Evaluation of Cardiac Dose Distribution and Prediction of Cardiovascular Risk Increase in Breast Cancer Radiotherapy for Georgian Women

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Breast Cancer Radiotherapy, Mean Cardiac Dose, Probability of Percentage

ABSTRACT
This study aims to evaluate cardiac dose distribution in breast cancer radiotherapy and predict the increase in cardiovascular risk among the Georgian female population.
Patients: We analyzed the treatment records of 100 female patients (40 with right-sided breast cancer, and 60 with left-sided) who underwent radiation therapy at the Kutaisi Christina Kiri Cancer Centre between 2017 and 2018.
Dose Evaluation: Radiotherapy was planned using conformal 3D and intensity-modulated radiation therapy (IMRT) techniques (ZXOX20) on the Eclipse planning system, based on diagnostic CT scans and virtual simulations (ZXOX30). A total dose of 50Gy was delivered in 2Gy fractions, with an additional 10Gy boost. Multi-leaf collimators (MLC) were used to protect surrounding tissues. The minimum, maximum, and mean heart doses were recorded.
Data Analysis: To enhance the accuracy of the results, Bayesian statistical approach was applied. We employed a hierarchical Bayesian model with lognormal distribution assumptions for heart dose data, using prior information from European studies (1977–2017) on cardiac doses in breast cancer radiotherapy. Posterior distributions, updated with clinical data, were used to estimate cardiac dose distributions for Georgian patients. Statistical significance was assessed using ANOVA, Chi-square, Shapiro-Wilk test for normality, and Grubbs' test.
Results: The mean heart doses for left-sided patients were 2.95Gy (SD =2.69), and for right-sided patients, 1.30Gy (SD = 0.80). Lognormal approximation yielded mean heart doses of 0.87 (SD=0.69) for left-sided and -0.23 (SD=0.82) for right-sided patients. The predicted increase in cardiovascular risk was 19% for left-sided and 6% for right-sided breast cancer patients.
Conclusion: Left-sided breast cancer radiotherapy is associated with a higher cardiovascular risk. Further research is needed to refine the "benefit-risk" assessment in radiotherapy and validate these findings.

1. Introduction:

According to the World Health Organization (WHO), 2.3 million women worldwide were diagnosed with breast cancer in 2020, resulting in 685,000 deaths. By the end of that year, approximately 7.8 million women who had been diagnosed with breast cancer in the previous five years were still alive, making it the most prevalent form of cancer globally. Breast cancer significantly impacts the quality of life, often leading to disability. In Georgia, breast cancer accounts for 29-32% of all registered cases of malignant neoplasms among women. The highest incidence of new cases is observed in women aged 50-70. Notably, the breast cancer incidence in Georgia, measured per 100,000 women, is lower than that in the European region and the European Union but higher than the average rate in the European Union (EU) [1].

Radiation therapy is essential in treating various cancers, especially breast cancer, with more than 50% of patients undergoing this treatment. Radiation causes direct damage to cancer cells, leading to immediate and long-term complications [2]. According to the International Commission on Radiological Protection (ICRP), radiation exposure can induce so-called "long-term tissue reactions",

which are linked to significant increases in cardiovascular risk [3]. This emphasizes the importance of personalized treatment strategies, considering individual radio sensitivity, especially in cases where radiation therapy targets vital organs such as the heart and brain. [3, 4].

Considering these factors and the increasing number of individuals at risk, assessing both individual and population radiation risks has become a significant focus in modern life and medical sciences. This field of research is currently undergoing extensive investigation [5]. Ongoing randomized population-based trials are investigating various aspects of radiotherapy. These studies focus on the radiation dose delivered, its correlation with long-term complications, and the impact of different risk factors. They aim to understand the effects of irradiating specific functional areas of the heart and to identify predictors and markers of cardiac risk [6-10].

Early studies indicated a dose-dependent relationship between radiation exposure and cardiovascular risk, with an estimated risk of 7.4% per 1Gy [7]. However, more recent data suggest a significantly higher risk (16% per 1Gy), with the onset of complications often occurring within five years. Recent studies suggest a threshold dose of approximately 5Gy, beyond which complications may arise, indicating a non-linear dose-effect relationship. However, other recent research has reported no significant increase in cardiac complications. This lack of increase may be due to optimizing radiotherapy protocols and using reduced radiation doses [11].

Motivation

Despite these findings, there is still no agreement on the predictors of late-onset complications or early indicators for their development. Additionally, the influence of individual and population-specific factors on the risk of cardiac complications is not well understood, especially concerning cancer development and the effectiveness of chemotherapy and radiotherapy interventions [12]. Given the gaps in understanding, studying the cardiological risks associated with radiotherapy dosages and procedures in breast cancer patients is particularly relevant, especially in Georgia.

Objective

This research aims to refine the methodology for assessing the benefit-risk balance of radiological procedures and optimization strategies and tactics for therapeutic interventions. The specific objectives of the study include:

- Evaluation of cardiac risk in patients undergoing radiotherapy and combined chemo-radiotherapy. This objective focuses on the optimal management of heart diseases in cancer patients receiving radiation treatments.
- Analysis of population variability in cardiotoxicity. The study will investigate the mechanisms behind radiotherapy-induced cardiotoxicity and explore how findings from this research can be integrated into current international efforts in this field.

2. Materials And Methods

Patients

This study involved a retrospective analysis of the patient's medical records who underwent radiation therapy, or combined chemo-radiotherapy, at the Kutaisi Christina Kiri Cancer Center from 2017 to 2018. A total of 1,000 patient cases were reviewed, of which 4 cases involved right-sided breast cancer and 60 cases involved left-sided breast cancer.

Inclusion Criteria:

Patients were included in the study if they met the following criteria: no pre-existing cardiac complications at the time of irradiation; a transmission fraction greater than 50%, as assessed by echocardiographic examination; a potential cardiac complication was defined as a reduction in the ejection fraction by approximately 5 to 10 units following treatment; Patient consent was obtained for

their medical data collection and analysis.

Radiation Dose Evaluation

Radiation therapy planning and dose evaluation were carried out using 3D conformal radiation therapy (CRT) and intensity-modulated radiation therapy (IMRT) planning systems (ZXOX20 and Eclipse, respectively). Diagnostic CT scans and virtual simulations (ZXOX30) were used to create detailed treatment plans.

The total prescribed dose was 50Gy, delivered in daily fractions of 2Gy, with an additional boost dose of 10Gy. Multi-leaf collimators (MLC) were employed to minimize radiation exposure to surrounding healthy tissues. The following dosimetry parameters were evaluated: Minimum Dose (D_{min}), Maximum Dose (D_{max}), and Mean Dose (MHD).

Statistical Analysis of Dosage Variations

To assess the statistical significance of differences in radiation doses between right and left breast irradiation, an Analysis of Variance (ANOVA) was performed. Grubbs' test was used to identify any outlier values within the dataset. Given the observed asymmetry in the histograms of dose distribution, the numerical evaluation of key distribution parameters was conducted using a log-normal distribution model. These results were then compared with existing literature data to assess consistency and identify any deviations:

$$\boldsymbol{Ln(D)=N(\mu,\sigma^2)} \quad (1)$$

$$\boldsymbol{(D|\mu,\rho)}=\frac{\sqrt{\rho}}{D\sqrt{2\pi}} * e^{-\frac{\rho}{2}*[\ln(D)-\mu]^2} \;;\; \rho=\frac{1}{S^2} \quad (2)$$

Where $\boldsymbol{\mu}$ and $\boldsymbol{\sigma}$ are the mean and standard deviations of the normal distributions corresponding to the logarithm-normal distribution. The relationship of these characteristics to the mean of the lognormal distribution ($\boldsymbol{m}$) and the standard deviation (s) was established using the following equations:

$$\boldsymbol{\mu}= \ln\left(\frac{m^2}{\sqrt{S^2+m^2}}\right) \quad (3)$$

$$\boldsymbol{\sigma}=\sqrt{ln\left[\frac{S^2}{m^2}+1\right]} \quad (4)$$

The Shapiro-Wilk test was used to assess the normality of the filtration results. A Bayesian approach was applied to integrate our data with results from various national and international studies to enhance the representativeness and accuracy of our findings. This integration allowed for a more comprehensive analysis of the data.

For prior information, we utilised data from previous studies [4, 5, 13-17] that focused on the distribution of cardiological dose loads within the relevant population. The posterior dose distributions were then considered the updated probability distribution, incorporating data from our clinical cohort.

We performed the calculations within a Bayesian hierarchical model, which assumes the variance of the log-normally distributed random variable to be known. In this framework, the relationship between the means of the posterior and prior distributions, and the accuracy of the posterior estimates, becomes straightforward to analyse [18].

$$\boldsymbol{m'}=\frac{mp+n\rho\frac{\sum_{i=1}^{n}\ln(D_i)}{n}}{p+n\rho} \;;\; \mathbf{p'}=p+n\rho \quad (5)$$

where $\boldsymbol{m}$' and $\boldsymbol{p}$', $\boldsymbol{m}$ and $\boldsymbol{p}$ are the means and accuracy of the posterior and a priori distributions, respectively, and $\boldsymbol{D_i}$ is the mean dose of cardiac irradiation. Finally, for a posterior distribution, we obtained the following equation:

$$\mathbf{P^{i}_{apost}}\left(D|, m'_{i,}\ \sigma_i\right) = \frac{1}{D\ \sigma_i\ \ +\sqrt{2\pi}} * e^{\frac{1}{2\sigma_i^2}*\left[\ln(D)-m'_i\right]^2} \quad (6)$$

I- indicates the irradiation side (left-right).

We tested the statistical reliability of the difference between the mean values of the dose distribution characteristics in the a priori, posterior, and study cohorts using a t-test.

Assessment of the Increase in Major Adverse Cardiovascular Event (MACE) Rate After Breast Cancer Radiotherapy for the Georgian Female Population

The rate of major coronary events following radiotherapy was modelled using the equation:

$$\boldsymbol{MACE\ Rate=Bs(1+KD)}$$

where: ***Bs*** represents the baseline rate of major coronary events in the absence of radiotherapy; ***D*** is the dose of cardiac radiation (in grey); ***K*** is the percentage increase in the rate of major coronary events per 1Gy of radiation exposure [7].

In this context, ***K*** reflects the percentage increase in the rate of major adverse cardiovascular events (MACCE) for typical radiation doses used in Georgia. The mean value of the ***K*** coefficient, along with its 95% confidence interval (CI), was derived from the literature, with the value ***K***=7.4% (95% CI, 2.9% to 14.5%; P<0.001) [7]. These values indicate a rightward skew in the density distribution of ***K***, suggesting that it follows a lognormal distribution.

As a random variable, ***K*** can be interpreted as having a distribution that matches the density of the MACCE rate increase (Eff) under the condition where ***D***=1Gy.

Using this, and applying simple transformations, it can be shown that the conditional probability density of the ***Eff*** distribution for any given dose ***D*** is given by the following equation:

$$\boldsymbol{P}(\boldsymbol{Eff}|, \mu_{\text{Eff}}, \sigma_{\text{Eff}}, D) = \frac{1}{\boldsymbol{Eff}\ \sigma_{\text{Eff}}\ \sqrt{2\pi}} * \boldsymbol{e}^{-\frac{1}{2\sigma^2_{Eff}}*\left[\boldsymbol{ln}(\boldsymbol{Eff})-(\mu_{\boldsymbol{Eff}}+\boldsymbol{ln}(\boldsymbol{D}))\right]^2} \quad (7)$$

Finally, by combining and integrating the distributions of ***Eff*** and dose ***D***, we can derive the expected probability of a percentage increase in the MACCE rate in both the left and right-sided breast cancer populations in Georgia. This is expressed as:

$$\boldsymbol{P^{i}_{post}} = \iint_{Eff,D}^{\cdot} Eff \cdot P(Eff|\mu_{\text{Eff}}, \sigma_{\text{Eff}}, D) \cdot\ P^{i}_{post}\ (D) \cdot dD \cdot dEff \quad (8)$$

3. Results

Fig. 1 shows the mean values, standard errors, 95% confidence intervals, and outliers of cardiac doses in radiotherapy for left-sided (*l*) and right-sided (*r*) breast cancer. The difference between the two groups is statistically significant, however, the presence of outliers suggests a deviation from normal distribution conditions.

The histograms presented in **Fig. 2 show the asymmetry** in the dose distribution. To facilitate comparison with results from other studies, we deemed it appropriate to approximate the histograms using parametric theoretical distributions.

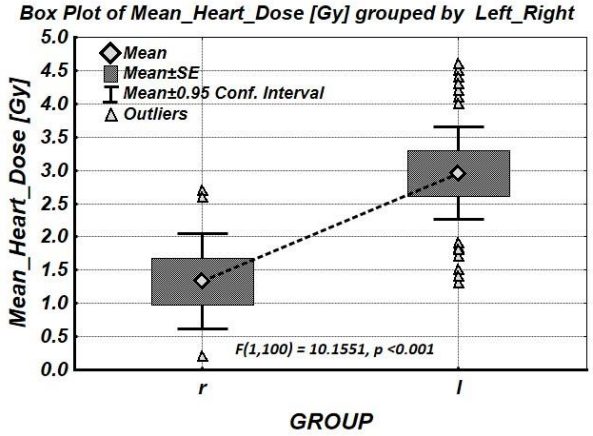


Fig.1. Mean value, standard error, 95% confidentiality interval and outliers of cardiac doses in radiotherapy of the left (*l*) and right-sided (*r*)breast cancer

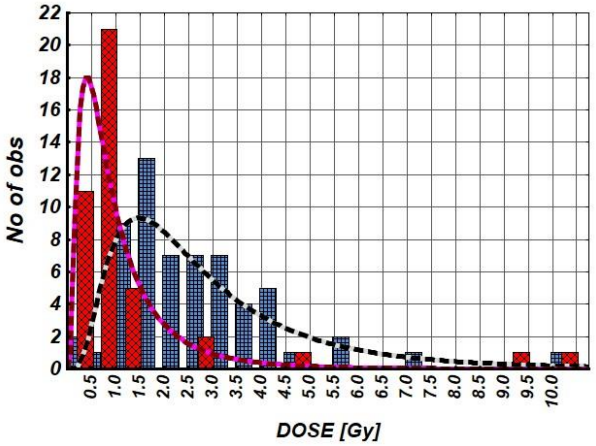


Fig.2. Histograms of cardiac dose distribution and their lognormal approximation in radiotherapy of the left (dotted line) and right-sided (solid line) breast cancer

To simplify the calculations at this stage and facilitate the interpretation of the results, we adopted the log-normal model as the optimal choice (see Table 1).

Table 1. The value and standard deviation (STD) of the distribution of mean heart doses, the mean and standard deviation of the normal (N) distribution associated with the lognormal approximation of mean heart dose distribution, and the value of the Shapiro-Wilk Test of normality

	Mean Hearth Dose (Left)	**Mean Hearth Dose (Right)**
M	2.95	1.33
STD	2.69	2.28
Mean _N	0.85	-0.23
STD_N	0.69	0.82
SW-W; p	0.97; p=0.33	0.95; p=0.35

The log-normal distribution is an important continuous probability distribution in statistics. It is characterized by positive skewness, and its variability arises from the multiplicative effects of various independent factors influencing the distribution.

4. Discussion

It should be noted that the asymmetry of the distribution of mean heart doses, the mean and standard deviation of the normal (N) distribution associated with the lognormal approximation of mean heart dose distribution (Table 1) is considered with individual cancer anatomy and treatment planning [14].

This asymmetry may reflect both population-specific aspects of carcinogenesis and the specifics of therapy, and, in this regard, can serve as a criterion for inter-population analysis. However, this falls outside the scope of the present article, and we will not address it further.

As shown in Fig. 2, a significant proportion of anomalous doses and excesses were observed in the study cohort. The legal case could significantly change the average dose distribution patterns within the population. This is especially true when the analysis is based on a limited number of cohorts from a single clinic. Equally important is the issue of cohort representativeness.

The Food and Drug Administration of USA FDA has recommended using Bayesian statistics in clinical trials for medical devices [19, 20]. Traditional (frequentist) statistical methods typically incorporate information from previous studies at the design stage. In contrast, Bayesian methods formally combine prior information with current data on a quantity of interest. The Bayesian approach treats prior information and trial results as part of an ongoing data stream, continuously updating inferences as new data become available [19, 21].

In our study, a priori information was taken from data from EU countries' cardiac doses in breast cancer radiotherapy (Table 2). There is a clear trend towards reducing cardiac doses during radiotherapy, possibly related to adopting new technologies. These technologies, such as three-dimensional treatment planning with dose-volume histograms, intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), and active breathing control (ABC) radiotherapy, have the potential to reduce the risk of radiation-induced heart problems.

Table 2. The time range of the examinations selected by us covers the years 1977-2017 and reflects the dynamics of optimization of radiotherapy procedures [4-10]

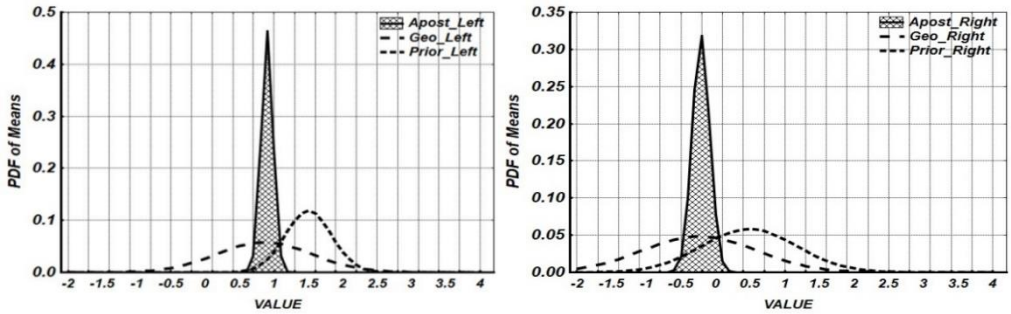
Country	Year	Side	MHD (Gy)	STD
German	1998-2008	*Left*	4.6	3.1
German	1998-2008	*Right*	1.7	1.2
Danish	1977-1981	*Left*	6.1	3.3
Danish	1977-1981	*Right*	2.9	1.6
Danish	1982-1988	*Left*	5.7	2.3
Danish	1982-1988	*Right*	2.9	1.6
Danish	1989-2001	*Left*	5.8	1.2
Danish	1989-2001	*Right*	2.1	0.5
BACCARAT	2015-2017	*Left*	2.95	1.49
BACCARAT	2015-2017	*Right*	0.46	0.12

Based on the preceding analysis, the average dose load value can be considered an updated reference for the literature and a characteristic of the dose load in the Georgian population, at least in the initial approximation. It is important to note that the dose loads on the heart during left-sided radiation in Georgia align closely with the results of the latest BACCARAT study (Breast Cancer and Cardiotoxicity Induced by Radiotherapy) study. However, doses to the right side are nearly three times higher. The interpretation of this discrepancy warrants further investigation.

As shown in Table 3 and Figure 3, the posterior mean of the average heart dose is nearly identical to the cohort mean. However, the mean dispersion and, consequently, the informational value of the estimate are increased approximately sevenfold.

Table 3. Cardiac dose logarithm distribution means the end standard deviation in radiotherapy of left and right-sided breast cancer

	Left		**Right**	
	Mean	***STD***	***Mean***	***STD***
Prior	1.5	0.34	0.48	0.68
Georgian population	0.86	0.69	-0.23	0.82
Posterior	0.9	0.086	-0.2	0.12



a **b**

Fig. 3. Probability Density Function of the logarithm of prior, cohort and posterior cardiac doses logarithm distribution in radiotherapy of left (a) and right-sided (b) breast cancer

The conditional probability of a percentage increase shows a pronounced peak in the relatively low dose range. As the dose increases, the range of percentage increases widens, which indicates a high level of uncertainty regarding cardiac risk in the higher dose range. This complicates the prognosis of cardiac risk in individuals receiving high doses of radiation.

By integrating equation (8), we obtain the expected value of the percentage increase in the MACE rate in the Georgian population, concerning the cardiac dose. This increase is approximately 19% for left-sided radiation and about 6% for right-sided radiation. Left-sided irradiation is primarily concentrated in the 10-40% range, corresponding to a dose range of 2-4Gy, while right-sided irradiation is mostly localized in the 5-10% range. These data provide a preliminary cardiovascular risk assessment, which should be considered when planning radiotherapy procedures.

Figures 4 and 5 illustrate the theoretical dose-dependence functions, representing the conditional probability of percentage increase and the dose-dependence distribution functions for left- and right-sided radiation in Georgia, as calculated using equation (8).

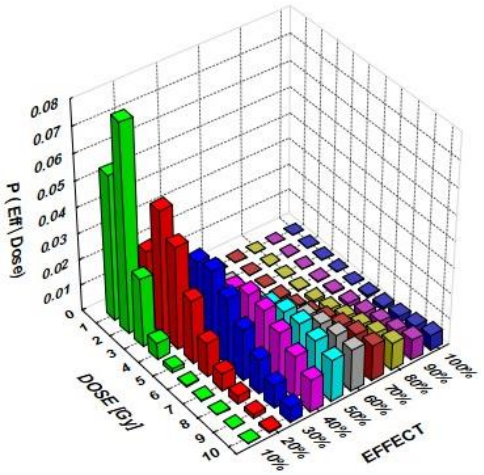


Fig.4. Conditional probability density function of percentage increase of Macerate effect forgiven dose

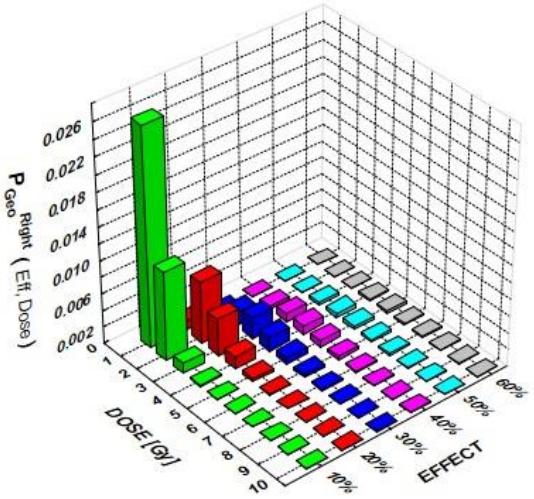


Fig. 5. Expected distribution of the probability density function for the percentage increase in MACE rate effect due to dose in Georgian breast cancer patients.

5. Conclusion

Based on the obtained results, potential avenues for further optimization of breast cancer radiotherapy include a more detailed assessment of distant cardiological risk within the lower dose range of radiotherapy. Furthermore, enhancing the "benefit-risk" evaluation methodology for radiotherapy is essential. This should include a thorough assessment of the long-term impacts on distant tissues associated with radiotherapeutic treatments.

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