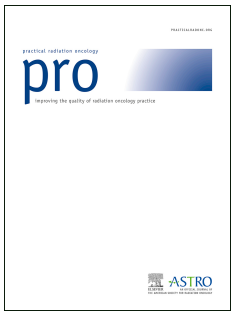

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Development of an Illustrated Scale for Acute Radiation Dermatitis in Breast Cancer Patients

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Development of an Illustrated Scale for Acute Radiation Dermatitis in Breast Cancer Patients

Abstract

Purpose

Scales for rating acute radiation dermatitis (ARD) have not been validated despite decades of clinical use, and little is known regarding the relationship between toxicity scores and patient-reported symptoms. Skin tone also complicates assessment of ARD, and as such we sought to design an illustrated scale to consistently describe ARD across several skin tone types in breast cancer patients undergoing radiation (RT).

Methods

Patients undergoing RT for breast cancer were enrolled on a prospective study with photographs obtained at 2-week intervals. Photographs were clustered according to the apparent severity of acute radiation dermatitis and a descriptive photonumeric scale was developed. Four clinically experienced raters used both the illustrated photonumeric scale and the CTCAE to independently score the collection of photographs in two independent sessions.

Results

Among 80 unique patients with 192 photographs, 47 patients (59%) completed questionnaires about their symptoms during RT. Physicians completed toxicity forms at the point-of-care for 52 patients (65%).

Photonumeric ratings compared against patient reports of dry and moist desquamation demonstrated high specificity (95% and 93%, respectively) and negative predictive value (84% and 92%), indicating correct identification of patients who did not report dry or moist desquamation. The sensitivity and positive predictive value for separate measures of dry and moist desquamation were considerably lower. A combined measure of any desquamation (dry or moist) portrayed higher diagnostic accuracy, resulting in 72% sensitivity, 93% specificity, 75% PPV, and 92% NPV.

Photonumeric ratings of dry or moist desquamation were significantly associated with patient reports of itching, burning/stinging, hurting, and swelling.

Conclusion

The xxx scale for acute radiation dermatitis is a simple grading rubric that is distinguished by characterization of its intra- and inter-rater reliability and diagnostic accuracy, correlation with patient-reported symptoms of bother and pain, and applicability across the spectrum of skin pigmentation.

Introduction

Acute radiation dermatitis is a common problem during whole breast radiotherapy, with as many as 29% of patients experiencing moist desquamation during treatment when using conventional fractionation.[1] Accurate assessment of acute radiation dermatitis (ARD) is important to be able to relate dosimetry and treatment technique to the severity of skin reaction, for reliable reporting in clinical trials, and to guide supportive care. However, the ability to accurately and reproducibly describe ARD is compromised by the lack of a scale that is validated and universally accepted.[2]

Many differing scoring systems have been developed for reporting acute radiation dermatitis, including CTCAE,[3] RTOG/EORTC,[4,5] WHO,[6] Danish,[7] European,[8] ECOG,[9] STAT,[10] Biomed2,[11] and RISRAS.[12-14] Reported rates of severe ARD vary substantially depending on which scoring system is used.[2] The toxicity scale most commonly used to report ARD in recent clinical trials, the CTCAE, has not undergone formal reliability and validity testing despite decades of clinical use, and little is known regarding the relationship between toxicity scores and patient-reported symptoms. Furthermore, none of the existing toxicity scales account for hyperpigmentation as a component of ARD, and are therefore not wholly applicable to patients of color.

Given the limitations of existing toxicity scales for ARD, we sought to develop and evaluate a new scale with clear delineation of the severity of toxicity, high reliability, and simplicity. In most studies, the assessment of ARD has been accomplished using only the descriptive written scales described above. Reliability between evaluators has been reported to be superior for scales that include photographic depiction of toxicity, in addition to a descriptive scale.[15-18] Our objective was to develop and evaluate a new scale with both photographs and a descriptive numerical rating system (thus, "photonumeric") to reliably describe acute radiation dermatitis in breast cancer patients undergoing radiotherapy (RT) including patients of color. We also sought to evaluate the correlation between the photonumeric scale rating and patient- and physician reported symptoms of bother and pain.

Methods

Sample

Women undergoing whole breast or post-mastectomy RT at two institutions (xx Hospital and the University of xx) provided informed consent to participate on a prospective, IRB approved protocol to obtain photographs at baseline and 2, 4, 6 and 10 weeks after initiating RT. Images were systematically obtained in three standard views to clearly visualize the breast and inframammary fold/chest wall, and axilla. At each photo session, colorimetric measurements were obtained from the 4 breast/CW quadrants, axilla, inframammary fold, and medial chest wall, using a Konica Minolta CR400 chromameter (Ramsey, New Jersey). Between these two institutions, photograph sets (3 photos at each session) were obtained from 94 unique patients at 418 unique sessions. From this sample, we excluded the majority of photographs that did not

demonstrate visible toxicity (grade 0), primarily at baseline and at the 10-week time points. This resulted in 14 patients being removed from the analyzed dataset due to lack of evaluable data. The final sample for development of the scale for acute radiation dermatitis consisted of 192 photographs from 80 unique patients, with the majority of the sessions at 2-, 4-, and 6-weeks (N=41, 69, and 55, respectively).

From this cohort, many patients from both institutions participated in the xx Radiation Oncology Quality Consortium (xx). xx is a prospective, multicenter collaboration of radiation oncology practices throughout the state of xx that collects detailed data for patients receiving adjuvant breast radiotherapy after lumpectomy, including physician-assessed and patient-reported toxicity. It is funded by Blue Cross Blue Shield of xx/Blue Care Network and collects data on eligible patients at participating centers regardless of insurance type. Among the 80 patients included in the cohort to develop the toxicity scale, 47 patients (58.8%) completed questionnaires about their symptoms as part of xx participation. From this group of 47 patients, there were 113 photographs during RT that link to a corresponding xx patient questionnaire at the same time. Physicians were also asked to complete toxicity forms at the point-of-care for patients in xx, which were available for 52 out of the 80 patients (65%). From these 52 patients, 127 photographs link to a corresponding physician questionnaire at the same time point.

Because the photonumeric scale was developed as a collaboration between two hospitals in the state of xx, and was developed as a component of xx, it is hereafter referred to as the “xx scale.”

Scale Development

The 3 photographs taken at each of the 192 sessions were printed using a high-resolution printer and high gloss photographic paper. Photographs were then clustered according to the apparent severity of acute radiation dermatitis, and a descriptive photonumeric scale was developed via an iterative process involving a committee of radiation oncologists and dermatologists. Erythema and hyperpigmentation were graded on a scale of 0-3 for none, mild, moderate and severe. Desquamation was graded as intact (I), dry (D), or moist (M) (figure 1A and supplementary data). The toxicity grade consisted of a composite of both scores, for example “2M” would refer to moderate erythema or hyperpigmentation with moist desquamation. The “+” modifier was used to indicate a large area of desquamation or remarkably severe toxicity. One representative patient was identified to illustrate each ARD grade on the illustrated photonumeric scale (figure 1B).

Scale Evaluation

Four physicians with experience evaluating ARD in breast cancer patients used the illustrated scale as a reference to independently score the entire collection of photographs in two rating sessions separated by at least one week. To assess both inter- and intra-observer reliability, physicians were blinded to their own previous ratings and those of other raters. Prior to each rating session, photos were re-sequenced using a random number generator.

Measures

Patients who participated in xx completed a weekly questionnaire during RT that has previously been described in detail.[1] Questions included a modified Brief Pain Inventory[19] to describe breast pain, a modified Skindex questionnaire[20] that was customized to inquire about bother related to breast RT, and patient ratings of radiation skin reaction. Breast pain was scored by asking patients to rate it "at its worst in the last 24 hours" on a scale from 0-10, with 10 representing the worst imaginable pain. Bother from breast skin irritation was assessed by asking patients how often they had been bothered by itching, burning or stinging, hurting, or swelling of the treated breast within the last week, with 5 response options ranging from "never" to "all the time." We also evaluated a composite measure of any reported bother symptom. Patients who reported erythema were asked to rate it as "very faint," "moderately pink," or "bright red." Similarly, hyperpigmentation was rated as "very faint," "moderately dark," or "very dark." Patient-reported desquamation was evaluated by asking if there was any skin peeling in the treated breast, and if it was "wet/weeping, or dry."

For patients who participated in xx, their physicians completed a weekly questionnaire with reporting of dry and moist desquamation based on clinical evaluation at the point of care. CTCAE grade of ARD was also reported at the point of care. Physician-reported ratings obtained at the point of care were then compared with ratings from the photonumeric scale.

Statistical analysis

We evaluated the reproducibility of toxicity scores between 2 rating sessions for four individual raters, as well as between raters. We report the agreement fractions and weighted kappa scores for each domain of the scale, including erythema/hyperpigmentation, dry desquamation, moist desquamation, and any desquamation (dry or moist). We evaluated the relationship between photonumeric scale scores and patient-reported bother and pain using Pearson correlation. The diagnostic accuracy of the photonumeric scale was evaluated by comparing against patient self-reports of erythema, hyperpigmentation, and desquamation, as well as from physician ratings at the point-of-care. Statistical analyses were performed using the SAS system version 9.4 [Cary, NC, USA]. P-values 5% or less were considered significant.

Results

Table 1A presents the characteristics of the 80 patients in our sample. The majority of patients (75%) were treated with breast conserving surgery followed by conventionally fractionated whole breast radiotherapy. Most (85%) were treated with a boost; few (29%) received treatment to the regional lymph nodes. Table 1B reports the maximum grade of dermatitis reported during the radiation treatment course. In our cohort of 80 patients with 192 photos, 18 photos were graded with the "+" modifier to indicate a severe skin reaction.

Table 2 reports the reliability results of two separate rating sessions with the entire collection of 192 photographs. Unsurprisingly, the agreement fractions and kappa values were consistently slightly lower for inter-rater reliability than for intra-rater reliability. The agreement fractions for erythema and hyperpigmentation were generally lower than those for

desquamation (dry or moist). The lowest kappa values were consistently observed for the intra- and inter-rater evaluation of dry desquamation.

In general, the sensitivity and positive predictive value (PPV) of physicians using the illustrated scale to report desquamation versus patient self-report were lower than the specificity and the negative predictive value (NPV) (supplementary table 1). Sensitivity was 33% and 38% for dry and moist desquamation. The low sensitivity for desquamation measures suggests that there are many false negatives (i.e. instances in which patients reported desquamation, but it was not identified with review of photos using the photonumeric scale). The low positive predictive values for dry and moist desquamation (67% and 42%, respectively) indicate that rating photographs with the xx scale resulted in several false positives, instances in which desquamation was identified from photo review and reported using the xx scale, but was not corroborated by patient report. However, these numbers are limited by a relatively low event rate. Despite survey reports from 47 patients at 112 photo sessions, there were only 24 sessions at which dry desquamation and 13 sessions at which moist desquamation were reported by patients.

The favorable specificity for dry and moist desquamation (95% and 93%, respectively) is the result of a high true negative rate, indicating that ratings of toxicity in photographs using the xx scale correctly identified most patients who did not report dry or moist desquamation. The favorable negative predictive value for dry and moist desquamation (84% and 92%) suggests that there were very few false negatives, and that most ratings of absence of desquamation from photographs using the xx scale corresponded to patient reports of absent desquamation.

A combined measure of any desquamation (dry or moist) portrayed higher diagnostic accuracy relative to patient reports, with fewer type I and type II errors, resulting in 72% sensitivity, 93% specificity, 75% PPV, and 92% NPV.

A very similar pattern was apparent in the diagnostic accuracy of the xx scale compared against physician ratings of dry and moist desquamation at the point-of-care (supplementary table 2). In general, there was more discordance in ratings of dry desquamation than for moist desquamation. Ratings of dry and moist desquamation on photographs were associated with low sensitivity (27% and 77%, respectively) due to several patients who were identified with dry or moist desquamation by the treating physician but were missed on photographic review. Photonumeric ratings of dry and moist desquamation were associated with low positive predictive value (46% and 59%) due to overcalling desquamation on photographs from many patients for whom desquamation was not reported by physicians at the point of care. Specificity and NPV were >90% for dry desquamation, moist desquamation, and any desquamation (with the exception of NPV 86% for dry desquamation). As with the comparison to patient ratings, the scale reported strong diagnostic accuracy relative to physician ratings for a composite measure of any desquamation (dry or moist), with sensitivity 88%, specificity 91%, PPV 71%, and NPV 97%.

Due to a high rate of missing patient and physician reports of erythema/hyperpigmentation, the diagnostic accuracy was not able to be calculated, and is only reported for desquamation.

We evaluated a cross-comparison of physician-reported CTCAE ratings of ARD from the point-of-care (N=124 survey reports from 52 unique patients) compared against ratings of erythema and hyperpigmentation on the xx scale from photographs at corresponding time points (table 3). We found that among 105 survey reports of physician-rated grade 0-1 CTCAE toxicity, there were 47 with grade 2 and 3 erythema or hyperpigmentation on toxicity ratings using the xx scale. This indicates that many patients who were reported to have moderate to severe erythema or hyperpigmentation based on photographic review were rated as having either no ARD or mild erythema using CTCAE ratings, suggesting notable under-reporting of moderate to severe erythema using the CTCAE scale. In other words, moderate to severe erythema is more often rated by physicians as grade 0-1 toxicity on the CTCAE scale, despite the scale specifying that it should be rated as grade 2 or higher.

As an additional measure of validity, we sought to determine if ARD ratings on the xx scale correspond with patient-reported symptoms of bother and pain. We found that desquamation (dry or moist) was significantly associated with patient reports of itching, burning/stinging, hurting, and swelling (Table 4). Moderate or severe erythema/hyperpigmentation did not appear to correspond with individual measures of bother, but was significantly associated with a composite measure of any bother symptom. Patient reports of moderate or severe breast pain were significantly associated with grade 2 or 3 erythema/hyperpigmentation and desquamation (table 5).

The distribution of toxicity grade according to Fitzpatrick score is reported in supplementary table 3.

Quantitative measurements of ARD using colorimetry revealed a step-wise progression in the intensity of erythema and hyperpigmentation that corresponded well with the 0 to 3 gradations of the xx scale (supplementary figures 1 and 2).

Discussion

The primary strength of our study is prospective evaluation of acute radiation dermatitis from several vantage points simultaneously, including patient-reported symptoms, physician-reported toxicity, and photographs throughout the course of radiotherapy. This allowed us to evaluate the intra- and inter-rater reliability of our scale, as well as its diagnostic performance against the gold standard of patient-reported symptoms and physician-reported toxicity at the point-of-care. We are not aware that any other method of grading ARD has been developed or rigorously evaluated in this way. Our findings distinguish the xx scale as a meaningful step toward creating a reliable, objective and standardized method of grading toxicity. The scale corresponds to patient-reported symptoms of bother and pain, is simple yet granular, and applicable to light and dark skin patients alike.

Although many different scales for reporting radiation dermatitis have been developed over the last 35 years, very few have undergone reliability testing,[21,22] and even fewer have been evaluated relative to any type of patient-reported outcome measure. The British Columbia

Cancer Agency reported the results of reliability and validity testing for an ARD toxicity scale, the STAT, that incorporated observer scoring, patient reported symptoms, and patient and treatment characteristics for 27 patients.[10] A group from New Zealand developed a scale, the RISRAS, that also incorporated both physician ratings of toxicity and patient-reported symptoms and underwent reliability testing using 4 photographs from different disease sites.[12-14] These commendable efforts illustrate key differences between scales and highlight the importance of accounting for the relationship between toxicity scoring and patient-reported symptoms. However, there is very little data assessing the reliability or validity of the CTCAE scale for rating ARD, which is the scale that has been most commonly used in recent clinical trials.

There are three significant limitations to the CTCAE scale that merit discussion in the context of our data. First, the wide spectrum of toxicity that is grouped into the same grade of toxicity may be associated with vastly different patient experience and symptoms. Faint erythema may be associated with minimal symptoms, whereas our data suggest that dry desquamation may be associated with symptoms of bother and pain, yet both are considered equivalent in the CTCAE scale as grade 1 toxicity. Similarly, CTCAE grade 2 toxicity encompasses a wide spectrum of toxicity ranging from moderate erythema with intact skin, to brisk erythema with moist desquamation in the skin folds. Our data suggest that the patient experience with the different types of toxicity encompassed within a single CTCAE grade may in fact be quite different. This observation is supported by findings from a prospective clinical trial with Alliance that found little intercorrelation between CTCAE and patient-reported outcome measures.[23]

Second, our findings indicate that grouping erythema together with desquamation into the same grade of toxicity on the CTCAE scale results in under-reporting of erythema, and is not clinically informative regarding the rate of desquamation. In practice, the CTCAE scale functions essentially as a binary scale, with nearly all patients who experience radiation dermatitis in our study rated as grade 1 or grade 2 toxicity, similar to what others have reported.[21] As we were developing the xx scale, a key observation was that erythema and desquamation appear to be somewhat independent of each other, and that there is not always a linear progression from erythema to desquamation. For example, a patient with mild erythema may still experience moist desquamation (supplementary figure 3A), and not all patients with severe erythema will experience desquamation (supplementary figure 3B). The CTCAE scale is not designed to isolate the incidence of desquamation, which limits its usefulness for both research and patient care. In order to accurately report the full range of ARD reactions, we found it imperative to grade erythema separately from desquamation in the xx scale.

Third, because the CTCAE scale only accounts for erythema and desquamation in assigning a grade of toxicity, it is of limited relevance to patients of color, who often experience acute hyperpigmentation as the predominant skin reaction. In the xx scale, we therefore considered acute erythema and hyperpigmentation as equivalent forms of toxicity, and both are graded 0 to 3 on the same scale of mild, moderate, and severe. The xx scale is distinguished by excellent participation and wealth of data from patients of color. This represents an original contribution to the literature that has not previously been evaluated in other scales of ARD.

We also note the limitations of our data and the precision of toxicity scales in general. We discovered that the ability to differentiate dry and moist desquamation in photographs appeared limited. When evaluated against patient and clinician reports, the sensitivity and positive predictive value of separate dry and moist desquamation ratings were suboptimal due to poor diagnostic accuracy with high false positive and false negative rates. It is interesting to note that when dry and moist desquamation were combined together as a measure of any desquamation (dry or moist), the diagnostic accuracy of the scale improved significantly, suggesting difficulty in differentiating dry and moist desquamation on photographic review. Additionally, the consistently lower positive predictive value of the scale compared against patient and physician ratings (75% and 71%, respectively) indicates a tendency to overcall desquamation in photographs when it was not reported by either the patient or the treating physician. Notwithstanding these findings, dry and moist desquamation were retained as separate entities in the final version of the scale because the diagnostic accuracy for desquamation is anticipated to be higher when used for real-time toxicity assessment at the point of care, in which differentiation of dry versus moist desquamation is more readily discernable by visual inspection and physical examination. While the use of photographs was imperative for development and assessment of an illustrated scale, these findings indicate the limited utility of obtaining photographs as a routine method of grading acute radiation dermatitis. The illustrated scale is intended for use at bedside, without the need to obtain photographs.

We note that although the intra- and inter-rater reliability of our scale were similar to what has been reported for other photonumeric scales,[15-18] they were not particularly strong. This may partially relate to uncertainties introduced by use of photographs rather than clinical evaluation at the point-of-care, as well as the relatively low event rate of toxicity. Colorimetric measurements were used during development of the scale to corroborate the subjective grade 0 to 3 scale, but are not required to clinically implement the scale.

Finally, despite our best efforts to clearly define and illustrate gradations of toxicity with the photonumeric scale, systematic differences between raters remained. Differences between raters were observed on the first rating session, and persisted on the second rating session as well. In general, the intra- and inter-rater reliability for erythema/hyperpigmentation were lower than for ratings of desquamation. This may partially relate to the inherent subjectivity in assigning a discrete grade of toxicity for something that exists on a continuum, as opposed to desquamation, which was considered to be either present or absent. Our findings suggest that a certain amount of persistent subjective biases remain in the way that raters assign a grade of toxicity, notwithstanding the use of written instructions and photographic depiction of toxicity grades in trained raters. These findings highlight the limitations of physician-reported toxicity, and the importance of simultaneously assessing patient-reported outcomes, which have been found to capture a more comprehensive range of patient experiences and symptoms.[24,25]

While acknowledging these limitations, we consider the xx scale to represent a step forward in the ability to accurately describe and report acute radiation dermatitis in the context of a

prospective clinical trial. The results reported in the current analysis provide information on the diagnostic accuracy of the xx scale when it is used to grade photographs. Future efforts may be directed toward further evaluation/validation of the xx scale at the point-of-care and identification of patient- and treatment-related factors that can be used to predict which patients are most susceptible to ARD. Our data provide the most rigorous evaluation of an ARD toxicity scale to date, with a simple grading scale that is distinguished by characterization of its intra- and inter-rater reliability, diagnostic accuracy, and correlation with patient-reported symptoms of bother and pain.

Figure 1. The xx scale for grading acute radiation dermatitis (A) with photographic depiction of each grade of toxicity (B).

Table 1. Sample description by (A) patient, tumor and treatment characteristics, and (B) frequency of acute radiation dermatitis.

Table 2. Reliability evaluation for the illustrated scale of radiation dermatitis.

Table 3. Cross-comparison of physician-reported CTCAE ratings at the point-of-care versus ratings of erythema/hyperpigmentation (A) and desquamation (B) from photographs using the xx scale.

Table 4. Evaluation of the relationship between ratings of acute radiation dermatitis on the illustrated scale and patient-reported bother and pain.

Table 5. Association between patient-reported breast pain and toxicity grade of acute radiation dermatitis using the xx scale.

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Figures and Tables

Figure 1. The Xx scale for grading acute radiation dermatitis with photographic depiction of each grade of toxicity.

Table 1. Sample description by (A) patient, tumor and treatment characteristics, and (B) frequency of acute radiation dermatitis.

A.

Characteristic (N=80)	
Age, mean (SD) [Min. – Max.]	59.7 (12.1) [33 – 82]
Race, No. (%)	
White	30 (37.5)
Black	45 (56.3)
Other	5 (6.3)
T stage, No. (%)	
T1	60 (75.0)
T2	14 (17.5)
T3/T4	6 (7.5)
N stage, No. (%)	
NX	5 (6.25)
N0	50 (62.5)
N1	18 (22.5)
N2/N3	7 (8.75)
Surgery, No. (%)	
Breast conserving surgery	60 (75.0)
Mastectomy	20 (25.0)
Chemotherapy, No. (%)	31 (38.8)
Total radiation dose to the breast or chest wall, mean (SD) [Min. – Max.]	56.8 (6.3) [37.8 – 66.0)
Total radiation dose to the breast or chest wall, No. (%)	
<40 Gy	1 (1.3)
42.56 Gy	1 (1.3)
45-52.72 Gy	23 (28.8)
60-66 Gy	55 (68.8)
Daily radiation fraction size No. (%)	
1.8 Gy	29 (36.3)
2 Gy	42 (52.5)
2.67 Gy	9 (11.3)
Boost delivered, No. (%)	68 (85.0)

Nodes treated as part of radiation plan, No. (%)	23 (28.8)

B.

Photonumeric rating of acute radiation dermatitis	
Maximum Erythema/hyperpigmentation†	
None (0)	0
Mild (1)	22 (27.5%)
Moderate (2)	33 (41.3%)
Severe (3)	25 (31.3%)
Maximum Desquamation†	
None (I)	43 (53.8%)
Dry (D)	20 (25.0%)
Moist (M)	17 (21.3%)
†Refereed/consensus scoring across the raters.	

Table 2. Reliability evaluation for the photonumeric scale of radiation dermatitis.

	Intra-rater Reliability			**Inter-rater Reliability**	
	Agreement % (range)	**Kappa**		**Agreement % (range)**	**Kappa**
Erythema and/or Hyperpigmentation	79% (73-82%)	0.59		67% (54-73%)	0.47
Moist Desquamation	93% (91-96%)	0.65		90% (83-94%)	0.51
Dry Desquamation	85% (83-88%)	0.46		81% (71-86%)	0.29
Desquamation (Dry or Moist)	88% (85-90%)	0.71		86% (72-89%)	0.64

Table 3. Cross-comparison of physician-reported CTCAE ratings at the point-of-care versus ratings of erythema/hyperpigmentation (A) and desquamation (B) from photographs using the Xx scale.

A)

	Physician-reported CTCAE Radiation Dermatitis			
Photonumeric rating of erythema/ hyperpigmentation	0	1	2	
0	1	0	0	1
1	29	28	4	61
2	18	15	12	45
3	9	5	3	17
	57	48	19	124

*N=124 survey reports from 52 unique patients.

B)

	Physician-reported CTCAE Radiation Dermatitis			
Photonumeric rating of desquamation (dry or moist)	0	1	2	
Absent	48	38	8	94
Present	9	10	11	30
	57	48	19	124

*N=124 survey reports from 52 unique patients.

Table 4. Evaluation of the relationship between photonumeric ratings of acute radiation dermatitis and patient-reported bother and pain.

During the past week, how often have you been bothered by…	**Number of patient reports of bother symptoms** (N=113 survey reports from 47 unique patients)	**Number of patient reports of bother symptoms with corresponding desquamation (dry or moist) rated with the photonumeric scale**	**p-value for association between patient-reported bother symptom and desquamation (dry or moist) rated with the photonumeric scale**	**Number of patient reports of bother symptoms with corresponding grade 2 or 3 erythema/ hyperpigmentation rated with the photonumeric scale**	**p-value for association between patient-reported bother symptom and erythema/ hyperpigmentation rated with the photonumeric scale**
Itching of the skin of your treated breast	17	8	0.006	11	0.49
Burning or stinging of the skin of your treated breast	11	8	<0.001	9	0.10
Your treated breast hurting	13	9	<0.001	9	0.12
Swelling of your treated breast	24	11	0.001	16	0.14
Any bother symptom (itching, stinging, hurting, or swelling)	37	17	<0.001	25	0.03

Patients who reported “sometimes, often, or all the time” to the questions above were considered to have experienced bother related to the reported symptom

Table 5. Association between patient-reported breast pain and toxicity grade of acute radiation dermatitis using the Xx scale.

Patient rating of "breast pain at its worst in the last 24 hours" (N=113 survey reports from 47 unique patients)		**p-value for association with photonumeric scale rating**
Distribution of pain ratings on scale of 0-10	0-1: 54 2-3: 38 ≥4: 21	
Number of patient reports of moderate to severe breast pain (≥4) with corresponding grade 2 or 3 erythema/ hyperpigmentation rated with the photonumeric scale	14/21	0.03
Number of patient reports of moderate to severe breast pain with corresponding desquamation (dry or moist) rated with the photonumeric scale	9/21	0.007

Erythema or Hyperpigmentation Grade	Desquamation Grade
0 None	I Intact skin
1 Mild/faint hyperpigmentation or erythema	D Dry desquamation *only*
2 Moderate hyperpigmentation or erythema	M Moist desquamation ± dry desquamation
3 Severe hyperpigmentation or erythema	

Optional: Large Desquamation Size

\+ Width of desquamation >5cm (dry and/or moist)