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RESEARCH ARTICLE

Optimizing Cardiac Safety: Dosimetric Analysis of Advanced Radiation Techniques in Left Breast Cancer Therapy

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Abstract

Purpose: This study aims to assess the incidental dose distribution to critical structures such as the heart, left anterior descending artery (LAD), and lungs using various external beam radiation techniques specifically, 3DCRT, IMRT, and VMAT plans. **Methods:** Following approval from the Institutional Scientific Review Board (ISRB) and ethics committee, a meticulous statistical analysis was conducted based on a prospective enrolment of 60 patients. Written consent was obtained from all participants. The process involved CT simulation and precise contouring, generating three radiation plans for each individual. **Results:** The study showed PTV 95 coverage was better achieved in VMAT (PTV95=99%). When coverage of VMAT was compared with 3D-CRT, P Value was statistically significant (P=0.007). The mean Dose to LAD was 15.29Gy with VMAT. The p-value obtained by comparing VMAT vs 3D-CRT was statistically significant (P=0.001). The volume of left Lung receiving 5%, 10%, and 20% of the dose is better achieved with 3D-CRT. **Interpretation and Conclusion:** This comparative dosimetric analysis of 3DCRT, IMRT, and VMAT in adjuvant radiotherapy for carcinoma of the left breast highlights the distinct advantages of VMAT in terms of superior PTV coverage and dose conformity. Notably, VMAT achieved a significantly lower mean dose to the LAD compared to 3DCRT, which is clinically relevant given the established correlation between radiation dose to the LAD and long-term cardiac morbidity. The reduction in LAD dose with VMAT strongly co-relates to a lower risk of radiation-induced ischemic heart disease and other late cardiac complications, reinforcing its role as an optimized treatment approach. While careful consideration of low-dose exposure to surrounding lung tissue remains essential, the overall benefits of VMAT in enhancing target coverage while minimizing cardiac risks make it a highly favorable technique in modern breast radiotherapy especially in left sided breast cancer treatment with preexisting heart diseases.

Keywords: Left breast- radiotherapy- VMAT- IMRT- 3DCRT- LAD dose

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Introduction

The historical perspective on heart irradiation considered it a "parallel subunit," allowing for tolerance to small volumes receiving high radiation doses. However, this paradigm overlooked the inherent vulnerability of coronary arteries, designated as a "serial subunit." Radiation damage to any segment of the coronary artery can result in stenosis, challenging the prior assumption of acceptable high doses in limited heart regions [1].

Cardiotoxicity stands out as a severe consequence of cancer therapy, encompassing both radiotherapy and chemotherapy. Despite achieving local and systemic control, the compromised quality of life can lead to heightened morbidity and mortality due to cardiac complications. Recognizing the heart's radio sensitivity in the early 1970s has elevated its status as one of the foremost dose-limiting organs in contemporary radiotherapy. Notably, women with breast cancer undergoing Adjuvant Radiotherapy post Breast Conservation surgery or Mastectomy experience a reduced risk of Local Recurrence and potentially enhanced Overall Survival. However, this benefit comes with an augmented risk of mortality

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attributed to Radiation-induced Ischemic Heart Disease [2].

The evolution of radiation therapy techniques, spanning from the 1960s to modern approaches such as 3D-CRT, incorporates advanced strategies like respiratory gating and deep inspiratory breath hold, particularly beneficial for left-sided breast cancer patients. Despite these advancements, the efficacy of these techniques in mitigating Cardiac Mortality remains unproven, with incidental cardiac irradiation persisting at 1-5 Gy [3, 4].

Meta-analyses, including one by Cuzick et al. involving 8,000 women with breast cancer, reveals a 62% increase in cardiac mortality for those receiving adjuvant radiotherapy. A meta-analysis by the Early Breast Cancer Trialist's Collaborative Group (EBCTCG) with 20,000 breast cancer patients reports a 30% rise in vascular mortality among those undergoing adjuvant radiotherapy [5, 6].

Cardiac irradiation induces significant pathological alterations, leading to diverse clinical manifestations such as Coronary Artery Disease (CAD), pericarditis, cardiomyopathy, valvular heart disease, and conduction disturbances [7-9]. The pathophysiology of Radiation-induced Heart Disease (RIHD) involves macroangiopathy of coronary arteries and microangiopathy of small blood vessels, resulting in fibrosis of the coronary artery and myocardium [10].

Several clinical studies have identified adverse clinical consequences of radiation-induced heart disease (RIHD) as outcomes of long-term cancer survivors. Development of RIHD is likely to increase by ~ 40% in cancer survivors at least 10 years post radiotherapy [11]. RIHD may manifest a wide range of deleterious effects, like coronary artery disease (CAD), myocardial infarction (MI), valvular heart disease, rhythm abnormalities, and conduction system damage.

Studies from Yu X et al and Marks LB et al shows radiation induced decreased cardiac perfusion in the SPECT scans, which was more evident on longer follow up. Thus showing subclinical cardiac injury in patients receiving adjuvant RT for carcinoma left breast [4, 12, 13]. Duke University did a prospective study in 130 patients. The study found close to 50% SPECT abnormalities and this was dependent on the Left ventricle volume which was irradiated and primarily confined to the RT beam, which reflects microvascular injury [14].

This study responds to the imperative need for a comprehensive assessment of potential cardiac complications associated with different radiotherapy techniques. Focusing specifically on adjuvant radiotherapy for left breast cancer, the study aims to compare the dosimetry of 3DCRT, IMRT, and VMAT, contributing valuable insights for optimizing treatment strategies and minimizing cardiac exposure.

Objectives of the Study

1.To evaluate Incidental dose to Heart and Left Anterior Descending artery by 3DCRT, IMRT and VMAT plans.

2.To evaluate doses to Left Lung, Right Lung and Right breast.

Materials and Methods

Methodology

Sixty breast cancer patients scheduled for adjuvant radiotherapy in our institution were recruited between January 2019 to June 2020. Patients meeting inclusion criteria underwent thorough investigations, excluding those with prior chest irradiation or certain medical conditions. All patients underwent a baseline complete hemogram and biochemistry, baseline chest x-ray, ECG, Echo Cardiogram, Baseline ultrasound abdomen and pelvis, along with a post-operative Histopathological examination report.

The patients who are willing to give informed written consent, who are suitable for breast adjuvant radiotherapy with KPS more than or equal to 70, and well-controlled diabetes or hypertension patients on medication are included in the study patients who are not willing to give informed consent, prior breast or thoracic RT for any condition, uncontrolled diabetes or hypertension in patients and patients with cardiovascular disorders are excluded.

Radiotherapy Planning and Standardization

Each patient underwent CT simulation, and target volumes and organs at risk (OARs) were contoured following standardized contouring guidelines to ensure consistency across plans. Three treatment techniques 3DCRT, IMRT, and VMAT were planned for each patient using the same target volume definitions and optimization parameters.

Predefined dose constraints for OARs, including the heart, left anterior descending artery (LAD), lungs, and contralateral breast, were applied uniformly across all plans to ensure objective dosimetric comparisons. To minimize inter-observer variability, two independent radiation oncologists contoured the target volumes and OARs, with discrepancies resolved through consensus. All plans were reviewed for adherence to institutional protocols and dosimetric standards.

Follow-up: At each visit, clinical history was updated; clinical breast examination, ECG, and Echo were done. Investigations were advised as and when required.

Sample Size of Estimation

Based on a review of the literature regarding studies comparing 3D Dose Volume of Heart and Coronary artery in 3D-CRT, IMRT, and VMAT plans for Adjuvant Radiotherapy in Carcinoma Left Breast, the minimum sample size required for this study was 60. This was calculated based on the ANOVA(Analysis of Variance) Formula. The analysis of variance was done, to compare 3 groups by considering 80% power and a confidence limit of 5%(level of significance).

Results

In this study involving 60 recruited patients, three treatment plans (3D-CRT, IMRT, and VMAT) were generated for each participant, and dosimetric comparisons were conducted using Dose Volume Histogram (DVH). Patient characteristics are outlined in detail in Table 1.

The study demographic reveals that 60% of the patients fall within the age group of 31 to 50 years, with a mean age of 45.6 years. Tumor distribution indicates that 57% of the cases were located in the upper outer quadrant. Additionally, 40% of patients had Invasive Ductal Carcinoma, Not Otherwise Specified, Grade 2. All patients who underwent surgery for breast carcinoma had negative margins, and none presented with an Extensive Intra-Ductal component.Regarding pathological characteristics, 70% of patients did not exhibit Peri-Nodal invasion, while 21.66% had Lympo-Vascular Space Invasion. The KI-67 proliferative index was within 21 to 40 in 28.33% of cases, and 53.33% and 56.66% had ER and PR positive statuses, respectively. Moreover, 30% of patients were Her-2 positive, and 28.33% belonged to Stage IIA.

Treatment adherence was notable, with 70% of patients completing the treatment within 28 days of initiating radiation. Follow-up assessments at 3, 6, and 9 months revealed no changes in either ECG or Echo compared to baseline findings for those who completed the follow-up protocol.

The dosimetric analysis demonstrated variations in PTV 95, with 93% in 3D-RT, 98.9% in IMRT, and 99% in VMAT plans. Mean doses to LAD were 34 Gy, 16.3 Gy, and 15.2 Gy in 3D-RT, IMRT, and VMAT plans, respectively. The mean heart dose remained relatively consistent across all techniques (6.6 Gy for 3D-CRT, 6.3 Gy for IMRT, and 6.4 Gy for VMAT). However, a closer analysis of heart dose distribution patterns revealed that VMAT effectively reduced high-dose exposure (≥20% of prescribed dose) compared to 3D-CRT (13%), aligning with its potential for improved cardiac sparing. Conversely, low-dose exposure (V5 and V10) was notably higher in IMRT and VMAT, with the volume of the heart receiving 5% of the prescribed dose increasing from 37.6% (3D-CRT) to 78.8% (IMRT) and 77% (VMAT).

While VMAT successfully minimized high-dose exposure to the LAD and heart, potentially reducing long-term ischemic heart disease risk, careful evaluation of the impact of increased low-dose exposure is necessary for optimizing treatment selection on individual patient basis (Table 1).

Regarding the left lung, the mean dose varied, recording 13 Gy in 3D-RT, slightly increased to 15.6 Gy with IMRT, and reached 15.4 Gy with VMAT plans. The volume of the left lung receiving 5% of the prescribed dose was 75% in 3D-RT, notably higher at 93% with IMRT, and slightly reduced to 88% with VMAT plans. Similarly, the volume of the left lung receiving 10% of the prescribed dose was 46% in 3D-RT, substantially increased to 78% with IMRT, and slightly reduced to 76% with VMAT plans. Moreover, the volume of the left lung receiving 20% of the prescribed dose was 32% in 3D-RT, increased to 39% with IMRT, and slightly reduced to 35.8% with VMAT plans.Although VMAT showed superior PTV coverage, the increased low-dose lung exposure is clinically significant as it may contribute to a higher risk of radiation pneumonitis. This finding underscores the importance of carefully balancing dosimetric advantages with potential pulmonary toxicities, particularly in patients with pre-existing lung conditions.

In terms of the right lung and right breast, the mean doses exhibited variations. For 3D-CRT, the mean dose to the right lung was 2.54 Gy, increased to 5.0 Gy with IMRT, and further elevated to 6.1 Gy with VMAT plans. Similarly, the mean dose to the right breast was 3.0 Gy in 3D-CRT, elevated to 5.0 Gy with IMRT, and further increased to 6.1 Gy with VMAT plans. These detailed dosimetric findings provide a comprehensive understanding of the radiation exposure to critical organs in different radiotherapy modalities, aiding in the assessment and optimization of treatment plans.

Discussion

Comparative analysis of three radiotherapy techniques for left breast cancer 3D-CRT, IMRT, and VMAT reveals that all three meet clinical requirements.In terms of heart and LAD exposure, VMAT significantly reduces the high-dose volume (V20) for the heart and the mean dose to LAD. VMAT demonstrates advantages in protecting normal tissues on the affected side wth increased coverage. For the lung, spinal cord, contralateral lung, and contralateral breast, VMAT shows no significant advantage over the other plans.

Clinical Implications of Reduced LAD Dose with VMAT

One of the most clinically significant findings is the substantial reduction in mean LAD dose with VMAT (15.2 Gy) compared to 3D-CRT (34 Gy) and IMRT (16.3 Gy, p=0.001). The LAD is highly radiosensitive, and emerging evidence suggests a linear increase in

Table 1. Evaluation of the Impact of Increased Low-dose Exposure

Dosimetric Parameter	3D-CRT	IMRT	VMAT
PTV 95 Coverage (%)	93%	98.90%	99%
Mean LAD Dose (Gy)	34 Gy	16.3 Gy	15.2 Gy
Mean Heart Dose (Gy)	6.6 Gy	6.3 Gy	6.4 Gy
Left Lung Mean Dose (Gy)	13 Gy	15.6 Gy	15.4 Gy
Right Lung Mean Dose (Gy)	2.54 Gy	5.0 Gy	6.1 Gy
Right Breast Mean Dose (Gy)	3.0 Gy	5.0 Gy	6.1 Gy

major coronary events with mean heart doses as low as 3–5 Gy, particularly in younger patients and those with pre-existing cardiovascular risk factors [15]. The observed reduction in LAD dose with VMAT is therefore clinically meaningful, as it may lower the long-term risk of ischemic heart disease and radiation-induced coronary events, potentially improving cardiac-related morbidity and overall survival.

Despite this advantage, VMAT and IMRT increased low-dose exposure to the heart (V5, V10) and lungs (V5, V10, V20) compared to 3D-CRT. While high-dose LAD sparing is beneficial, the clinical impact of increased low-dose spread remains an area of concern, requiring further evaluation in long-term follow-up studies.

Secondary Malignancy Risks with VMAT

An important consideration with VMAT is the increased low-dose radiation scatter to surrounding normal tissues, including the contralateral lung and breast, which may elevate the risk of radiation-induced secondary malignancies. Studies have suggested that IMRT and VMAT, due to their greater number of monitor units (MUs) and increased integral dose, may be associated with a higher relative risk of secondary cancers compared to conventional 3D-CRT [16, 17].

Our findings confirm that VMAT resulted in the highest mean dose to the right lung (6.1 Gy) and right breast (6.1 Gy) compared to IMRT (5.0 Gy) and 3D-CRT (2.54 Gy, 3.0 Gy, respectively). These dosimetric differences may be particularly relevant for younger breast cancer patients, who have a longer post-treatment life expectancy, increasing their cumulative risk of developing secondary malignancies. While the absolute risk remains low, further research integrating secondary cancer risk models is essential to refine patient selection for VMAT-based radiotherapy.

Future Directions

AI-Driven Planning for Further Optimization

Advancements in AI-driven treatment planning hold promise in optimizing dose distributions while minimizing exposure to critical structures. AI-based auto-segmentation and machine learning–based dose prediction models have demonstrated the ability to generate highly conformal plans with lower normal tissue doses, potentially overcoming some of the current limitations of VMAT and IMRT [18].

Future research should explore

• AI-assisted VMAT planning to reduce low-dose spread while maintaining LAD sparing.

• Deep-learning models for predicting long-term cardiac and pulmonary toxicity based on patient-specific dosimetric data.

• Personalized radiotherapy selection algorithms integrating patient-specific factors (e.g., age, cardiovascular risk profile, tumor location) to optimize technique selection between 3D-CRT, IMRT, and VMAT.

In conclusion, among the three radiotherapy techniques analyzed, VMAT emerges as a highly promising modality for left breast cancer treatment, demonstrating superior target coverage, dose conformity, and efficiency. Its ability to significantly reduce LAD dose and high-dose cardiac exposure suggests a potential reduction in long-term radiation-induced cardiac morbidity. Additionally, VMAT optimizes treatment efficiency by minimizing monitor units and reducing overall treatment time, which may improve patient comfort and workflow feasibility.

However, increased low-dose exposure (V5, V10) to surrounding normal tissues with VMAT raises concerns regarding secondary malignancy risks and pulmonary toxicity. While dosimetric advantages are evident, their clinical significance must be further validated through long-term follow-up studies and real-world clinical outcomes. Future prospective trials integrating cardiac event monitoring and late toxicity assessments will be crucial in confirming whether VMAT's dosimetric benefits translate into tangible patient survival and quality-of-life improvements.

Additionally, advancements in AI-driven treatment planning hold potential for further optimizing VMAT by reducing low-dose spread while maintaining high precision. Continued research into personalized radiotherapy selection and adaptive planning will help refine the role of VMAT in balancing treatment efficacy and toxicity risks, ensuring better outcomes for breast cancer patients.

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Statement of Transparency and Principals

• Author declares no conflict of interest

• Study was approved by Research Ethic Committee of author affiliated Institute.

• Study's data is available upon a reasonable request.

• All authors have contributed to implementation of this research.

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