 1.016 (95 % CI, p=0.016).The LV- V5 for the no ACEs group was 16.85, and for the ACE group was 29.32. Reshma Jagsi et al. (261) compared IMRT-DIBH versus standard, free breathing in patients with left-sided breast cancer. The LV V5 averaged 15.8 % among patients on the 3D arm and 5.6 % among those on the IMRT-DIBH arm (p<0.001). Bradford S et al. [15] ensured that the mean dose to the LV is <15 Gy and that they have minimized the volume of coronary vessels receiving doses of 20 Gy and higher. The average LV V5 (%) in our study for 3DCRT, IMRT, and VMAT was 35.44, 30.72, and 22.70, respectively (95 % CI, p<0.000). The average LV mean(Gy) for 3DCRT, IMRT, and VMAT was 11.69, 6.86, and 5.28, respectively (95 % CI, p<0.01). Nicolini et al. [13] calculated a mean V20 of 9.7 % with Rapid Arc VMAT and 12.8 % with IMRT for the left lung, similar to those for the right lung. In the above study, the mean V20 for the ipsilateral lung was 29.1 % with Rapid Arc VMAT and 19.9 % with IMRT for the entire group and 25.9 % and 19.9 % for the left-sided disease subgroup. According to Mirjam E Mast et al. [8], the average lung mean (Gy) and V20(%) for the lung in FB for 3D-CRT Vs IMRT were 3.3 Vs 2.9 and 6.8(±2.8) VS 5.7(±2.6) respectively. Schubert et al(132) demonstrated significant reductions in lung V20 Gy (three-dimensional conformal radiotherapy [3D CRT] Vs IMRT: 14.8 % Vs 11.8 %, P<0.001), lung V5 Gy (3D CRT Vs IMRT: 28.1 % Vs 24.1 %, P<0.001), and lung Dmean (3D CRT Vs IMRT: 8.1 Vs 6.6 Gy, P<0.001).

Heping Xu et al. [16] reported that VMAT and FinF had similar HI and CI; V5 of the left lung was much higher in VMAT than that in Fin F; no significant difference was found between VMAT and Fin F in the left lung V20 and the heart V5; the right breast received much higher dose in VMAT. Plans showed that PTV coverage in VMAT and Fin F was statistically similar, with VMAT demonstrating better dose conformity to target volumes. However, VMAT produced lessV20 for the left lung in chest-wall patients. It is noted that a better PTV coverage in VMAT was achieved at the expense of

higher V5 for the lungs, hearts and right breast. The average Left lung V20 for IMRT Vs FinF plans was 20.1 % Vs 23.2 %. Right lung V5 was 24.6 % for IMRT and 0.0 % for FinF and Right breast V5 for IMRT 44.0 % Vs FinF 0.0 %.

In our study, the average left lung V20 (%) for 3DCRT, IMRT, and VMAT was 23.67, 26.20, and 21.72, respectively (95 % CI, p<0.01). The average right lung V5 (%) for 3DCRT, IMRT, and VMAT was 0.000, 21.08, and 14.57, respectively (95 % CI, p<0.000).The contralateral breast V3 (%) for 3DCRT, IMRT, VMAT was 0.32, 41.01, 36.50 respectively (95 % CI, p<0.01).

In our study, the average CI for IMRT and VMAT was 0.8807, 0.8678 respectively (95 % CI, p=0.092), the HI being 1.073 Vs 1.077 for IMRT and VMAT respectively(p=0.173)The average PTV 95 %(Gy) for 3DCRT, IMRT, VMAT was 41.01, 41.96, 41.76 respectively (95 % CI, p<0.01) (Table 5).

Table 5

Dosimetry from literature

Author	Parameter	TECHNIQUE		
		3DCRT	IMRT	VMAT
Badakshi et al. [11]	Mean heart dose(Gy)	12.41	8.78	6.55
	Left lung V20Gy (%)	25.06	19.81	21.9
	HI		0.13	0.16
Heping Xu et al. [16]	Left lung V20Gy (%)	23.2	20.1	–
	Right lung V5Gy (%)	0	24.6	–
	Right breast V5 %	0	44	–
Mirjam E Mast et al [8]	Heart mean(Gy)	3.3	2.7	–
	Heart max(Gy)	29.9	24.7	–
	Heart V20Gy (%)	5	3.5	–
	Lung V20 %	6.8	5.7	–
Veerle A B et al [14]	LV V5Gy(%)	15.8	5.6	–
Jagsi et al [9]	Mean LAD (Gy)	8.95	5.29	–
Nicolini et al. [13]	Left lung V20Gy(%)	–	12.8	9.7

Limitations of the study.

1) Although the same radiation oncologist did all the contouring, we can understand that there will be certain intra-observer bias in the contouring of the PTV and OARs. This will give rise to potential uncertainties, the impact of which can be estimated accurately.

2) We at our institute do not have respiratory gating or breath hold techniques associated with a further decrease in heart doses[146]. Therefore, assessment of the influence of motion artefacts and the need for a definition of a safety margin around the LAD is necessary. Moreover, no firm human data allows us to answer the question of which doses are most damaging to the coronary arteries, i.e. the "a lot to a little or a little to a lot" question.

3) Irrespective of the breast volume(large or small), we at our institute position patients in the supine position through data for prone positioning is also encouraging.

4) We at our institute practice 7-field IMRT, but the same was not found in the comparative literature.

5) In our study, we did not account for the electron boost to the tumour bed.

6) All the patients were of early-stage BC, so the IMN was not treated. The treatment to which further increases the dose to the heart.

7) Although radiation pneumonitis as a complication of breast/chest-wall cancer treatment only affects 1 % of patients. The main concern when using VMAT is the spreading of low dose radiation to normal tissues and hence integral dose.

8) Except for acute and late radiation damage induced by high-dose radiation, low-dose irradiation raises the concern of radiation-induced secondary malignancy.

9) Every effort was taken to avoid bias towards a plan, but it cannot be ignored in a comparative study like this.

10) Longer follow-up is needed to assess the benefit of these techniques in reducing chronic toxicity rates and secondary malignancies.

Prospects for further research. It will be important for future research to identify patient and treatment characteristics associated with substantially increased risk for cardiac morbidity and mortality so that choices may be considered in such situations.

6. Conclusion

Patients treated with left-sided radiation as a component of breast conservation have an increased risk of late, radiation-associated coronary damage. Treatment with modern radiation techniques may reduce the risk of cardiac injury. We report that using the VMAT technique in radiotherapy for left-sided breast cancer can significantly reduce radiation doses to the heart and LAD, potentially reducing cardiac risk. For all patients, the cardiac doses are considerably decreased for all dose levels without compromising the dose coverage to PTV, which is an advantage over IMRT and 3DCRT.

The present study found a lower mean heart dose of 5.46Gy and a lower mean LAD dose of 7.54Gy.In addition to dose reduction to the whole heart, individualized dose distributions can be created, which spare the left ventricle and left anterior descending coronary artery.

Hypertension alone is associated with a three-fold increased risk for developing coronary artery disease, representing a much greater risk factor than radiation exposure. Women treated for left-sided breast cancer

should be monitored long-term for hypertension and other risk factors and treated appropriately. However, for most women who receive Breast Cancer Radio Therapy, the benefits in terms of reduction in Breast Cancer outcomes far out way the risk. Therefore, the risk-benefit analysis may not be favourable for all women. Some women may achieve a small absolute gain from Radio Therapy, for example, women receiving Radiotherapy for Carcinoma in situ. Thus, even a small cardiac risk from radiotherapy may outweigh the benefit for such women.

As RT techniques evolve, the focus on survival, control, recurrence, and tissue toxicities remains. Treatment options must consider the patient's schedule, QOL, and the financial impact of different techniques. It will be important for future research to identify patient and treatment characteristics associated with substantially increased risk for cardiac morbidity and mortality so that choices may be considered in such situations.

Conflict of interest

The authors declare that they have no conflict of interest concerning this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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References

1. Fitzmaurice, C., Allen, C., Barber, R. M., Barregard, L., Bhutta, Z. A., Brenner, H. et. al. (2017). Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life- years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JA JAMA Oncology, 3 (4), 524–548. doi: https://doi.org/10.1001/jamaoncol.2016.5688

2. Torre, L. A., Siegel, R. L., Ward, E. M., Jemal, A. (2016). Global Cancer Incidence and Mortality Rates and Trends – An Update. Cancer Epidemiology, Biomarkers & Prevention, 25 (1), 16–27. doi: https://doi.org/10.1158/1055-9965.epi-15-0578

3. Torre, L. A., Islami, F., Siegel, R. L., Ward, E. M., Jemal, A. (2017). Global Cancer in Women: Burden and Trends. Cancer Epidemiology, Biomarkers & Prevention, 26 (4), 444–457. doi: https://doi.org/10.1158/1055-9965.epi-16-0858

4. Malvia, S., Bagadi, S. A., Dubey, U. S., Saxena, S. (2017). Epidemiology of breast cancer in Indian women. Asia-Pacific Journal of Clinical Oncology, 13 (4), 289–295. doi: https://doi.org/10.1111/ajco.12661

5. Prosnitz, R. G., Hubbs, J. L., Evans, E. S., Zhou, S.-M., Yu, X., Blazing, M. A. et. al. (2007). Prospective assessment of radiotherapy-associated cardiac toxicity in breast cancer patients: Analysis of data 3 to 6 years after treatment. Cancer, 110 (8), 1840–1850. doi: https://doi.org/10.1002/cncr.22965

6. Langer, M., Brown, R., Urie, M., Leong, J., Stracher, M., Shapiro, J. (1990). Large scale optimization of beam weights under dose-volume restrictions. International Journal of Radiation Oncology*Biology*Physics, 18 (4), 887–893. doi: https://doi.org/10.1016/0360-3016(90)90413-e

7. Darby, S. C., Ewertz, M., McGale, P., Bennet, A. M., Blom-Goldman, U., Brønnum, D. et. al. (2013). Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer. New England Journal of Medicine, 368 (11), 987–998. doi: https://doi.org/10.1056/nejmoa1209825

8. Mast, M. E., van Kempen-Harteveld, L., Heijenbrok, M. W., Kalidien, Y., Rozema, H., Jansen, W. P. A. et. al. (2013). Left-sided breast cancer radiotherapy with and without breath-hold: Does IMRT reduce the cardiac dose even further? Radiotherapy and Oncology, 108 (2), 248–253. doi: https://doi.org/10.1016/j.radonc.2013.07.017

9. Jagsi, R., Griffith, K. A., Moran, J. M., Ficaro, E., Marsh, R., Dess, R. T. (2018). A Randomized Comparison of Radiation Therapy Techniques in the Management of Node-Positive Breast Cancer: Primary Outcomes Analysis. International Journal of Radiation Oncology*Biology*Physics, 101 (5), 1149–1158. doi: https://doi.org/10.1016/j.ijrobp.2018.04.075

10. Maslyukova, E., Korytova, L., Bondarenko, A., Zhabina, R., Korytov, O., Odintsova, S. (2017). The radiation doses to the heart and the left anterior descending coronary artery for various modes of radiation treatment of the breast cancer patients. Journal of Clinical Oncology, 35 (15_suppl), e12092–e12092. doi: https://doi.org/10.1200/jco.2017.35.15_suppl.e12092

11. Badakhshi, H., Kaul, D., Nadobny, J., Wille, B., Sehouli, J., Budach, V. (2013). Image-guided volumetric modulated arc therapy for breast cancer: a feasibility study and plan comparison with three-dimensional conformal and intensity-modulated radiotherapy. The British Journal of Radiology, 86 (1032), 20130515. doi: http://doi.org/10.1259/bjr.20130515

12. Taylor, C. W., Wang, Z., Macaulay, E., Jagsi, R., Duane, F., Darby, S. C. (2015). Exposure of the Heart in Breast Cancer Radiation Therapy: A Systematic Review of Heart Doses Published During 2003 to 2013. International Journal of Radiation Oncology*Biology*Physics, 93 (4), 845–853. doi: https://doi.org/10.1016/j.ijrobp.2015.07.2292

13. Nicolini, G., Clivio, A., Fogliata, A., Vanetti, E., Cozzi, L. (2009). Simultaneous integrated boost radiotherapy for bilateral breast: a treatment planning and dosimetric comparison for volumetric modulated arc and fixed field intensity modulated therapy. Radiation Oncology, 4 (1). doi: https://doi.org/10.1186/1748-717x-4-27

14. van den Bogaard, V. A. B., Ta, B. D. P., van der Schaaf, A., Bouma, A. B., Middag, A. M. H., Bantema-Joppe, E. J. et. al. (2017). Validation and Modification of a Prediction Model for Acute Cardiac Events in Patients With Breast Cancer Treated With Radiotherapy Based on Three-Dimensional Dose Distributions to Cardiac Substructures. Journal of Clinical Oncology, 35 (11), 1171–1178. doi: https://doi.org/10.1200/jco.2016.69.8480

15. Hoppe, B. S., Bates, J. E., Mendenhall, N. P., Morris, C. G., Louis, D., Ho, M. W. et. al. (2020). The Meaningless Meaning of Mean Heart Dose in Mediastinal Lymphoma in the Modern Radiation Therapy Era. Practical Radiation Oncology, 10 (3), e147–e154. doi: https://doi.org/10.1016/j.prro.2019.09.015

16. Xu, H., Hatcher, G. (2016). Treatment planning study of Volumetric Modulated Arc Therapy and three dimensional field-in-field techniques for left chest-wall cancers with regional lymph nodes. Reports of Practical Oncology & Radiotherapy, 21 (6), 517–524. doi: https://doi.org/10.1016/j.rpor.2016.07.005

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Nindra Armugam, Associate Professor, Department of Radiotherapy, SV Medical College, Tirupati, Andhra Pradesh, India, 517507

Zoha Mohd Saleem, DNB (RT), Consultant Radiation Oncologist, Omega Hospital, Rain bazar, Hyderabad, India, 500023

Chandipriya Veluru, DNB (RT), Assistant Professor, Department of Radiotherapy, SV Medical College, Tirupati, Andhra Pradesh, India, 517507

Erukula Ramanjaneyulu, Assistant Professor, Department of Hospital Administration, SV Medical College, Tirupati, Andhra Pradesh, India, 517507

***Corresponding author:** Zoha Mohd Saleem, e-mail:* dr.zohamohdsaleem@gmail.com