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CLINICAL TRIAL

Evaluation of radiation-induced cardiac toxicity in breast cancer patients treated with Trastuzumab-based chemotherapy

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Abstract

Purpose Patients with Her2-positive breast cancer treated with trastuzumab have higher rates of cardiotoxicity (CT). Left-breast radiation might increase the risk for CT from cardiac exposure to radiation. The goal of our study is to evaluate the contribution of radiotherapy (RT) in the development of CT in breast cancer patients receiving trastuzumab.

Methods Two hundred and two patients were treated with RT and trastuzumab from 2000 to 2014. The RT plans for left-side disease were recalled from archives. The heart, each chamber, and left anterior descending artery (LAD) were independently contoured. New dose-volume histograms (DVH) were generated. Their serial left-ventricular ejection fractions (LVEF) were studied. CT for left and right side were compared using Fisher's exact test. The DVH data were correlated with the predefined cardiac events using actuarial Cox regression analysis.

Results Compared to the right sided, the left-side cases showed statistically significant development of arrhythmia (14.2%) versus (< 1%) ($p<0.001$). Cardiac ischemia was found in 10 patients in left and one patient in right side ($p=0.011$). The equivalent uniform dose (EUD) to the left ventricle (LV), right ventricle (RV), and LAD was significantly associated with decrease in LVEF by > 10% ($p=0.037$, $p=0.023$ and $p=0.049$, respectively).

Conclusions Among patients treated for left-sided lesions, there were no significant differences in EF decline. However, there was a higher rate of ischemia and arrhythmia compared to those with right-sided disease. The EUD index of LV, RV, and LAD could be considered as a parameter to describe the risk of radiation-induced CT.

Keywords Radiotherapy · Trastuzumab · Cardiotoxicity · Dose-volume histograms

Introduction

Although breast cancer is among the most common malignancies worldwide [1], contemporary treatments herald excellent disease control [2, 3]. Thus, there is a growing global community of breast cancer survivors who were treated with surgery, chemotherapy, and radiation, and for whom long-term toxicities are of concern. Radiation therapy (RT) yields locoregional control and overall survival (OS) benefits [3], yet it is not without significant long-term risks.

RT-associated cardiac toxicity has been reported among breast cancer survivors [4]. This late adverse effect may manifest as various cardiac injuries including left-ventricular dysfunction, decreased myocardial perfusion/ischemia, heart failure, pericarditis, and/or valvular dysfunction [5]. Reports suggest that many RT-associated cardiac effects are irreversible, and that time to symptom development varies

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depending on disease nature, pre-existing susceptibility, and age [6]. These toxicities could be a function of the volume and location of the part of the heart exposed to specific dose of radiation [7]. Reducing cardiotoxicity could be achieved by manipulating radiation delivery techniques, planning, and dosimetry.

In addition to RT, systemic therapies (e.g., doxorubicin and trastuzumab) have also been linked to adverse cardiac outcomes. For example, trastuzumab has been shown to manifest a reversible cardiac event [8] in 4% of patients [9], including those without pre-existing cardiac disease.

Therefore, the routine combination of RT with cardiotoxic systemic therapies may increase morbidity. Here, we aim to evaluate the association of breast/chest wall and regional lymph node irradiation with the development of cardiac toxicity in breast cancer patients receiving relevant systemic therapy (trastuzumab based). By elucidating the potential cardiotoxic interaction between RT and systemic agents, we hope to further inform the application of adjuvant radiotherapy in a risk-adjusted manner.

Methods

The study was approved by the institutional review board. RT metrics and cardiac outcomes were collected for 202 patients who were treated between 2000 and 2014 at our institution. Patients with HER2 + breast cancer confirmed by immunohistochemistry (3+) or fluorescent in-situ hybridization were included. All patients received RT, trastuzumab, and chemotherapy. All evaluable patients underwent baseline cardiac imaging via echocardiogram and/or nuclear imaging and at least one study in the first year post treatment. It should be noted that a baseline EKG was not routinely available for all patients. To make sure that any reported cardiac events in the EKG post treatment are de novo, all patients had baseline assessment of their past medical history including any cardiac morbidity in their medical notes.

Radiation plans and segmental metrics were evaluated for 106 patients with left-sided disease including overall heart dose, dose to each chamber, and dose to the left anterior descending artery (LAD) space. We contoured the heart and the different structures according to the RADCOMP atlas [10]. We used the XiO Treatment Planning System by CMS Inc for photon plans and MiM 6 by MiM Software Inc for proton plans. New DVH-based dosimetric indices, including V10, V20, mean, median, max dose, and equivalent uniform dose (EUD), were created and evaluated for an association with cardiac toxicity.

Cardiac outcomes were collected for each patient, including the development of cardiac ischemia, arrhythmia, heart failure, wall motion abnormalities, left-ventricular ejection fraction (LVEF) decline of more than 15% or 10%, and other miscellaneous cardiac events as noted. Right-sided breast cancer cases were used as a control.

Descriptive statistics were used to characterize baseline patient and treatment characteristics. The crude rates of cardiac events for left and right-sided cancers were compared using Fisher's exact test. Logistic regression multivariate analysis was used to identify predictors of cardiac toxicity. Dose-volume histogram indices including the EUD (which assumes that any two dose distributions are equivalent if they cause the same radiobiological effect which takes into account the inhomogeneity of the dose distribution) [11] for left-sided cases were correlated with the predefined cardiac events using actuarial Cox regression analysis. The Kaplan–Meier method was used to estimate overall survival (OS) and disease-free survival (DFS). For all analyses, two-sided p values of < 0.05 were considered statistically significant.

Results

Patient and treatment characteristics

Among 202 evaluable patients, 106 had left-sided disease (Arm A), and 96 were right sided and considered the control arm (Arm B). Median follow-up was 81 months among left-sided cases vs 84 months for the right-sided group. About 55% of patients underwent lumpectomy with 58.5% and 52% of the left- and right-sided cases underwent axillary lymph node dissection ALND, respectively ($p = 0.4$), while sentinel lymph node was done in 49% in left side and 58.3% in right side ($p = 0.2$). Baseline clinicopathologic data are noted in Table 1.

There were no significant differences between groups regarding adjuvant or neoadjuvant systemic therapies (Table 2). Among both groups, trastuzumab was administered for a median of 49 weeks. Survival analyses (Fig. 1) similarly demonstrated no differences in 5 years DFS or OS (The 5-year DFS was 91.8% (95% CI 84.1–95.8%) for left side and 92.3% (95% CI 84.4–96.2%) for the right side (log-rank test $p = 0.7$). The 5-year OS was 98.7% (95% CI 91.4–99.8%) for left side and 97.5% (95% CI 90.3–99.4%) for right side (log-rank test $p = 0.9$). Systemic and locoregional treatments are detailed in Table 2.

The majority of patients received whole breast/chest wall RT ($n = 105$, 99.1% in left side and $n = 93$, 96.9% in right side); one patient in Arm A and three patients in Arm B received accelerated partial breast irradiation (APBI). The deep-inspiration breath-hold technique was used among 26.4% of study patients (Arm A), 82.1% of them treated during or after 2010. A boost was administered to 87.7% of patients in Arm A and 84.4% in Arm B ($p = 0.54$). There were no significant differences between groups in the

Table 1 Clinicopathological data

	Left side (106)	Right side (96)	*p* value
Median age	47	51	0.14#
BMI	27	27	0.68#
Surgery			1.0*
Lumpectomy	58 (54.7%)	53 (55.2%)	
Mastectomy	48 (45.3%)	43 (44.8%)	
Final pathologic stage			0.092*
Stage 0	18 (16.98%)	7 (7.29%)	
Stage 1	32 (30.19%)	39 (40.63%)	
Stage 2	41 (38.68%)	32 (33.3%)	
Stage 3	15 (14.15%)	18 (18.8%)	
Tumor grade			0.53*
Grade 1	1 (0.9%)	1 (1%)	
Grade 2	26 (24.5%)	29 (30.2%)	
Grade 3	73 (68.9%)	64 (66.7%)	
Not assessed	6 (5.7%)	2 (2.1%)	
ER receptors			0.88*
Positive	71 (67%)	66 (68.8%)	
Negative	35 (33%)	30 (31.2%)	
Pre-existing cardiac condition			0.77*
Yes	7 (6.6%)	5 (5.2%)	
No	99 (93.4%)	91 (94.8%)	
Pre-existing hypertension			0.1*
Yes	21 (19.8%)	29 (30.2%)	
No	85 (80.2%)	67 (69.8%)	

*Fisher's exact

#Wilcoxon rank-sum

delivery of supraclavicular nodal irradiation (60.4% Arm A vs 61.5% to Arm B; $p=0.89$) or internal mammary fields (20.8% to Arm A vs 13.5% to Arm B; $p=0.2$). Patients were treated with photons except for five in Arm A and one patient in Arm B who received protons.

Cardiac outcomes by disease laterality and cardiac doses

Among patients treated for left-sided lesions and with baseline and post-treatment cardiac imaging, there were no significant differences in EF decline between groups ($p=0.74$ for the decrease in EF with > 10% and 0.79 for the decrease in EF with > 15%). However, there was a higher rate of ischemia diagnosed by EKG than those with right-sided disease (9.4% vs 1%; $p=0.011$). Similarly, the rate of arrhythmias was higher for patients with left-sided disease (14.2% vs 1%; $p<0.001$) Table 3.

Multivariate analysis demonstrated that increasing age at diagnosis was a significant factor for the development of arrhythmia [$p=0.017$, odds ratio (OR) 1.07], and, as above, left-sided treatment was more likely to yield arrhythmia

Table 2 Treatment received

	Left side (106)	Right side (96)	*p* value
Neoadjuvant			0.20*
Yes	48 (45.3%)	34 (35.4%)	
No	58 (54.7%)	62 (64.6%)	
Chemotherapy median duration	15 weeks	15 weeks	0.46#
Trastuzumab median duration	49 (36, 52)	49 (36, 51)	0.74#
Radiation therapy			0.35*
Whole breast	105(99.1%)	93(96.9%)	
Partial breast	1(0.9%)	3(3.1%)	
Supraclavicular field			0.89*
Yes	64 (60.4%)	59 (61.5%)	
No	42 (39.6%)	37 (38.5%)	
Internal mammary field			0.20*
Yes	22 (20.8%)	13 (13.5%)	
No	84 (79.2%)	83 (86.5%)	
Boost			0.54*
Yes	93 (87.7%)	81 (84.4%)	
No	13 (12.3%)	15 (15.6%)	

#Wilcoxon rank-sum

*Fisher's exact

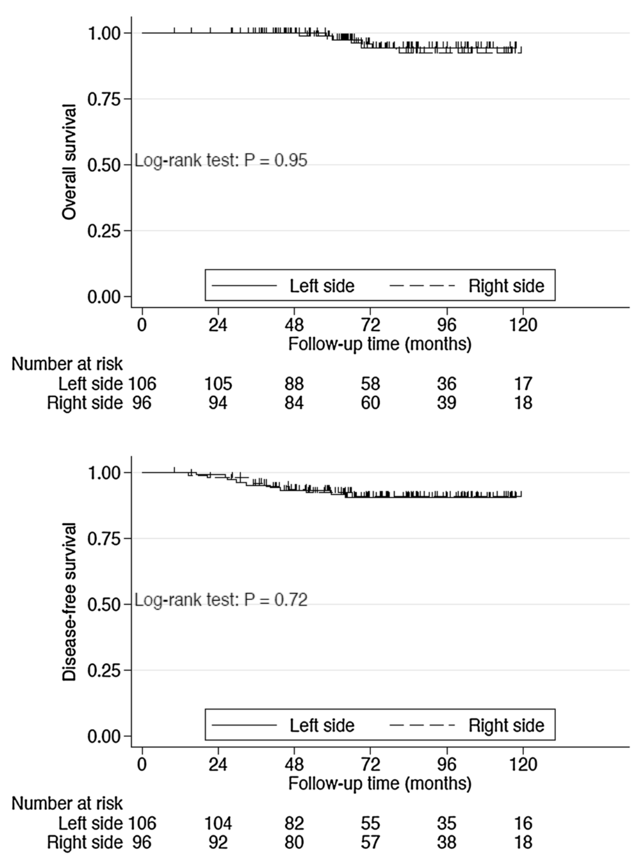

Fig. 1 A and B disease-free and overall survival curves

Table 3 Comparison of cardiac toxicity

	Left side (106)	Right side (96)	*p* value
Arrhythmia			< 0.001*
No	91 (85.8%)	95 (99%)	
Yes	15 (14.2%)	1 (1%)	
Ischemia			0.011*
No	96 (90.6%)	95 (99%)	
Yes	10 (9.4%)	1 (1%)	
EF decrease more than 10%			0.74*
No	83 (78.3%)	73 (76%)	
Yes	23 (21.7%)	23 (24%)	
EF decrease more than 15%			0.79*
No	98 (92.5%)	90 (93.8%)	
Yes	8 (7.5%)	6 (6.2%)	

($p=0.005$) and ischemia ($p=0.021$) than right-sided treatment (Table 5).

With regard to cardiac metrics illustrated in Table 4, right ventricle (RV) Dmax and EUD15 were each significantly correlated with > 10% decrease in EF ($p=0.017$ and 0.023, respectively); however, no RV metrics were associated with ischemia or arrhythmias. For the left ventricle (LV), significant associations were observed between the LV V10, EUD3, and > 10% decrease in EF ($p=0.023$ and $p=0.037$, respectively) (Table 5). As with the RV, no LV metrics were significantly predictive of the development of arrhythmia or ischemic events.

The LAD space Dmax, EUD3, EUD5, and EUD15 were all significantly associated with > 10% decrease in EF ($p=0.036$, $p=0.049$, $p=0.04$ and $p=0.035$, respectively), while the LAD V10 and D-mean approached significance ($p=0.067$ and 0.066, respectively). Of note, no significant correlation was seen between LAD dosimetry and the development of arrhythmia or ischemia.

Table 4 Cardiac dosimetric study for decrease in EF more than 10%

Factor	EF_ decrease > 10% (yes) (23)	EF_ decrease > 10% (No) (83)	*p* value
Heart_V10, median	1.65 (0.50, 3.47)	0.68 (0.06, 2.24)	0.094
Heart_V20, median	0.29 (0.07, 1.57)	0.17 (0.00, 1.04)	0.26
Heart_dmax, median	45.90 (27.10, 54.50)	35.80 (20.70, 47.80)	0.086
Heart_dmean, median	1.41 (1.00, 1.99)	1.06 (0.78, 1.82)	0.17
Heart_eud3, median	5.75 (3.17, 8.91)	4.20 (2.02, 7.23)	0.11
Heart_eud5, median	9.70 (6.26, 16.90)	8.00 (3.42, 12.86)	0.11
Heart_eud15, median	24.30 (14.76, 34.56)	18.35 (10.12, 28.23)	0.087
Ventricle_R_V10, median	0.69 (0.03, 4.37)	0.06 (0.00, 3.47)	0.090
Ventricle_R_V20, median	0.04 (0.00, 0.85)	0.00 (0.00, 0.59)	0.29
Ventricle_R_dmax, median	25.50 (14.00, 49.80)	17.10 (5.40, 36.00)	**0.017**
Ventricle_R_dmean, median	1.69 (1.06, 2.47)	1.31 (0.76, 2.53)	0.15
Ventricle_R_eud5, median	7.46 (3.49, 14.97)	3.87 (1.68, 11.16)	0.058
Ventricle_R_eud15, median	13.05 (7.06, 32.05)	9.44 (3.15, 20.62)	**0.023**
Ventricle_L_V10, median	2.48 (0.48, 6.74)	0.62 (0.01, 3.01)	**0.023**
Ventricle_L_V20, median	0.28 (0.00, 2.67)	0.09 (0.00, 0.86)	0.15
Ventricle_L_dmax, median	41.60 (19.40, 54.10)	29.90 (11.00, 47.70)	0.068
Ventricle_L_dmean, median	1.75 (1.26, 3.71)	1.45 (1.04, 2.43)	0.11
Ventricle_L_eud3, median	5.87 (3.26, 12.48)	4.06 (1.74, 7.14)	**0.037**
Ventricle_L_eud5, median	9.29 (5.44, 21.04)	6.38 (2.58, 12.35)	0.053
Ventricle_L_eud15, median	22.73 (9.58, 37.01)	15.82 (5.77, 27.47)	0.064
LAD_V10, median	23.22 (4.31, 46.93)	8.01 (0.00, 37.14)	0.067
LAD_V20, median	5.13 (0.00, 30.50)	0.65 (0.00, 17.67)	0.14
LAD_dmax, median	41.10 (17.20, 51.80)	26.90 (8.90, 46.89)	**0.036**
LAD_dmean, median	7.09 (4.26, 14.84)	4.55 (2.54, 12.09)	0.066
LAD_eud3, median	12.12 (6.07, 26.98)	7.75 (3.30, 19.20)	**0.049**
LAD_eud5, median	17.16 (7.88, 33.15)	10.96 (4.05, 24.77)	**0.040**
LAD_eud15, median	27.91 (10.49, 42.92)	16.92 (5.90, 35.05)	**0.035**

Table 5 Multivariate analysis for cardiac toxicity

	Arrhythmia OR (95% CI)	p value	Ischemia OR (95% CI) p value	Decrease in EF more than 10% OR (95% CI) p value	Decrease in EF more than 15% OR (95% CI) p value
Left side versus right side	0.05 (0.006–0.39)	0.005	0.08 (0.01–0.69) 0.021	1.10 (0.57–2.15) 0.772	0.77 (0.25–2.33) 0.644
Age at diagnosis	1.07 (1.01–1.13)	0.017	1.05 (0.99–1.12) 0.094	1.00 (0.97–1.04) 0.809	1.01 (0.96–1.07) 0.651
Pathological stage	0.85 (0.61–1.17)	0.320	1.31 (0.96–1.79) 0.087	1.04 (0.88–1.23) 0.662	1.10(0.84–1.45) 0.488
Neoadjuvant chemotherapy	1.39 (0.43–4.48)	0.581	0.43 (0.12–1.62) 0.213	1.16 (0.57–2.34) 0.686	1.15 (0.36–3.69) 0.820

Discussion

Although contemporary radiation approaches are designed to mitigate cardiac toxicity, our results are consistent with prior reports: there were no appreciable differences in LVEF decrease between left- and right-sided cases ($p = 0.74$ for LVEF decrease > 10% and $p = 0.79$ for LVEF decrease > 15%); however, patients with left-sided cancers who received trastuzumab did exhibit more ischemia and arrhythmias than their right-sided counterparts. In addition, multivariate analyses demonstrated that RT was not an independent predictor of heart failure.

Until now, there existed only a few studies evaluating the cardiac safety from radiotherapy in patients who received trastuzumab and these studies are limited by their relatively short periods of follow-up. In contrast, our study median follow-up period was 81 months, thereby providing extensive data about the long-term cardiotoxic effects of this therapeutic combination.

Many prior studies focused on a decline in left ventricle ejection fraction as the main manifestation of trastuzumab/RT cardiotoxicity. In a prospective study involving 106 patients, only 4% developed symptomatic heart failure (median follow-up of 28 months) after adjuvant treatment with trastuzumab and radiation [12]. Similarly, in a retrospective analysis of patients who were treated with trastuzumab, higher incidence of cardiac events mainly diagnosed with LVEF decline was associated with left-breast irradiation, though not right-breast irradiation (21% vs.7% patients, respectively) [13]. A subgroup analysis of NCCTG N9831 showed no significant differences in cardiac side effects between patients receiving concomitant RT and trastuzumab and patients receiving only trastuzumab with no RT [14]. A study published by Shaffer et al. found no difference in cardiotoxicity when comparing the laterality of RT among patients also receiving trastuzumab. In this study, only three out of 59 patients developed clinical congestive heart failure, none of whom received left-sided IMC RT [15]. Notably, a more recent report evaluating early cardiac toxicity following adjuvant radiotherapy of left-sided breast cancer with or without concurrent trastuzumab concluded that left-side RT with trastuzumab was well tolerated in comparison to patients receiving left-side RT with no trastuzumab [16].

Myocardial ischemia is another radiation cardiac effect that requires more investigation. Darby et al. was the first to show a linear correlation between increased heart dose irradiation and the risk of developing ischemic heart disease (IHD) [17]. The same results were reported in the metaanalysis done by Yun-Jiu Cheng et al who found that exposure of the heart to radiotherapy in breast cancer patients increase the risk of coronary heart disease [18]. These results are comparable to our findings which demonstrated a significant difference between the two groups with left-sided RT patients showing a higher incidence of IHD. Another recent report from Wu SP et al. showed higher rates of IHD in a group receiving no left RT in comparison to left-side RT [19]. However, these conflicting results could be attributed to the patients' baseline cardiac risk factors, while both groups in our study had comparable baseline cardiac risk factors.

Interestingly, the same study highlighted the risk of developing arrhythmia after left-side RT. Among 559 patients receiving RT, 18 (3.2%) developed arrhythmia vs zero patients in the no radiation group ($p = 0.01$). Our results similarly found that 15/106 (14.2%) patients in the left-side RT group developed arrhythmia compared to 1/96 (1%) in right-side control group ($p < 0.001$) [19].

In order to assess the effect of RT on different heart structures, we conducted a dosimetric study on robust dose-volume histograms (DVH) and EUD for each heart chamber and LAD. Our results showed significant correlation between LV V10 and EUD3 to > 10% decrease of LVEF after 81 months of follow-up for 106 patients. Our results are comparable to those of Cao et al., who found that continuous increase of LV dose statistically correlates with LVEF dysfunction within 7-month follow-up of 64 patients [16].

It should be noted that there is a discrepancy in our study between correlation of dosimetric analysis and development of ischemia and/or arrhythmia in patients receiving left-side RT, and the overall correlation between the effect of radiation and ischemia and/or arrhythmia development in the same cohort. Such a discrepancy could be explained by the fact that the overall ischemia assessed may be originated from the right coronary or any small coronary branches which have not been included in the dosimetric analysis. Furthermore, the constraints for physiological sinus nodes of the heart were not included in the dosimetry. Therefore, there was no significant correlation between each heart chamber RT dose and arrhythmia development.

The strengths of our study include a reasonable number of patients for the comparative and dosimetric analyses, a relatively long period of follow-up of the patients for late cardiac toxicity, all patients treated with 3DCRT, and both groups had almost the same baseline conditions and received mostly the same modalities of treatment.

These findings must be interpreted in the context of the study design. The retrospective nature of these analyses is susceptible to confounding if unaccounted-for measures were instituted for left-sided cases more frequently than for their right-sided counterparts. We attempted to account for this using multivariate analysis of expected confounding variables. Baseline EKG was not routinely done in order to compare with subsequent cardiac evaluation. Regarding the endpoints, the identification of a nominal decline in LVEF without other clinical findings remains of uncertain significance, although it may serve as a relevant surrogate for longer-term cardiac morbidity. Lastly, radiographic identification of the LAD is challenging on non-contrast planning CT images, such that LAD dosimetry in this study was estimated by contouring the presumed LAD space and may not reflect true LAD dose.

Conclusion

The addition of left-breast RT to HER2-directed therapy might increase the risk of arrhythmia and ischemia; however, there was no significant reduction in EF. The EUD index of the LV, RV, and LAD merits further study as a parameter to describe the risk of radiation-induced cardiac toxicity. Routine baseline EKG should be considered for patients receiving trastuzumab and left-side radiation.

Compliance with ethical standards

Conflict of interest All the authors declare that he/she has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the IRB.

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