Introduction

The majority of women with in situ and early-stage breast cancer receive adjuvant breast radiation therapy (RT) after breast-conserving surgery. 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. In some cases, the skin reaction can progress to desquamation, either dry or moist, which is often more uncomfortable and poses a risk, albeit small, of infection and/or treatment breaks. Mild erythema is very common, occurring in up to 95% of patients, as is brisk erythema with or without moist desquamation, ranging from 5% to 69%, whereas moist desquamation is less common, ranging from 11% to 47% [1–8]. Several predictive factors for more severe skin toxicity have been identified, including body mass index (BMI), breast size, and radiation technique including fractionation regimen and dosimetric homogeneity [1, 4, 6–9].

Our institution serves a racially and ethnically diverse population of breast cancer patients, and we have been interested in studying racial and ethnic variation in radiation-related skin toxicity in breast cancer patients.
We previously published a series evaluating predictors of skin toxicity in a cohort of patients receiving postmastectomy radiation (PMRT), and identified black/AA race, postmenopausal status, and higher BMI as predictors for moist desquamation [10]. Interestingly, these same factors did not predict for higher grade skin toxicity by the National Cancer Institute’s Common Toxicity Criteria for Adverse Events (CTCAE) skin toxicity scale, which does not clearly differentiate between patients who do and do not develop moist desquamation. The observed variation in skin toxicity in that series was thus seen primarily in rate of moist desquamation, rather than other skin toxicity characteristics such as the degree of erythema. Moist desquamation is much less common in patients receiving radiation to the intact breast after lumpectomy, as compared to patients receiving radiation to the chest wall after mastectomy. We therefore sought to determine if the same factors, particularly race, predicted for more severe skin toxicity in the setting of radiation to the intact breast in a similarly diverse cohort of patients from the same institution.

Materials and Methods

In this study, we evaluated 392 consecutive breast cancer patients enrolled during December, 2008 to July, 2014 in a prospective study assessing RT-induced skin toxicity to the intact breast in the Radiation Oncology Department at the University of Miami. The study was approved by the Institutional Review Board. Women (≥18 years) with newly diagnosed breast carcinoma, stage 0–III (American Joint Committee on Cancer) who underwent breast-conserving surgery were scheduled to receive RT to the intact breast with or without regional nodal radiation were eligible. At the time of enrollment, patients signed informed consent either in English or Spanish, and completed a baseline assessment form, including self-identification of race and ethnicity, breast cancer risk factors including reproductive and family history, as well as comorbidities, height, weight, and smoking habits. Other patient, disease, and treatment characteristics, including detailed information on radiation delivery, were prospectively collected.

Skin toxicity was assessed by the treating physician. As previously described [10], we used both NCI CTCAE (v3.0), and a modified variation in the NCI CTCAE (v3.0) skin toxicity scale which breaks CTCAE “grade 2” into three subcategories, seeking to capture more detailed information including the presence and extent of dry and moist desquamation. The scale divides skin reaction into six categories as follows: 1 – faint or dull erythema and/or follicular reaction and/or itching (CTCAE grade 1); 2 – bright erythema and/or tender to touch (CTCAE grade 2); 3 – dry desquamation with or without erythema (CTCAE grade 1 or 2); 4 – small or moderate amount of wet desquamation (CTCAE grade 2); 5 – confluent moist desquamation (CTCAE grade 3); 6 – ulceration, hemorrhage, and/or necrosis (CTCAE grade 4). Skin toxicity was captured at midpoint to RT completion. 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.

We used Pearson’s chi-squared test or Fisher’s exact test to compare differences in the distributions of patient and disease characteristics as well as skin toxicity grade by race/ethnicity. Wilcoxon signed-rank test was performed to evaluate progression of RT-induced skin toxicity from midpoint to RT completion. Multiple logistic regression analyses were conducted to evaluate the association between multiple predictors and the risk of higher grade skin toxicity using both grading scales. Statistical analysis was performed using SAS version 9.3 for Windows (SAS Institute, Cary, NC) and significance level was set at two-sided α = 0.05.

Results

Patient demographic and tumor characteristics

In Table 1, we summarize overall patient, tumor, and treatment characteristics by race and ethnicity, presented as 15% non-Hispanic white (NHW), 62% Hispanic white (HW), 20% AA, and 3% other, as well as condensed to 80% non-AA and 20% AA. Mean age at the time of enrollment was 56.2 years (range 27–85 years). Thirty-three percent were pre or perimenopausal, and 67% postmenopausal. A higher proportion of AA patients were obese (61% vs. 35% in non-AA; P < 0.001), had at least two comorbidities (31% vs. 22%; P = 0.013), had stage II-III disease (43% vs. 28%; P = 0.022), had ER-negative tumors (34% vs. 21%; P = 0.013) or triple-negative tumors (27% vs. 12%; P < 0.001), and had above-median breast volume (72% vs. 45%; P < 0.001).

Treatment characteristics

All patients received breast-conserving surgery, and patients with invasive disease had axillary dissection or sentinel node biopsy. As shown in Table 1, 51% received systemic chemotherapy (8% neo-adjuvant and 43% adjuvant) and 66% received hormone therapy. A higher proportion of AA patients did not receive hormone therapy (51% vs. 30%; P < 0.001). RT was delivered to the breast with or without regional nodes based on clinical indications.
Table 1. Patient characteristics by race/ethnicity.

| Variable                                | Total | NHW | HW | AA | Other | Non-AA | AA |
|-----------------------------------------|-------|-----|----|----|-------|--------|----|
| Study population                        | 392   | 100 | 59 | 15 | 241   | 62     | 79 | 20 |
| Age at consent (years)                  |       |     |    |    |       |        |    |
| <50                                     | 98    | 25  | 18 | 30 | 58    | 24     | 20 | 25 |
| 50–59                                   | 156   | 40  | 21 | 36 | 94    | 39     | 34 | 43 |
| ≥60                                     | 138   | 35  | 20 | 34 | 89    | 37     | 25 | 32 |
| Mean (SD)                               | 56.2  | 9.1 | 55.9| 9.1| 56.5  | 9.0    | 55.5| 9.4|
| Menopausal status                       |       |     |    |    |       |        |    |
| Pre/Peri                                | 128   | 33  | 24 | 41 | 76    | 32     | 25 | 32 |
| Post                                    | 264   | 67  | 35 | 59 | 165   | 68     | 54 | 68 |
| BMI (kg/m²)                             |       |     |    |    |       |        |    |
| <25                                     | 101   | 26  | 28 | 47 | 55    | 23     | 13 | 16 |
| 25–29.99                                | 133   | 34  | 17 | 29 | 94    | 39     | 18 | 23 |
| ≥30                                     | 158   | 40  | 14 | 24 | 92    | 38     | 48 | 61 |
| Mean (SD)                               | 29.4  | 6.4 | 27.0| 6.6| 29.0  | 5.2    | 32.5| 8.4|
| Smoking history                         |       |     |    |    |       |        |    |
| Never                                   | 260   | 66  | 38 | 64 | 156   | 65     | 56 | 71 |
| Ever                                    | 132   | 34  | 21 | 36 | 85    | 35     | 23 | 29 |
| Number of comorbidities²                |       |     |    |    |       |        |    |
| 0                                       | 154   | 39  | 27 | 46 | 102   | 42     | 20 | 25 |
| 1                                       | 146   | 37  | 20 | 34 | 87    | 36     | 35 | 44 |
| 2                                       | 66    | 17  | 7  | 12 | 36    | 15     | 20 | 26 |
| ≥3                                      | 26    | 7   | 5  | 8  | 16    | 7      | 4  | 5  |
| Disease stage                           |       |     |    |    |       |        |    |
| 0                                       | 79    | 20  | 7  | 12 | 53    | 22     | 15 | 19 |
| I                                       | 193   | 49  | 38 | 64 | 120   | 50     | 30 | 38 |
| II–III                                  | 120   | 31  | 14 | 24 | 68    | 28     | 34 | 43 |
| Histology                               |       |     |    |    |       |        |    |
| DCIS (ductal carcinoma in situ)          | 85    | 22  | 8  | 14 | 57    | 24     | 16 | 20 |
| IDC (invasive ductal carcinoma)          | 289   | 74  | 48 | 81 | 172   | 71     | 60 | 76 |
| ILC (invasive lobular carcinoma)         | 17    | 4   | 3  | 5  | 11    | 5      | 3  | 4  |
| Other                                   | 1     | 0   | –  | –  | 1     | 0      | –  | –  |
| ER Positive                              | 299   | 76  | 43 | 73 | 193   | 80     | 52 | 66 |
| ER Negative                              | 92    | 24  | 16 | 27 | 47    | 20     | 27 | 34 |
| PR Positive                              | 263   | 67  | 37 | 63 | 169   | 71     | 48 | 61 |
| PR Negative                              | 127   | 33  | 22 | 37 | 70    | 29     | 31 | 39 |
| HER2 Positive                            | 38    | 12  | 5  | 9  | 24    | 12     | 8  | 12 |
| HER2 Negative                            | 285   | 88  | 50 | 91 | 169   | 88     | 58 | 88 |
| Triple negative                         |       |     |    |    |       |        |    |
| No                                      | 317   | 85  | 48 | 86 | 201   | 89     | 57 | 73 |
| Yes                                     | 56    | 15  | 8  | 14 | 25    | 11     | 21 | 27 |
| Chemotherapy therapy                    |       |     |    |    |       |        |    |
| No                                      | 191   | 49  | 28 | 48 | 119   | 49     | 41 | 52 |
| Yes                                     | 201   | 51  | 31 | 52 | 122   | 51     | 38 | 48 |
| Hormone therapy                         |       |     |    |    |       |        |    |
| No                                      | 133   | 34  | 17 | 29 | 75    | 31     | 40 | 51 |
| Yes                                     | 257   | 66  | 42 | 71 | 165   | 69     | 39 | 49 |

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Patients were treated using standard or partially wide photon tangents with both conventionally fractionated and hypofractionated schemes. The dose range to the breast was 42.4–50.4 Gy, in fraction sizes of 1.8–2.7 Gy. The most common conventionally fractionated approach was 50 Gy in 2 Gy per fraction, and the most common hypofractionated approach was 42.4 Gy in 2.65 Gy per fraction. For the purposes of statistical analysis, total dose of <45 Gy in fraction size >2 Gy was considered hypofractionated, and total dose ≥45 Gy in fraction size of ≤2 Gy was considered conventionally fractionated.

Seventeen percent of patients were treated with a hypofractionated approach, and 83% with a conventionally fractionated approach. Regional nodal radiation including supra/infraclavicular +/− axillary and internal mammary nodes was delivered in 15% of patients, dose range 45–50.4 Gy in 25 fractions. Anterior oblique supraclavicular +/− axillary fields were most commonly matched monoisocentrically with the breast tangents. Eighty-eight percent of patients received a boost to the lumpectomy cavity of 10–16 Gy. 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. Dosimetric analysis showed that the mean percentage breast volume receiving >105% of prescription dose was 35% and >110% was 16%. There were no significant differences in RT treatment parameters by race or ethnicity.

**Skin toxicity**

Table 2 demonstrates the progression of skin toxicity grades from midpoint to RT completion (P < 0.001). Using the modified grading scale, changes in skin toxicity from midpoint to RT completion were: (1) grade 0: decreased from 11% to 1%; (2) grade 1 (mild erythema): decreased from 82% to 42%; (3) grade 2 (brisk erythema without desquamation): increased from 4% to 20%; (4) grade 3 (dry desquamation with or without erythema): increased from 1% to 15%; (5) grade 4 (moist desquamation with or without erythema): increased from 3% to 20%; (6) grade 5 (confluent moist desquamation): increased from 0% to 2%. Using the NCI CTCAE grading scale, changes in skin toxicity from midpoint to RT completion were as follows: (1) grade 0: decreased from 11% to 1%; (2) grade 1 (mild erythema): decreased from 83% to 46%; (3) grade 2: increased from 6% to 51%; and (4) grade 3: increased from 0% to 2%. No patient developed grade 6 by the modified study scale or grade 4 or greater by CTCAE scale at RT completion.
Table 3 presents skin toxicity at RT completion using both the modified scale of 0–6, as well as the NCI CTCAE scale of 0–4, broken down by patient, disease, and treatment characteristics. In general, the two scales identified similar predictors of more severe skin toxicity, including higher BMI, more advanced tumor stage and invasive ductal histology, progesterone receptor (PR) negative status, conventionally fractionated regimens with RT dose to whole breast ≥ 45 Gy, the use of a lumpectomy cavity boost, and above-median breast volume. Breast volume and BMI were significantly correlated. Neither race nor ethnicity predicted for more severe skin toxicity grade, although there was a higher crude rate of severe skin reaction in AA patients compared to non-AA: 28 versus 19% for modified grade 4–5 (moist desquamation) and 58 versus 50% for CTCAE grade 2–3 toxicity. Skin toxicity grade did not vary with age, menopausal status, the use of chemotherapy, and dosimetric factors.

As shown in Table 4, multivariate analyses were performed to evaluate the association between skin toxicity and age, race, breast volume, BMI, stage, ER and PR status, fractionation approach, and breast volume. For the modified scale, analysis was performed for two separate groupings, grade 2–3 versus 0–1, and 4–5 versus 0–1; the first grouping separates patients with lower versus higher degrees of erythema or hyperpigmentation, whereas the latter specifically separates out patients with moist desquamation. For grade 2–3 versus 0–1, the following factors were significant: higher stage (OR = 1.82, 95% CI = 1.00, 3.31), ER-positive/PR-negative status (OR = 3.00 95% CI = 1.25, 7.21), and conventionally fractionated regimens (OR = 2.98; 95% CI = 1.52, 5.84); higher BMI was not significantly associated with higher grade toxicity. For 4–5 versus 0–1, higher BMI (OR = 2.99, 95% CI = 1.29, 6.92), ER-positive/PR-negative status (OR = 3.50, 95% CI = 1.29, 9.48), and conventionally fractionated regimens (OR = 4.81, 95% CI = 1.77, 13.05) were significantly associated with higher grade skin toxicity - specifically moist desquamation.

Using the NCI CTCAE grading scale, higher BMI (OR = 2.09; 95% CI = 1.15, 3.82), higher stage (OR = 1.82; 95% CI = 1.06, 3.11), ER-positive/PR-negative status (OR = 3.50; 95% CI = 1.29, 9.48), and conventionally fractionated regimens (OR = 3.25; 95% CI = 1.76, 6.01) were significantly associated with higher grade RT-induced skin toxicity (2–3 vs. 0–1). After controlling for all predictors, age, race, and breast volume were not significant predictors of severe skin toxicity by either grading scale.

**Discussion**

In this prospectively followed tri-racial/ethnic cohort of breast cancer patients receiving adjuvant RT to the intact breast after breast-conserving surgery, the overall incidence of NCI CTCAE grade 2 or greater skin toxicity was 52%, and 21% developed moist desquamation, consistent with the majority of published series [1–8]. We identified higher BMI, higher disease stage, PR-negative tumor status, and conventionally fractionated regimens as predictors for higher skin toxicity grade. Age, race, ethnicity, and breast volume did not predict for skin toxicity. Additionally, a more detailed skin toxicity scale designed to specifically capture desquamation identified BMI as a predictor specifically for moist desquamation, but not dry desquamation.
Table 3. Skin toxicity grade at post-RT by patient and clinical variables.

| Variable                  | Skin toxicity (modified grade) | Skin toxicity (CTCAE grade) |
|---------------------------|-------------------------------|-----------------------------|
|                           | 0  1  2  3  4  5  | 0  1  2  3  4  5  | 0  1  2  3  4  5  |
| Total patients            | 4 169 77 59 74 9  | 173 44 136 35 83 21  | 4 184 195 9  |
| Age at consent (years)    |                               |                             |                             |
| <50                       | – 39 15 18 24 2  | 0.221 39 40 33 34 26 27  | 0.367 – 43 53 2 0.308 43 44 55 56 0.332 |
| 50–59                     | 1 65 37 23 24 6  | 66 42 60 38 30 19  | 1 71 78 6  |
| ≥60                       | 3 65 25 18 26 1  | 68 49 43 31 27 20  | 3 70 64 1  |
| Menopausal status         |                               |                             |                             |
| Pre/Peri                  | – 56 19 23 27 3  | 0.433 56 44 42 33 30 23 0.719 – 61 64 3 0.966 61 48 67 52 0.933 |
| Post                      | 4 113 58 36 47 6  | 117 44 94 36 53 20  | 4 123 131 6  |
| Race/ethnicity            |                               |                             |                             |
| NHW                       | – 28 17 7 6 1  | NE 28 47 24 41 7 12 0.451 – 31 27 1 0.286 31 53 28 47 0.610 |
| HW                        | 2 107 41 40 48 3  | 109 45 81 34 51 21 2 116 120 3 118 49 123 51 |
| AA                        | 2 28 16 11 17 5  | 30 38 27 34 22 28 2 31 41 5 33 42 46 58 |
| Other                     | – 6 3 1 3 – 6 46 4 31 3 23 – 6 7 – 6 46 7 54 |
| Non-AA                    | 2 141 61 48 57 4 0.080 143 46 109 35 61 19 0.230 2 153 154 4 0.019 155 50 158 50 0.218 |
| AA                        | 2 28 16 11 17 5  | 30 38 27 34 22 28 2 31 41 5 33 42 46 58 |
| BMI (kg/m²)               |                               |                             |                             |
| <25                       | – 56 18 15 10 2  | 0.008 56 55 33 33 12 12 0.001 – 62 37 2 0.004 62 61 39 39 0.002 |
| 25–29.99                  | 1 62 28 20 21 1  | 63 47 48 36 22 17 1 63 68 1 64 48 69 52 |
| ≥30                       | 3 51 31 24 43 6  | 54 34 55 35 49 31 3 59 90 6 62 39 96 61 |
| Smoking history           |                               |                             |                             |
| Never                     | 2 111 45 39 56 7 0.227 113 43 84 32 63 24 0.093 2 121 130 7 0.738 123 47 137 53 0.717 |
| Ever                      | 2 58 32 20 18 2 60 45 52 39 20 15 2 63 65 2 65 49 67 51 |
| No. of comorbidities      |                               |                             |                             |
| None                      | 1 67 34 25 24 3  | NE 68 44 59 38 27 18 0.821 1 72 78 3 0.642 73 47 81 53 0.993 |
| 1                         | – 66 27 20 31 2  | 66 45 47 32 33 23 – 71 73 2 71 49 75 51 |
| 2                         | 3 25 10 12 14 2 28 42 22 33 16 24 3 29 32 2 32 48 34 52 |
| ≥3                        | – 11 6 2 5 2 11 42 8 31 7 27 – 12 12 2 12 46 14 54 |
### Table 3. Continued.

| Variable                          | Skin toxicity (modified grade) |                                      | Skin toxicity (CTCAE grade) |                                      |
|-----------------------------------|--------------------------------|-------------------------------------|-----------------------------|-------------------------------------|
|                                   | 0 1 2 3 4 5                    | 0–1 2–3 4–5                         | 0–1 2–3                     |                                     |
| Disease stage                     | N N N N N N                   | N %                                 | N %                         |                                     |
| 0                                 | 2 45 11 10 10 1               | 0.099                               | 47 59 21 27 11 14           | 0.013                               |
| IA–B                              | 1 83 35 29 40 5               | 0.013                               | 2 47 29 1 0.022             | 49 62 30 38 0.005                   |
| IIA–III                           | 1 41 31 20 24 3               | 0.022                               | 1 92 95 5 0.044             | 93 48 100 52                       |
| Histology                         |                                |                                      |                             |                                     |
| DCIS (ductal carcinoma in situ)   | 2 49 10 11 11 2               | NE 0.004                             | 2 51 30 2 0.002             | 53 62 32 38 0.002                   |
| IDC (invasive ductal carcinoma)   | 2 108 64 47 61 7              | 0.005                               | 2 121 159 7 0.005           | 123 43 166 57                      |
| ILC (invasive lobular carcinoma)  | – 11 3 1 2 –                  |                                      | 0.002                       |                                     |
| Other                             | – 1 – – – – –                 |                                      |                             |                                     |
| ER                                |                                |                                      |                             |                                     |
| Positive                          | 3 133 54 46 55 8              | 0.493                               | 136 45 100 33 63 21 0.518   | 145 143 8 0.275 148 49 151 51 0.233 |
| Negative                          | 1 35 23 13 19 1               | 0.150                               | 1 36 39 36 39 20 22 1 38 52 1 39 42 53 58 |
| PR                                |                                |                                      |                             |                                     |
| Positive                          | 3 123 46 38 46 7              | 0.150                               | 3 133 120 7 0.044           | 136 52 127 48 0.022                |
| Negative                          | 1 44 31 21 28 2               | 0.063                               | 1 49 75 2 0.044             | 50 39 77 61                        |
| HER2                              |                                |                                      |                             |                                     |
| Positive                          | – 17 7 6 8 –                 | 0.836                               | – 19 19 – 0.503             | 19 50 19 50 0.500                  |
| Negative                          | 2 112 62 43 58 8              | 0.855                               | 2 124 151 8 0.051           | 126 44 159 56                      |
| Triple negative                   |                                |                                      |                             |                                     |
| No                                | 3 140 60 48 58 8              | 0.336                               | 3 153 153 8 0.145           | 156 49 161 51 0.062                |
| Yes                               | – 18 15 8 14 1               | 0.192                               | – 20 35 1 0.36             | 20 36 36 64                        |

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| Variable                       | Skin toxicity (modified grade) | Skin toxicity (CTCAE grade) |
|--------------------------------|--------------------------------|-----------------------------|
|                                | 0 | 1 | 2 | 3 | 4 | 5 | 0–1 | 2–3 | 4–5 | 0–1 | 2–3 | 0–1 | 2–3 |
|                                | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Chemotherapy                   | 3 | 86 | 37 | 27 | 34 | 4 | 0.909 | 89 | 47 | 64 | 34 | 38 | 20 | 0.622 |
| No                             | 1 | 83 | 40 | 32 | 40 | 5 | 0.966 | 56 | 42 | 47 | 35 | 30 | 23 | 0.784 |
| Yes                            | 2 | 46 | 10 | 45 | 9 | 0.001 | 48 | 72 | 14 | 21 | 5 | 7 | 0.001 |
| Hormone therapy                | – | 56 | 27 | 20 | 27 | 3 | – | 60 | 70 | 3 | 0.668 |
| No                             | 1 | 131 | 49 | 39 | 46 | 6 | 117 | 48 | 88 | 34 | 52 | 20 | 0.628 |
| Yes                            | 4 | 113 | 49 | 39 | 46 | 6 | 0.784 | 124 | 123 | 6 | 0.379 |
| Fractionation                  | 2 | 46 | 10 | 4 | 5 | – | 0.001 | 48 | 72 | 14 | 21 | 5 | 7 | 0.001 |
| Hypofractionated               | – | 56 | 27 | 20 | 27 | 3 | – | 60 | 70 | 3 | 0.668 |
| Conventional fractionated     | 2 | 122 | 67 | 54 | 69 | 9 | 0.001 | 124 | 38 | 121 | 37 | 78 | 24 | 0.005 |
| Lumpectomy cavity boost        | 1 | 30 | 5 | 5 | 5 | 2 | 0.024 | 31 | 65 | 10 | 21 | 7 | 15 | 0.009 |
| No                             | 3 | 138 | 72 | 53 | 69 | 7 | 0.001 | 124 | 181 | 7 | 154 | 45 | 188 | 55 |
| Yes                            | 4 | 94 | 34 | 30 | 27 | 1 | 0.005 | 99 | 51 | 66 | 34 | 28 | 15 | 0.003 |
| Breast volume <881.3 CC (median) | 2 | 118 | 48 | 42 | 45 | 5 | 0.607 | 121 | 46 | 90 | 34 | 50 | 19 | 0.438 |
| No                             | 3 | 118 | 48 | 42 | 45 | 5 | 0.003 | 126 | 127 | 5 | 0.581 |
| ≥881.3 CC (median)             | 2 | 118 | 48 | 42 | 45 | 5 | 0.607 | 121 | 46 | 90 | 34 | 50 | 19 | 0.438 |
| Percentage of breast volume with >105% prescription dose <51.3 (75th percentile) | 1 | 43 | 15 | 9 | 19 | 1 | 0.003 | 129 | 49 | 132 | 51 | 0.644 |
| ≥51.3                          | 1 | 43 | 15 | 9 | 19 | 1 | 0.003 | 129 | 49 | 132 | 51 | 0.644 |
| Percentage of breast volume with >105% prescription dose >0 | 2 | 89 | 29 | 29 | 33 | 2 | 0.634 | 91 | 49 | 58 | 32 | 35 | 19 | 0.710 |
| No                             | 2 | 72 | 33 | 22 | 31 | 4 | 0.634 | 91 | 49 | 58 | 32 | 35 | 19 | 0.710 |
| Yes                            | 2 | 72 | 33 | 22 | 31 | 4 | 0.634 | 91 | 49 | 58 | 32 | 35 | 19 | 0.710 |

NE, not estimable.

1P-value from chi-squared test or Fisher’s exact test with grade 0–1 grouped.
2P-value from chi-squared test or Fisher’s exact test.

Bold values indicate statistically significant findings at p < 0.05.
or degree of erythema, a finding the NCI CTCAE scale was not able to detect.

One of the most important findings of this series is that race and ethnicity were not associated with variation in skin toxicity. In our previously published series of patients receiving PMRT, the incidence of moist desquamation was much higher, 53.7% overall, and AA race was found to be a significant predictor of moist desquamation but not of higher grade skin toxicity by the CTCAE scale [10]. In the current series, there was a nonsignificantly higher rate of severe skin toxicity in AA versus non-AA patients – 58 versus 50% for CTCAE grade 2–3 toxicity, and 28 versus 19% for moist desquamation. AA patients were more likely to have other potential risk factors for skin toxicity, including higher BMI, higher disease stage, and larger breast volume; when these factors were considered in multivariate analysis, race ultimately did not predict for skin toxicity grade or moist desquamation. There are two possible interpretations. One is that this study has limited statistical power to identify variation in skin toxicity by race, given the low incidence of moist desquamation and severe skin toxicity in patients receiving radiation to the intact breast. However, it is also possible that race only predicts for moist desquamation at the higher skin doses achieved using PMRT, and is not associated with skin toxicity grade in the postlumpectomy setting. We look forward to analysis of additional cohorts to determine if differences are seen with larger patient numbers and different populations.

It is also important to note that this cohort includes a large number of HW patients, who make up the majority (62%) of the non-AA comparison group, demonstrating no increased risk of skin toxicity severity in this population as compared to NHW and AA patients.

The relationship between BMI and higher grade skin toxicity is supported by previous studies [6, 8, 9]. However, our findings on multivariate analysis using the modified scale additionally demonstrated that BMI is specifically associated with moist desquamation, rather than dry desquamation or greater degree of erythema or hyperpigmentation. While both breast volume and BMI predicted for higher skin toxicity grade in univariate analysis, only BMI retained statistical significance on multivariate analysis, suggesting this is a more important predictor than breast volume. This finding likely relates the bolus effect of skin folds seen in obese patients, as well as the abrasive effect of friction within skin folds; nonobese patients with larger breasts often have fewer skin folds than obese patients, explaining why BMI may be more predictive than breast volume. Skin toxicity is usually addressed with one of any number of topical agents, or in some cases with subcutaneous amifostine, [6, 11, 12], but recent data suggest that a protective barrier approach may also reduce desquamation [13]. The premise of the barrier film approach is that skin reaction forms from an accumulation of microabrasions on the skin surface, in tissue that is sensitized to injury by radiation. The finding that BMI is specifically correlated with moist desquamation points to a barrier approach as a potentially more effective approach in these patients, an important subject for future investigation.

Large breast separation (a surrogate for large breast volume and/or BMI) has long been considered a relative contraindication to hypofractionated treatment regimens, based on the concept that such patients are at higher risk of more

| Table 4. Associations between multiple variables and post-RT skin toxicity. |
|--------------------------------------|------------------|------------------|------------------|
| Variable                          | Category                | Skin toxicity (modified grade) | Skin toxicity (CTCAE Grade) |
| Age at enrollment (years)         | <50 versus ≥50         | OR (95%CI) | P       | OR (95%CI) | P       |
| Race AA versus Non-AA             | 0.95 (0.50, 1.78)     | 0.861 | 1.13 (0.56, 2.29) | 0.735 | 1.01 (0.58, 1.76) | 0.975 |
| BMI 25–29.99 versus <25           | 1.32 (0.71, 2.47)     | 0.378 | 1.62 (0.70, 3.77) | 0.262 | 1.84 (1.03, 3.27) | 0.038 |
| ≥30 versus <25                    | 1.53 (0.79, 2.98)     | 0.210 | 2.99 (1.29, 6.92) | 0.011 | 2.09 (1.15, 3.82) | 0.016 |
| Stage I–III versus 0              | 1.82 (1.00, 3.31)     | 0.050 | 2.10 (0.98, 4.50) | 0.058 | 1.82 (1.06, 3.11) | 0.029 |
| ER/PR ER+/PR− versus ER+/PR+      | 3.00 (1.25, 7.21)     | 0.014 | 3.50 (1.29, 9.48) | 0.014 | 2.74 (1.26, 5.98) | 0.001 |
| Er−/PR− versus ER+/PR+            | 1.66 (0.93, 2.97)     | 0.087 | 1.45 (0.72, 2.96) | 0.300 | 1.57 (0.93, 2.66) | 0.095 |
| Fractionation Conventional versus Hypo | 2.98 (1.52, 5.84) | 0.001 | 4.81 (1.77, 13.05) | 0.002 | 3.25 (1.76, 6.01) | ≤0.001 |
| Breast volume (CC) ≥Median versus <Median | 1.29 (0.74, 2.23) | 0.371 | 1.87 (0.96, 3.63) | 0.067 | 1.38 (0.84, 2.27) | 0.200 |

OR: odds ratio; CI: confidence interval; Model 1: multinomial logistic regression with generalized logit link function. Model 2: logistic regression.

Bold values indicate statistically significant findings at p < 0.05.
severe skin reaction. One of the reasons for the risk of skin toxicity in patients with large breast separation has been the difficulty in achieving dose homogeneity in this setting, and the awareness that dosimetric “hotspots” are likely to increase the risk of desquamation [1]. However, this series demonstrates that relatively homogeneous plans can be achieved even in patients with large breast volume and/or high BMI. About 40% of our patients were obese. Nonetheless, the mean percent of the breast volume receiving >105% of prescription dose was 35%, and >110% was 16%. Dosimetric factors were not associated with skin toxicity, possibly because reasonably homogeneous plans were achieved. The finding that higher BMI predicted for moist desquamation, whereas dosimetric factors did not, again suggests skin folds as an important underlying cause of moist desquamation.

The majority of data evaluating toxicity related to fractionation scheme has focused on late rather than acute toxicity. However, a recent large analysis from the Michigan Radiation Oncology Quality Consortium found that conventionally fractionated radiation was associated with higher skin toxicity grade compared to hypofractionated regimens [8], and our study corroborates this finding. The reasons for this likely relate to the lower total dose prescribed with hypofractionated regimens, and this finding lends greater support for the use of this approach in appropriately selected patients [8, 14].

There are a number of interesting findings in our analysis, in particular associations between skin toxicity and disease characteristics including stage and receptor status. It is interesting that PR-negative status predicted for higher skin toxicity grade in this series, whereas in our series evaluating risk factors for skin toxicity in the setting of PMRT, PR-negative status was protective. There is no clear explanation for these findings; we are not aware of any literature that identifies hormone receptors as a predictor of RT-induced skin reaction [15]. The fact that PR status emerged as a significant predictor in both series, but in opposite directions, suggests that it is possible that these relationships are treatment specific or related to the statistical limitations of these relatively small series. To better evaluate the relationship identified in this series, we conducted additional analyses and found that ER and PR status were significantly associated with each other on univariate analysis (data not shown); thus in the multivariate model we included ER and PR status as a combined variable, to avoid collinearity. PR status was analyzed as ER+/PR− versus ER+/PR+, and as ER−/PR− versus ER+/PR+ to account for this, and in the context of ER positivity, PR-negative status retained its significance as a risk factor for more severe skin toxicity. Thus, it seems the strength of this relationship is maintained despite the collinearity of ER and PR. These relationships between PR status and skin toxicity may thus be a novel finding, which requires further investigation.

Our analysis also showed that more severe skin toxicity was associated with invasive disease as compared to DCIS, but not chemotherapy or hormone therapy. There may be underlying changes in the skin of the breast in the setting of invasive breast cancer or more locally advanced breast cancer that predispose to radiation sensitivity. It would seem logical that the skin toxicity grade would relate to the more frequent use of chemotherapy in patients with invasive disease, but there have been mixed findings on this correlation [16, 17], and these associations may also relate to the time interval between chemotherapy and radiation.

Overall this series identified a number of factors that were associated with skin reaction that are not readily explained, including relationships between tumor subtype, stage, and skin reaction. While there is no known mechanism for such relationships, we hypothesize that these findings may relate to patient factors such as inflammatory or other cytokines related to the various conditions – obesity, presence of invasive breast cancer, and PR status, among others, that might link these factors to skin toxicity. Our prospective analysis also includes collection of genomic DNA, serum, and urine specimens at the start and completion of RT, and we are optimistic that future studies may begin to elucidate molecular and genetic mechanisms [18]. Indeed, our preliminary analysis has uncovered a relationship between C-reactive protein and skin reaction [19]. However, the relationships identified in this study must be interpreted cautiously, and are simply hypothesis-generating at this time.

In this series, the NCI CTCAE scale captured the majority of the findings that the modified scale did, however, the more nuanced analysis of the study scale was able to differentiate between factors that increased the risk of higher grade skin toxicity overall (including erythema, hyperpigmentation, and desquamation), as well as factors that specifically predict for moist desquamation. These findings lend additional support to the need to capture additional skin toxicity data beyond the CTCAE scale.

We continue to expand this study cohort and will conduct additional analyses as our data matures. With a rate of moist desquamation of 21%, we hope that we may be able to strengthen the statistical analysis and more clearly identify novel predictors of this endpoint as our series continues to grow over time. As a component of our study we are also collecting patient-reported outcomes in the form of the Breast Cancer Treatment Outcome Scale (BC-TOS) and we are currently conducting an analysis of quality of life (QOL) data in this patient cohort, relating QOL outcomes to acute skin toxicity factors, to help put the acute toxicities identified in this study in context of the patient-reported outcomes and to guide priorities for future treatment decision making and intervention studies.
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Conflict of Interest

None declared.

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