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The Impact of Obesity on Acute Skin Toxicity from Radiation Treatment for Breast Cancer: Opportunities to Predict and Address

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ABSTRACT

Rationale: *As radiation therapy techniques have improved, skin toxicity from breast radiation is less common. However, as the rates of metabolic syndrome and obesity increase, we sought to determine the impact of obesity on acute skin toxicity following radiation therapy for early-stage breast cancer and explored potential strategies for mitigating toxicity.*

Objectives: *A retrospective analysis was conducted on 355 early-stage breast cancer patients who underwent radiation therapy. Patient demographics, clinical characteristics, radiation details, and skin toxicity were recorded. Logistic regression models were used to assess the association between obesity (BMI ≥ 30) and skin toxicity, considering treatment variables such as radiation dose, boost, and wedge use.*

Findings: *Higher BMI was significantly associated with increased odds of grade 2 or higher skin toxicity (OR = 4.24, $p < 0.001$). The use of wedges showed a potential protective effect against toxicity in overweight patients (OR = 0.48, $p = 0.060$). Multivariable analysis revealed that younger age, higher BMI, and an increased number of radiation segments were associated with a higher likelihood of toxicity. Recurrence rates did not differ significantly between BMI groups.*

Conclusion: *Obesity is a significant risk factor for acute skin toxicity in breast cancer patients undergoing radiation therapy. Strategies to mitigate toxicity, such as personalized treatment planning incorporating wedges and optimizing radiation dose, are crucial for improving patient outcomes. Future research is warranted to explore the role of dietary interventions or personalized therapies to minimize acute radiation toxicity for patients living with metabolic dysfunction or obesity.*

Keywords

Breast cancer, Cancer, Radiation therapy, Skin toxicity.

Introduction

Breast cancer, the most common malignancy in women in the United States, is a serious disease associated with substantial medical and economic burden [1]. More than 3.7 million US women were living with breast cancer in 2019, and it is estimated that 290,560 women will be newly diagnosed with the disease in 2022[2,3]. In 2019, out of pocket patient cost in the United States was highest for those with breast cancer, at 3.14 billion dollars [4]. A significant portion of this economic burden is derived from surveillance and treatment for treatment-related adverse events [5].

As improvements are made in breast cancer treatment, quality of life after cancer care becomes the focus of treatment. As of 2021, there were more than 3.8 million breast cancer survivors living in the US with the death rate from breast cancer decreasing by

1% per year from 2013 to 2018 [3,6]. Ionizing radiation often plays a crucial role in the adjuvant treatment of breast cancer, reducing local recurrence and improving 15-year overall survival by reducing breast cancer metastases [7]. Unfortunately, toxicity incurred by normal tissues during radiation therapy can limit the therapeutic dose and cause significant morbidity and detriments to quality of life. Tissue radiosensitivity is highly dependent on cell proliferation making skin, a tissue with significant regenerative capacity, particularly sensitive to the effects of radiation. As such, radiodermatitis is the most common side effect of radiation for breast cancer. Through the course of radiation treatment and in the weeks to months following it can be a significant source of physical and emotional discomfort [8]. In addition, it may be the cause of premature interruption of radiation therapy, resulting in inadequate disease treatment [9].

Despite a well-established radiation treatment guidelines which is informed by patient and tumor specific factors, the toxicities and severity each patient experiences can vary significantly. Prior literature examining predictors of radiation-induced skin toxicity have had varied results when looking at patient demographics, tumor characteristics and treatment variables. Wright el al., identified BMI, disease stage, and conventionally fractionated radiation as a predictor for higher skin toxicity grade [10]. Other factors identified that serve as predictors of increased skin toxicity include age, BMI ≥25, breast size, regional nodal irradiation, chemotherapy, and current smoking [11-14]. As radiation treatment plans become more sophisticated and complex, there is also a question as to whether treatment factors have an effect on skin toxicity. A more recent systematic review by Yee et al. demonstrated that specific radiotherapy techniques such as intensity-modulated radiotherapy, hypofractionation, simultaneous integrated boost and prone positioning have been consistently demonstrated to decrease rates of radiation dermatitis, although the number of studies in which they were evaluated is limited [15].

As skin toxicity develops, radiation oncology health practitioners can intervene and escalate supportive care as necessary to address acute pain, discomfort and wound problems. As radiation oncologists prescribe more hypofractionated radiation therapy, we will continue to observe this increase in delayed toxicity occurring following completion of RT and the weekly visits with radiation oncology health practitioners [16]. Unfortunately, due to the timing of when toxicity begins for these patients, patients may seek cost-ineffective medical care for their treatment-related pain, skin wounds, or other maladies through acute care centers or the emergency departments. Using the concept of alpha/beta ratio, it is been long believed that an increase in fraction size (hypofractionation) impacts late normal tissue toxicity. Most of our current long-term data on late toxicity from breast cancer treatment comes from conventional fraction sizes and it is imperative we are vigilant in identifying those at risk for late toxicity in the modern era. There has been data supporting that patients getting acute radiation toxicity predicts for the risk of late toxicity [17,18].

By identifying patients prone to skin toxicity with breast radiation, prevention may be emphasized, interventions can be executed early, preventive measures can be put in place and a line of communication can be established between radiation provider and patient to avoid unnecessary emergency department visits and hospitalizations. In this study we sought to assess the impact of obesity (body mass index kg/m^2 ≥30) at the time of diagnosis on acute skin toxicity in early stage breast cancer patients being treated with breast-conserving treatment.

Methods

On an IRB approved protocol, a retrospective analysis of skin toxicity as it relates to radiation treatment was conducted. Clinical characteristics (e.g., age, T-stage, BMI) were summarized by counts and percentages. The radiation details of dose, boost and wedges was recorded. Skin toxicity was documented according to the common terminology criteria for adverse events (CTCAE)-score.

The relationship between skin toxicity and BMI was assessed via univariable logistic regression comparing the odds of a grade 2 or 3 event to a grade 0 or 1 event. Additionally, to assess the impact of wedge use within each BMI group, a logistic model of skin toxicity by BMI and wedge use was fit, allowing for interactions between BMI and wedge use. A multivariable model adjusting for BMI group, age, total dose, wedges, number of segments and chemotherapy was fit. Interaction terms between BMI group and intervention variables (total dose, wedges, number of segments and chemotherapy) were subject to a backwards selection and retained if $p < 0.05$. Differences in risk of recurrence by BMI groups were assessed by the log-rank test. All analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

Between 2008 and 2014 a total of 355 breast cancer patients were included in analyses. Table 1 shows baseline patient characteristics. Median follow-up time was 9.1 years (range: 7.3 – 11.2 years). Ninety (25.4%) women had a BMI <25; 33.8% were considered overweight (BMI between 25 and 30) and the remaining 40.8% were considered obese (BMI of 30 or more). Most women had localized disease (21.4% Tis; 62.5% T1). Patients included in the study ranged in age from 33 to 89 years old with a mean age of 58.7 years (SD: 10.1). 101 patients (28.5%) had a whole breast dose <50Gy and 254 patients (71.5%) had ≥50Gy. An additional photon boost to the tumor bed was given to 94.4% of the patients, most commonly 10 Gy in 5 fractions. 30.7% of cases were planned using wedges with slightly less than half of plans using 4 fields/segments or less and the other half 5 or more.

Toxicity

Table 2 summarizes treatment-related side effects. All but 3 patients experienced skin toxicity. 37.5% had a grade 1 skin toxicity event; 61.4% had a grade 2 event. Only 1 individual had a grade 3 skin toxicity event. 105 women (29.6%) experienced grade

1 dry desquamation; 87 (24.5%) had moist desquamation (grade 1: 84; grade 2: 3). Fatigue was present in 239 (67.3%) women (grade 1: 226; grade 2: 13). Table 3 depicts the parameters associated with acute G2+ dermatitis, in univariate analysis.

Table 1: Baseline Patient Characteristics.

Patient Characteristics	N	%
No. Patients	355	100
Age		
30-49	70	19.7
50-59	126	35.5
60-69	113	31.8
70+	46	13
Race		
Asian	17	4.8
Black	96	27.1
Hispanic	9	2.5
White	233	65.6
BMI		
Normal/Under† (<25)	90	25.4
Overweight (25.0-29.9)	120	33.8
Obese (30.0+)	145	40.8
T-Stage		
T1	222	62.5
T2/T3‡	57	16.1
Tis	76	21.4
ER receptor status		
Negative	72	20.3
Positive	278	78.3
Unknown	5	1.4
PR receptor status		
Negative	100	28.2
Positive	249	70.1
Unknown	6	1.7
Her2 status		
Negative	261	73.5
Positive	60	16.9
Unknown	34	9.6

Table 2: Radiation treatment-related toxicity summary.

Toxicity Summary	All	
	N	%
Skin Toxicity		
0	3	0.8
1	133	37.5
2	218	61.4
3	1	0.3
Dry Desquamation		
0	250	70.4
1	105	29.6
Moist Desquamation		
0	268	75.5
1	84	23.7
2	3	0.8
Fatigue Toxicity		
0	116	32.7
1	226	63.7
2	13	3.7

Table 3: Associations between patient- and systemic therapy-related characteristics and acute G2+ dermatitis.

Clinical Characteristics	All	CTCAE Radiation Dermatitis		Chi-sq
		G0-1	G2+	
	N (%)	N (%)	N (%)	
No. Patients	355 (100)	136 (38.3)	219 (61.7)	
Age				**<0.001**
30-49	70 (19.7)	15 (21.4)	55 (78.6)	
50-59	126 (35.5)	46 (36.5)	80 (63.5)	
60-69	113 (31.8)	46 (40.7)	67 (59.3)	
70+	46 (13.0)	29 (63)	17 (37)	
BMI				**<0.001**
Normal/Under† (<25)	90 (25.4)	50 (55.6)	40 (44.4)	
Overweight (25.0-29.9)	120 (33.8)	53 (44.2)	67 (55.8)	
Obese (30.0+)	145 (40.8)	33 (22.8)	112 (77.2)	
T-Stage				0.521
T1	222 (62.5)	88 (39.6)	134 (60.4)	
T2/T3‡	57 (16.1)	18 (31.6)	39 (68.4)	
Tis	76 (21.4)	30 (39.5)	46 (60.5)	
ER receptor status				0.63
No	72 (20.3)	26 (36.1)	46 (63.9)	
Yes	278 (78.3)	109 (39.2)	169 (60.8)	
Unknown	5 (1.4)	1 (20)	4 (80)	
PR receptor status				0.409
No	100 (28.2)	35 (35)	65 (65)	
Yes	249 (70.1)	99 (39.8)	150 (60.2)	
Unknown	6 (1.7)	2 (33.3)	4 (66.7)	
Her2 status				0.554
No	261 (73.5)	98 (37.5)	163 (62.5)	
Yes	60 (16.9)	25 (41.7)	35 (58.3)	
Unknown	34 (9.6)	13 (38.2)	21 (61.8)	
Other Therapies				
Chemotherapy				0.063
No	245 (69.0)	102 (41.6)	143 (58.4)	
Yes	106 (29.9)	33 (31.1)	73 (68.9)	
Unknown	4 (1.1)	1 (25)	3 (75)	
Herceptin				0.907
No	319 (89.9)	123 (38.6)	196 (61.4)	
Yes	32 (9.0)	12 (37.5)	20 (62.5)	
Unknown	4 (1.1)	1 (25)	3 (75)	
Endocrine therapy				0.164
No	98 (27.6)	32 (32.7)	66 (67.30	
Yes	253 (71.3)	103 (40.7)	150 (59.3)	
Unknown	4 (1.1)	1 (25)	3 (75)	

†includes 2 underweight (BMI < 18.5)
‡includes 4 T3.

Body Mass Index

Women with higher BMI were more likely to have grade 2 (or 3) skin toxicity than those with lower BMI. The odds of an obese woman having a grade 2 skin toxicity were 4.24 times that of a woman with normal BMI ($p < 0.001$)(Table 4). Figures 1 and 2 highlight maximum CTCAE dermatitis by BMI and a scatterplot of CTCAE dermatitis and BMI. 112 (77.2%) patients with a BMI ≥30 experienced grade 2+ skin toxicity while 67 (55.8%) of patients BMI 25-30 and 40 (44.4%) of patients with a BMI <25 experienced the same toxicity. The use of wedges overall was not associated with toxicity; however, wedge use appears to

have a protective effect in the overweight group (OR = 0.48, p = 0.060). On multivariable analysis, age, BMI group and number of segments were significantly associated with having a higher-grade toxicity (2+ vs 0/1). Higher BMI, younger age and more segments were associated with increased likelihood of a higher-grade toxicity. While this interaction is non-significant in the multivariable analysis, the unadjusted data (as seen in table 5) seem to indicate a protective effect of wedges in the overweight group that does not exist in the normal or obese BMI groups.

Table 4: Odds of experiencing more severe skin toxicity (grade 2/3 vs. grade 0/1) by BMI. (Results of univariable logistic regression).

	Odds Ratio	95% Confidence Interval		p-value
Body Mass Index (BMI)				<0.001
Normal* (<25)	1.00	REF	REF	--
Overweight (25.0-29.9)	1.58	0.91	2.74	0.103
Obese (30.0+)	4.24	2.40	7.49	<0.001

*includes 2 underweight (BMI <18.5)

Table 5: Acute dermatitis by BMI and use of wedges.

	Wedges							
	No				Yes			
	Skin Toxicity				Skin Toxicity			
	G0-1		G2+		G0-1		G2+	
	N	%	N	%	N	%	N	%
BMI								
Normal (<25)	32	57.1	24	42.9	18	52.9	16	47.1
Overweight (25.0-29.9)	30	38.0	49	62.0	23	56.1	18	43.9
Obese (30.0+)	26	23.4	85	76.6	7	20.6	27	79.4

***1** includes three grade 0 events; **2** includes one grade 3 event.

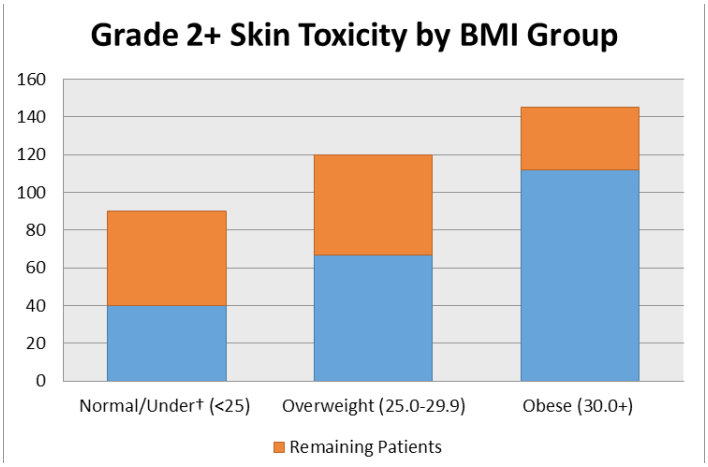

Figure 1: CTCAE dermatitis by BMI group. A Stacked-column bar graph was used to compare the Grade 2+ skin toxicity among the body mass index groups.

Radiation Treatment Characteristics

Table 6. shows associations between radiation therapy-related characteristics and acute G2+ dermatitis. A number of characteristics specific to the radiation therapy employed conveyed varying rates of skin toxicity. We identified the number of segments, radiation dose, and use of a boost as predictors for higher skin toxicity grade. The radiation dose, both to the whole breast and to a more focal boost, significantly correlated with the occurrence of grade 2 dermatitis (G2D). Total doses below 6000 cGy conferred a 40.5% chance of developing G2D, while total doses of 6000, 6040 and greater than 6040 cGy resulted in G2D incidences of 62.2%, 66.4% and 66.7%, respectively (p=.022). 50.5% of patients receiving a whole breast dose of less than 5000 cGy developed G2D, while whole breast doses of 5000 and 5040 cGy resulted in 67.9% and 64.2% incidences of G2D (p=.02). Furthermore, the presence of a boost conferred a higher rate of G2D (63.9% vs 25.0%, p<.001). The energy utilized did not correlate with G2D. Of patients undergoing external beam radiation therapy (EBRT), 166 received 6mV, 36 received 10mV, 7 received 15 mV, 1 received 18mV and 145 received mixed energy radiation (6mV and 10, 15, or 18). This resulted in G2D of 62.6% for 6mV, compared to 52.8%, 71.4% and 62.1% G2D for 10mV, 15mV and mixed energy EBRT, respectively (p = 0.67).

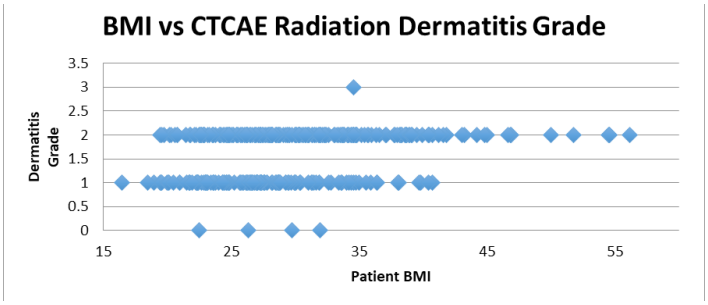

Figure 2: BMI vs CTCAE radiation dermatitis grade. A scatter plot was used to highlight the relationship between patients' body mass index and CTCAE radiation dermatitis grade.

Table 6: Associations between radiation therapy-related characteristics and acute G2+ dermatitis.

Radiation Summary	All		Skin Tox				Chi-sq
			G0-1		G2+		
	N	%	N	%	N	%	
Total Dose							**0.022**
<6000	42	11.8	25	59.5	17	40.5	
6000	143	40.3	54	37.8	89	62.2	
6040	110	31.0	37	33.6	73	66.4	
>6040	60	16.9	20	33.3	40	66.7	
Whole breast dose							**0.020**
<5000	101	28.5	50	49.5	51	50.5	
5000	131	36.9	42	32.1	89	67.9	
5040	123	34.6	44	35.8	79	64.2	
Boost?							**<0.001**
No	20	5.6	15	75.0	5	25.0	
Yes	335	94.4	121	36.1	214	63.9	
Boost dose							**0.003**
None	20	5.6	15	75.0	5	25.0	
<1000	7	2.0	4	57.1	3	42.9	
1000	240	67.6	82	34.2	158	65.8	
>1000	88	24.8	35	39.8	53	60.2	
Number of total fields/segments							**0.002**
2	38	10.7	21	55.3	17	44.7	
3	58	16.3	30	51.7	28	48.3	
4	72	20.3	30	41.7	42	58.3	
5	12	3.4	5	41.7	7	58.3	

6	104	29.3	34	32.7	70	67.3	
7	13	3.7	5	38.5	8	61.5	
≥8	58	16.4	11	19.0	47	81.0	
Wedges							0.140
No	246	69.3	88	35.8	158	64.2	
Yes	109	30.7	48	44.0	61	56.0	
Max Energy Used							**0.671**
6	166	46.8	62	37.4	104	62.6	
10	36	10.1	17	47.2	19	52.8	
15	7	2.0	2	28.6	5	71.4	
18	1	0.3	1	100	0	0	
Mixed (6 and 10,15 or 18)	145	40.8	55	37.9	90	62.1	

Recurrence

Disease recurrence was noted in 20 cases; 26 have died. Recurrence rates were not statistically different between BMI groups. In patients with a BMI <30, 6.7% of patients recurred while 4.5% of patients with a BMI ≥30 recurred. Of those patients that have died 5 had a BMI <25, 5 had a BMI 25-30 and 16 had a BMI >30 at the time of our initial analysis.

Discussion

As the prevalence of obesity continues to grow to include more than a third of the current US adult population, the biological link between body habitus and malignancies of the breast will continue to more profoundly impact the incidence, treatment and outcomes of the disease [19].

Dermatitis is a frequent and distressing side effect of radiation therapy that may necessitate a treatment interruption when evolving towards more severe forms such as moist desquamation. In this cohort of breast cancer patients receiving adjuvant RT to the breast after breast conserving therapy, the overall incidence of NCI CTCAE grade 2 or greater skin toxicity was 61.7%. Moist and dry desquamation was observed in 24.5% and 29.6% of study participants, consistent with recent published series [20,21].

Patient factors associated with increased toxicity include age and increasing BMI. The relationship between BMI and higher-grade skin toxicity is supported by previous studies [22]. However, our findings on multivariate analysis using the modified scale additionally demonstrated that BMI is specifically associated with moist and dry desquamation. Additionally, our study is unique in identifying younger age as a significant predictor for developing a higher grade of skin toxicity. Although younger patients are more likely to require a boost, 94.4% of patients in our study required a boost allowing for this analysis.

The obese state has been shown to propagate a proinflammatory endocrinologic milieu altering cellular signaling between adipocytes, immunologic cells, and epithelial cells through various hormones and cytokines [23]. Visceral adipocytes secrete a variety of endocrinologically active molecules, including the adipokines leptin and adiponectin, the cytokines tumor necrosis factor (TNF)-α, transforming growth factor (TGF)-β and interleukin-6 (IL-6), augmenting insulin resistance and stimulating an assortment of immunologic cells [24]. Acute radiation skin toxicity has been correlated with increased formations of the aforementioned cytokines [25]. Furthermore, the transendothelial migration of leukocytes and various immune cells from circulation to irradiated skin is recognized as a crucial mechanism of radiation-induced skin injury. Future interventions aimed to decrease systemic inflammation may work to decrease radiation induces skin toxicity.

In addition, medical physics factors associated with less skin toxicity include fewer segments, less dose, and the use of wedges in obese patient in the present study. By identifying patients that are more prone to developing acute skin toxicities, radiation oncologists can work with dosimetry and physics colleagues to apply additional caution to ensure dose constraints are met in breast radiation treatment planning and radiation dose in uniform manner.

Overweight and obese breast cancer patients should be considered as a high-risk group for developing severe radiation dermatitis and its resulting sequela. In an effort to save health care resources, precise post-RT screening for radiation dermatitis or desquamation could be implemented. Furthermore, this screening could be conducted with phone interventions or telehealth. Our institution screens and identifies at risk patients during on treatment visits (OTVs) and initiates intervention. Physicians and nurses educate patients on the timeline of skin toxicity, focusing on patients understanding that the peak side effect may occur after treatment is complete in many cases. In addition to standard treatments including skin care, creams, and infection prevention, our staff will schedule nurse skin checks and 1-week post treatment follow-ups for those patients deemed high risk for skin toxicity. We have also previously piloted completing these types of follow-ups leveraging telehealth [26].

Furthermore, our findings stress the importance of continuing to study the role of metabolism in carcinogenesis and cancer treatments. Given that the obese state alters the tumor microenvironment through inflammatory and immunologic mechanisms, targeting the underlying metabolic dysfunction is a logical therapeutic strategy and avenue to decrease toxicity. Dietary interventions have shown promise in this regard, as calorically restricted or ketogenic diets have been shown to have beneficial effects on body composition and subsequent chemokine expression, with the potential to have normal tissue radiation protection [27-29]. Given these findings, it is logical to consider a more targeted approach inclusive of diet modification as an adjuvant therapy for patients in the setting of cancer. Current and future clinical trials are needed to explore the safety and the impact of personalized dietary interventions as an adjuvant therapy to conventional radiation and chemotherapies and to further elucidate the mechanisms by which dietary intervention may enhance cancer cell therapeutic responses and decrease normal tissue toxicity.

Declarations

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