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Cardiac Dose Risk Stratification and Determinants of Radiation Exposure in Breast Cancer Patients Undergoing Advanced Radiotherapy

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ABSTRACT

Background: Cardiac exposure during breast cancer radiotherapy is one of the well-known causes of late cardiovascular morbidity. The present secondary analysis was conducted with the aim of stratifying the risk of exposure to cardiac radiations and defining clinical and treatment specific determinants of increased cardiac dose among patients with breast cancer using three-dimensional conformal radiotherapy (3D-CRT). **Methods:** The treatment planning data of 126 female breast cancer patients given 3D-CRT in a tertiary cancer center was performed by secondary analysis. The Cardiac exposure was classified as being of low-, moderate-, and high-dose groups depending on clinically significant mean heart dose (MHD) exposure thresholds. The chi-square test, independent t-tests, and one-way ANOVA were used to test associations between cardiac dose category, laterality, surgical procedure and patient age with the level of statistical significance ($p<0.05$). **Results:** In general, patients who were classified within the moderate-high levels of cardiac exposure were 38.1%. The association between cardiac dose risk and left-sided breast cancer was significant as more than 85% of all the high-risk patients were identified to have left-sided treatment ($p < 0.001$). The type of surgery influences cardiac exposure since radical mastectomy was found to have a higher dose of risk than breast-conserving surgery ($p < 0.001$). **Conclusion:** This secondary review illustrates that there is no homogeneous distribution of cardiac radiation exposure during 3D-CRT but highly dependent on the tumor laterality and method of surgery as opposed to patient age. The cardiac dose in the form of risk-based interpretation may offer more clinically useful evidence as compared to absolute mean dose alone, endorsing personalized radiotherapy planning for managing cardiovascular risk.

Keywords: Breast Neoplasms, Cardiovascular Diseases, Radiotherapy, Heart, Radiation Dosage, Cardiotoxicity, Risk Assessment, Mastectomy, Treatment Outcome, Retrospective Studies

Introduction

Breast cancer is the most commonly diagnosed malignancy in women across the world, and radiotherapy is an essential part of its management [1]. Although improvements in radiation technology have greatly resulted in a better control of local tumor, survival, there are concerns regarding unintended radiation dose reaches neighboring vital organs especially heart [2,3]. Radiation-induced cardiac toxicity can be mentioned as a clinically relevant delayed effect, which can develop many years after the end of the treatment and lead to long-term morbidity and mortality [4].

Three- dimensional conformal radiotherapy (3D-CRT) remains a common usage in low- and middle-income nations because of its accessibility, cost-efficiency as well as acceptable tumor coverage [5]. Nonetheless, 3D-CRT is related to increased variability of cardiac dose exposure as opposed to more developed methods particularly in patients with left-sided breast cancer [6]. Even small increases in mean heart dose (MHD) have been demonstrated to be linked with the relative increase in the significant coronary incidents, suggesting the significance of dose optimization and methodologic cardiac hazard evaluation throughout the treatment planning process [7,8]. The majority of published research about cardiac exposure in breast radiotherapy is based on the reporting of absolute dose values or a comparison of differences based on laterality [9,10]. Such approaches though informative, may not adequately measure clinically relevant dose distributions or classify patients based on their potential risk of being at long-term cardiac risk. Secondary analyses of radiotherapy through classification and using procedural modifiers is an opportunity to derive more clinical information without recreating the original findings.

The paper uses a secondary analytical model to analyze the previously retrieved 3D-CRT planning information to assess trends in cardiac exposures using the MHD as a surrogate measure of cardiovascular risk. The analysis is based on dose stratification based on how the dose varies depending on laterality and surgical approach level, as opposed to just comparing dose averages, which allows cardiac safety profiles to be interpreted in a more insightful manner. By determining subgroups that have increased cardiac exposure, the study will help to justify tailored treatment and encourage future research on importance of cardiac-sparing strategies in standard clinical practice. The study aims to provide a valuable information regarding improvements in radiotherapy planning to reduce long-term cardiac complication among breast cancer survivors who have undergone 3D-CRT.

Methodology

This secondary analysis research is carried out at INMOL Cancer Hospital, Lahore, using the data of previously treated radiotherapy planning of breast cancer in the course of six months (July 2024 -December 2024). Ethical clearance of using secondary data was given by the Institutional Review Board (INMOL-128, dated 15-06-2024). No physical contact with patients was involved and all the identifiers were anonymized before analysis.

There were 126 women patients who were selected according to the predetermined qualification criteria. The sample included histopathological proved 18 years old patients with I-III breast cancer stage and an Eastern Cooperative Oncology Group (ECOG) of 0-2 performance status. Patients who underwent curative-intent 3D-CRT were eligible. The study excluded patients who had bilateral breast cancer, those with metastatic disease, recurrent tumors or those who had been treated through palliative intent. The same number of left-sided (n=63) and right-sided (n=63) breast cancers was used in order to enable balanced comparative evaluation. The treatment planning system of the radiotherapy institution was used to access radiotherapy planning data.

Each patient had been simulated on a wide-bore CT simulator with 5-mm slice thickness, starting at the clavicle up to the upper abdomen. The 6-MV beams were used to produce treatment plans based on full 40 Gy in 15 fractions delivered 5 days a week. It calculates the dose by a pencil beam algorithm with the correction of tissue heterogeneity, no deliberate cardiac shielding, field borders.

In this secondary analysis, the entire heart was contoured on the axial CT images based on conventional standard anatomical delimitations. Mean heart dose (MHD) was determined on each patient and then fitted in predetermined cardiac exposure risk classes (low, moderate, high) to facilitate interpretation of risks other than absolute dose report. Other variables that were observed included the tumor laterality and the type of surgery performed. The statistical analysis was conducted to use SPSS version 21 [11]. The continuous variables were reported in mean ± standard deviation, and the categorical variables were reported in frequencies and percentages. The independent t-tests, Chi-square tests, and one-way ANOVA were used to conduct group comparisons. The p-value of less than 0.05 was subject to statistical significance.

Results

In this secondary analysis, 126 breast cancer patients, who underwent 3D-CRT, were used. Exposure to cardiac dose was diverse among the patients, as almost one-third of patients fell under high-risk group levels according to the mean heart dose limits. Tumor laterality is linked to high risk of cardiac exposure favouring increased dose in case of the left sided disease. The use of surgical modality also affected cardiac dose delivery especially in left sided mastectomy. These results highlight that the determinants of cardiac radiation burden are procedure- and laterality-based determinants. The distribution of patents between predetermined cardiac radiation risks categories depending on the mean heart dose are illustrated in Table 1. A significant number of patients fell in moderate-to-high risk categories, showing the importance of the cardiac exposure to clinically significant levels, despite the usual 3D-CRT delivery.

Table 1. Cardiac Radiation Exposure Risk Stratification Based on Mean Heart Dose

Tumor Laterality	Low Risk n (%)	Moderate Risk n (%)	High Risk n (%)	Total	p-value
Left-sided	6 (7.9)	31 (40.8)	39 (51.3)	76	
Right-sided	46 (92.0)	3 (6.0)	1 (2.0)	50	<0.001*
Total	52	34	40	126	

**Chi-square test, n = No. of patients, % = Percentage, p = Value of Significance*

Such stratification offers a risk-biased interpretation (as opposed to mere dose reporting). Almost a third of the patients belong to the high cardiac exposure risk category, which means that the percentage of patients who received clinically significant cardiac radiation, despite standard 3D-CRT planning, is considerable. Table 2 depicts a statistically significant relationship between the tumor laterality and cardiac dose risk rates (Chi- square, $p < 0.001$).

Table 2. Association Between Tumor Laterality and Cardiac Dose Risk Categories

Tumor Laterality	Low Risk n (%)	Moderate Risk n (%)	High Risk n (%)	Total	p-value
Left-sided	6 (7.9)	31 (40.8)	39 (51.3)	76	
Right-sided	46 (92.0)	3 (6.0)	1 (2.0)	50	<0.001*
Total	52	34	40	126	

**Chi-square test, n = No. of patients, % = Percentage, p = Value of Significance*

The high-risk group had an over-representation of left-sided cancer patients of the breast, and the right-sided tumors were matched with low-risk cardiac exposure. It was found that tumor laterality had an extremely important relationship with the stratification of cardiac dose risk (Chi-square, $p < 0.001$). Over a half of the left breast cancer patients were in the high-risk cardiac exposure category and remaining patients with tumors on the right were mainly linked with low-risk exposure. Table 3 provides a comparison of MHD and high-risk category of various surgical procedures.

Table 3. Influence of Surgical Procedure on Mean Heart Dose (MHD) and Risk Category

Surgical Procedure	MHD (Gy) Mean ± SD	High-Risk Category n (%)	p-value
Left MRM	5.21 ± 0.55	28 (70.0)	
Left BCS	4.11 ± 0.62	11 (27.5)	
Right MRM	0.21 ± 0.19	1 (2.5)	<0.001†
Right BCS	0.10 ± 0.15	0 (0.0)	

†One-way ANOVA, MHD = Mean Heart Dose, MRM = Modified Radical Mastectomy, BCS = Breast-Conserving Surgery, Gy = Gray, n = No. of patients, % = Percentage, p = Value of Significance

The type of surgical procedure had a great effect on the exposure to radiation on the heart (ANOVA, $p < 0.001$). Left-sided modified radical mastectomy turned out to record the largest MHD and the biggest proportion of cardiac risk exposure instances, whereas right-sided breasts conserving surgery exhibited insignificant cardiac dose.

Discussion

Through this secondary analysis, a meaningful insight of cardiac radiation exposure of breast cancer patients under 3D-CRT is offered whose mean heart dose is contextualized in relation to clinically relevant risk groups. The discovery supports the historical finding that when the breast is irradiated at left, the cardiac exposure is significantly greater as compared to when the breast is irradiated at right. Moreover, the paper extends the comparison of laterality to reveal the influence of surgical technique as an additional contributor to the burden of cardiac exposures [12,13]. The mean cardiac doses were greatest in patients who underwent a left-sided modified radical mastectomy, indicating that in cardiac exposure, the positioning of the anatomical fields and the geometry of the chest wall have a decisive influence in cardiac exposure during 3D-CRT [14,15].

The variation in the mean dose of heart observed in different categories of surgery illustrates the need to have a personalized radiotherapy planning [16,17]. The practice of chest wall irradiation after mastectomy can potentially require broad tangential fields and greater penetration of the beam, which can contribute to higher incidence of incidental cardiac irradiation than the practice of breast-conserving irradiation [18]. In this regard, increased cardiac vigilance in the planning process is emphasized especially when dealing with cases of left-sided post-mastectomy where cumulative cardiac risk may prove to be significantly important [19,20].

Interestingly, patient age was not statistically proven to be correlated with MHD which implies that anatomical and technical aspects are the most common factors affecting cardiac exposure in 3D-CRT as opposed to demographic factors [21,22]. This result explains why cardiac-sparing strategies should be based on the treatment geometry, and not on patient-related aspects only [23,24]. The findings are consistent with other radiobiological data also showing that even low to moderate accumulation of MHD could be associated with quantifiable long-term cardiovascular risk amongst newer clinical implications of dose minimization [25].

Through the restructuring of the data, using an additional analytical prism, the present paper focuses on the risk stratification, not on absolute dose coverage. This method has practical application in standard clinical practice where sophisticated methods are not available and one can effectively use meaningful decisions on high-risk subgroups and make efforts to reduce cardiac exposure such as beam angle optimization and selective dose limits.

There are various limitations of this study. It was a secondary analysis hence dependent on prior planning data collection thus had no control over imaging protocols and contouring variability. MHD alone might not be the most accurate way of incorporating the regional cardiac dose heterogeneity or coronary artery exposures. Also, there are no longitudinal clinical cardiac-based outcomes limiting straight correlation of dosimetric results with cardiovascular occurrences. The single-center design could also be restrictive in terms of generalization. Despite these limitations, the analysis will offer clinically significant data on patterns of cardiac risks in breast cancer patients receiving 3D-CRT therapies.

Conclusion

This secondary analysis has shown that laterality and surgical approach are some critical factors that determine the MHD during the 3D-CRT of breast cancer, irrespective to the patient's age. The cardiac radiation exposure to left-sided breast cancer patients especially those who have undergone modified radical mastectomy surgery is significantly higher than that of right-sided breast cancer patients and patients undergoing breast-conserving surgery.

The results suggest that cardiac dose at 3D-CRT mostly rely on the treatment geometry and field arrangement, underlining the importance of dose monitoring around the time of planning radiotherapy in cases of anatomic high risk. These findings point towards the clinical significance of risk-based radiotherapy planning particularly in the environment where high technology-based cardiac-sparing radiotherapy is not regularly made. The addition of secondary dosimetric assessment enables the clinician to establish susceptible sub groups and implement specific planning to minimize incidental cardiac irradiation occurrence. This practice advocates informed decision-making, patient safety optimization, and it is also associated with better long-term cardiovascular risk management of radiotherapy of breast cancer.

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Conflict of Interest

None

Authors' Contribution

Iqra Iftikhar contributed all ICMJE roles.

Ethical Statement

This secondary analysis research is carried out at INMOL Cancer Hospital, Lahore, using the data of previously treated radiotherapy planning of breast cancer in the course of six months (July 2024 -December 2024) under Ref#INMOL-128, dated 15-06-2024.

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