ORIGINAL RESEARCH

Risk Factors for the Development of Acute Radiation Dermatitis in Breast Cancer Patients

Jennifer J. Parker, MD PhD[a], Alfred Rademaker PhD[b], Eric D. Donnelly MD[a], Jennifer N. Choi, MD[c]

Northwestern University Feinberg School of Medicine, Chicago, IL
[a]Department of Radiation Oncology, Robert H. Lurie Comprehensive Cancer Center
[b]Department of Preventative Medicine, Division of Biostatistics
[c]Department of Dermatology, Division of Oncodermatology, Robert H. Lurie Comprehensive Cancer Center

ABSTRACT

Objective: Adjuvant breast radiation increases the risk of acute dermatitis. We aimed to identify patient and treatment characteristics that may increase this risk to help individualize the prevention and management of radiation-induced skin toxicities.

Methods/Materials: We analyzed 320 women with breast cancer who received adjuvant radiation for increased risk of acute dermatitis based upon age, BMI, histology, stage, chemotherapy, radiation fractionation, whole breast dose, tumor bed boost dose, total dose, diuretics use, smoking, diabetes, autoimmune disease, and chronic immunosuppression. Univariate logistic regression was used to compare each factor across the dermatitis groups. Significant factors were analyzed in a multivariate analysis.

Results: On univariate analysis, grade 3 dermatitis was more likely with a 1 unit BMI increase (OR 1.084, p=0.005). Grade 2 dermatitis risk increased with each 100 cGy increase in breast dose (OR 1.14, p=<0.001). Every 100 cGy total dose increase resulted in higher grade 2 and 3 dermatitis risks (OR 1.13 and 1.45, p=<0.001). There was decreased risk of grade 2 and 3 dermatitis with hypofractionated radiation (grade 2: OR 0.16, p=<0.0001; grade 3: OR 0.08, p=0.017).

On multivariate analysis, higher risk of grade 2 (OR 1.06, p=0.014) and 3 dermatitis (OR 1.12, p=<0.001) remained with increasing BMI. Higher total dose increased grade 3 dermatitis (OR 1.35, p=0.019). Hypofractionated radiation continued to decrease the risk of grade 2 dermatitis (OR 0.08, p=<0.001).

Conclusion: Lower BMI, lower total dose, and hypofractionated radiation were beneficial to decrease dermatitis risk. The other risk factors were not significant within our patient population.

INTRODUCTION

Adjuvant radiation therapy following breast-conserving surgery for invasive breast cancer is widely utilized. After long-term follow-up in large randomized trials, this approach showed equal efficacy to mastectomy without significant differences in survival.[1-3] A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group analyzed data from multiple randomized trials that showed decreased 10-year recurrence and 15-year breast cancer death with radiation therapy after breast-conserving surgery.[4] In addition, adjuvant radiation therapy has been studied extensively in noninvasive breast cancer and has been shown to have a local control benefit after breast-conserving surgery as well.[5-6]

As a result, many patients undergo radiation therapy for their noninvasive and invasive breast cancer. One of the most common side effects is the development of acute skin toxicities. Up to 90% of patients develop dose-dependent skin reaction within the treated area that may include mild erythema, dry desquamation, moist desquamation, and, rarely, ulceration.[7] Studies have shown acute skin reactions are associated with the development of late skin toxicities that lead to poor cosmetic outcomes and decreased quality of life, including pain, impaired body image, and impaired functioning.[8] One prospective study showed that in long-term follow-up, patients who developed acute skin toxicities were at a higher risk of telangiectasias and fibrosis.[9]

This study seeks to better determine which patient and/or treatment factors are detrimental or protective against developing acute dermatitis in breast cancer patients. Understanding these factors could help individualize the prevention and management of radiation-induced skin toxicities in patients undergoing breast cancer treatment.

METHODS

The medical records of 320 breast cancer patients treated between 2011 and 2014 with histologically confirmed ductal carcinoma in situ, invasive ductal carcinoma, or invasive lobular carcinoma were obtained. Patients who were American Joint Committee on Cancer (AJCC) stage 0 to 3 were included. Those with metastatic disease were excluded. Patients may or may not have received chemotherapy. The patients received radiation therapy treatment in the Northwestern Memorial Hospital Department of Radiation Oncology after breast-conserving surgery. The patients were either treated in the supine or prone position with three-dimensional conformal radiotherapy (3D-CRT) administered daily, Monday through Friday, as whole breast photon radiotherapy using standard or hypofractionation. Patients may or may not have received a tumor bed boost using photon or electron radiotherapy. Patients who received nodal radiotherapy were excluded.

Acute skin toxicity was measured using The National Cancer Institute−issued Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Dermatitis from radiation was categorized from grades 1 to 5. Faint erythema or dry desquamation were classified as grade 1. Moderate to brisk erythema; patchy, moist desquamation mostly confined to skin folds and creases; and moderate edema were recorded as grade 2. Moist desquamation in areas other than skin folds and creases and bleeding induced by minor trauma or abrasion were classified as grade 3. Life-threatening

consequences, skin necrosis or ulceration of full thickness dermis, spontaneous bleeding from involved site, and skin graft indicated were recorded as grade 4; death was recorded as grade 5. This information was retrospectively evaluated in Mosaiq (Radiation Oncology Care Management Software). EPIC, the electronic medical record, was used to obtain the patient's cancer and noncancer clinical history, including patient-specific parameters (age, body mass index [BMI], medications, smoking status, comorbidities), tumor-specific parameters (tumor histology and stage), and treatment-specific parameters (whole breast fractionation schedule and dose, tumor bed boost dose).

Descriptive data were summarized using means and standard deviations for continuous data and percentages for categorical data. For both univariate and multivariate analysis of correlates of dermatitis, logistic regression with a generalized logit related the 3-category measure of dermatitis to either categorical or continuous correlates. Odds ratios for the relationship between dermatitis grades 2 and 3 relative to the reference category grade 1 were calculated from the regression model. Both a global p-value for the 3 category dermatitis variable and individual p-values for each of grades 2 and 3 were calculated. P-value <0.05 was deemed significant.

RESULTS

Patient, Tumor, and Treatment Characteristics

The average age was 56.4 years and average BMI was 28.4. Most patients did not have a history of diuretic use, type 2 diabetes mellitus, autoimmune disease, or chronic immunosuppression. In addition, the majority of patients were nonsmokers. These patients most often had noninvasive or early-stage breast cancer and did not receive chemotherapy. Furthermore, the majority of patients were treated with standard whole breast radiation therapy (WBRT) fractionation (Table 1).

Univariate Analysis of Dermatitis Risk Factors

Univariate analysis was performed to determine if age, weight, height, BMI, WBRT dose, tumor bed boost dose, total breast dose, WBRT dose fractionation, chemotherapy use, smoking status, years smoked, diuretic use, history of type 2 diabetes mellitus, history of autoimmune disease, and chronic immunosuppression were risk factors (Table 2). Weight was found to be a risk factor for the development of grade 3 dermatitis as compared to grade 1 dermatitis. Weight was related to grade 3 dermatitis, with odds ratios being the fold-increase in odds for every 10-pound increase in weight (OR 1.114, 95% CI 1.002-1.020, p=0.017).

In addition, for a 1-unit increase in BMI, grade 3 dermatitis was more likely (grade 3: OR 1.084, 95% CI 1.025-1.146, p=0.005). For every 100-cGy increase in whole breast dose, grade 2 dermatitis was more likely (OR 1.14, 95% CI 1.06-1.23, p=<0.001). A similar phenomenon was seen with a 100-cGy increase in tumor bed boost dose. A 100-cGy increase in total dose (WBRT and tumor bed boost dose) resulted in a higher risk of grade 2 and grade 3 dermatitis (grade 2: OR 1.13, 95% CI 1.06-1.22, p=<0.001 and grade 3: OR 1.45, 95% CI 1.17-1.80, p=<0.001). When patients received hypofractionated RT, they were less likely to have grade 2 or grade 3 dermatitis (OR grade 2: OR 0.16, 95% CI 0.08-0.32, p=<0.0001 and grade 3: OR 0.08, 95% CI 0.01-0.42, p=0.017). Autoimmune disease increased the risk of grade 3 dermatitis as compared to grade 1 (OR 4.89, 95% CI 1.92-2.33, p=0.05). Age, height, smoking status, years smoked, diuretic use, chemotherapy, diabetes, and chronic immunosuppression did not affect risk for development of dermatitis.

Table 1. Patient, tumor, and treatment characteristics

	ALL PATIENTS		DERMATITIS=1		DERMATITIS=2		DERMATITIS=3	
	N	MEAN (SEM)	N	MEAN(SEM)	N	MEAN(SEM)	N	MEAN(SEM)
Age	320	56.4 (0.6)	91	56.7 (1.1)	200	56.4 (0.7)	28	56.5 (2.1)
Weight (lb)	319	165.7 (2.5)	91	159.4 (4.2)	200	166.3 (3.2)	28	182.4 (7.9)
Height (in)	316	64.0 (0.2)	90	64.4 (0.3)	198	63.8 (0.2)	28	63.8 (0.4)
BMI	316	28.4 (0.4)	90	27.0 (0.7)	198	28.6 (0.5)	28	31.4 (1.2)
WBRT dose	320	4732 (19)	91	4627 (41)	201	4775 (21)	28	4768 (53)
Tumor bed boost dose	311	1224 (17)	86	1193 (31)	197	1219 (22)	28	1357 (50)
Total dose	311	5963 (19)	86	5841 (44)	197	5993 (21)	28	6125 (43)
Years Smoking	91	18.6 (1.3)	23	21.1 (2.6)	62	18.0 (1.7)	6	15.3 (3.6)
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
TNM Stage								
0	111	34.6	29	31.9	75	37.3	6	21.4
1	135	42.1	42	46.2	80	39.8	13	46.4
2	72	22.4	20	22.0	43	21.4	9	32.1
3	3	0.9	0	0	3	1.5	0	0
Histology								
IDC	196	61.1	57	62.6	120	59.7	19	67.9
DCIS	111	34.6	29	31.9	75	37.3	6	21.4
ILC	8	2.5	3	3.3	4	2.0	1	3.6
Mixed	5	1.6	2	2.2	2	1.0	1	3.6
Other	1	0.3	0	0	0	0	1	3.6
Chemotherapy given								
1 Yes	65	21.0	15	17.2	41	21.1	9	32.1
2 No	244	78.0	72	82.8	153	78.9	19	67.9
Missing	12							
Diuretics								
1 Yes	44	13.8	12	13.2	29	14.4	3	11.1
2 No	275	86.2	79	86.8	172	85.6	24	88.9
Missing	2							
Current Smoker								
1 Yes	9	2.8	1	1.1	7	3.5	1	3.6
2 No	311	97.2	90	98.9	194	96.5	27	96.4
Former Smoker								
1 Yes	97	30.9	27	30.0	64	32.5	6	22.2
2 No	217	69.1	63	70.0	133	67.5	21	77.8
Missing	7							
Diabetes mellitus								
1 Yes	22	6.9	5	5.5	16	8.0	1	3.6
2 No	298	93.1	86	94.5	185	92.0	27	96.4
Missing	1							
Autoimmune disease								
1 Yes	10	3.1	3	3.3	3	1.5	4	14.3
2 No	309	96.9	88	96.7	197	98.5	24	85.7
Missing	2							
Chronic Immunosuppresion								
1 Yes	6	1.9	2	2.2	3	1.5	1	3.6
2 No	313	98.1	89	97.8	197	98.5	27	96.4
Missing	2							
WBRT Dose Fractionation								
Hypofractionated	42	13.1	28	30.8	13	6.5	1	3.6
Standard	278	86.9	63	69.2	188	93.5	27	96.4
Missing	1							

Table 2. Univariate analysis of dermatitis risk factors

	UNIVARIATE GENERALIZED LOGISTIC REGRESSION			
	Odds Ratio (OR) definition	**OR**	**95% CI**	**p-value***
Age				0.97
	Grade 2 vs Grade 1, odds ratio of Grade 2 for a 5 year increase in age	0.997	0.973 - 1.021	0.80
	Grade 3 vs Grade 1, odds ratio of Grade 3 for a 5 year increase in age	0.998	0.958 - 1.040	0.92
Weight (lb)				0.058
	Grade 2 vs Grade 1, odds ratio of Grade 2 for a 10 pound increase in weight	1.042	0.979 - 1.010	0.20
	Grade 3 vs Grade 1, odds ratio of Grade 3 for a 10 pound increase in weight	1.114	1.002 - 1.020	0.017
Height (in)				0.28
	Grade 2 vs Grade 1, odds ratio of Grade 2 for a 3 inch increase in height	0.82	0.63 - 1.06	0.12
	Grade 3 vs Grade 1, odds ratio of Grade 3 for a 3 inch increase in height	0.80	0.53 - 1.21	0.29
BMI				0.018
	Grade 2 vs Grade 1, odds ratio of Grade 2 for a 1 unit increase in BMI	1.037	0.997 - 1.079	0.07
	Grade 3 vs Grade 1, odds ratio of Grade 3 for a 1 unit increase in BMI	1.084	1.025 - 1.146	0.005
WBRT dose				0.002
	Grade 2 vs Grade 1, odds ratio of Grade 2 for a 100 cGy increase in WBRTDOSE	1.14	1.06 - 1.23	<0.001
	Grade 3 vs Grade 1, odds ratio of Grade 3 for a 100 cGy increase in WBRTDOSE	1.13	0.99 - 1.29	0.06
Tumor bed boost dose				0.044
	Grade 2 vs Grade 1, odds ratio of Grade 2 for a 100 cGy increase in BOOST	1.03	0.95 - 1.13	0.49
	Grade 3 vs Grade 1, odds ratio of Grade 3 for a 100 cGy increase in BOOST	1.19	1.04 - 1.37	0.014
WBRT + BOOST				<0.001
	Grade 2 vs Grade 1, odds ratio of Grade 2 for a 100 cGy increase in TOTAL DOSE	1.13	1.06 - 1.22	<0.001
	Grade 3 vs Grade 1, odds ratio of Grade 3 for a 100 cGy increase in TOTAL DOSE	1.45	1.17 - 1.80	<0.001
Years Smoking				0.49
	Grade 2 vs Grade 1, odds ratio of Grade 2 for a 1 year increase in years smoked	0.98	0.95 - 1.02	0.34
	Grade 3 vs Grade 1, odds ratio of Grade 3 for a 1 year increase in years smoked	0.96	0.89 - 1.04	0.32
TNM Stage	No odds ratios calculated due to small sample sizes in the multiple subcategories			0.69
Histology	No odds ratios calculated due to small sample sizes in the multiple subcategories			0.85
Chemotherapy given				0.25
	Grade 2 vs Grade 1, odds ratio of Grade 2 for chemo vs no chemo	1.29	0.67 - 2.48	0.45
	Grade 3 vs Grade 1, odds ratio of Grade 3 for chemo vs no chemo	2.27	0.86 - 5.99	0.10
Diuretics use				0.88
	Grade 2 vs Grade 1, odds ratio of Grade 2 for diuretic use vs no diuretic use	1.11	0.54 - 2.29	0.78
	Grade 3 vs Grade 1, odds ratio of Grade 3 for diuretic use vs no diuretic use	0.82	0.21 - 3.16	0.78
Current Smoker				0.54
	Grade 2 vs Grade 1, odds ratio of Grade 2 for current smoker vs not current smoker	3.25	0.39 - 16.8	0.27
	Grade 3 vs Grade 1, odds ratio of Grade 3 for current smoker vs not current smoker	3.33	0.20 - 55.1	0.40
Former Smoker				0.55
	Grade 2 vs Grade 1, odds ratio of Grade 2 for former smoker vs not former smoker	1.12	0.65 - 1.93	0.67
	Grade 3 vs Grade 1, odds ratio of Grade 3 for former smoker vs not former smoker	0.67	0.24 - 1.84	0.43
Diabetes mellitus (DM)				0.58
	Grade 2 vs Grade 1, odds ratio of Grade 2 for DM vs no DM	1.49	0.53 - 4.19	0.45
	Grade 3 vs Grade 1, odds ratio of Grade 3 for DM vs no DM	0.64	0.07 - 5.69	0.69
Autoimmune disease (AID)				0.01
	Grade 2 vs Grade 1, odds ratio of Grade 2 for AID vs no AID	0.45	0.09 - 2.26	0.33
	Grade 3 vs Grade 1, odds ratio of Grade 3 for AID vs no AID	4.89	1.02 - 23.3	0.05
Chronic Immunosuppresion (CI)				0.74
	Grade 2 vs Grade 1, odds ratio of Grade 2 for CI vs no CI	0.68	0.11 - 4.13	0.67
	Grade 3 vs Grade 1, odds ratio of Grade 3 for CI vs no CI	1.65	0.14 - 18.9	0.69
WBRT Dose Fractionation				<0.0001
	Grade 2 vs Grade 1, odds ratio of Grade 2 for hypofractionation vs standard	0.16	0.08 - 0.32	<0.0001
	Grade 3 vs Grade 1, odds ratio of Grade 3 for hypofractionation vs standard	0.08	0.01 - 0.42	0.017

*p≤0.05 significance level

Table 3. Multivariate analysis of dermatologic risk factors

MULTIVARIATE GENERALIZED LOGISTIC REGRESSION				
	Odds Ratio (OR) definition	OR	95% CI	p-value*
BMI				0.002
	Grade 2 vs Grade 1, odds ratio of Grade 2 for a 1 unit increase in BMI	1.06	1.01 - 1.11	0.014
	Grade 3 vs Grade 1, odds ratio of Grade 3 for a 1 unit increase in BMI	1.12	1.05 - 1.19	<0.001
Total dose				0.006
	Grade 2 vs Grade 1, odds ratio of Grade 2 for a 100 cGy increase in total dose	0.92	0.80 - 1.07	0.29
	Grade 3 vs Grade 1, odds ratio of Grade 3 for a 100 cGy increase in TOTAL DOSE	1.35	1.05 - 1.74	0.019
Fractionation				0.002
	Grade 2 vs Grade 1, odds ratio of Grade 2 for hypofractionation vs standard	0.08	0.02 - 0.31	<0.001
	Grade 3 vs Grade 1, odds ratio of Grade 3 for hypofractionation vs standard	0.53	0.02 - 6.16	0.64

*p≤0.05 significance level

Multivariate Analysis of Dermatologic Risk Factors

Multivariate analysis assessed variables significant in the univariate analysis including BMI, total dose, and fractionation schedule. The variables selected did not include those from univariate analysis that were related to another variable and did not pass the p-value test for multivariate analysis. Thus, weight, WBRT dose, and tumor bed boost dose were not included in the analysis. Autoimmune disease was not examined due to the small number of patients. The higher risk of grade 2 (OR 1.06, 95% CI 1.01-1.11, p=0.014) and grade 3 dermatitis (OR 1.12, 95% CI 1.05-1.19, p=<0.001) persisted with increasing BMI. Total breast dose still increased the risk of grade 3 dermatitis (OR 1.35, 95% CI 1.05-1.74, p=0.019). Hypofractionated RT still decreased the risk of grade 2 dermatitis. However, decreased risk of grade 3 dermatitis as compared to standard fractionated RT was no longer statistically significant (Table 3).

DISCUSSION

Significant progress has been made over the years to reduce potential toxicities of external beam radiation therapy after breast-conserving surgery. There are now improved radiation techniques including 3D-CRT and intensity-modulated radiation therapy, which allow for better dose homogeneity.[10-12] Hypofractionated courses of radiation therapy to the breast have been found to have better long-term cosmetic outcomes in randomized control trials.[13]

There are also cardiac-sparing techniques to reduce potential late side effects from breast radiotherapy.[14]

Despite these significant advances in reducing potential toxicities from radiation therapy, patients continue to frequently have acute skin reactions while undergoing breast radiotherapy. Previous studies have sought to examine which patient and treatment factors play a role in acute skin reaction from breast radiation therapy. Radiation fractionation schedule, patient position, 3D-CRT, IMRT, concomitant hormone treatment, and patient-related factors including high BMI, large breast volumes, smoking during treatment, and single nucleotide polymorphisms in genes involved in DNA repair pathways have all been examined. Increased risk of acute dermatitis was found with standard fractionation schedules, 3D-CRT technique compared to IMRT, largest breast size, high BMI, and smoking.[10,15-17]

Across these studies there was significant disagreement on the most significant factors for the development of acute breast radiation dermatitis, likely due to the smaller study number of these retrospective reviews. In our study, BMI, total radiation dose, and radiation fractionation schedule appear to be the most important factors for development of breast radiation dermatitis. Unlike current studies available, our study also determined specific thresholds significant for the development of breast dermatitis, including a 1-unit increase in BMI and a 100-cGy increase in dose to the breast for the development of moderate to severe acute dermatitis.

In addition, a hypofractionated course of radiation therapy seems to be beneficial for decreasing acute dermatitis risk and would support using this regimen over a standard fractionated course of radiation therapy. Though autoimmune disease was not analyzed on multivariate analysis given the smaller sample size of patients, it may be a significant risk factor for the development of radiation dermatitis if a large enough sample size of patients with autoimmune disease can be obtained.

Understanding when these risk factors affect the development of acute dermatitis may help physicians to counsel the patients who are more likely to develop these skin toxicities. In addition, it may lead physicians to re-examine their treatment approach to help minimize the moderate to severe skin reactions that ultimately could lead to worse cosmetic outcomes in the long-term. Finally, individuals at high risk of such toxicity may benefit from additional and earlier skin-directed interventions to potentially mitigate acute skin toxicity.

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Corresponding Author:
Jennifer J. Parker, MD, PhD
Department of Radiation Oncology
Robert H. Lurie Comprehensive Cancer Center
Northwestern University Feinberg School of Medicine
Arkes Pavilion
676 North Saint Clair Street, Suite 1820
Chicago, IL 60611
312-926-3521
jennifer.parker@northwestern.edu

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