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Effect at One Year of Adjuvant Trastuzumab for HER2+ Breast Cancer Combined with Radiation or an Anthracycline on Left Ventricular Ejection Fraction

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Abstract

To determine the impact of radiation therapy (XRT) in addition to trastuzumab (TZB) adjuvant chemotherapy for HER2+ breast cancer on left ventricular systolic function, we assessed demographics, oncologic treatment history including XRT exposure, and serial measurements of left ventricular ejection fraction (LVEF) in 135 consecutively identified women receiving TZB for treatment of adjuvant breast cancer. Longitudinal mixed effects models were fit to identify baseline to treatment changes in LVEF among those receiving TZB with or without concomitant

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Mousumi M. Andersen: Original writing, Data procurement and analysis **Jessie Bowers:** Data procurement, Radiation dosimeter calculations **Banks W. Kooken:** Participant chart reviews and Gathering data **Ralph B. D'Agostino, Jr.:** All statistical analysis **Jennifer H. Jordan:** Image parameter assessments for CV tests, Review and establishing LV dysfunction measurements **Sujethra Vasu:** Defining Cardiotoxicity, Study design measures **Alexandra Thomas:** Breast cancer expertise **Heidi D. Klepin:** Breast cancer adverse events in older patients. **Doris R. Brown:** Supervision of all radiation dosimeter assessments **W. Gregory Hundley:** Overall study design, Study funding, Writing assistance

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

anthracycline or XRT. Women averaged 53 ± 3 years in age, 77% were white, 62% patients had 1 or more cardiovascular risk factors at baseline, and mean duration of TZB was 11 ± 5 months. Seventy-seven women were treated with XRT and received between 4000 and 5500 cGy of radiation. The LVEF declined by an average of 3.4% after 1 year for those in the study. Relative to baseline upon completion of adjuvant TZB, LVEF remained reduced for those receiving anthracycline with or without XRT (p=0.002 for both), or XRT alone (p=0.002), but not in those without these therapies. Amongst patients treated only with XRT and TZB, LVEF declined 3.1% on average in those with left-sided disease and 6.9% on average in those with right-sided disease (p= 0.06, p= 0.008 respectively). Among women receiving TZB for adjuvant treatment of HER-2 positive breast cancer, the administration of XRT, anthracycline, or the combination of the 2 is associated with a persistent post-treatment as opposed to a temporary treatment related decline in LVEF.

Keywords

Radiation therapy; trastuzumab; cardio-oncology; cardiotoxicity

Introduction:

Trastuzumab (TZB) (Herceptin, Genentech, USA), a humanized monoclonal antibody that binds to the extracellular juxtamembrane domain of the human epidermal growth factor-2 (HER2) receptor and inhibits the proliferation and survival of HER2-dependent breast tumors, is often associated with a temporary treatment-associated decline in left ventricular ejection fraction (LVEF) in women receiving adjuvant therapy for breast cancer.[1–3] Several studies and position papers suggest a possible relationship between the administration of radiation therapy (XRT) and inflammation/injury to cardiac muscle and a possible association between trastuzumab, radiation, and adverse cardiovascular events.[4–6] We surmised that the concomitant administration of XRT with trastuzumab might associate with a persistent decline in LVEF in women receiving adjuvant treatment for breast cancer.

Methods:

The study was approved by the Institutional Review Board of Wake Forest Health Sciences and consisted of a consecutive review and collection of data from the medical records of women who received TZB for HER2+ breast cancer between 2000 and 2016. Inclusion criteria included those who also received serial assessments of LVEF before, during and upon completion of their cancer treatment. Data including patient demographics, breast cancer treatment history, and non-invasive cardiac imaging were collected. The total prescribed dose of radiation was obtained from the radiation plan. Upon review of the cancer treatment history, patients were separated into 1 of 4 mutually exclusive groups including those receiving: 1) TZB + anthracycline, 2) TZB + anthracycline + XRT, 3) TZB + XRT, 4) TZB without XRT or an anthracycline.

Risk factors for the development of a future CV event were identified including hypertension, diabetes, smoking and pre-existing coronary artery disease. Definitions of hypertension,[7] diabetes,[8] and coronary artery disease[9] were accomplished according to

published studies. Current smoking was defined as having smoked a cigarette in the last 30 days.

The LVEF was collected from the electronic medical records as an absolute value measured from radioisotope, echocardiographic, or cardiovascular magnetic resonance methods. Patients receiving an echocardiographic assessment did so with either a Phillips or GE system with images acquired in standard parasternal and apical 2-and 4-chamber views using the modified Simpson's biplane method.[10]

For cardiovascular magnetic resonance, patients underwent scanning on a 1.5-T Magnetom Avanto scanner (Siemens Medical Solutions USA, Malvern, PA) using cine white blood steady-state free precession techniques with a 256×128 matrix, a 40-cm field of view, a 10-ms repetition time, a 4-ms echo time, a 20-degree flip angle, a slice 8-mm thick, and a 40-ms temporal resolution. According to previously published techniques, LV endocardial and epicardial contours were drawn at end-diastole and end-systole on offline workstations and summed using Simpson's rule.[11]

For nuclear medicine acquired studies, standard gated equilibrium blood pool scintigraphy was implemented in nearly all patients.[12]

Descriptive statistics were calculated for variables examined. These included means and standard deviations for continuous variables and counts and percentages for categorical variables. Each measure was shown in 1 of the 4 treatment groups of interest. Next, longitudinal mixed effects models were fit where patients were considered as random effects and fixed effects for group (4 levels), time, age, race (white/non-white), diabetes status and hypertension were included. We examined the time by group interaction to estimate the baseline to 6 month and baseline to 12-month changes in LVEF. Since the data were not collected based on a specific pre-specified time window, measures taken 3-months to 8-months post baseline were considered as the 6-month assessment and measures taken between 10 months and 13 months were considered as the 12-month assessment. Additional mixed effects models were fit adjusting for duration of Herceptin use and side (left/right) of the breast cancer. Finally, models were fit examining radiation dose (4000-4700 cGy, 4800-5040 cGy, and 5100+ cGy) both overall and then stratified by anthracycline use (yes/no).

Results:

The demographic data of the study population including cardiovascular comorbidities and medications are included in Table 1. The mean age at diagnosis was 53 ± 3 years.

Baseline left ventricular structure and volume data are also summarized in Table 1. The LVEF declined by 3.4% for all women after 1 year during receipt of TZB, going from an average of 60.2% to 56.8%. Among all patients, 19.1% of patients experienced a 1-year drop in LVEF of 10% (or more) or had an LVEF under 50% after 1-year. Figure 1 illustrates the LVEF at baseline, 6 months, and 1 year for each subgroup.

Details of breast cancer treatment are summarized in Table 2. In patients treated for left-sided breast cancer, there was a 3.4% decline in LVEF at 1 year (p = 0.0006), and in patients with right-sided disease, there was a 3.1% decline in LVEF (p= 0.005) at 1 year. Fifty-five percent of left-sided patients and 66% percent of right-sided patients were treated with anthracycline. Fifty-five percent of left-sided patients and 61% of right-sided patients were treated with radiation. The change in LVEF stratified by the side with breast cancer and radiation with or without anthracycline is shown in Figure 2.

Seventy-seven patients (57% of total) received XRT, either alone or in combination with anthracycline. Radiation dosage data was available in 57 patients, and of these 46 had a baseline EF and an EF measure at 1 year. Change in LVEF at 1 year based on dose of radiation received is shown in Figure 3. A test for a dose response relationship for radiation dose was not significant (p=0.59); however the dose range was relatively limited (4600 to 6020 cGy) and there were few patients at the higher or lower ranges of dose delivered.

When we compared 1-year changes in LVEF for patients with left or right sided breast cancer with radiation doses between 4800 to 5100 (n=23 for each side) we found the groups to have similar declines in LVEF (2.0% for those that experienced left side and 4.6% drop for those that experienced right side, p=0.15). The fact that the right sided breast cancer group experienced a 4.6% decline in LVEF suggests that radiation may have a detrimental effect on LVEF regardless of the side of administration.

Three patients received 4000–4700 cGy XRT but did not receive anthracycline, and in these patients, there was an 8.6% decline in LVEF at 1 year (p = 0.06). Eighteen patients received 4800–5100 cGy of XRT but did not receive anthracycline, and there was a 2.5% decline in LVEF at 1 year (p = 0.09). One patient received 5100+ cGy of XRT but did not receive anthracycline, and there was a 10% decrease in LVEF at 1 year. Three patients received 4000–4700 cGy of XRT and also received an anthracycline agent. In these patients, there was an overall increase in LVEF at 1 year as compared to baseline. Twenty-seven patients received 4800–5100 cGy of XRT as well as anthracycline, and there was a 3.8% decline in LVEF at 1 year (p = 0.004). Five patients received 5100+ cGy of radiation in addition to treatment with anthracycline and had a 3.8% decline in LVEF at 1 year (p = 0.16).

Discussion:

The results of this single institution retrospective study suggest that treatment of HER2+ breast cancer with TZB and XRT with or without anthracycline chemotherapy may result in a persistent decline in LVEF after treatment as compared to patients treated with TZB alone. The observed declines in LVEF occurred in women with both right-and left-sided breast cancer. Additionally, there appears to be an association with cumulative radiation dose received as it relates to the magnitude of the persistent post-treatment decline in LVEF.

Our results indicate that on average the persistent decline in LVEF in those receiving TZB and an anthracycline with or without radiation begins within 6 months. This seemed to differ from those receiving TZB and XRT without an anthracycline that on average experienced a significant decline in LVEF at 12 months (Figure 1). The additive side effects of

anthracycline in addition to TZB have been demonstrated previously.[13] TZB duration was similar amongst the 4 groups and so reversal of cardiac dysfunction in the setting of discontinuation of the medication likely does not explain our findings. Also, our findings persisted after accounting for age, race, stage, hormone receptor status, duration of treatment, diabetes mellitus, and hypertension, suggesting that the presence of cardiac risk factors alone do not account for the cardiac dysfunction observed.

All patients experienced a similar decline in LVEF regardless of whether they possessed right-or left-sided disease. Similarly, all women in our cohort receiving XRT, whether right- or left-sided, experienced a decline in LVEF at 1 year (Figure 2). Notably, the magnitude of the average change in LVEF for those receiving radiation only was larger in the right-sided patients (6.9%) as compared to left-sided patients (3.1%). This suggests that despite advances in radiation oncology, cardiac dysfunction may be as much a risk to right-sided patients as left-sided.

We found that those receiving 5100+cGy of radiation started with a higher baseline LVEF as compared to the other 2 groups. In the lowest radiation dose therapy group, there was no persistent decline in LVEF at 1 year, regardless of concomitant anthracycline treatment. Those receiving 4800–5040 cGy of radiation alone had a similar absolute decline in LVEF as those receiving radiation and anthracycline, suggesting the cardiotoxicity demonstrated for this dose was not solely driven by anthracycline use.

TZB disrupts myofibrillar structure but does not appear to cause extensive cardiomyocyte death, resulting in an often-reversible side effect profile.[14,15] Anthracyclines bind to the DNA of replicating cells causing fragmentation and polymerase inhibition, and they also decrease DNA-RNA protein synthesis.[16] Myocyte destruction is thought to result from the generation of free oxygen radicals and from an increase in oxidative stress, which leads to lipid peroxidation of membranes, and to vacuolation.[17,18] In humans, HER2 expression on myocytes is low, however there is involvement of mitogen-activated protein kinase/ extracellular signal-regulated kinase and AKT pathways.[14] Such pathways may explain anthracycline and TZB additive toxicity on myocytes. The anthracycline-induced apoptotic phenomena might increase with the addition of TZB inhibiting AKT and extracellular signal-regulated kinase signal transduction.[19]

Few studies have examined the mechanisms of XRT associated LV dysfunction.[20–26] The exact mechanism of radiation induced cardiotoxicity is unknown, though it is suspected that diffuse myocardial interstitial fibrosis, microcirculatory damage leading to ischemia and fibrosis, fibrous thickening of the pericardium, valvular fibrosis, and accelerated atherosclerosis all are contributors.[27] Perhaps XRT results in an additional inflammatory response in patients already treated with TZB and/or anthracyclines, resulting in acute cellular injury and necrosis in addition to programmed apoptosis. Future studies in animals and perhaps with techniques in human subjects may help clarify the etiology of the left ventricular dysfunction related to XRT therapy in combination with TZB. Additionally, while this study focused on LVEF, contemporary measurements of LV longitudinal strain with echocardiography or measures of serum biomarkers have been used in single center studies to identify those at risk of LVEF decline after cancer treatment.[28,29] Further research

is warranted from multicenter initiatives to determine the utility of these methods for identifying increased CV risk in those receiving radiation and trastuzumab.

Our study has some limitations. First, we did not randomize patients into treatment groups. As a result, differences in stage and hormone receptor status of breast cancer are present, though persistent declines in LVEF were observed after adjusting for these differences. Second, we obtained LVEF values calculated using 1 of 3 methodologies. Interestingly, this would likely introduce variance into our results compared to a situation in which each patient would receive single imaging method (e.g., MRI). The fact that we were able to demonstrate a statistically significant change suggests that we might expect a greater effect if we were to use a single method with lower variance in future studies. Third, we do not have comprehensive data regarding the amount of anthracycline administered to every participant and therefore we are unable to evaluate the effect of variances in dosing on our study outcomes. Similarly, radiation dose was missing in 20 of the 77 (26%) patients who received XRT, and information regarding the use of dose-sparing techniques was not available in any patients. Further analysis which includes this information will be helpful to elucidate dose-related or technique-related changes in cardiac function.

In conclusion, our cohort treatment of HER2+ breast cancer with any combination of TZB, anthracycline, and XRT resulted in a persistent decline in LVEF that on average does not return to pre-treatment levels at the conclusion of adjuvant therapy as is often observed when women who receive TZB without anthracyclines or XRT. Women with right-sided breast cancer equally experience persistent declines in LVEF after TZB relative to women with left-sided breast cancer. There may be an association with cumulative radiation dose received and the magnitude of LVEF decline in the setting of concomitant receipt of TZB.

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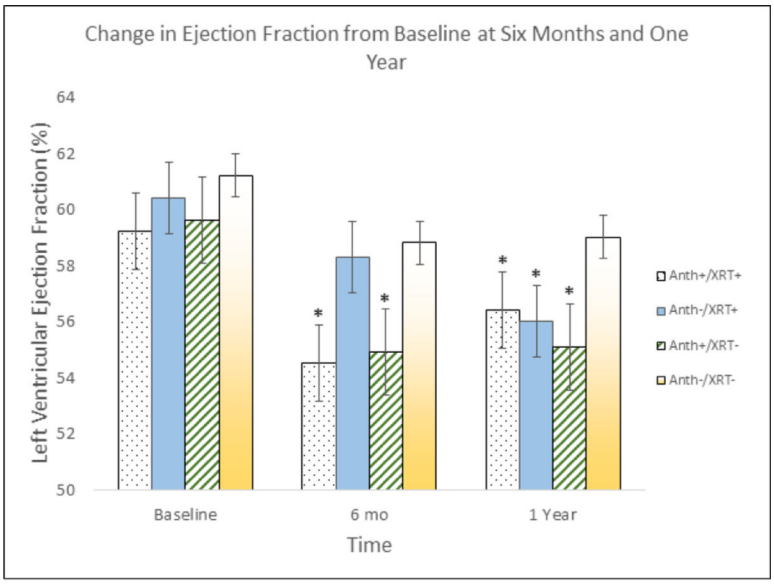
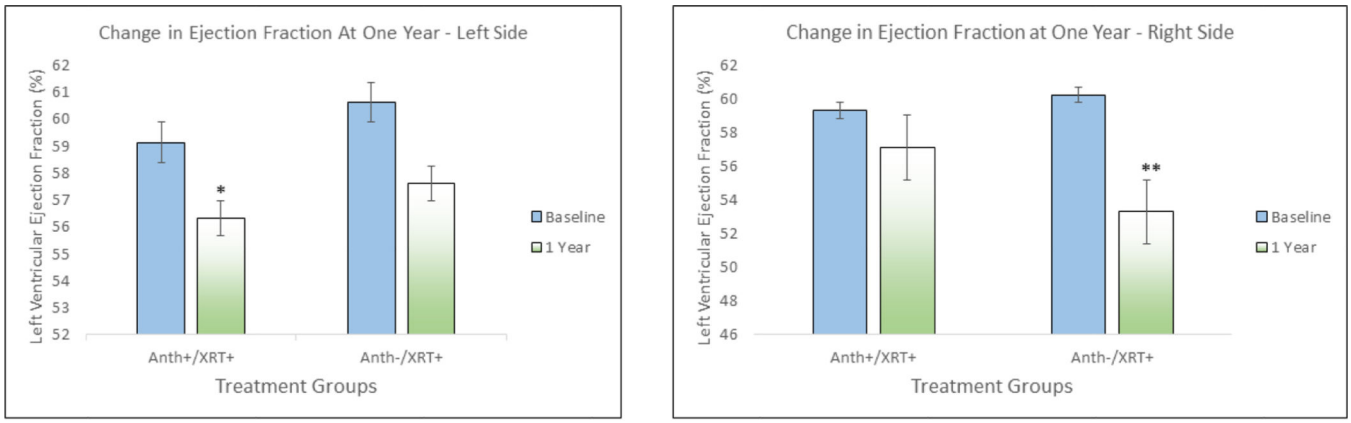


Figure 1.

Left ventricular ejection fraction (LVEF) shown on the y-axis versus average measures for each group (x-axis) at baseline, 6 months, and 1 year. Shaded bars represent different forms of cancer treatment. For each of the similarly shaded bars, the changes from baseline are shown at 6 months and 1 year after accounting for age, race, stage, hormone status, diabetes mellitus, and hypertension (* $p \leq 0.006$). Note that at 1 year, groups receiving trastuzumab with either an anthracycline or XRT experienced a decline in LVEF relative to baseline ($p \leq 0.006$); whereas those receiving trastuzumab only did not.



* $p \leq 0.05$
** $p \leq 0.008$

Figure 2.

Change in left ventricular ejection fraction (LVEF) at 1 year in those patients receiving trastuzumab therapy by breast cancer side. In patients with cancer involoving the breast (left panel),there was nearly a decline in LVEF in the radiation only group (3.1%, p=0.06) and there was a decline in patients treated with both (2.8%, p=0.05). In patients with cancer involving the right breast, there was a decline in the average LVEF in those receiviging radiation (6.9%, *p=0.0008).

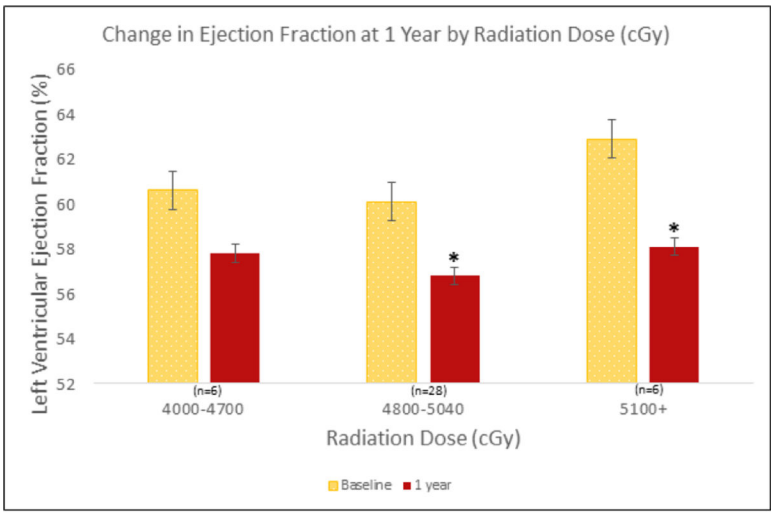


Figure 3.

Change in left ventricular ejection fraction (LVEF) at 1 year in those receiving trastuzumab by radiation dose. There was a decline in LVEF in those patients receiving 4800–5040 cGy of radiation (p=0.001) and 5100+ cGy (p=0.05).

Table 1:

Baseline Characteristics and Left Ventricular Data -N (%) or Mean ± SD

Variable	Anthracycline (−) Radiation (−) (N = 27)	Anthracycline (+) Radiation (−) (N = 31)	Anthracycline (−) Radiation (+) (N = 27)	Anthracycline (+) Radiation (+) (N = 50)
Age at Diagnosis (years ± SD)	54 ± 10	52 ± 12	56 ± 14	51 ± 11
•White •Black •Other	20 (74%) 3 (11%) 4 (15%)	25 (81%) 5 (16%) 1 (3%)	22 (81%) 5 (19%) 0	37 (74%) 10 (20%) 3 (6%)
Body mass index >30 (kg/m^2)	6 (22%)	4 (13%)	7 (26%)	13 (26%)
Hyperlipidemia	5 (19%)	9 (29%)	6 (22%)	11 (22%)
Hypertension	9 (33%)	8 (26%)	13 (48%)	22 (44%)
Diabetes Mellitus II	2 (7%)	1 (3%)	5 (19%)	10 (20%)
Coronary Artery Disease	0	0	0	0
Tobacco Abuse	10 (37%)	13 (42%)	5 (19%)	10 (20%)
Medications				
• ACE-Inhibitor	5 (19%)	5 (16%)	6 (22%)	9 (18%)
• Angiotensin Receptor Blocker	2 (7%)	1 (3%)	1 (4%)	6 (12%)
• Beta Blocker	0	2 (6%)	5 (19%)	7 (14%)
• Calcium Channel Blocker	3 (11%)	0	5 (19%)	6 (12%)
• Diuretic	4 (15%)	6 (19%)	8 (30%)	11 (22%)
• Metformin	2 (7%)	0	1 (4%)	3 (6%)
• Statin	4 (15%)	5 (16%)	3 (11%)	6 (12%)
Ejection Fraction (%)	61 ± 5	60 ± 6	61 ± 6	59 ± 5
Posterior Wall Thickness (mm)	10 ± 1	11 ± 2	10 ± 1	11 ± 2
Ventricular Septal Thickness (mm)	10 ± 2	11 ± 2	10 ± 2	11 ± 2
Left Ventricular Internal Dimension-Diastole (mm)	43 ± 6	40 ± 5	43 ± 6	41 ± 5
Left Ventricular Internal Dimension-Systole (mm)	31 ± 6	27 ± 7	28 ± 7	28 ± 5
End Diastolic Volume (mL)	72 ± 27	67 ± 22	80 ± 29	77 ± 29
End Systolic Volume (mL)	27 ± 14	25 ± 10	31 ± 13	31 ± 16
Stroke Volume (mL)	45 ± 28	41 ± 18	49 ± 22	47 ± 22

SD =standard deviation, **BMI** =body mass index

Table 2:

Breast Cancer Treatment Data -N (%)

Variable	Anthracycline (−) Radiation (−) (N = 27)	Anthracycline (+) Radiation (−) (N = 31)	Anthracycline (−) Radiation (+) (N = 27)	Anthracycline (+) Radiation (+) (N = 50)
Side				
• Left	16 (59%)	17 (55%)	17 (63%)	24 (48%)
• Right	10 (37%)	13 (42%)	10 (37%)	26 (52%)
• Bilateral	1 (4%)	1 (3%)	0	0
Stage				
• I	9 (33%)	8 (26%)	9 (33%)	2 (4%)
• II	6 (22%)	16 (52%)	6 (22%)	18 (36%)
• III	2 (7%)	3 (9%)	8 (30%)	28 (56%)
• IV	10 (37%)	4 (13%)	4 (15%)	2 (4%)
Hormone Receptor Status				
• ER/PR (−)	9 (33%)	12 (39%)	8 (30%)	25 (50%)
• ER (+) only	8 (30%)	8 (26%)	4 (14%)	10 (20%)
• PR (+) only	2 (7%)	3 (9%)	1 (4%)	2 (4%)
• ER/PR (+)	8 (30%)	8 (26%)	14 (52%)	13 (26%)
Surgery				
• None	6 (22%)	4 (13%)	0	1 (2%)
• Lumpectomy	2 (7%)	3 (9%)	15 (56%)	15 (30%)
• Mastectomy	19 (71%)	24 (78%)	12 (44%)	34 (68%)
Average Trastuzumab Duration (months ± SD)	12 ± 5	11 ± 4	13 ± 6	11 ± 4
Recurrent Disease	6 (22%)	5 (16%)	0	6 (12%)
• Prior Anthracycline	0	4 (13%)	0	4 (8%)
• Prior Trastuzumab	0	0	0	0
• Prior Radiation Therapy	4 (15%)	3 (9%)	0	2 (4%)
Radiation Dose (cGy)	n/a	n/a		
• Unknown			5 (19%)	15 (30%)
• 4000–4700			3 (11%)	3 (6%)
• 4800–5040			18 (66%)	27 (54%)
• 5100+			1 (4%)	5 (10%)

SD = standard deviation, **ER** = estrogen receptor, **PR** = progesterone receptor