Original Article

Radiobiological estimation of radiation-induced heart complication of postmastectomy radiation therapy patients using the relative seriality model

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Abstract

Background and Aim: In Nigeria today, most radiotherapy (RT) centers do manual planning using anatomical landmarks rather than precise planning using imaging modalities such as Computerized Tomography and Magnetic Resonance Imaging. This puts the collateral organs at a greater risk of damage. The objective of this study is to carry out a comparison of the risk of cardiac complication in the right and left breasts of postmastectomy radiation therapy patients using radiobiological evaluation tools.

Methods: Ninety-six patients treated in the University of Benin Teaching Hospital, RT Center, Nigeria, between January 2012 and March 2014 were recruited for this study. The relative seriality model was used to compute the risk of cardiac mortality to the breast of these patients.

Results: The results showed that the equivalent uniform dose (EUD) to the heart for patients with left breast cancer is significantly ($P < 0.05$) higher than the EUD to the heart of patients with right breast and also the risk of cardiac mortality is significantly ($P < 0.05$) higher in the left breast than the right breast; due to proximity to the heart to the left side.

Conclusion: This implies that the long-term risk of having cardiac disease should be of particular concern for women treated for left-sided breast cancer. As a result of this, care should be taken in planning patients using computerized treatment planning system that embraces imaging simulation rather than the conventional anatomical landmark; this will go a long way to prevent cardiac-induced mortality especially in cancer of the left breast.

Keywords: Cardiac, cardiovascular, ionizing radiation, mortality, radiobiology

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INTRODUCTION

Breast cancer is becoming a progressively survivable disease with increasing number of long-term survivors due to advances in its diagnosis and treatment. The focus of study is now shifting from radiation toxicity to toxicity due to long-term therapy. Although randomized trials have shown that breast irradiation significantly decreases the prevalence of recurrence in the ipsilateral breast of women with either invasive or *in situ* breast cancer,[1-5] long-term survivors may develop late radiation toxicity due to the doses delivered

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to the heart and the coronary arteries. During the second part of the 20th century, the radiation doses delivered to these structures were high; for example, it was estimated that breast or chest wall radiotherapy (RT) resulted in whole heart doses of 0.9–14.0 Gy for left-sided and of 0.4–6.0 Gy for right-sided irradiation. Internal mammary chain RT delivered heart doses of 3–17 Gy and 2–10 Gy for left- and right-sided irradiation, respectively.[4]

Radiation therapy (RT) plays a central role in the treatment of breast and other thoracic malignancies. Statistics has it that >50% of these patients receive RT at some point of time.[6] As a matter of great concern is the long-term toxicity from RT, as early diagnosis and the improvement in the treatment of these cancers has increased the survival of patients. One of the indices is radiation-induced heart disease (RIHD) which can offset the progress in cancer specific mortality. Most thoracic malignancies such as mediastinal lymphoma, breast, esophageal, and lung delivers significant radiation dose to the heart.

Survivors of breast cancer and Hodgkin disease (HD) are at a greater risk of RIHD because they have a relatively longer cancer specific survival.[6] This disease condition usually occurs with a latent period of 10–15 years and in younger patients, it is of special concern as they tend to survive longer. RIHD includes a range of cardiovascular complications ranging from subclinical microscopic changes to overt heart failure. These complications can be further divided into pericardial, myocardial, vascular, valvular, or conduction abnormalities. While the most common complications are pericardial, conduction abnormalities are the least common. Pericardial complications range from asymptomatic pericardial effusion to constrictive pericarditis. Symptomatic cardiac disease after radiation occurs in approximately 10% of the patients.[7]

In developed countries, this risk is decreasing as a result of dose reduction which is a consequence of conformal treatment.[8] The most common end-point of RIHD is pericarditis but myocardial insufficiency and ischemic HD may also occur. Long-term follow-up is essential as the incidence of RIHD begins to increase 10 years after the treatment and is progressive with time. Addition of cardiotoxic chemotherapeutic agents can further aggravate cardiac disease development.

The risk of developing cardiovascular disease after whole-body exposure to radiation was first demonstrated in Japanese atomic bomb survivors. First convincing evidence that radiation can cause HD is reported by the Stockholm group.[9] Later, it was reported that the incidence of HD was increased in those atomic bomb survivors who received a moderate dose of around 0.5–2 Gy. RIHD has been traditionally reported in patients who received RT for breast cancer and HD because of relatively better survival and follow-up in these patients. Radiation dose received to the heart depends on the technique, patient positioning, beam energy, and total dose used for treatment.[10]

In 1987, Cuzick *et al*. reported that patients who received RT for breast cancer had excess noncancer-related mortality after 10 years of completion of treatment.[11] The study included 8000 breast cancer patients who were randomized to receive RT or not. They reported that cardiac mortality was the primary cause of excessive mortality in these patients after 10 years. The surveillance, epidemiology, and end results cancer registry database was the first to report cardiovascular risk in left versus right-sided breast cancer patients.[12] It was inferred that patients who received postmastectomy RT for left-sided breast cancer were 2–3 times at a higher risk of developing cardiovascular disease. The risk was higher in those patients who received RT to internal mammary lymph nodes.

The aim of this study is not only to compare the risk of cardiac complication in the right and left breasts of postmastectomy radiation therapy patients using radiobiological evaluation tools; however, the need to emphasize the need to embrace computerized treatment planning system; as in obtained in many developed countries. This will help to eliminate or reduce to barest minimum the risk of cardiac mortality.

MATERIALS AND METHODS

Ninety six patients treated in the University of Benin Teaching Hospital RT Center, Nigeria, between January 2012 and March 2014 for breast cancer after mastectomy were recruited for this study. All patients underwent computed tomography simulation in the supine position on an angled board, with both arms placed above the head, which was rotated to the contralateral side (GET Brightspeed CT-scanner, GE Medical Systems). Patients received 50 Gy in 25 fractions over 5 weeks to the primary site chest wall, corresponding axillae and supraclavicular region using tangential field anterior-posterior-posterio-anterior and direct anterior, respectively. The direct anterior was given to the supraclavicular lymph node. The tangential fields were to treat the internal maxillary and axillary lymph nodes. The Elekta PrecisePlan was used for this process. The patients were treated on a linear accelerator with two 6 MV photon beams.

Theory

Equivalent uniform dose

This is defined as the uniform dose that, if delivered over the same number of fractions as the nonuniform dose distribution of interest, yields the same radiobiological effect.[13]

The phenomenological formula for the generalized EUD (i.e., normal and tumor cells) as proposed by[14] is

$$\mathrm{EUD} = \left(\sum_{i}^{n} v_{\mathrm{i}} D_{\mathrm{i}}^{\mathrm{a}} \right)^{\frac{1}{\mathrm{a}}} \qquad (1)$$

Where v_{i} is fractional organ volume receiving a dose of D_{i}, n is the number of bins in the DVH and a is tissue-specific parameter that describes the volume effect. The organ under discourse in this study is the heart.

Relative seriality model

The biological model used in this study was the RS model,[15] which is based on Poisson statistics to describe cell survival. The model was chosen because it accounts for both serial and parallel architecture of the functional subunit (FSU) and for the binomial nature of cell kill. For a heterogeneous dose distribution, the complication probability is given by

$$\mathrm{NTCP} = \left(1 - \prod_{i=1}^{n} \left[1 - P\left(D_{\mathrm{i}}\right)^{\mathrm{s}} \right]^{\mathrm{v_i}} \right)^{\frac{1}{\mathrm{s}}} \qquad (2)$$

$$P\left(D_{\mathrm{i}}\right) = 2^{-\mathrm{e}\cdot\gamma\left(1-\frac{D_{\mathrm{i}}}{D_{50}}\right)} \qquad (3)$$

Where v_{i} is the fractional organ volume receiving a dose D_{i}, n is the number of subvolumes in the dose volume histogram (DVHs), s is the RS of the organ which is defined as the ratio between the number of serial FSUs to the total number of FSUs (serial organ: $s = 1$, parallel organ: $s = 0$). D_{50} is the dose associated with 50% complication probability. P (D_{i}) is the probability of complication; γ is the slope parameter with impact on the steepness of the sigmoid-shape dose-response curve. Parameters used in this study was retrieved from Gagliardi *et al*.[16] The calculated normal tissue complication probability (NTCP) value is a radiobiological index used in this study to estimate the risk of complication.

Data analysis

BioSuite™ (version 12.2) was used to read the absolute differential DVHs files from the computerized treatment planning system; which runs a Linux Red Hat operating system. On importing the DVH files into the Biosuite software helps to compute the EUD and NTCP. Descriptive statistics (percentage, median, interquartile range [IQR]) was used to analyze the EUD and NTCP. Kolmogorov–Smirnov (KS) test of normality was used to test the normality of the continuous dataset, where there was a significant difference from normality, nonparametric test statistics was used, if not significant, the parametric statistics was used. Mann–Whitney U test statistics was used to compare between the left and right breast NTCP and EUD for statistically significant difference. The level of significance was set at $P < 0.05$. The analyses were done using STATA version 12 (StataCorp, Texas, USA).

RESULTS

To check for the distribution of EUD and NTCP, a normality plot was done on a histogram, before subjecting it to normality test statistics. The histogram showed that the data (EUD and NTCP) is skewed from classical normal distribution [Figures 1 and 2]. The KS normality statistics for EUD was 0.838 with a $P = 0.002$, while for NTCP was 0.238; $P = 0.000$.

Figure 3 shows the box-plot of the EUD for the left and right breasts of the patients. The median (IQR) EUD for the right breast was 83.55 (59.85–150.68) cGy; while that of the left breast is 211.20 (108.50–319.50) cGy. The difference in EUD is statistically significantly different (Mann–Whitney $U = 19.00$; $P = 0.039$).

Figure 4 shows the Box-plot of the NTCP for the left and right breasts of the patients. The median IQR NTCP for the right breast was 0.40 (0.40–0.48) cGy; while that of the left breast is 0.60 (0.50–0.80) cGy. The difference in NTCP is statistically significantly different (Mann–Whitney $U = 13.00$; $P = 0.007$).

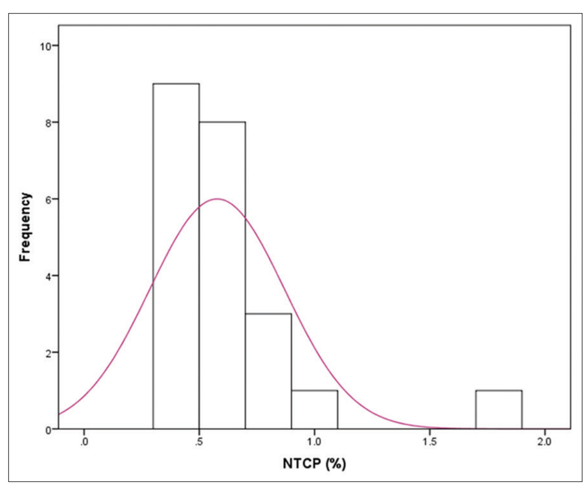

Figure 1: Histogram showing normality plot for normal tissue complication probability

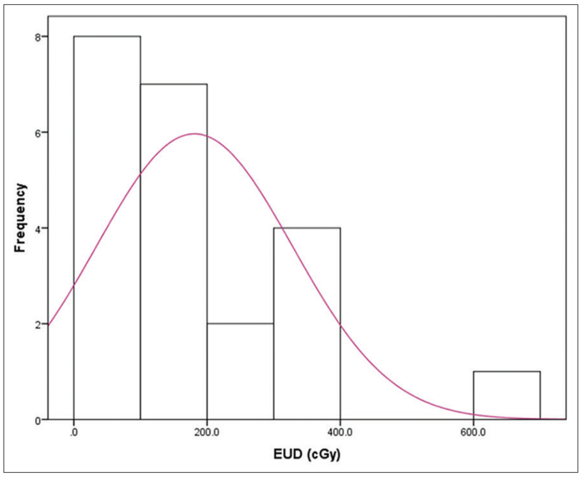

Figure 2: Histogram showing normality plot for equivalent uniform dose

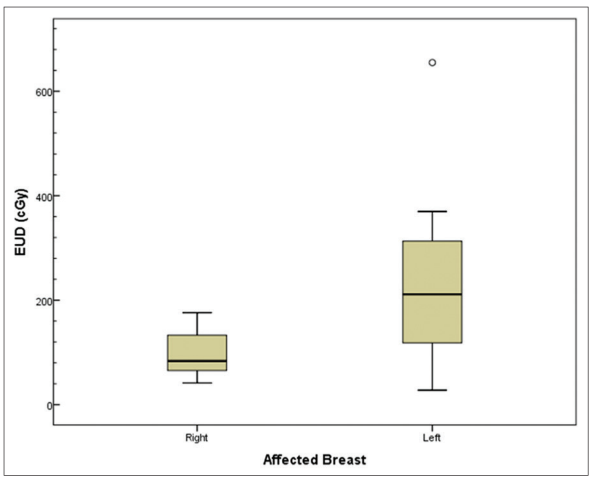

Figure 3: Box-plot showing the equivalent uniform dose of the heart for the left and right breasts of the patients

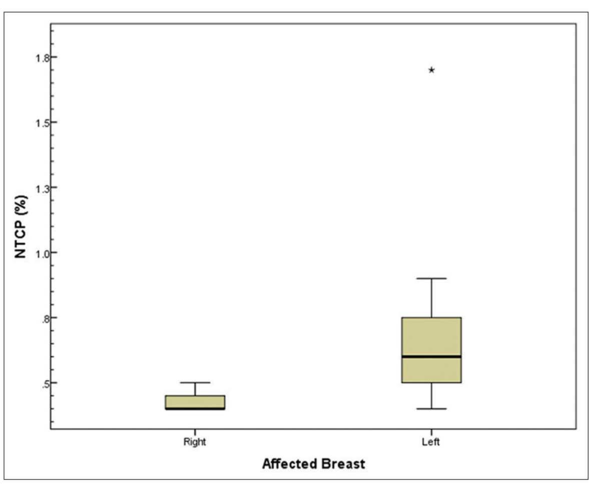

Figure 4: Box-plot showing the normal tissue complication probability of the heart for the left and right breasts of the patients

DISCUSSION

The median EUD of the hearts calculated in this study for patients with right breast was 0.83 Gy; while for those patients with left breast cancer was 2.11 Gy. The difference in equivalent uniform dose was significantly higher in the left breast cancer patients than the right breast cancer patients. These values are low compared to that reported by Taylor *et al.*,[17] who reported that HD risk for women with mean heart dose of 5 Gy and 5–15+ Gy increased by 15% and 108%, respectively. Therefore, there is nothing to worry about from the point of view of heart complications.

Our results validate higher risk of cardiac induced mortality among left breast cancer patients than the right. The result are consistent with several randomized,[1,18-20] observational studies,[21-23] and systematic reviews[3,24,25] In this study, the risk of cardiac disease due to RT was estimated to be 0.4% and 0.6% for the right and left breast cancer patients, respectively. These values are in agreement with those obtained in other studies, most of which demonstrated higher cardiac mortality following RT for a left-sided breast cancer than for a right-sided lesion.[22,23,26-28] This risk value is also in agreement with the study of Bouillon, *et al.*,[29] who estimated a relative risk of cardiac mortality following RT for a left-sided tumor versus a right-sided tumor was 1.28 (95% CI: 0.92–1.78) and increased with increasing follow-up.

CONCLUSION

We determined the risk of cardiac mortality of post-mastectomy patients that have undergone external beam radiotherapy in Nigerian facility. The results showed that the dose to the heart of patients treated for the left breast cancer is significantly higher than the right and also the risk of cardiac mortality is significantly higher in the left breast cancer patients than the right breast cancer patients. The heart is mostly located on the left side of the thoracic cage and thus in closer to the left breast than the right breast. The heart therefore receives more radiation from the left breast than the right breast during radiation therapy. This shows that the long-term risk of having radio-induced cardiac complications is of concern in women treated for left-sided breast cancer; and the use of computerized treatment planning system in African countries will go a long way to increase or eliminate this risk.

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Conflicts of interest

There are no conflicts of interest.

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