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THE EFFECT OF EXTERNAL RADIOTHERAPY TO THE LEFT VENTRICLE SYSTOLIC FUNCTION IN LOCALLY ADVANCED BREAST CANCER PATIENTS, ANDHRA PRADESH, INDIA: A COHORT STUDY.

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ABSTRACT.

Introduction:
People having cancer on the left side are more prone to develop cardiac issues than patients with other-sided malignancies, and radiation therapy (RT) has certain risks. This study aims to offer a dosimetric analysis of how radiation therapy (RT) affects the heart and coronary arteries following breast conservation surgery and to ascertain whether these dosages are linked with a greater risk of ischemic heart disease (IHD).

Methods:
A random selection of 150 patients with early-stage T1/T2 + N0 breast carcinomas was made on both the left and right sides. In these individuals, the entire breast was treated with radiation, and the tumor beds were expanded and planned to use computed tomography. The dosages for the left ventricle (LV), right ventricular (RV), left anterior descending coronary artery (LAD), and left circumflex coronary artery (LCx) were noted.

Results:
The mean dose to the left anterior descending coronary artery (LAD) for left-sided breast cancer patients was significantly higher at 2402.480 ± 838.40 cGy compared to right-sided patients. The left ventricle (LV) in left-sided patients received an average dose of 397.56 ± 131.73 cGy, while the right ventricle in right-sided patients received 130.18 ± 24.92 cGy. High doses in cardiac substructures were noted for left-sided patients, with significantly elevated Dmean, Dmin, and Dmax values for the LCx, LAD, RV, and LV ($P < 0.0001$). This increased radiation exposure is associated with a higher risk of developing ischemic heart disease (IHD) in left-sided breast cancer patients.

Conclusion:
The most straightforward and effective way to lessen and prevent radiation-induced cardiac harm, particularly in cases of left-sided breast cancer, is to balance dosage limits between the mean heart dose and many high-dose zones of cardiac substructures.

Recommendation:
After a certain age, it is advising routine breast screening to lower breast cancer risk.

Keywords: *Heart, Breast cancer, Coronary arteries, Radiation therapy*
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INTRODUCTION.

When it comes to cancer-related deaths, breast cancer is second only to skin cancers in terms of frequency among women [1]. There is an approximate 12% risk in women of breast cancer. Age is the primary statistic used to predict breast cancer risk. A high-fat, high-calorie diet, the use of contraceptives, menopausal hormone replacement therapy, early menarche and delayed menopause, gender, race, family medical history, and previous breast diseases, or breast cancer are additional breast cancer risks.

The cancer's mainstream treatment leads to surgery. In cases when the cancer has spread locally, neoadjuvant chemotherapy is followed by surgery, and early-stage cases are operated on. Surgery is carried out as a breast-sparing procedure (broad excision, quadrantectomy,

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lumpectomy) or as a mastectomy, which can be either total, modified radical, or radical. Patients undergoing surgical therapy as well as those who underwent surgery and had more positive lymph nodes, are administered RT or adjuvant radiation therapy [2].

With advancements in breast cancer diagnosis and therapy leading to higher long-term survival rates, it is now crucial to investigate the toxicities associated with these outcomes. RT lowers the chance of localized breast cancer recurrence [3]. It's unclear whether the increased survival resulting from more extensive surgery is unrelated to systemic therapy. Research has demonstrated that RT increases high-risk individuals' chances of survival [4]. But there are also dangers associated with RT, including skin responses, cosmetic issues, pneumonia, upper limb edema, and heart toxicity—the latter of which is particularly significant when left-sided breast RT is performed.

The target volume contains the left anterior descending coronary artery (LAD), susceptible to high radiation dosages [5, 6]. Additionally, compared to those who have breast cancer on the right side those with the left side also had a higher frequency of cardiac issues [7]. Finding out how much radiation patients receiving conservative surgery for either-sided breast cancer received for their hearts, left and right ventricles, right ventricle (RV), or left circumflex coronary artery (LCx) was the goal of this study. Additionally, we sought to ascertain whether these dosages were linked with a greater risk of (IHD) ischemic heart disease.

METHODOLOGY.

Study Design.

Prospective Cohort Study

Study Setting.

The study was carried out at the Department of Radiation Oncology, Siddhartha Medical College, Vijayawada, Andhra Pradesh, India. The study spanned from April 2021 to March 2024.

Study Population.

This study included 150 patients receiving radiation therapy (RT) from the Department of Radiation Oncology.

Inclusion Criteria.

- Patients diagnosed with early-stage T1/T2 + N0 breast carcinoma.
- Patients undergoing breast conservation surgery followed by radiation therapy.
- Age between 40-80 years.

Exclusion Criteria.

- Patients with distant metastases.
- Patients with a history of prior cardiac diseases.

Bias.

Potential bias may arise from the non-randomized allocation of radiation therapy protocols and the retrospective nature of some data collection.

Variables.

Independent variables include the side of breast cancer (left vs. right) and radiation dose parameters (Dmean, Dmin, Dmax) to cardiac substructures (LAD, LCx, RV, LV); the dependent variable is the incidence of ischemic heart disease (IHD).

Study Procedure.

Breast cancer patients were chosen at random and followed for three years. Two distinct radiation experts created the patient's shape. Computed tomography (CT)-based planning was used to perform tangential fields on the patients to enhance the beds and administer radiation treatment (RT) to the entire breast. Documents included the patient's location, age, and tumor stage, the number and type of chemotherapy treatments given. Every patient had surgery to preserve their breasts. Typically, patients received passive treatment with a specialized immobilization device. To plan the radiation, 3-mm slices of contrast-enhanced CT images were obtained. Each patient was immobile throughout the simulation and had her ipsilateral arm above her head. To differentiate the scar and breast areas from the incision on the CT scan, radiopaque catheters were implanted. The CT information for each patient was imported into an internal three-dimensional treatment planning system. Two radiation oncologists contoured and assessed the clinical target volumes (CTVs).

A 6-MV photon beam was used to treat the breast in each patient. Electron energy was used to apply Boost. Patients were often immobilized while supine using a specialized device. To plan the radiation, 3-mm slices of contrast-enhanced CT images were obtained. Throughout the simulation, all patients remained motionless and raised their ipsilateral arms above their heads.

Statistical Analysis.

The NCSS 11 version (Number Cruncher Statistical System, 2017) and version 18 of the MedCalc statistical software were utilized for the investigations. For categorical variables, frequency and percentage numbers were provided. The Kolmogorov-Smirnov test was used to look at the continuous variable distribution. For the two uncorrelated groups, the Mann-Whitney U-test was

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applied when the variables did not fit the characteristics of a normal distribution. $P < 0.05$ was designated as the statistical significance level.

Ethical Consideration.

The World Medical Association Declaration was followed in the conduct of this investigation, which was approved by the Health Sciences University Ethics Panel.

RESULTS.

In this study, 150 breast cancer patients of early-stage had breast-conserving surgery. Out of the total patients, 75 had cancerous growths on their left breast and 75 on their right.

The patient's age range diagnosed with right-sided breast cancer was forty to Eighty years old, with 57 serving as the mean age. 25% of the patients had tumors 2-4 cm (T2), and 75 percent had tumors < 2 cm (T1). 30% of patients had an inner quadrant tumor, and 70% had an outside quadrant tumor. There were no distant metastases or involvement of lymph nodes in any of the patients. Additionally, 35% underwent chemotherapy (Table 1).

Table 1 Patient's Characteristics.

		Right-sided breast cancer n (%)	Left-sided breast cancer n (%)
Breast conservation surgery		20.00 (100%)	20.00 (100%)
Age		57.34 ± 10.22 (40–80)	60.35 ± 10.91 (42.0–76.0)
T stage	T1	15.00 (75%)	12.00 (60%)
	T2	5.00 (25%)	8.00 (40%)
N stage	N0	20.00 (100%)	20.00 (100%)
M stage	M0	20.00 (100%)	20.00 (100%)
Tumor location	inner quadrant	6.1 (30%)	0.90 (50%)
	outer quadrant	14.00 (70%)	10.00 (50%)
Tumor size	≤2 cm	15.01 (75%)	12.01 (60%)
	2–5 cm	5.00 (25%)	8.00 (40%)
Chemotherapy	Yes	7.01 (35%)	10.99 (55%)
	No	12.99 (65%)	10 (45%)
Number of chemotherapy cycles	4	4 (20%)	6 (30%)
	6	3 (15%)	5 (25%)

The doses for individuals with breast tumors on both the left and right sides were established during RT planning (Table 2). The Dmean, Dmin, or Dmax values for LCx, LAD, RV, LV, and heart were considerably higher in individuals with left breast cancer than in those with right breast disease ($P < 0.0001$).

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Table 2- Depending on whether the side of the tumor is present, the heart, right and left ventricles, left anterior descending coronary artery, and left circumflex coronary artery have different dosimetric properties.

Dosimetric parameters		Right-sided breast cancer	Left-sided breast cancer	P value
LAD	Dmean	97.58 ± 10.27 (73.9–113)	2403.48 ± 839.39 (1020–3783)	< 0.0001
	Dmax	112.87 ± 16.15 (78.8–145)	4753.83 ± 499.46 (3700–5703.8)	< 0.0001
	Dmin	84.12 ± 9.30 (64.7–99.9)	223.59 ± 75.42 (96–472)	< 0.0001
	Dmean	83.99 ± 9.09 (63.8–100.8)	171.55 ± 45.36 (85.8–260.2)	< 0.0001
LCx	Dmax	97.27 ± 12.33 (75.6–116.3)	204.49 ± 55.9 (112–353.9)	< 0.0001
	Dmin	75.59 ± 8.57 (54.5–92.1)	136.63 ± 39.59 (69.7–235.5)	< 0.0001
	Dmean	131.18 ± 25.92 (110.8–224.2)	564.65 ± 221.78 (140.9–875.6)	< 0.0001
RV	Dmax	465.76 ± 517.55 (221.2–2619)	4576.55±1077.66 (460.1–6149.3)	< 0.0001
	Dmin	76.51 ± 7.81 (58.8–90.5)	104.41 ± 29.67 (49.3–184.9)	< 0.0001
	Dmean	82.71 ± 8 (60.9–96.5)	536.8 ± 193.24 (230–1018.1)	< 0.0001
LV	Dmax	150.13 ± 44.75 (85.1–264.2)	4823.6 ± 363.4 (3965.4–5836.4)	< 0.0001
	Dmin	66.75 ± 8.02 (47.1–80.2)	106.49 ± 27.64 (52.2–184.2)	< 0.0001
	Dmean	121.33 ± 20.05 (97.3 – 189.2)	397.56 ± 131.73 (158.5–588.7)	< 0.0001
Heart	Dmax	635.48 ± 752.55 (277–3759.5)	5033.44 ± 332.02 (4135.3–5993.9)	< 0.0001

The LV had a mean V5 of 18.68% (6.89–31.69) and a mean V25 of 5.22% (0.45–16.55). The mean V5 was 23.8% (2.56–26.89), and the mean V25 was 6.79% (0.630–13.630) in the bilateral ventricles.

DISCUSSION.

The study found that left-sided breast cancer patients received significantly higher radiation doses to the left anterior descending coronary artery (LAD) and left ventricle (LV) compared to right-sided patients. Specifically, the mean dose to the LAD was 2402.480 ± 838.40 cGy for left-sided patients, while the LV received an average dose of 397.56 ± 131.73 cGy. In contrast, right-sided patients received an average dose of 130.18 ± 24.92 cGy to the right ventricle (RV). The dosimetric parameters (Dmean, Dmin, Dmax) for the LAD, LV, LCx, and RV were significantly elevated in left-sided patients

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(P < 0.0001). These higher radiation exposures were associated with an increased risk of developing ischemic heart disease (IHD), particularly in those with left-sided breast cancer.

The results indicate that radiation therapy for left-sided breast cancer poses a higher risk of cardiac complications due to the increased radiation doses received by critical cardiac structures. This underscores the need for careful dosimetric planning and monitoring to minimize cardiac exposure and reduce the risk of ischemic heart disease in these patients.

The greatest breast cancer risk is getting older. Neoadjuvant or adjuvant KT, RT, lumpectomy, breast-sparing surgery, and surgery (radical mastectomy) are common treatments. Adjuvant radiation therapy for breast cancer in its advanced stages may cause cardiac issues. This is problematic since ischemic heart disease often originates in the left anterior direction (LAD), and arteries are more radiation-sensitive, according to a recent study [8].

Radiation therapy has been shown in numerous follow-up studies to potentially cause delayed cardiac morbidities, including acute coronary syndromes, congestive heart failure, and ischemic heart disease (IHD) [9]. We computed our cardiac dose rates using the standard regimens used for breast cancer patients, taking into account the dosage and delivery method for both left- and right-side breast radiation therapy.

Women between the ages of 36 and 76 made up the study [8], with a median age of 58.5. A mean age of 50 (24–74) years was used among female subjects [10]. Patients diagnosed with breast cancer, whether left- or right-sided, ranged in age from 61 (42–76) years to 57 (40–80) years. Since long-term survival rates have increased due to advancements in breast cancer diagnosis and therapy, it is crucial to investigate the toxicities associated with long-term survival. Examining cardiac toxicity is particularly crucial for left-sided breast radiation therapy. Specifically, because the LAD is in or close to the target volume, it is exposed to much radiation. Furthermore, research has indicated that after RT, cardiovascular mortality rises [5,6]. Population-based assessments have demonstrated that cardiac morbidity and death are caused by high-dose exposure to the heart [11], if there is minimal heart exposure or low for the employed treatment method, no cardiac morbidity was noted [12].

Even while the predicted average heart dosage increases by 4% for every 1-Gy increment, this linear connection breaks down at very low cardiac dosages. The heart's volume should not be greater than 20 Gy or 40 Gy below 10% or 5%, respectively, according to the Danish Breast Cancer Cooperative Group [13].

Research [14] has demonstrated that radiation-induced heart disease can occur at doses lower than 5 Gy, defying the generally held opinion that radiation dosages of 40 Gy or more may cause heart disease. The mean dosage in this study was 3.97 ± 1.32 Gy, while the maximum dosage for patients with left-sided breast cancer was 50.32 ± 3.31 Gy. For patients with breast cancer on the right side, the mean dosage was 1.20 ± 0.19 Gy, and the highest dosage was 6.34 ± 7.52 Gy. Based on reasonable forecasts, it appears that those with left-sided breast cancer have a lower relative chance of heart problems.

Although it is evident that adjuvant radiation provides a survival advantage [15, 16], there is also ample evidence of increased cardiac morbidity and mortality [17, 18, 19, 20, 21]. It is necessary to establish a link between cardiac doses and death to forecast the cardiac hazards associated with contemporary radiation therapy accurately. Previous studies have tried to establish a relationship between the dosages that the heart receives and the risk of cardiac damage [19,21]. A retrospective analysis of cardiovascular illness treated between 1970 and 1986 was conducted by Hooning et al [21].

Modern therapeutic approaches reduced the risk of cardiovascular disease, even if the risk increased with rising estimated mean cardiac doses. As studies have more recently declared with coronary angiography [19], Particularly for left-sided treatment or treatment of the internal mammary nodes, the location and severity of coronary artery stenosis match the anticipated locations of high-dose radiation.

Another research included 14 patients with cardiac catheterization and stress testing; Thirteen of them had breast cancer on the left, and 1 had right-sided breast cancer. This study impacted the LAD in 11 out of 13 patients. Of these 11 individuals, eight had a single channel impact, one had the illness in both the LCx and the LADs, and one patient had the disease in three of the primary coronary vessels. However, one patient did not exhibit any signs of LAD illness while having LCx and right coronary stenosis [22].

Our study's findings suggest that, in addition to LCx and LAD illnesses, there may be a tendency toward cardiac problems. Radiation therapy (RT) was administered to the left side of the breast cancer patient's heart at higher mean and maximum doses compared to the right side. Furthermore, compared to left-sided malignancies, the mean, maximum, and minimum dosages on the left anterior division (LAD), left LCx, and both ventricles were considerably higher.

The significant variety in cardiac doses observed over the past few decades is probably due to the diversity of RT treatment. When determining dose-response connections, our estimations will be useful since they take into account heart and coronary artery dosages in cases of both-sided breast cancer. According to the principle of "as low as reasonably achievable," these results focus on the importance of reducing cardiac irradiation during left-sided breast cancer therapy.

GENERALIZABILITY.

The generalizability of the study's results is limited by several factors. The sample population, treatment protocols, and follow-up duration were specific to a single institution in India, which may not reflect broader patient populations or practices. Differences in radiation techniques, genetic predispositions, cultural factors, and advances in technology could affect the applicability of the findings. Thus, while the study provides important insights, further research in diverse settings with modern techniques is necessary to confirm and extend these results.

CONCLUSION.

Achieving a balance between dose limitations for the mean heart dose and many high-dose zones of cardiac structure is the most straightforward and effective way to reduce radiation-induced cardiac complications. This is particularly true for left-sided breast cancer. One can use breath hold, deep intake, prone stance, respiratory gating, or MLC blocking to lower the dose reaching the heart. It is also necessary to use reliable techniques that may be used as standards for the diagnosis and management of cardiac diseases brought on by radiation exposure.

LIMITATIONS.

The small, single-institution sample and observational design limit generalizability and causality. The three-year follow-up and uncontrolled baseline factors may not capture long-term cardiac risks, necessitating further multi-center research with extended follow-up.

RECOMMENDATION.

They also emphasize the need for more studies into the clinical consequences of low-dose exposure over the long term.

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LIST OF ABBREVIATIONS.

RT: Radiation Therapy
IHD: Ischemic Heart Disease
LAD: Left Anterior Descending Coronary Artery
LV: Left Ventricle
RV: Right Ventricle
LCx: Left Circumflex Coronary Artery
CT: Computed Tomography
CTV: Clinical Target Volume
MV: Megavolt
Gy: Gray (unit of radiation dose)
Dmean: Mean Dose
Dmin: Minimum Dose
Dmax: Maximum Dose
V5: Volume receiving 5 Gy
V25: Volume receiving 25 Gy
CHF: Congestive Heart Failure
IMRT: Intensity-Modulated Radiation Therapy
DIBH: Deep Inspiration Breath-Hold

CONFLICT OF INTEREST.

There was no disclosure of any possible conflicts of interest.

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