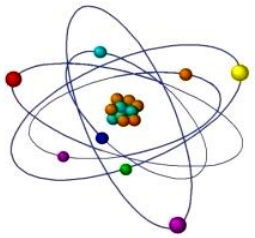
EVALUATION OF DISTRIBUTION OF CARDIAC DOSES IN BREAST CANCER RADIOTHERAPY AND PREDICTION OF PERCENTAGE INCREASE IN CARDIOVASCULAR RISK IN THE GEORGIAN FEMALE POPULATION



(Preliminary Results)

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ABSTRACT: *The purpose of this article is the preliminary Evaluation of cardiac doses distribution in breast cancer radiotherapy and Prediction of Percentage Increase in Cardiovascular Risk in the Georgian Female Population. Patients: The histories of 100 patient cases (40 right breast cancer, 60 left breast cancer) who underwent a course of radiation therapy at the Kutaisi Christina Kiri Cancer Centre in the years 2017-2018, were analysed.*

Dose Evaluation: Patient irradiation program and dose evaluation were performed using conformal 3D and IMRT planning (ZXOX20) and eclipse system based on diagnostic CT scan and virtual simulation (ZXOX30). Total dose 50 Gy, fractional dose 2 Gy, additional dose 10 Gy. MLC blocking was used to protect surrounding tissues. The minimum, maximum and mean dose (MHD) of the heart were recorded.

Data analysis and statistics: Bayesian approach for parameters updating were used to increase the representativeness and accuracy of our survey results. Calculations was performed within hierarchical Bayesian model for a lognormally distributed random value with known variance. As a prior information was used literary data on cardiac doses in breast cancer radiotherapy in EU countries in years 1977-2017. In this case, a posterior distribution function, represents updated with clinical data a prior function, and with crude accuracy can be considered as a dos's distribution in a breast cancer patient in Georgia. The statistical significance of the results was tested with the methods of parametric and non-parametric statistics (ANOVA, Xi2, Shapiro-Wilk test for normality, Grubbs' test and so on).

Results: The mean values of the left and right- sided breast cancer doses and its standard deviations in clinic patients are equal to 2.95 Gy and 2.69, and 1.3Gy, 0.8, respectively. The mean and standard deviation of the normal distribution associated with lognormal approximation of mean heart doses distribution for the left and right sides is equal to 0.87, 0.69 (SW-W = 0.98, p = 0.34) and -0.2328, 0.8236, (SW-W = 0.95, p = 0.07), respectively. The posterior values of the left and right-side doses and their standard deviation are equal respectively to 0.9, 0.08 and -0.2328, 0.12, the mean values of the posterior doses are practically no different from the means of the study cohorts, although their estimation error was reduced practically by 4-7 fold. In the case of doses used in the breast cancer patients of Georgia, the expected total probability of Percentage Increase of Major Adverse Cardiovascular Event Rate is equal to 19% and 6% for the left and right sides, respectively. From the standpoint of the results obtained, the priority areas of our further research are the validation of these results and further refinement of the radiotherapy "benefit-risk" evaluation methodology with consideration of distant tissue effects after radiotherapy

Key words: breast cancer radiotherapy, mean cardiac dose, probability of percentage

INTRODUCTION

According to the World Health Organization, worldwide 2.3 million women were diagnosed with breast cancer worldwide in 2020, of whom 685,000 died. By the end of 2020, there were 7.8 million women alive who had been diagnosed with breast cancer in the last 5 years, making it the most common localization of cancer in the world. Globally, breast cancer is associated with a deterioration in the quality of life associated with disability.

According to the Georgian Cancer Population Register, 29-32% of all cases of malignant neoplasms registered are in women (table 1).

Table 1. Cases of malignant neoplasms registered in women

(Georgian Cancer Population Register) [1]

Number of new cases of breast cancer in Georgia by years 2015-2018				
Years	2015	2016	2017	2018
Total amount	1919	1793	1661	1603

The number of new cases is prevalent in the age group of 50-70 years. At the same time, it should be noted that the incidence of breast cancer in Georgia per 100,000 women, is less than the rate in the European region and the European Union and higher than the average rate in the CIS countries [1]. Radiation therapy is an effective adjunct treatment for many malignant neoplasms, including breast cancer. In fact, over 50% of cancer patients receive radiation therapy. Exposure to radiation causes damage and death of cancer cells, which is the cause of the development of both immediate and distant complications[2].

In the 118 recommendations of the International Commission on Radiological Protection, in the form of an independent radiobiological effect, the so-called long-term tissue reactions [3]. This finding is based on the analysis of long-term complications of radiotherapy in cancer patients and lies in a significant increase in cardiovascular risk. Considering these circumstances, in radiation oncology, it is recommended to take into account the individual factor of the patient's radiosensitivity when selecting the strategy and tactics of therapeutic procedures, especially in the therapy of localizations accompanied by irradiation of the heart muscle and the brain [3,4].

Given the above, and the growth rate of the risk group contingent, the problem of individual and population radiation risk assessment has been made a top priority in modern life sciences and medical sciences, and is currently the subject of large-scale research [5].

Initial and ongoing large-scale population randomized trials will study population dose loads in radiotherapy [4-10], the dependence of the risk of long-term complications on exposure dose, the role of various risk factors, including the role of the development of complications due to irradiation of various functional areas of the heart and concomitant cardiac anomalies, the study of predictors and markers of cardiac risk [11-15]. It should be noted that if in early studies the dose-dependence ratio of cardiological risk was (7.4% 1/Gy) [12], there are data according to which the risk is significantly higher (16% 1/Gy) and its manifestation is within 5 years. They also indicate the presence of a certain limit dose (5 Gy), after which a complication develops - that is, non-linear dependence of the dose-effect. However, according to a number of recent studies, there is no significant increase in cardiac complications [16], the probable explanation for this circumstance is the optimization of radiotherapy procedures and the reduction of the dose range used. There is no unified view on both predictors of distant complications and early markers of complication development.

Finally, the role of individual and population specificity in the risk of cardiac complications is unclear, the role of this factor in terms of both the risk of developing cancer and the effectiveness of its chemotherapeutic and radiotherapeutic interventions [17].

From all the above positions, the study of cardiological risks related to radiotherapy dosage loads and procedure in breast cancer patients is relevant in the population of Georgia: To refine the radiology procedure benefit/risk assessment methodology and to further optimize the strategy and tactics of therapeutic procedures: 1) For evaluations of the flow of cardiac patients related to radiotherapy and combined chemo and radiotherapy of oncological patients and for the optimal treatment of heart diseases олотой. 2) Analysis of population variability of cardiotoxicity of radiotherapy in terms to study its pathogenesis and integration of Georgia into current international studies in this area.

MATERIALS AND METHODS

Patients: The hystories of patients who underwent a course of radiation and combined radiation therapy and chemotherapy at the Kutaisi Christina Kiri Cancer Center in 2017-2018 were analyzed retrospectively.

A total of 1000 patient cases were analyzed (4 right side breast cancer, 60 left side breast cancer). Inclusion criteria: no cardiac complication at the time of irradiation, transmission fraction with echocardiological examination> 50. A potential case of cardiac complication was considered to be a reduction of the delay fraction by about 5–10 units. Information is collected with the consent of patients from their medical history.

Dose Evaluation: Patient irradiation program and dose evaluation were performed using conformal 3D and IMRT planning (ZXOX20) and eclipse system based on diagnostic CT scan and virtual simulation (ZXOX30). Total dose - 50 Gy, fractional dose - 2 Gy, additional dose - 10 Gy. MLC blocking was used to protect surrounding tissues. The minimum, maximum and mean dose (MHD)

Dosage loads in breast cancer radiotherapy:

Variation analysis (ANOVA) was used to assess the statistical reliability of the difference between the mean doses of right and left breast irradiation, and Grubbs' test was used to identify anomalous (outlier) values. Taking into account the asymmetry of the histograms of the dose distribution in patients, the numerical evaluation of the characteristic parameters of the distribution and their comparison with the existing literature data was performed by logarithm-normal distribution:

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

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

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 expressions:

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

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

The Shapiro-Wilk-test was used to assess the validity of the filtration results.

The Bayesian approach was used to integrate the data obtained by us with the results of various national and international surveys and thus to increase the representativeness and accuracy of our survey results. As a prior information was used [4-10] material published in the works on the distribution of cardiological dose loads in the respective populations. Aposterial dose distributions were considered as the updated probability distribution with the inclusion of a clinical cohort.

We performed the calculations within the Bayesian hierarchical model, approaching the known variance of a logarithmically-normally distributed random quantity. In this approximation, the relationship between the means of posterior and a priori distribution and the accuracy of its becomes simple[18]:

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

where m' and **p'**; m and p are the means and accuracy of the a posterior and a priori distributions, respectively, $D_i$is the mean dose of cardiac irradiation.Finally, for a posterior distribution we obtained the followingexpression:

$$P^i_{apost}(D|, m'_i, \sigma_i) = \frac{1}{D\sigma_i\sqrt{2\pi}} * e^{-\frac{1}{2\sigma_i^2}*[ln(D)-m'_i]^2} \quad (6)\ ;$$

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, a posteriori, and study cohorts using a ***t***-test.

Assessment of increase of Major Adverse Cardiovascular Event (MACCE) Rate After Breast Cancer Radiotherapy for the Georgian Female Population

The rate of major coronary events was modeled as **Bs(1+KD),** where **Bs** was the rate of major coronary events in the absence of radiotherapy, **D** was the dose of cardiac radiation (**in Gy**),and **K** was the percentage increase in the rate of major coronary events per gray[12].
From these positions, KD represents the percentage increase in major adverse cardiovascular event rate for typical dose loads for Georgia;
The mean value of the K coefficient and its 95% CI was taken [12] from the paper K = 7.4%, (95% CI, 2.9 to 14.5; P <0.001). These values clearly indicate the existence of right asymmetry in the density distribution function of K, which allows us to approximate its lognormal distribution.
By its definition, K can be thought of as a random value whose distribution coincides with the density of the MACCE rate increase (Eff) distribution under the condition D = 1Gy.
With this in mind and simple transformations, it can be shown that the conditional probability of Eff distribution density in the case of D-dose irradiation is described by the following expression:

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

finally, by combining and integrating the (6) and (7) distributions, we obtain the expected probability of a percentage increase in the major adverse cardiovascular event (MACCE) rate in the left and right sides of the Georgian population.

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

RESULTS AND DISCUSSION

Fig. 1 presentsMean values, standard errors, 95% confidentiality intervals and outliers of cardiac doses in radiotherapy of left (l) and right sided (r) breast cancer. The difference between them is statistical significant, however outliers indicate disturbed conditions of normalities of distribution.

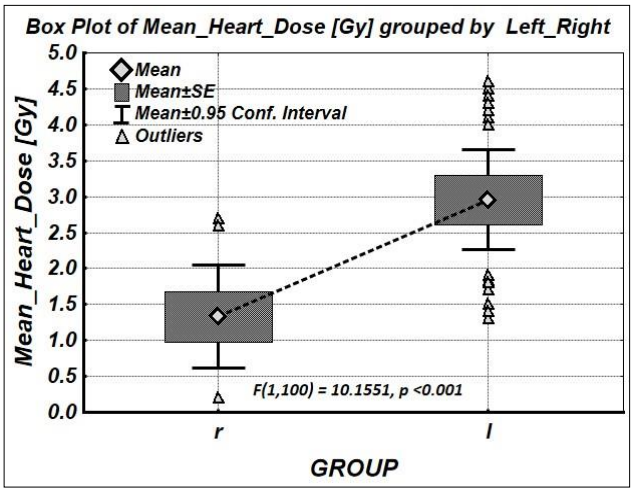


Fig.1. Mean value, standard error, 95% confidentiality interval and outliersof of cardiac doses in radiotherapy of left (l) and right sided (r) breast cancer

Asymmetry in distributions is clearly evident in dose distribution histograms (Fig.2). In order to compare the results of different studies, we considered it expedient to approximate histograms according to parametric theoretical distributions.

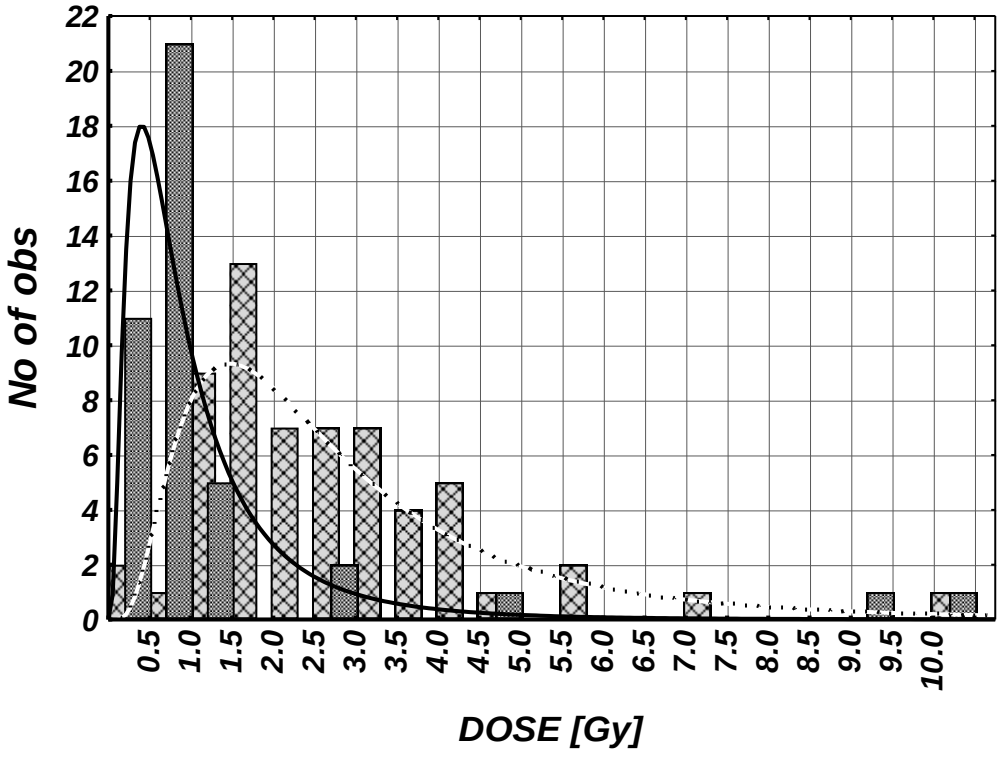


Fig.2. Histograms of cardiac doses distribution and their lognormal approximation in radiotherapy of left (dotted line) and right-sided (solid line) breast cancer

In order to simplify the calculations at this stage and to simplify the interpretation of the results, we considered the logarithmic-normal model to be optimal (Tab.1). The lognormal distribution is one of the important continuous distributions in statistics and due to the fact that it is positively skewed and the effect of a variety of forces working independently on the variability of the lognormal distribution is multiplicative.

Table 1. Meanvalue and standard deviation of distribution of mean heart doses, the mean and standard deviation of the normal distribution associated with lognormal approximation of mean heart doses distribution end value of the Shapiro-Wilk Test of normality

	M	**STD**	**Mean_N**	**Std_N**	**SW-W; p**
Mean Hearth Dose (Left)	2.95	2.69	0.85	0.69	0.97; p=0.33
Mean Hearth Dose (Right)	1.33	2.28	-0.23	0.82	0.95; p=0.07

It should be noted that the asymmetry of the distribution are considered as individual cancer anatomy and its treatment planning [7] and it can reflect both the population-specific aspects of carcinogenesis as well as the specifics of its therapy and in this regard can be used as a criterion for inter-population analysis.However, this is not the subject of this article and we will not discuss it at this point of view. As presented above, a significant proportion of anomalous doses and excesses are observed in the study cohort. Of particular importance in this regard is the assessment of stability, as each new individual case can make significant changes in revealing the patterns of average dose loads for the population and their distribution. Especially if it is based on a study of a limited number of cohorts in one particular clinic. No less important is the question of the representativeness of the cohorts. Considering similar and many other factorsthe US Food and Drug Administration (FDA) has recommended the use of Bayesian statistics in clinical trials of medical devices [21]. Traditional (frequentist) statistical methods may use information from previous studies only at the design stage. In contrast, the Bayesian to formally combine prior information with current information on a quantity of interest. The Bayesian idea is to consider the prior information and the trial results as part of a continual data stream, in which inferences are being updated each time new data become available [21]. In our study, a priori information was taken from data from European Union Countriesabout cardiac dosesIn breast cancer radiotherapy (*Table 2.*)

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	**Y**	**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

There is a clear tendency to reduce cardiac doses, which is explainedwith the introduction of new technologies in radiotherapy. These technologies, such as three-dimensional treatment planning with dose-volume histogram, intensity-modulated radiotherapy (IMRT) image-guided radiotherapy (IGRT), and active breathing controlled (ABC) radiotherapy have the potential to reduce the risk of radiation-related heart problems.

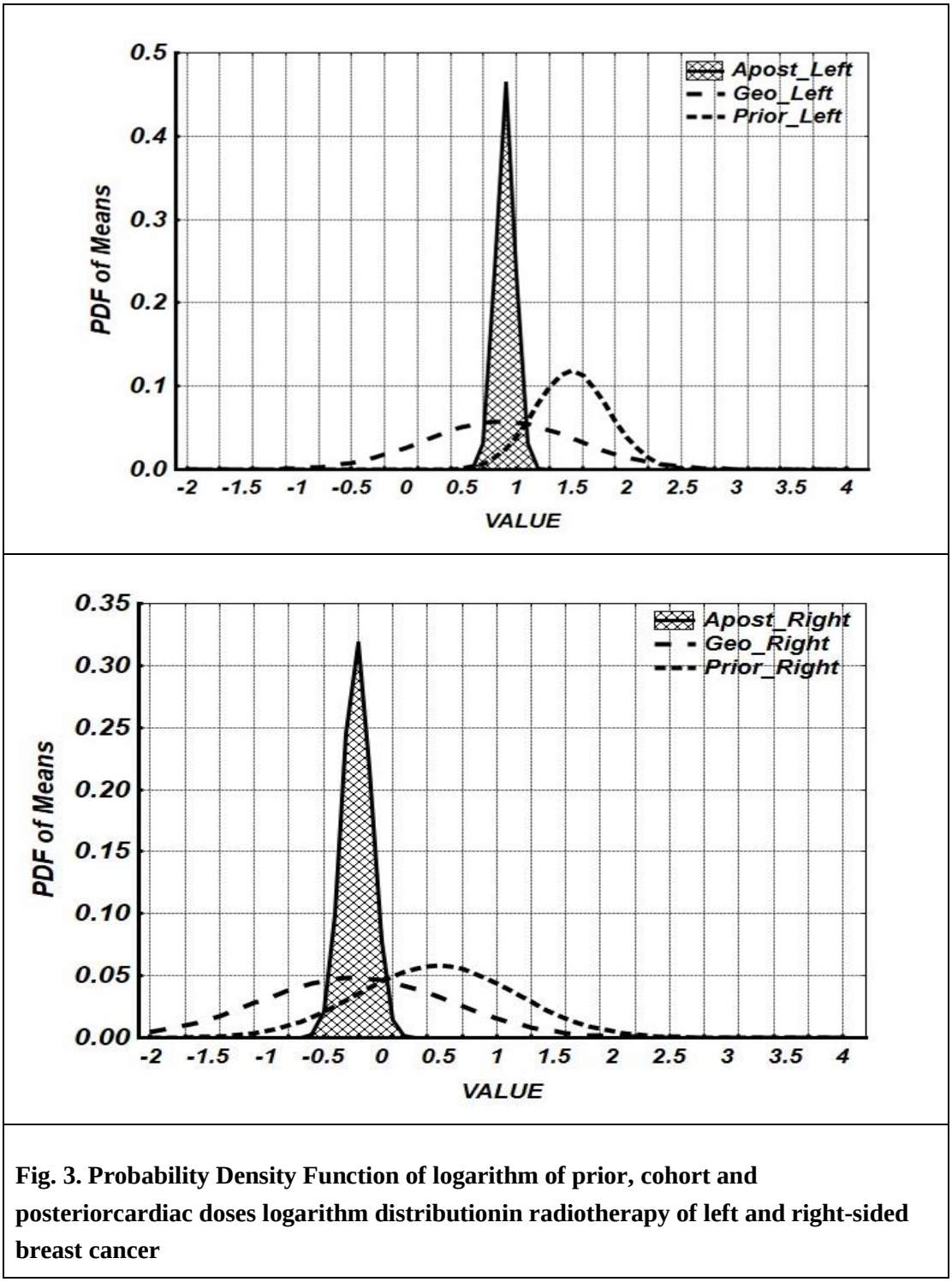


Fig. 3. Probability Density Function of logarithm of prior, cohort and posteriorcardiac doses logarithm distributionin radiotherapy of left and right-sided breast cancer

As shown in Table 2 and Figure 3, the posterior means of the mean heart dose is practically no different from the mean of the cohort, although the mean dispersion and consequently the informational value of the estimate is increased approximately 7-fold

Table 3. Cardiac doses logarithm distribution mean 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

Based on the above, theaverage value of the dose load can be considered as an updated value of the literature and a characteristic of the dose load in the Georgian population in the first approximation. It should be noted that the dose loads on the heart during left-sided radiation in Georgia practically coincide with the results of the latest (BACCARAT) examinations, although the right-sided doses are almost three times higher. Interpretation of this fact requires further analysis.

Figures 4, 5 represents the theoretical function of the dose dependence of conditional probability of percentage increase and dose dependence functions of distribution of this indicator for left and right side radiation in Georgia, calculated by expression (8).

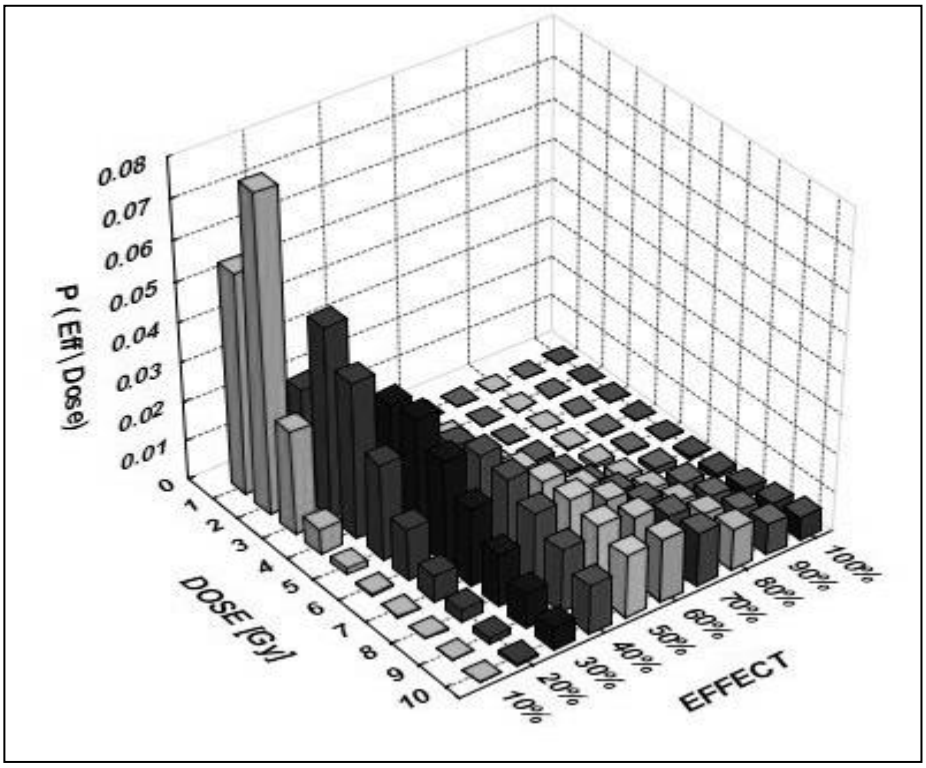
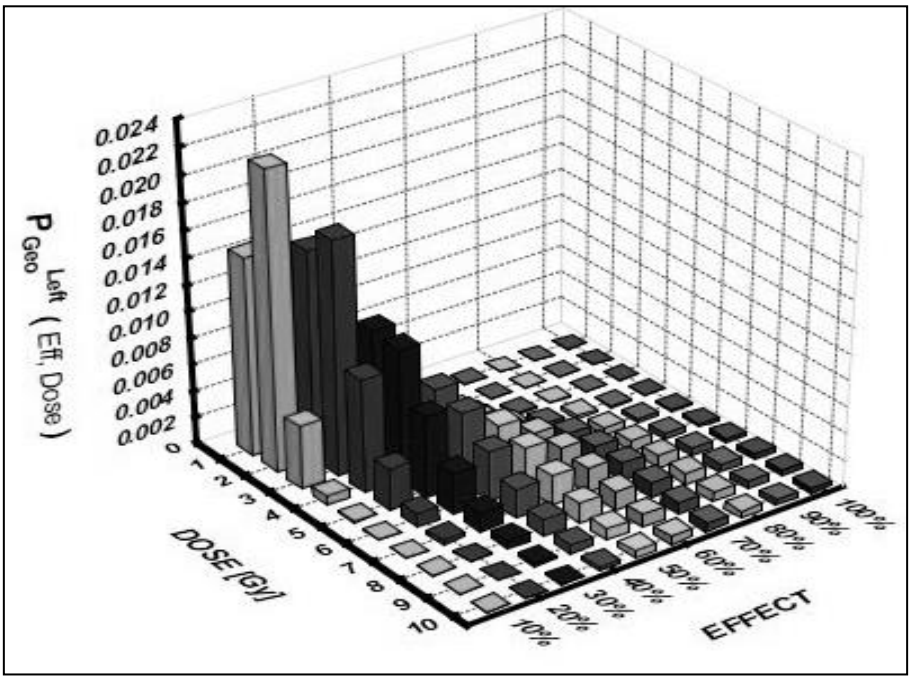


Fig.4Conditional probability density function of Percentage Increase of Major Adverse Cardiovascular Event Rate (EFFECT) for given dose

The conditional probability of percentage increase is characterized by a pronounced peak in the relatively small dose range, while the range of percentage increase varies with increasing dose, indicating a high degree of cardiac risk uncertainty in the high dose range. This complicates the prognosis of cardiac risk in the high-dose radiation range.

By integrating expression (8), we obtain the expected value of major adverse cardiovascular event (MACCE) rate percentage increase in the Georgian population in terms of cardiac dose, it is about 19% for left-sided radiation, and about 6% for right-sided radiation. Left-sided irradiation is Mostly localized in the 10-40% range (dose range 2-4 Gy), while left-sided irradiation is mostly localized in the 5–10% range. These data provide a somewhat remote cardiovascular risk assessment when planning a radiotherapy procedure.



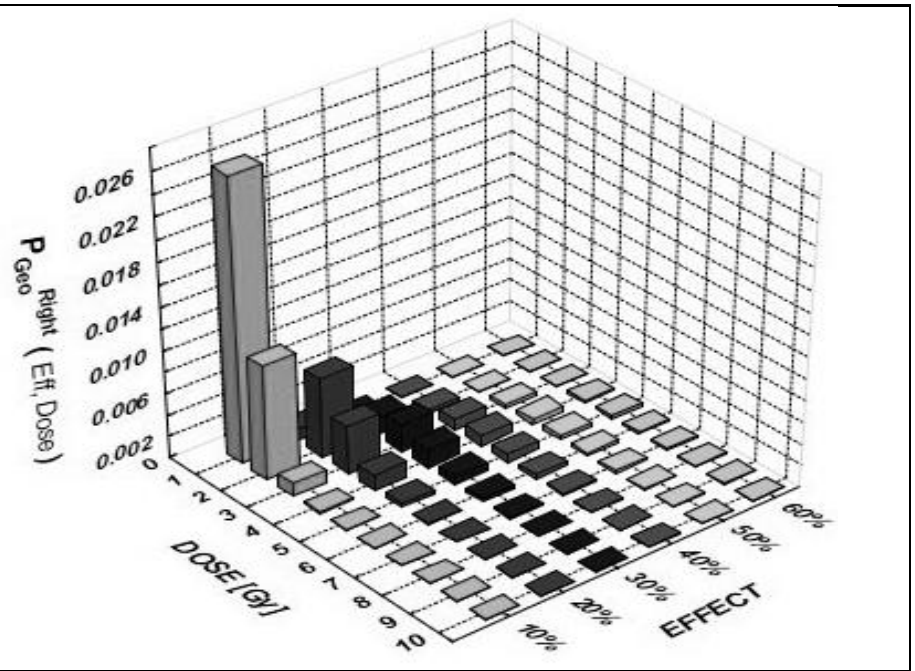


Fig.5. Expected distribution of Probability Density Function of Percentage Increase of Major Adverse Cardiovascular Event Rate (EFFECT) from the dosein Georgian breast cancerpatients

CONCLUSION

From the obtained results, the ways of further optimization of breast cancer radiotherapy are the further clarification of the distant cardiological risk in the relatively small dose range of radiotherapy, further refinement of the radiotherapy "benefit-risk" evaluation methodology with consideration of distant tissue effects after radiotherapeutic effects.

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