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Characterization of Risk Factors for Adjuvant Radiotherapy-Associated Pain in a Tri-Racial/Ethnic Breast Cancer Population

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Abstract

Pain related to cancer or treatment is a critical quality of life (QOL) issue for breast cancer survivors. In a prospective study of 375 breast cancer patients (enrolled during 2008–2014), we characterized the risk factors for adjuvant radiotherapy (RT)-associated pain. Pain score was assessed at pre- and post-RT as the mean of four pain severity items (i.e., pain at its worst, least, average, and now) from the Brief Pain Inventory (BPI) with 11-point numeric rating scale (0–10). Pain scores of 4–10 were considered clinically-relevant pain. The study consists of 58 non-Hispanic whites (NHW; 15%), 78 black or African Americans (AA; 21%), and 239 Hispanic whites (HW; 64%). Overall, the prevalence of clinically-relevant pain was 16% at pre-RT, 31% at post-RT, and 20% RT-associated increase. In univariate analysis, AA and HW had significantly higher pre- and post-RT pain compared to NHW. In multivariable logistic regression analysis, pre-RT pain was significantly associated with HW and obesity; post-RT pain was significantly associated with AA, HW, younger age, ≥2 comorbid conditions, above median hotspot volume receiving >105% prescribed dose, and pre-RT pain score ≥4. RT-associated pain was significantly associated with AA (odds ratio [OR]=3.27; 95% confidence interval (CI)=1.09–9.82), younger age (OR=2.44, 95% CI=1.24–4.79), and 2 or ≥3 comorbid conditions (OR=3.06, 95%CI=1.32–7.08; OR=4.61, 95%CI=1.49–14.25, respectively). These risk factors may help to guide RT decision making process, such as hypo-fractionated RT schedule. Furthermore, effective pain management strategies are needed to improve QOL in breast cancer patients with clinically-relevant pain.

Keywords

breast cancer; radiotherapy; pain; cancer disparities; cancer survivorship

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INTRODUCTION

Breast cancer is the most frequently diagnosed cancer and the second leading cause of cancer death in American women [11]. Post-surgical adjuvant radiotherapy (RT) significantly reduces local-regional recurrence of early-stage breast cancer, so currently most breast cancer patients receive RT after breast-conserving surgery (BCS). Breast RT is generally well tolerated, but acute skin toxicity is a common side effect which can result in bothersome symptoms including burning sensation, itching, tenderness and pain. Pain is one of the most common symptoms affecting more than half of the breast cancer survivors [5; 15; 22; 27; 41] and it may last for decades after completion of treatment [25]. Pain may contribute to depression, sleep disturbances, and deteriorate performances and quality of life (QOL) [8; 41].

Multiple factors may influence the development and persistence of pain in breast cancer survivors, including younger age, chemotherapy, axillary lymph-node dissection (ALND), and acute postoperative pain [2; 5; 14; 19; 22; 27; 39]. There were multiple studies evaluating the impact of adjuvant RT on pain but there have been inconsistent findings [2; 13; 15; 17; 21; 22; 26; 41]. Dose inhomogeneity measured by “hotspot” volume has emerged as an important risk factor for RT-associated pain or skin toxicity [10; 27]. However, many of these studies were either retrospective or cross-sectional, lacking temporal relationship and subject to recall bias. Therefore, we designed a prospective study to monitor pain at pre- and post-RT as a critical QOL issue in breast cancer patients. In our previous report of breast cancer patients receiving post-mastectomy RT, nearly 80% of patients developed grade 2+ skin toxicity at the end of RT and more proportions of black or African American (AA) race experienced higher skin toxicity [42].

The goal of this study was to characterize the risk factors associated with clinically-relevant pain in breast cancer patients undergoing post-surgery adjuvant RT. We have used a prospective study design to target a tri-racial/ethnic breast cancer patient population undergoing RT. Investigating risk factors related to acute RT-associated pain, which occurs immediately after RT, is highly relevant to QOL of breast cancer patients undergoing RT. Given the importance of patient-reported QOL outcomes and generalizable evidence of comparative effectiveness from breast cancer patients treated outside the context of clinical trials, our study provides the critical information regarding the prevalence of RT-associated pain in breast cancer patients, particularly in underserved minorities with worse treatment-related QOL [43].

METHODS AND MATERIALS

Study Population

In a prospective study of breast cancer patients undergoing RT, newly-diagnosed female breast cancer patients (≥ 18 yrs) with Stage 0-III breast cancer (American Joint Committee on cancer 6th edition) after BCS and planning to receive adjuvant breast RT on their intact breast were recruited from the Radiation Oncology clinics at the Sylvester Comprehensive Cancer Center and Jackson Memorial Hospital in Miami, FL. All patients underwent BCS with or without sentinel lymph-node biopsy (SLNB) or axillary lymph-node dissection

(ALND). Adjuvant hormonal therapy was allowed prior to, during, or after RT at the discretion of medical oncologist, however concurrent chemotherapy was not allowed for study entry. This study was approved by both institutions' review board. After receiving a detailed description of the study protocol, signed informed consent in English or Spanish was obtained from each participant.

Patient and Clinical Characteristics

At the time of study entry, patients completed a baseline assessment form which includes data on age, self-identification of race and ethnicity, marital status, comorbidities, smoking history and status, and medication. Body mass index (BMI) was calculated from the self-reported height and weight. Tumor–related characteristics were collected from pathology reports regarding tumor-stage, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and surgery information including lymph-node examination. Detailed information about other hormone therapy and chemotherapy prior to or during RT was obtained from medical records.

Radiation Treatment

RT was administered 4–6 weeks after surgery or completion of chemotherapy. The breast was irradiated using standard or partially wide photon tangents using 6 and/or 10 MV photons with a conventionally fractionated schedule (45–50.4 Gy in 25–28 fractions over 5–6 weeks, mostly 50 Gy in 25 fractions), a hypofractionated schedule (40–45Gy in 15–16 fractions over 3 weeks, most commonly 42.4 Gy in 16 fractions) or partial breast irradiation (38.5 Gy in 10 fractions over 1 week). In general, the duration of RT was 4 or 6 weeks depending on the fractionation scheme used. The patients in our cohort were uniformly managed with topical aloe vera applied to the breast throughout treatment, with silver sulfadiazine applied to areas of desquamation as needed. Additional boost dose (concurrent or sequential) of 10–20 Gy without bolus was delivered to the lumpectomy cavity in 88% of patients. Target volumes including the breast and lumpectomy cavity were contoured by radiation oncologists. Treatment planning was completed on the Eclipse or Pinnacle planning system depending on the institutional center, and forward planned field-in-field technique was used to maximize dose homogeneity. The detailed information on radiation delivery including target breast volume and breast volume receiving >105% of prescribed dose (hotspot volume, V105) were analyzed from the dose-volume histogram.

Pain Assessment

We have collected QOL data at the same day of RT before initiation of RT (pre-RT) and the last day of RT immediately after RT (post-RT) using the NSABP B-39/RTOG 0413 protocol QOL questionnaire either in English or Spanish. It has extracted 4 questions from the Brief Pain Inventory (BPI) which was developed by The Pain Research Group of the World Health Organization (WHO) Collaborating Centre for Symptom Evaluation in Cancer as a widely used pain assessment tool for cancer patients. The BPI has been translated into many languages and has shown both reliability and validity across cultures and languages, including English and Spanish [1; 9]. Also it has been validated in many different patient populations, including breast cancer patients [6]. Pain severity score was assessed as mean of the four pain items (i.e., pain at its worst, least, average, and now) using an 11-point

numeric rating scale, from 0 (no pain) to 10 (the worst imaginable pain). There is no clear consensus on cut off points for clinically relevant pain. We decided to either use pain score as a continuous variable or use pain score 4 as the cutoff for clinically relevant pain. This cut-off value is supported by previous studies in breast cancer patients [15; 29; 37]: the data from a recent study that identified pain score 4 as the tolerable pain threshold [16]; and the National Comprehensive Cancer Network guidelines for cancer pain management using pain intensity ≥ 4 to initiate opioids treatment [31]. The RT-associated clinically relevant pain was considered "yes" when mean pain severity score increased from <4 to ≥ 4 during RT. We have also collected other physician-reported acute skin adverse reactions using the National Cancer Institute Common Toxicity Criteria.

Statistical Analysis

Descriptive statistics were computed to describe patient-, tumor-, and treatment-related characteristics of the study population. Analysis of variance was used to compare group differences in pain score while Pearson's chi square or Fisher's exact test was performed to compare prevalence of clinically relevant pain by study variables. The variables with significant level $p<0.1$ in the univariate analyses were included in the multivariable logistic regression analyses to evaluate the independent risk factors associated with pre-RT, post-RT, or RT-associated clinically-relevant pain. The nine patients with accelerated partial breast irradiation (APBI) were included only for pre-RT pain analysis and excluded from all the subsequent analyses because APBI is different from conventional or hypo-fractionated whole breast irradiation in terms of dose, duration, and delivery technology. In addition, there is a difference in eligibility for APBI favoring small locally confined tumors, so the comparison with other regimens is not relevant. All statistical analyses were performed using SAS version 9.3 for Windows (SAS Institute, Cary, NC, USA) and significance level was set at two-sided alpha=0.05.

RESULTS

Distribution of Study Variables by Race/Ethnicity

The target study sample size is 1,000. As of July, 2014, we have screened 438 patients and enrolled 399 patients (response rate 91%). For this study, we excluded 24 patients: 13 other race/ethnicity, 3 did not finish RT, 4 stage IV or with concurrent chemotherapy, and 4 without any pain data. We analyzed the patient-reported pain outcomes of 375 patients recruited during December, 2008–July, 2014. Among the 375 study participants who completed the QOL questionnaire, we had data on pain from 358 (96%), 335 (89%), and 314 (84%) patients at pre-RT, post-RT, and both time points, respectively. The distributions of study variables by race/ethnicity were summarized in Table 1. The study consists of 58 non-Hispanic whites (NHW; 15%), 78 AA (21%), and 239 Hispanic whites (HW; 64%). The mean age at study entry was 56 years old (range 27.6–82.5). Significantly higher proportions of AA patients were obese (62 % vs. 24% in NHW vs. 38% in HW, $p<0.0001$), had diabetes (22 % vs. 5% in NHW vs. 10% in HW, $p=0.004$), had hypertension (60 % vs. 31% in NHW vs. 40% in HW, $p=0.001$), had ER negative tumors (32% vs. 24% in NHW vs. 19% in HW, $p=0.049$), had triple negative tumors (27% vs. 15% in NHW vs. 11% in HW, $p=0.002$), and above-median breast volume (73% vs. 36% in NHW vs. 48% in HW, $p<0.001$). Both AA

and HW patients were diagnosed with more advanced stage of disease relative to NHW (p=0.001).

Treatment Characteristics

About 33% (n=125) of patients had axillary lymph-node dissection (ALND), 175 (47%) patients had sentinel lymph-node biopsy (SLNB), and 75 (20%) had no axillary surgery. About half (n=175, 47%) received chemotherapy (8% neoadjuvant and 39% adjuvant) with combinations of chemotherapy drugs (44% taxanes and only 3% anthracyclines). In addition, 29 (8%) received monoclonal antibody therapy with trastuzumab for HER2-positive tumors. For adjuvant hormone therapy, 167 (44%) initiated hormone therapy prior to RT (27% aromatase inhibitor and 17% tamoxifen), and 27 (8%) started treatment during RT (4% aromatase inhibitor and 4% tamoxifen). Significantly higher proportion of HW patients had received hormone therapy (52% vs. 36% in AA vs. 26% in NHW, p=0.027) prior to RT. About 82% (n=308) patients received RT using the conventional schedule, 58 (16%) followed the hypo-fractionated schedule, and 9 (2%) received partial breast irradiation. A total of 331 patients (88%) received an additional boost of 10–20 Gy to the lumpectomy cavity. Dose-volume histogram analysis showed that average 313 cc of breast volume received > 105% of prescribed dose (V105, median: 241.7 cc, range: 0 to 1676.8 cc). There were no significant differences in treatment parameters in terms of dose and boost by race/ethnicity. However, target breast volume was significantly ($p<0.001$) larger among AA (mean±SD: 1224±641 cc) compared to that in NHW (816±481 cc) or HW (965±454 cc).

Pain Severity Score by Patient and Treatment Characteristics

As shown in Table 2, patients had a mean pain intensity score 1.6±2.1 and 2.8±2.6 (mean ±SD) at pre- and post-RT, respectively. Pain scores ranged from 0 to 10 at pre-and post-RT. Overall, there was a statistically significant increase in RT-associated pain score (mean±SD: 1.2±2.2; $p<0.001$). At pre-RT, AA/HW or patients with thyroid disease had a higher pain score (p=0.044 and p=0.039, respectively). At post-RT, pain score was higher in AA/HW, women with younger age (<50 years old), obesity (BMI≥30 kg/m^2), thyroid disease, and pre-RT pain score ≥4. Significantly higher RT-associated pain score change was observed in patients with diabetes (p=0.012) or pre-RT pain score < 4 ($p<0.001$). As shown in Table 3, at pre-RT, pain score was significantly higher in patients with IIA–IIIC tumor stage (p=0.038), HER2 positive tumors (p=0.014), prior trastuzumab treatment (p=0.027), axillary lymph node dissection (ALND) (p=0.048), and total RT dose ≥ 60 Gy (p=0.045). At post-RT, pain score was significantly higher in patients who had conventional RT type (p=0.002), total RT dose ≥60 Gy ($p<0.001$), above-median breast volume (p=0.004), and above-median V105 ($p<0.001$). RT-associated pain score change was significantly higher in patients who had conventional RT type (p=0.031) and above-median V105 (p=0.026).

Clinically-Relevant Pain by Patient and Treatment Characteristics

In Table 4, the prevalence of clinically-relevant pain (≥ 4) was 16% at pre-RT and 31% at post-RT, respectively. About 20% of patients experienced RT-associated clinically-relevant pain, defined as a change from no to yes for clinically-relevant pain during RT. At pre-RT, presence of clinically-relevant pain was more prevalent in AA or HW compared to NHW

(p=0.025), obese patients with BMI ≥ 30 (p=0.005), HER2 positive tumors (p=0.013), prior trastuzumab treatment (p=0.024), taxane chemotherapy with trastuzumab (p=0.036), and total RT dose ≥ 60 Gy (p=0.015). At post-RT, presence of clinically-relevant pain was more prevalent in AA or HW compared to NHW (p=0.003), younger age (p=0.024), obese (p=0.001), # of comorbid conditions ≥2 (p=0.010), thyroid disease (p=0.002), conventional RT type (p=0.014), total RT dose ≥60 Gy (p=0.016), and above-median V105 (p=0.011). RT-associated clinically-relevant pain was more prevalent in AA or HW compared to NHW (p=0.045), # of comorbid conditions ≥ 2 (p=0.027), thyroid disease (p=0.030), and conventional RT type (p=0.042).

Multivariable Logistic Regression Analyses

We selected risk factors from Table 4 with p<0.1 in univariate analyses for multivariable logistic regression models to determine which risk variables were independent. Some variables were not included in the multivariable models because they were redundant. As shown in Table 5, at pre-RT, two out of the four variables were significantly independently associated with clinically-relevant pain: HW (OR=5.06; 95%CI=1.17–21.83) and obesity (OR=2.46; 95%CI=1.34–4.50) after adjusting for taxane with trastuzumab chemotherapy and axillary surgery type. At post-RT, five out of the seven variables were significantly associated with clinically-relevant pain: AA or HW (OR=3.75, 95%CI=1.19–11.85 and OR=3.14, 95%CI=1.08–9.11, respectively), younger age (OR=3.09, 95%CI=1.57–6.10), # of comorbid conditions 2 or ≥3 (OR=3.04, 95%CI=1.31–3.08; OR=5.68, 95%CI=1.60–20.18, respectively), above-median breast volume receiving > 105% of prescribed dose (OR=1.80, 95%CI=1.00–3.23), and pre-RT pain score ≥4 (OR=4.65, 95%CI=2.30–9.38) after adjusting for BMI and RT type. RT-associated clinically-relevant pain was significantly associated with AA (OR=3.27, 95%CI=1.09–9.82), younger age (OR=2.44, 95%CI=1.24–4.79), and # of comorbid conditions 2 or ≥3 (OR=3.06, 95%CI=1.32–7.08 and OR=4.61, 95%CI=1.49–14.25, respectively) after adjusting for RT type.

DISCUSSION

This prospective study suggests that RT increased clinically-relevant pain (from 16% at pre-RT to 31% post-RT) in breast cancer patients. RT contributed to a 20% increase in the proportion of patients with clinically-relevant pain. Although we report acute pain developed during RT, the proportion of patients with RT-associated pain is consistent with the literature [15; 30]. Long-term follow-up of our patient population will shed light on whether RT-associated acute pain can predict chronic pain in breast cancer survivors.

It is noteworthy that there were significant racial/ethnic disparities in clinically-relevant pain at pre-RT and post-RT, as well as RT-associated change. The etiology of higher prevalence of pain in underserved minorities could be influenced by several cofactors. First, higher proportions of AA (62%) and HW (38%) were obese compared to NHW (24%) and obesity has been associated with chronic pain [20]. Second, higher proportions of AA and HW had more advanced tumor stage (IIA–IIIC) that may require more aggressive treatments, such as chemotherapy and/or ALND. Third, higher proportions of AA and HW had HER2 positive tumors and most likely received trastuzumab combined with taxane chemotherapy that may

contribute to pain and neuropathy [12]. Fourth, higher proportions of HW (36%) had received hormonal therapy with aromatase inhibitor, which is known to cause musculoskeletal pain in breast cancer patients [24], compared to 24% in AA and 21% in NHW. Lastly, higher proportions of AA (31%) reported # of comorbidities ≥2 compared to NHW (19%) and HW (21%). However, racial/ethnic differences remain significant after adjusting for all potential confounders in the multivariable logistic regression model.

It is not clear whether AA and HW experience higher level of pain or are more sensitive to pain in nature [4; 14; 28; 32; 33]. AA and Hispanics have been shown to have a lower threshold for pain as well as less tolerance of pain than NHW in the experimental pain response test [33] and AA patients reported higher intensity of pain compared to whites in a large colorectal and lung cancer cohort study [28]. This is not an issue with our study because the pain intensity score was assessed using questions from the culturally and linguistically validated BPI questionnaire in English and Spanish. The cultural differences in reporting pain may be considered as a potential measurement bias in patient-reported outcome measures [34]. Larger studies with more objective methods for pain measurement are warranted to further evaluate whether higher RT-associated pain reported by underserved minorities are related to susceptibility and/or sensitivity.

At pre-RT, clinically relevant pain was associated with prior trastuzumab treatment (OR=2.95; 95%CI=1.25–6.94) but not taxane (OR=1.61, 95%CI=0.91–2.85). There was a slightly stronger association between pre-RT pain and combined trastuzumab with taxane (OR=3.24; 95%CI=1.27–8.28). However, these associations were not significant in the multivariable analysis. It is not clear whether it is related to our limited sample size and statistical power. We will be able to validate these interesting study findings in our ongoing study targeting 1,000 breast cancer patients.

In general, chronic non-cancer pain has been associated with older age (>65 years) [20]. In this study, we reported that younger age (<50) is a risk factor for post-RT and RT-associated clinically-relevant pain. Our observation is consistent with the data from previous studies which demonstrate biological changes with aging and pain; the functioning of the nociceptive pathway may be reduced with age, or hormonal change related to age could affect the cytokine profiles involved in wound-healing processes [15; 26].

The number of patient-reported comorbidities has emerged as an important risk factor for RT-associated pain and this is in line with the literature that comorbidity may contribute to variations in pain [39]. Among the 11 comorbid conditions, diabetes, hypertension, or thyroid disease may increase pain intensity through modulating pain hypersensitivity/threshold, systemic inflammation, and/or radio-sensitivity [44]. Our previous study demonstrated that comorbid conditions increased inflammatory biomarker in radio-sensitivity and skin toxicity, particularly among obese breast cancer patients [35]. These comorbid conditions will need to be considered as part of the treatment decision making process and effective pain management strategies are needed to improve QOL in high-risk breast cancer patients with at least 2 comorbid conditions.

Recently, dose inhomogeneity measured by “hotspot” volume has been emerged as a significant independent risk factor for RT-induced adverse responses, but the relationship has not been consistent [7; 17; 27; 38; 42]. The reasons for this inconsistency could be explained by differences in study design, outcome endpoints, definition and cut-off point of hotspot volume, and adjustment of covariates. In our prospectively followed cohort from RT initiation to completion with comprehensive adjustment for covariates, above-median hotspot volume receiving > 105% of prescribed dose was identified as an independent risk factor for post-RT clinically-relevant pain. Therefore, minimizing hotspot volume receiving > 105% prescribed dose is warranted to reduce post-RT pain.

The predictive value of RT-related variables including total dose, boost, and fractionation in RT-associated pain has been explored [8; 21; 22]. Considering our study is not a randomized controlled trial, there may be differences related to selection criteria for RT dose and/or boost irradiation that are determined by patient’s age and tumor characteristics. Although an earlier study showed no differences in breast pain between hypo-fractionation and conventional schedule [21], the results from a large study of 2,309 evaluable patients showed that hypo-fractionation may reduce acute pain, fatigue, and skin toxicity [23]. In our current study, the conventional fractionation increased pain intensity during RT and contributed to higher pain prevalence compared to that in hypo-fractionation in the univariate analysis, but not in multivariable analysis. Larger studies are warranted to further evaluate whether hypo-fractionation RT will have the same efficacy as traditional RT and less RT-associated side effects in underserved minorities.

The current data suggest that pre-RT pain is an independent risk factor for post-RT pain, which is supported by previous studies [19; 37]. Furthermore, RT-associated pain can last for many decades [25; 27]. Therefore, pain management during RT may be an effective preventive measure. In terms of pre-RT pain management, both race/ethnicity and BMI should be taken into consideration because these are the two risk factors for pre-RT pain. Obesity is a well-established risk factor of chronic pain in the general population and cancer patients [13; 14; 18; 20], and obese patients have elevated pain, worse functional well-being during RT, and slower improvement compared to normal weight group [13]. The molecular mechanisms of obesity in pain may be related to the nociceptive process, anxiety, or systemic inflammation [3; 36; 40].

This study has several strengths and limitations. The major strength is the prospective study design that is suitable for comprehensive evaluation of pre-RT, post-RT, and RT-associated pain. We have followed patients over time and recorded patient-reported pain intensity at the first day and the last day of RT to minimize recall bias and we showed that pain severity and prevalence have increased during RT in a prospective observational study. More importantly, capitalizing on a diverse patient population, this is the first large study showing disparities, particularly in Hispanics, in RT-associated pain experience among breast cancer patients. Our study has some limitations. First, under the original study design, we have mainly focused on RT-associated acute pain. It is not clear whether results can predict which patients will develop chronic pain. Therefore, we are conducting a long-term follow-up study to assess RT-related late effects and clinical outcomes. Second, although we have an

adequate sample size for evaluating HW in RT-associated pain, our results will need to be validated in other study populations.

In conclusion, our data demonstrate that multiple risk factors contribute to pre-RT, post-RT, and RT-associated pain and underserved minorities (i.e. AA and HW) have significantly higher risk for pre-RT and RT-associated pain. Obesity, younger age, and comorbid conditions may contribute to racial/ethnic disparities in pre-RT and RT-associated pain. The slow transition from conventional to hypo-fractionated breast RT has recently become the subject of considerable attention. If hypo-fractionation RT can provide equivalent long-term tumor control but with reduced RT-associated side effects beyond the selected breast cancer patients, it may present a great cost-effective alternative treatment strategy to improve RT outcomes, particularly in underserved minorities with worse RT-associated side effects.

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Table 1

Study Population and Clinical Characteristics by Race/Ethnicity

Variable	Categories	Total		NHW		AA		HW		p[1]
		N	%	N	%	N	%	N	%	
Total		**375**		**58**	**15**	**78**	**21**	**239**	**64**	
Age (yrs)	<50	96	26	18	31	20	26	58	24	0.746
	50–59	150	40	22	38	34	44	94	39	
	≥60	129	34	18	31	24	31	87	37	
	Mean (SD)	56.0 (9.0)		55.6 (9.1)		55.3 (9.3)		56.4 (9.0)		
BMI (kg/m^2)	<25	97	26	29	50	12	15	56	23	**<0.0001**
	25–29.99	126	34	15	26	18	23	93	39	
	≥30	152	40	14	24	48	62	90	38	
	Mean (SD)	29.4 (6.5)		26.9 (6.6)		32.7 (8.3)		28.9 (5.3)		
Smoking status	Never	246	66	36	62	55	71	155	65	0.391
	Former	109	29	21	36	18	23	70	29	
	Current	20	5	1	2	5	6	14	6	
# Comorbidities[2]	0	150	40	28	48	20	26	102	43	0.068
	1	139	37	19	33	34	43	86	36	
	2	63	17	7	12	20	26	36	15	
	≥3	23	6	4	7	4	5	15	6	
Diabetes	No	332	88	55	95	61	78	216	90	**0.004**
	Yes	43	12	3	5	17	22	23	10	
Hypertension	No	214	57	40	69	31	40	143	60	**0.001**
	Yes	161	43	18	31	47	60	96	40	
Thyroid disease	No	336	90	50	86	74	95	212	89	0.197
	Yes	39	10	8	14	4	5	27	11	
Tumor stage	0	76	20	7	12	15	19	54	29	**0.001**
	IA–B	186	50	38	65	30	38	118	49	
	IIA–B	91	24	12	21	31	40	48	20	
	IIIA–C	22	6	1	2	2	3	19	8	
ER	Positive	291	78	44	76	53	68	194	81	**0.049**

Variable	Categories	Total		NHW		AA		HW		p[1]
		N	%	N	%	N	%	N	%	
Total		**375**		**58**	**15**	**78**	**21**	**239**	**64**	
	Negative	84	22	14	24	25	32	45	19	
HER2	Positive	32	12	3	7	7	12	22	13	0.458
	Negative	282	88	51	93	59	88	172	87	
Triple negative	No	304	85	47	85	56	73	201	89	**0.002**
	Yes	54	15	8	15	21	27	25	11	
Axillary surgery	None/SLNB	250	67	39	67	57	73	154	64	0.370
	ALND	125	33	19	33	21	27	85	36	
Chemotherapy	None	200	53	32	55	42	54	126	53	0.885
	Taxane	166	44	25	43	33	42	108	45	
	Other	9	3	1	2	3	4	5	2	
Hormone Therapy/Initiation time	None/after RT	181	48	37	64	44	56	100	41	**0.027**
	AI before RT	102	27	9	16	16	21	77	32	
	AI during RT	14	4	3	5	2	3	9	4	
	Tamoxifen before RT	65	17	6	10	12	15	47	20	
	Tamoxifen during RT	13	4	3	5	4	5	6	3	
RT type	Conventional	308	82	45	77	66	85	197	82	0.753
	Hypofractionation	58	16	12	21	9	11	37	16	
	Partial[3]	9	2	1	2	3	4	5	2	
Total RT dose (Gy)	<60	116	31	22	38	22	28	72	30	0.433
	≥60	259	69	36	62	56	72	167	70	
	Mean(SD)	57.7 (5.6)		58.0 (5.2)		57.9 (6.3)		57.6 (5.5)		
Boost	Yes	331	88	55	95	66	85	210	88	0.178
	No	44	12	3	5	12	15	29	12	
Breast volume (cc)	< 892.1(MD)	182	49	37	64	21	27	124	52	**<0.001**
	≥ 892.1	189	51	21	36	56	73	112	48	
	Mean(SD)	996 (517)		816 (481)		1224 (641)		965 (454)		
V105 (cc)[4]	<241.7 (MD)	167	50.2	33	60	35	50	99	48	0.262
	≥241.7	166	49.8	22	40	35	50	109	52	
	Mean(SD)	313 (288)		304 (318)		331 (298)		310 (276)		

[1] p values from chi-square test or Fisher's exact test excluding missing.

[2] Sum of 11 patient-reported comorbidity conditions: diabetes, hypertension, heart disease, lung disease, thyroid disease, cirrhosis liver, stroke, chronic bronchitis, hepatitis, tuberculosis, and other.

[3] The nine patients with partial breast irradiation were excluded from all subsequent analyses since they received only 1 week of RT.

[4] V105 (cc): Breast volume receiving > 105% of prescribed dose. SD: standard deviation, MD: median.

Table 2

Pain Score by Patient Characteristics

Variable	Pain Score[1]														
	Pre-RT					Post-RT					RT-Associated Change				
	N	Mean	SD	MD	P[2]	N	Mean	SD	MD	P[2]	N	Mean	SD	MD	P[2]
All	358	1.6	2.1	0.8		335	2.8	2.6	2.3		314	1.2	2.2	0.8	**<0.001**
Race/ethnicity															
NHW	55	1.0	1.3	0.3	**0.044**	50	1.9	1.7	1.5	**0.012**	47	1.0	1.7	1.0	0.818
AA	76	1.9	2.4	1.0		71	3.3	2.6	2.8		69	1.3	2.3	0.8	
HW	227	1.7	2.1	0.8		214	2.9	2.6	2.3		198	1.2	2.3	0.8	
Age (yrs)															
<50	93	1.9	2.2	1.0	0.090	85	3.4	2.6	2.8	**0.023**	82	1.3	2.2	0.9	0.428
≥50	265	1.5	2.0	0.5		250	2.6	2.5	1.9		232	1.1	2.2	0.8	
Menopausal status															
Pre/Peri	119	1.8	2.2	1.0	0.372	111	3.1	2.5	2.5	0.228	104	1.3	2.0	1.0	0.546
Post	239	1.6	2.0	0.7		224	2.7	2.6	2.0		210	1.1	2.3	0.5	
BMI (kg/m^2)															
<25	96	1.4	1.8	0.5	0.201	84	2.1	2.2	1.1	**<0.001**	83	0.8	1.9	0.3	0.078
25–29.99	117	1.6	1.9	0.8		113	2.5	2.3	1.8		101	1.0	2.1	1.0	
≥30	145	1.9	2.3	1.0		138	3.5	2.7	3.4		130	1.5	2.4	1.0	
Smoking history															
Never	236	1.5	2.0	0.5	0.145	223	2.7	2.6	2.0	0.333	210	1.2	2.2	0.5	0.879
Ever	122	1.9	2.2	1.0		112	3.0	2.5	2.5		104	1.2	2.2	0.9	
# Comorbidities[3]															
0	140	1.6	2.0	0.8	0.986	138	2.5	2.3	2.1	0.184	127	0.9	2.1	0.8	0.054
1	134	1.7	2.1	0.8		121	2.9	2.6	2.3		115	1.1	2.2	0.5	
2	61	1.7	2.1	0.5		56	3.1	2.8	2.5		53	1.5	2.3	1.0	
≥3	23	1.5	2.0	0.3		20	3.7	2.8	4.5		19	2.3	2.1	2.3	
Diabetes															
No	315	1.7	2.1	0.8	0.115	300	2.8	2.5	2.3	0.483	280	1.1	2.2	0.6	**0.012**
Yes	43	1.2	1.7	0.3		35	3.1	2.9	2.8		34	2.1	2.3	1.6	

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Variable	Pain Score[1]														
	Pre-RT					Post-RT					RT-Associated Change				
	N	Mean	SD	MD	P[2]	N	Mean	SD	MD	P[2]	N	Mean	SD	MD	P[2]
Hypertension															
No	202	1.7	2.2	0.8	0.454	192	2.7	2.4	2.3	0.301	179	1.0	2.1	0.8	0.051
Yes	156	1.5	2.0	0.5		143	3.0	2.8	2.3		135	1.4	2.3	1.0	
Thyroid disease															
No	319	1.6	2.0	0.8	**0.039**	298	2.7	2.5	2.3	**0.031**	278	1.1	2.2	0.8	0.257
Yes	39	2.3	2.3	2.0		37	3.7	3.0	4.0		36	1.6	2.1	1.0	
Pre-RT pain score															
<4	301	0.9	1.1	0.3	**<0.001**	264	2.3	2.2	1.8	**<0.001**	264	1.4	2.1	0.8	**<0.001**
≥4	57	5.5	1.4	5.0		54	5.2	2.8	5.3		50	0.0	2.2	0.0	

Abbreviations: NHW=non-Hispanic whites; AA=Black or African American; HW=Hispanic whites; BMI= body mass index; SD= standard deviation. MD= median.

[1]Defined as the mean score of the 4 pain severity items (i.e., pain at its worst, least, average, and now).

[2]P values from ANOVA; except for RT-associated change in the total population, paired-sample t test was used. Significant findings were in bold.

[3]Sum of patient-reported 11 comorbidity conditions: diabetes, hypertension, heart disease, lung disease, thyroid disease, cirrhosis liver, stroke, chronic bronchitis, hepatitis, tuberculosis, and other.

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Table 3

Pain Score by Tumor and Treatment Characteristics

Variable	Pain score[1]														
	Pre-RT					Post-RT					RT-Associated Change				
	N	Mean	SD	MD	P[2]	N	Mean	SD	MD	P[2]	N	Mean	SD	MD	P[2]
Tumor stage															
0	71	1.4	1.9	0.7	**0.038**	63	2.5	2.3	2.0	0.540	58	1.2	2.1	0.8	0.368
IA–B	177	1.5	2.0	0.3		165	2.8	2.6	2.5		153	1.3	2.3	0.8	
IIA–IIIC	110	2.0	2.2	1.3		107	3.0	2.6	2.3		103	0.9	2.2	0.8	
ER															
Positive	276	1.6	2.0	0.8	0.431	262	2.8	2.6	2.3	0.978	244	1.2	2.2	0.8	0.414
Negative	82	1.8	2.4	0.7		73	2.8	2.5	2.3		70	1.0	2.2	0.8	
PR															
Positive	242	1.6	2.0	0.8	0.376	228	2.9	2.6	2.3	0.641	214	1.3	2.2	0.8	0.110
Negative	115	1.8	2.2	0.8		107	2.7	2.4	2.3		100	0.9	2.1	0.5	
HER2															
Positive	30	2.6	2.7	1.8	**0.014**	27	3.4	2.9	3.0	0.343	21	1.2	1.8	0.8	0.917
Negative	269	1.6	2.0	0.8		257	2.9	2.2.	2.3		244	1.2	2.3	0.8	
Triple negative															
No	288	1.6	2.0	0.8	0.563	273	2.9	2.6	2.3	0.971	253	1.2	2.2	0.8	0.609
Yes	53	1.8	2.5	0.3		47	2.9	2.6	2.5		46	1.0	2.4	0.6	
Type of chemotherapy															
None	191	1.5	1.9	0.8	0.272	174	2.7	2.4	2.3	0.598	164	1.2	2.1	0.8	0.707
Taxane	159	1.8	2.2	0.8		152	2.9	2.7	2.3		142	1.2	2.4	0.5	
Other	8	1.2	1.4	0.8		9	3.5	2.2	3.8		8	1.8	1.5	2.0	
Trastuzumab															
No	331	1.6	2.0	0.8	**0.027**	310	2.8	2.5	2.3	0.334	295	1.2	2.2	0.8	0.720
Yes	27	2.5	2.7	1.0		25	3.3	3.0	2.8		19	1.3	1.8	1.3	
Taxane +Trastuzumab															
None/other chemo only	197	1.5	1.9	0.8	0.053	181	2.8	2.4	2.3	0.530	171	1.2	2.1	0.8	0.999
Either	136	1.7	2.1	0.6		131	2.8	2.7	2.3		125	1.2	2.4	0.5	

Variable	Pain score[1]														
	Pre-RT					Post-RT					RT-Associated Change				
	N	Mean	SD	MD	P[2]	N	Mean	SD	MD	P[2]	N	Mean	SD	MD	P[2]
Both	25	2.5	2.8	1.0		23	3.4	3.1	2.8		18	1.2	1.8	1.0	
Axillary surgery															
None/SLNB	240	1.5	2.0	0.6	**0.048**	221	2.7	2.5	2.3	0.386	210	1.2	2.2	0.8	
ALND	118	1.9	2.2	1.0		114	3.0	2.7	2.3		104	1.1	2.2	0.8	0.508
Hormone Therapy															
None/after RT	175	1.6	2.1	0.8	0.912	156	2.7	2.4	2.1	0.811	149	0.9	2.0	0.5	0.063
AI before RT	95	1.6	1.9	1.0		96	2.9	2.7	2.1		88	1.2	2.5	0.8	
AI during RT	14	1.1	1.8	0.0		14	3.5	2.9	3.8		14	2.4	2.7	2.1	
Tamoxifen before RT	61	1.7	2.2	0.8		56	2.9	2.5	2.4		50	1.7	2.4	1.1	
Tamoxifen during RT	13	1.8	2.6	0.3		13	2.9	2.7	2.5		13	1.1	1.1	0.5	
RT Type															
Conventional	294	1.7	2.1	0.8	0.331	286	3.0	2.6	2.5	**0.002**	268	1.3	2.3	1.0	**0.031**
Hypofractionation	55	1.5	2.0	0.8		49	1.8	2.0	1.0		46	0.5	1.8	0.0	
Total RT dose (Gy)															
<60	112	1.3	1.8	0.5	**0.045**	93	2.0	2.1	1.3	**<0.001**	87	0.8	2.0	0.3	0.109
≥60	246	1.8	2.2	0.8		242	3.1	2.7	2.6		227	1.3	2.3	1.0	
Boost															
No	44	1.1	1.6	0.5	0.087	32	2.0	2.1	1.1	0.059	31	1.0	2.0	0.3	0.621
Yes	314	1.7	2.1	0.8		303	2.9	2.6	2.3		283	1.2	2.2	0.8	
Breast volume (cc)															
<892.1 (MD)	178	1.4	1.9	0.5	0.097	162	2.4	2.3	1.8	**0.004**	152	1.0	2.1	0.8	0.183
≥892.1	176	1.8	2.2	1.0		169	3.2	2.7	2.8		158	1.3	2.3	0.8	
V105 (cc)[3]															
<241.7 (MD)	167	1.7	2.0	1.0	0.829	147	2.3	2.2	1.8	**<0.001**	139	0.8	1.9	0.3	**0.026**
≥241.7	154	1.7	2.2	0.6		153	3.2	2.7	2.8		143	1.4	2.4	0.8	

Abbreviations: ER=estrogen receptor; PR=progesterone receptor; HER2=human epidermal growth factor receptor 2; ALND=axillary lymph node dissection; SLNB=sentinel lymph node biopsy; AI=aromatase Inhibitor; SD: standard deviation. MD: median.

[1]Defined as the mean score of the 4 pain severity items (i.e., pain at its worst, least, average, and now).

[2]P values from ANOVA. Significant findings were in bold.

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$^{3}V_{105}$ (cc): Breast volume receiving > 105% of prescribed dose.

Table 4

Clinically-Relevant Pain by Selected Patient and Treatment Characteristics

Variable	Pre-RT Pain[1]						Post-RT Pain[1]						RT-Associated Pain[1]					
	Total	No (<4)		Yes (≥4)			Total	No (<4)		Yes (≥4)			Total	No		Yes		
	N	N	%	N	%	P[2]	N	N	%	N	%	P[2]	N	N	%	N	%	P[2]
Total	358	301	84	57	16		335	230	69	105	31		314	252	80	62	20	
Race/ethnicity																		
NHW	55	53	96	2	4	**0.025**	50	44	88	6	12	**0.003**	47	42	89	5	11	**0.045**
AA	76	63	83	13	17		71	42	59	29	41		69	49	71	20	29	
HW	227	185	81	42	19		214	144	67	70	33		198	161	81	37	19	
Age (yrs)																		
<50	93	76	82	17	19	0.470	85	50	59	35	41	**0.024**	82	60	73	22	27	0.061
≥50	265	225	85	40	15		250	180	72	70	28		232	192	83	40	17	
BMI (kg/m^2)																		
<25	96	87	91	9	9	**0.005**	84	67	80	17	20	**0.001**	83	71	85	12	15	0.305
25–29.99	117	103	88	14	12		113	83	73	30	27		101	81	80	20	20	
≥30	145	111	77	34	23		138	80	58	58	42		130	100	77	30	23	
# Comorbidities[3]																		
0	140	120	86	20	14	0.826	138	103	75	35	25	**0.010**	127	107	84	20	16	**0.027**
1	134	112	84	22	16		121	86	71	35	29		115	96	83	19	17	
2	61	51	84	10	16		56	32	57	24	43		53	37	70	16	30	
≥3	23	18	78	5	22		20	9	45	11	55		19	12	63	7	37	
Diabetes																		
No	315	263	83	52	17	0.412	300	209	70	91	30	0.243	280	229	82	51	18	0.051
Yes	43	38	88	5	12		35	21	60	14	40		34	23	68	11	32	
Hypertension																		
No	202	170	84	32	16	0.962	192	139	72	53	28	0.087	179	150	84	29	16	0.069
Yes	156	131	84	25	16		143	91	64	52	36		135	102	76	33	24	
Thyroid disease																		
No	319	271	85	48	15	0.196	298	213	71	85	29	**0.002**	278	228	82	50	18	**0.030**
Yes	39	30	77	9	24		37	17	46	20	54		36	24	67	12	33	

Variable	Pre-RT Pain[1]						Post-RT Pain[1]						RT-Associated Pain[1]					
	Total	No (<4)		Yes (≥4)			Total	No (<4)		Yes (≥4)			Total	No		Yes		
	N	N	%	N	%	P[2]	N	N	%	N	%	P[2]	N	N	%	N	%	P[2]
Clinical stage																		
0	71	63	89	8	11	0.276	63	45	71	18	29	0.852	58	47	81	11	19	0.973
IA–B	177	150	85	27	15		165	113	68	52	32		153	122	80	31	20	
IIA–IIIC	110	88	80	22	20		107	72	67	35	33		103	83	81	20	19	
HER2																		
Positive	30	20	70	10	30	**0.013**	27	16	59	11	41	0.352	21	17	81	4	19	1.000
Negative	269	228	84	41	16		257	175	68	82	32		244	193	79	51	21	
Type of Chemotherapy																		
None	191	165	86	26	14	0.150	174	124	71	50	29	0.419	164	135	82	29	18	0.269
Taxane	159	128	80	31	20		152	101	66	51	34		142	112	79	30	21	
Other	8	8	100	0	0		9	5	56	4	44		8	5	62	3	38	
Trastuzumab																		
No	331	283	85	48	15	**0.024**	310	215	69	95	31	0.332	295	237	80	58	20	0.775
Yes	27	18	67	9	33		25	15	60	10	40		19	15	79	4	21	
Taxane+Trastuzumab																		
None/other chemo only	197	172	87	25	13	**0.036**	181	128	71	53	29	0.566	171	140	82	31	18	0.623
Either	136	112	82	24	18		131	88	67	43	33		125	97	78	28	22	
Both	25	17	68	8	32		23	14	61	9	39		18	15	83	3	17	
Axillary surgery																		
None/SLNB	240	208	87	32	13	0.056	221	158	71.5	63	28.5	0.119	210	170	81	40	19	0.659
ALND	118	93	79	25	21		114	72	63.2	42	36.8		104	82	79	22	21	
Hormone Therapy																		
None/after RT	175	150	86	25	14	0.734	156	108	69	48	31	0.915	149	122	82	27	18	0.367
AI before RT	95	77	81	18	19		96	67	70	29	30		88	73	83	15	17	
AI during RT	14	13	93	1	7		14	8	57	6	43		14	9	64	5	36	
Tamoxifen before RT	61	50	82	11	18		56	38	68	18	32		50	37	74	13	26	
Tamoxifen during RT	13	11	85	2	15		13	9	69	4	31		13	11	85	2	15	
RT Type																		
Conventional	294	244	83	50	17	0.304	286	189	66	97	34	**0.014**	268	210	78	58	22	**0.042**

Variable	Pre-RT Pain[1]						Post-RT Pain[1]						RT-Associated Pain[1]					
	Total	No (<4)		Yes (≥4)			Total	No (<4)		Yes (≥4)			Total	No		Yes		
	N	N	%	N	%	P[2]	N	N	%	N	%	P[2]	N	N	%	N	%	P[2]
Hypofractionation	55	48	87	7	13		49	41	84	8	16		46	42	91	4	9	
Total RT dose (Gy)																		
<60	112	102	91	10	9	**0.015**	93	73	78	20	22	**0.016**	87	73	84	14	16	0.314
≥60	246	199	81	47	19		242	157	65	85	35		227	179	79	48	21	
V105 (cc)																		
<241.7 (Median)	163	140	86	23	14	0.219	143	110	77	33	23	**0.011**	136	115	85	21	15	0.156
≥241.7	156	126	81	30	19		156	99	63	57	37		145	113	78	32	22	

[1]Pain score <4 and ≥ 4 was considered no and yes for pain, respectively. RT-associated pain was based on change from no for pre-RT to yes for post-RT pain.

[2]P values from chi-square test or Fisher's exact test excluding missing. Significant findings were in bold.

[3]Sum of 11 conditions: diabetes, hypertension, heart disease, lung disease, thyroid disease, cirrhosis liver, stroke, bronchitis, hepatitis, tuberculosis, and other.

Table 5

Risk Factors Associated with Pre-RT, Post-RT and RT-Associated Clinically-Relevant Pain

Variable	Comparisons	OR (95%CI)	P[1]
Pre-RT Pain (Yes vs. No)[2]			
Race/ethnicity	AA vs. NHW	3.87 (0.82–18.44)	0.089
	HW vs. NHW	**5.06 (1.17–21.83)**	**0.030**
BMI (kg/m^2)	≥30 vs. <30	**2.46 (1.34–4.50)**	**0.004**
Taxane + Trastuzumab	Either vs. None/other chemotherapy	1.34 (0.69–2.58)	0.387
	Both vs. None/other chemotherapy	2.43 (0.88–6.73)	0.088
Axillary surgery	ALND vs. SLNB or None	1.53 (0.80–2.92)	0.198
Post-RT Pain (Yes vs. No)[2]			
Race/ethnicity	AA vs. NHW	**3.75 (1.19–11.85)**	**0.024**
	HW vs. NHW	**3.14 (1.08–9.11)**	**0.036**
Age (yrs.)	<50 vs. ≥50	**3.09 (1.57–6.10)**	**0.001**
BMI (kg/m^2)	≥30 vs. <30	1.26 (0.69–2.29)	0.460
# Comorbidities[3]	1 vs. 0	1.17 (0.59–2.33)	0.661
	2 vs. 0	**3.04 (1.31–3.08)**	**0.010**
	≥3 vs. 0	**5.68 (1.60–20.18)**	**0.007**
RT Type	Conventional vs. Hypofractionation	1.49 (0.58–3.82)	0.408
V105 (cc)	≥241.7 vs. <241.7	**1.80 (1.00–3.23)**	**0.050**
Pre-RT pain score	≥ 4 vs. <4	**4.65 (2.30–9.38)**	**<0.0001**
RT-Associated Pain (Yes vs. No)[4]			
Race/ethnicity	AA vs. NHW	**3.27 (1.09–9.82)**	**0.034**
	HW vs. NHW	2.08 (0.75–5.82)	0.162
Age (yrs.)	<50 vs. ≥50	**2.44 (1.24–4.79)**	**0.010**
# Comorbidities[3]	1 vs. 0	1.18 (0.58–2.43)	0.648
	2 vs. 0	**3.06 (1.32–7.08)**	**0.009**
	≥3 vs. 0	**4.61 (1.49–14.25)**	**0.008**
RT Type	Conventional vs. Hypofractionation	2.41 (0.80–7.19)	0.117

[1]P values from multi-variable logistic regression. Significant findings were in bold.

[2]Pain score <4 and ≥ 4 was considered no and yes for pain, respectively.

[3]Sum of 11 comorbidity conditions: diabetes, hypertension, heart disease, lung disease, thyroid disease, liver cirrhosis, stroke, chronic bronchitis, hepatitis, tuberculosis, and other.

[4]RT-associated pain was based on the change from no for pre-RT to yes for post-RT pain.