Scientific Article

Toward a Skin Dose-Area Metric Predictive of Moist Desquamation Using In Vivo Skin Dosimetry and Skin Assessments

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Purpose: Moist desquamation (MD) is a concerning acute side effect of radiation therapy for breast cancer, often seen in skin folds for patients having large or pendulous breasts. In vivo skin dosimetry, clinical assessments, and patient-reported skin reactions were used to determine a relationship between dose-area metrics and the development of MD, to lend insight into skin tolerances and possibly guide future treatment planning dose constraints.

Methods and Materials: Skin dose was measured using GafChromic film on the inner surface of an early prototype carbon-fiber accessory for breast support to remove the inframammary fold in 20 patients at high risk of developing MD undergoing adjuvant whole breast radiation therapy. Prescribed doses were 42.5 Gray (Gy) in 16 fractions or 50 Gy in 25 fractions using 6 to 15 MV x-rays. To account for fraction size differences, analysis was performed using the equivalent dose in 2 Gy fractions using $\alpha/\beta = 11$ ($EQD2_{11}$). MD was assessed out to 2 weeks post radiation therapy by trained therapists and by a patient-reported outcome questionnaire.

Results: Statistically significant differences in areas receiving 30 to 48 Gy ($EQD2_{11}$) were observed between patients who did and did not develop MD in the inframammary area. Patients receiving $EQD2_{11}$ maximum dose ≤ 46 Gy and ≥ 38 Gy to ≤ 50 cm^2 of their breast skin did not develop MD.

Conclusions: The findings of this study offer insight into the relationship between skin toxicity and areas of skin irradiated to doses up to 50 Gy. Potential skin dose constraints to test in future studies to prevent MD are suggested.

Introduction

Moist desquamation (MD) is a concerning acute side effect of radiation therapy (RT) for breast cancer, often seen in skin folds for patients having high body mass index and large or pendulous breasts.[1-6] Breast positioning to remove or reduce skin folds combined with a

suitable dose-area constraint to the skin during treatment planning is likely to reduce this side effect. Dose-volume constraints to the target breast tissue with the introduction of intensity modulated RT (IMRT) have achieved reductions in MD rates in recent years.[7,8] However, the problem still persists in up to 40% of patients depending on body type.[9] Dose buildup in the first millimeter of the epidermis follows an extremely steep gradient. This introduces a highly challenging situation for both in vivo dosimetry and accurate skin dose calculation during the treatment planning process. Skin dose is a function of beam energy, breast shape, incident beam angle, and the planned intensity modulation.[10] Thus, predicting skin dose for all breast sizes and shapes is challenging.

Skin folds place the skin in the high-dose region where it receives 95% or more of the prescribed dose to the breast, out of a necessity to ensure adequate target coverage in whole breast RT. The largest skin fold is often the inframammary fold (IMF), which is subject to sweating and rubbing during everyday activities, likely further increasing the severity of acute skin reactions and increasing the risk of infection in this area. Improving breast position to eliminate the IMF has been the subject of a number of investigations.[11] Recently, a novel carbon fiber adjustable reusable accessory for breast positioning (CARA) in supine positioning was introduced.[12] In a pilot study, this method of breast support has proven effective at eliminating both the IMF and lateral breast sag, repositioning the breast to reduce dose to the lung and normal body tissue.[13] This breast support device also provides a unique opportunity to perform in vivo skin dosimetry using radiochromic film in contact with the skin surface on the inner side of the carbon-fiber support cradle. This study examines the skin dose measured in the pilot study using the early prototype CARA V1.0 to determine an association between dose-area metrics and the development of MD. This study included only patients at high risk for this acute side effect due to the presence of inframammary skin folds or lateral breast ptosis.

Methods and Materials

Study design

This institutional research ethics board-approved 20-patient study (ClinicalTrials.gov NCT04543851) was designed to assess safety in preparation for a randomized controlled trial to assess the efficacy of the CARA device to reduce the incidence of MD in the IMF. The early prototype CARA V1.0 device is shown in Fig. 1. Patients were recruited in 2 treatment centers in British Columbia, Canada from May 2018 to September 2019. In vivo skin dosimetry was used to measure skin dose along the surface of the breast in contact with the
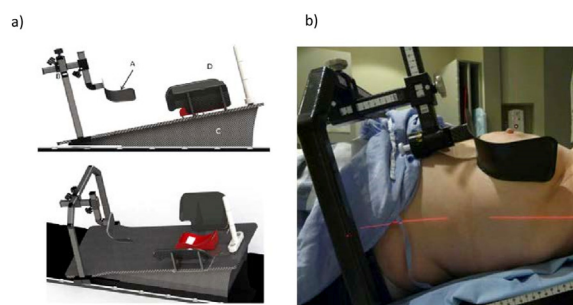

Figure 1 The carbon fiber adjustable reusable accessory for breast positioning device (a) in schematic form and (b) in use on a patient. The carbon fiber cradle is supporting the breast on the chest wall. Customized settings for each patient are determined using the indexing scales seen in the photograph for longitudinal, lateral, vertical, and angular position of the cradle.

carbon-fiber cradle to relate clinical outcomes with skin dose-area metrics.

Patients

Patients with stage I to III invasive breast cancer or ductal carcinoma in situ requiring adjuvant whole breast radiation with or without nodal coverage were recruited to this study. Patients receiving a boost to the breast tumor bed were included in this study if the boost was not in the IMF area. Additional patient eligibility criteria included the presence of an inframammary skin fold of ≥1 cm and/or lateral ptosis and breast cup size D and larger. Exclusion criteria included pre-existing skin conditions, use of Mepitel film,[14] and inability to return for follow-up skin assessments 1 and 2 weeks after treatment.

Treatment planning

Patients underwent computed tomography simulation on GE Lightspeed scanners in the supine position on a breast board. One center used a fixed breast board angle of 12.5° and the other used a breast board with a variable angle between 5° and 15°. As seen in Fig. 1, the CARA device consists of a carbon fiber frame that fits over the patient at hip level with the patient on a conventional angled breast board. A carbon fiber breast support cradle connects to the frame by means of a bracket that can be adjusted left-right, superior-inferior, anterior-posterior, and rotated to customize the fit for each patient. Treatment planning was performed using the Varian Eclipse AAA algorithm version 13.6 and a forward-planned, field-in-field, step and shoot dose optimization strategy. Whole breast dose prescriptions were either 42.5 Gy in 16

fractions or 50 Gy in 25 fractions. Patients requiring a boost received an additional 10 Gy in 5 fractions to the seroma volume. A tangential field technique was used to cover the whole breast. For patients requiring regional nodal irradiation, internal mammary nodes were covered using wide tangents, whereas axillary and supraclavicular nodes were covered using anterior and posterior fields. A 0.5-cm layer of tissue under the body contour was excluded from the planning target volumes to create treatment planning dose-evaluation volumes. Six, 10, or 15 MV photon beams were used. Dose constraints included: volume of lung receiving ≥20 Gy less than 35% (lung V20 Gy < 35%) and heart V25 Gy < 5%, and ≥95% of the dose-evaluation volumes were covered by ≥95% of the prescribed dose. There were no dose constraints on the skin. The maximum allowed point dose in the breast was 110% and V107% breast was limited to 20 cm^3. Left breast patients were treated using deep inspiration breath hold technique if they were able to hold their breath for 20 seconds or more.

Treatment

Patients were treated daily on weekdays using the CARA device on Varian TrueBeam linear accelerators. Imaging consisted of daily orthogonal kV imaging to match bony landmarks on digitally reconstructed radiographs and MV portal imaging on the first 3 days, then weekly, to assess the position of the breast and the amount of lung in the treatment field. Patients did not undergo bacterial decolonization.[15] The standard institutional skin care protocol was used in this study. Water-based moisturizer was recommended for daily care. In the event that MD developed, saline soaks were recommended as front-line treatment followed by β—methasone and/or antibiotic prescription on the advice of the radiation oncologist.

Film equipment and calibration

In vivo skin dose was measured using Gafchromic EBT3 (Ashland, NJ) film over 3 treatment fractions. Films were cut to the shape of the inner surface of the CARA support, with an area of 170 cm^2. Films were scanned using an Epson Expression 10000XL scanner following the 1-scan protocol.[16] All films in this study were scanned 48 hours or more after irradiation to ensure film darkening was stable.[17] A template was used to align CARA cradle-shaped films on the scanner to ensure consistent position in the middle of the scanner bed. Film calibration was performed with the Film QA Pro (Ashland, KY) software, which uses triple-channel film dosimetry,[18] and further analysis was conducted in MATLAB (Mathworks, MA). Sets of calibration films were made with 6, 10, and

15 MV photons, and calibration curves for the red, green, and blue channels were acquired using the color reciprocal linear versus dose function. The green channel calibration was the most consistent in the dose region >1.8 Gy, which is of most interest in this study and was used for all subsequent analysis. No corrections were applied to account for the physical depth or composition of the film in this study.[19]

In vivo skin dose measurements

Each of the 20 patients in this study had 3 film measurements taken on different treatment days over 3 weeks. Film was cut and secured to the inner surface of the carbon fiber cradle and wrapped in a single layer of plastic wrap for hygiene. This film was in place for the duration of that day's treatment, including imaging and treatment delivery. CARA supported the entire inferior portion of the breast despite varying breast size across the patient population. Patients who had mixed energy beams during treatment were analyzed with the 6 MV calibration strips. Six patients were given boost doses sequentially to the whole breast treatments. The film measurements were taken during whole breast treatment alone without the boost.

Skin assessments

Skin reactions were graded at baseline, 1 week before treatment end, at end of treatment, 1 week after treatment, and 2 weeks after treatment by trained therapists. National Cancer Institute Common Terminology Criteria for Adverse Events V4.03 skin assessment criteria were used for general assessment, and size and location of any areas of MD were recorded. Photographs taken during skin assessments were reviewed independently by a second trained observer and consensus opinion was reported.

Patient-reported skin assessments

A previously validated patient-reported outcome (PRO) questionnaire was completed by patients at similar timepoints as the staff skin assessments.[20] Patients were asked to report on whether they developed open skin in the fold under the breast. This included the inferior surface of the breast, the breast crease, and the chest wall below the breast when an inframammary breast fold was present. Thus, the patient-reported skin area exceeded the region where dose was measured under the CARA device. This was accounted for in the analysis. The questionnaire was administered electronically such that patients could complete it either in the clinic or from home.
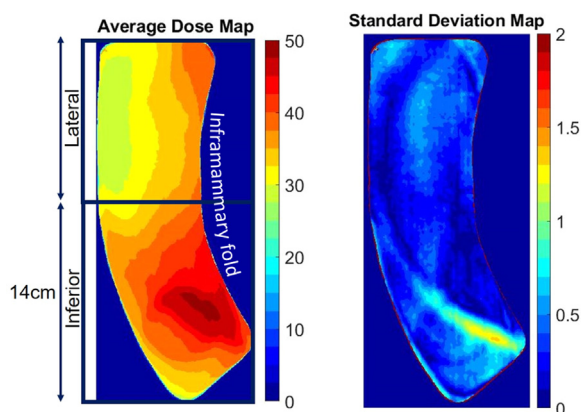
Figure 2   (Left) The color map is a pixel-by-pixel average of the 3 dose maps of 1 patient (patient 5), where the dose is given as equivalent total doses in 2-Gy fractions with $\alpha/\beta = 11$ Gy. The film is segmented into lateral and inferior sections to enable separate analysis of the lateral and the inferior breast skin. The total film area is 170 cm^2, with 76 cm^2 lateral area and 94 cm^2 inferior area. (Right) Pixel-by-pixel standard deviation (expressed as % of prescribed dose) of the 3 equivalent total doses in 2-Gy fractions with $\alpha/\beta = 11$ Gy maps of the same patient. Regions with high standard deviation indicate areas affected by variation in daily patient setup.

Analysis

As suggested by Devic et al,[19] a 5×5 median filter was applied to remove noise caused by spikes from dust or scratches on the film/scanner, then a 5×5 Wiener filter was applied to remove inherent scanner noise and non-uniformity in the film. The outer 2 pixels along the edges of each film were discarded in the analysis to avoid edge artefacts due to film cutting. Mean dose maps for each patient were created from the 3 film measurements, and the film area was segmented to allow separate analysis of the lateral (76 cm^2) and inferior (94 cm^2) breast skin areas, as shown in Fig. 2. Standard deviation maps were computed to demonstrate the reproducibility of the dose distributions, which would be affected by patient setup variability.

Taking into consideration the biologic effects of the 2 different dose fractionations, all film dose measurements were converted to equivalent total doses in 2-Gy fractions with $\alpha/\beta = 11$ Gy for MD (EQD2$_{11}$).[21,22] To assess the significance of α/β variation, all results were also computed using α/β of 5 and 15 Gy for comparison.

Cumulative dose-area histograms and boxplots were created from the mean dose maps, with the dose expressed as EQD2$_{11}$ for 2 groups of patients: those who did and those who did not develop MD. Staff assessments of MD were reported for the area of skin in contact with CARA, where the dose was measured. PROs of open skin include, but are not limited to, this area of skin. The primary dose-area analysis was based on the staff assessments and the PRO, using Boolean AND to identify cases of MD. This gives some weight to the patient's experience and is an acknowledgment that staff assessments are also subject to limitations. A sensitivity analysis was conducted to look at staff assessments alone and both combined. A comparison of the median dose-area results for the aggregated data for the 2 patient groups was performed and t test was used to validate statistical significance.

Results

Patient characteristics are shown in Table 1. Seventeen patients participated at center 1 with the fixed breast board and 3 patients participated at center 2 with the adjustable breast board. Nineteen out of 20 patients had body mass index > 25 and 16/20 had IMF skin folds ≥1-cm deep while the breast was unsupported in the supine position. Seven patients were left breast and treated with deep inspiration breath hold. Thirteen patients were right breast, all treated free breathing. Eleven patients were treated to 42.5 Gy/16 fractions and 9 were treated to 50 Gy/25 fractions using 6, 10, or 15 MV beams. Six patients received sequential boost dose to the breast (10 Gy/5 fractions). All patients completed treatment without interruption. Two patients completed their last 2 skin assessments remotely by telehealth or phone, and 1 patient was lost to follow-up after RT but they had developed a small area of patchy MD in the inferior breast area at last treatment.

Table 2 lists the assessed peak skin reactions using the National Cancer Institute Common Terminology Criteria for Adverse Events V4 scale, the study staff assessment of MD, and the PRO for open skin in the fold under the breast. Staff assessments determined that 7/20 patients developed some patchy MD on the inferior breast surface where the dose was measured. PROs determined that there were 9/20 cases of MD in the breast fold area. In 6/20 cases, both the staff and patient reported MD.

Figure 2 shows the average skin dose map and standard deviation map of 1 patient and demonstrates the segmentation of the film into lateral and inferior sections. Figure 3 displays average skin dose over 3 treatment fractions across the portion of breast in contact with the carbon-fiber cradle. Data are shown for all 20 study patients separated into 2 groups: those who developed MD in the inferior breast region and those who did not.

Figure 4 shows cumulative dose-area histogram data from the inferior film segment for each patient. Patients are color coded for MD and the dose prescription is indicated for each case. The maximum dose-area data from the lateral film segments are also indicated on Fig. 4 for reference. EQD2$_{11}$ ≥ 46 Gy was delivered to ≤1 cm^2 and

Table 1   CARA patient characteristics

Case	Age (y)	BMI	L/R breast	Unsupported breast fold depth (cm)	Bra size	Dose (cGy)/fractions	Boost
1	60	26.3	R	0	38 J	4250/16	N
2	55	52	L	3.5	46 DD	5000/25	N
3	58	34.4	R	1.3	42 DD	5000/25	N
4	47	33.9	R	1.0	26 G	5000/25	N
5	65	30.8	R	1.0	40 D	4250/16	N
6	46	41	L	0	40 C	4250/16	Y
7	51	32.7	L	2.0	38 DD	5000/25	Y
8	54	31.2	L	2.3	36 J	5000/25	N
9	71	28.6	R	4.0	40 B	4250/16	Y
10	48	32.6	R	2.0	40 DD	5000/25	Y
11	45	44.3	R	3.5	42 K	5000/25	Y
12	74	32.0	L	2.0	40 D	4250/16	N
13	57	35.1	R	1.8	40 DD	4250/16	N
14	63	32.6	L	2.1	42 DD	5000/25	Y
15	65	30.9	R	3.0	38 DD	4250/16	N
16	72	31.9	R	0.5	40 D	4250/16	N
17	56	34.5	R	2.0	40 D	4250/16	N
18	68	26.7	R	0	40 D	4250/16	N
19	58	23	L	4.6	34 EE	4250/16	N
20	41	41.7	R	2.0	40 H	5000/25	N

Abbreviations: BMI = body mass index; CARA = carbon fiber adjustable reusable accessory for breast positioning.

≥38 Gy was delivered to ≤31 cm^2 on the lateral breast skin for all patients. There were no reports of patients developing MD on the lateral breast surface.

Table 3 shows a comparison of dose-area versus MD in the inframammary area for the staff assessments alone and the Boolean AND for staff and PRO. Because only 1 case of staff-reported MD was not reported by the patient, the differences are insignificant. A *t* test was performed on the area measurements comparing cases of MD versus no MD at 2 Gy increments from 30 to 50 Gy. Statistically significant differences between patients who developed MD and those who did not are seen up to 48 Gy. There were no significant differences in findings using α/β of 5 or 15 Gy in comparison to α/β= 11 Gy.

The aggregate patient dose area data, presented as box plots in 2 Gy increments for both patient groups, are shown in Fig. 5. The boxplots provide a convenient representation of the statistically significant differences in skin areas receiving ≥30 to 48 Gy (EQD2$_{11}$) between patients who did and did not develop MD. Splitting the difference between the 75th percentile for patients who did not develop MD and the 25th percentile for those who did, a

convenient dose constraint for further evaluation to avoid MD could be ≥38 Gy to ≤50 cm^2, as shown in Fig. 5. A point maximum dose constraint of 46 Gy is also suggested by the data in Figs. 4 and 5. The full set of potential dose-area constraints ≥30 Gy are listed in Table 4, with the corresponding isodose levels for the 42.5 Gy/16 and 50 Gy/25 fractionations. For the 50 Gy/25 dose fractionation schedule, EQD2$_{11}$ 38 Gy corresponds to 79% of the prescribed dose and to 87% for the 42.5 Gy/16 fraction prescription. The suggested point maximum dose constraint of EQD2$_{11}$ 46 Gy corresponds to 93% of the prescribed dose for 50 Gy/25 fractions and to 103% for 42.5 Gy/16.

Discussion

This study demonstrates a relationship between skin dose-area metrics and the development of MD. This is the first study to associate measured dose-area data with staff- and patient-assessed skin reactions in external beam RT. Skin reactions in the current study are consistent with expectations for MD in this high-risk patient population

Table 2   Peak skin reactions and MD-positive cases for the dose-area analysis

Case	Peak NCI score	Staff assessed any patchy MD on the inferior breast surface where the dose was measured	Patient reported positive for open skin in the fold under the breast
1	2	No	No
2	2	Yes	Yes
3	2	Yes	Yes
4	3	Yes	Yes
5	2	Yes	Yes
6	2	No	No
7	1	No	No
8	3	Yes	Yes
9	2	No	No
10	2	No	Yes
11	2	Yes	Yes
12	2	No	Yes
13	2	No	No
14	2	No	Yes
15	2	No	No
16	3	No	No
17	2	Yes	No
18	1	No	No
19	3	No	No
20	2	No	No

Abbreviations: MD = moist desquamation; NCI = National Cancer Institute.
Highlighted cases reported MD by both staff and patients.

based on previous studies,[8,9] although those studies do not mention the use of a breast support to eliminate skin folds. An α/β value of 11 for MD is used in this study, as suggested by Turesson and Thames.[21] This approach links the 50 Gy/25 and 42.5 Gy/16 dose fractionation regimens and should help facilitate translation of the results to newer hypofractionated dose prescriptions.[22]

The inferior breast surface systematically received a higher dose than the lateral surface for all patients, a result of lateral scatter within the breast. There was no incidence of MD on the lateral breast surface in contact with the breast support for any patient. Statistically significant differences in skin areas receiving 30 to 48 Gy are seen when comparing patients developing MD with those not developing MD. This information might be leveraged in future treatment planning studies to reduce the incidence of this acute side effect. The data in Fig. 5 suggest potential dose area constraints to avoid MD. For example, a maximum skin dose of 46 Gy ($EQD2_{11}$) with an additional dose constraint of ≥38 Gy ($EQD2_{11}$) ≤50 cm^2 would be interesting to investigate in a future

study. An expanded set of potential dose constraints is provided in Table 4. These dose constraints should be achievable using IMRT in combination with effective breast support to remove large skin folds, without compromising target coverage.

This study was not designed to separate the effect of breast support on skin reactions from the effect of the IMRT dose optimization. No treatment planning dose constraints were applied to the skin for patients in this study. Phantom studies indicate that CARA support can reduce skin dose by alleviating large inframammary and lateral skin folds with minimal bolus effect and meet the dose constraints suggested in this study.[12]

There is a high degree of consistency in the staff and PRO data, with only 1 patient not reporting open skin when the staff assessment was positive for MD. As the PRO data encompassed more breast skin than the measured area, PRO alone was not sufficient for this analysis.

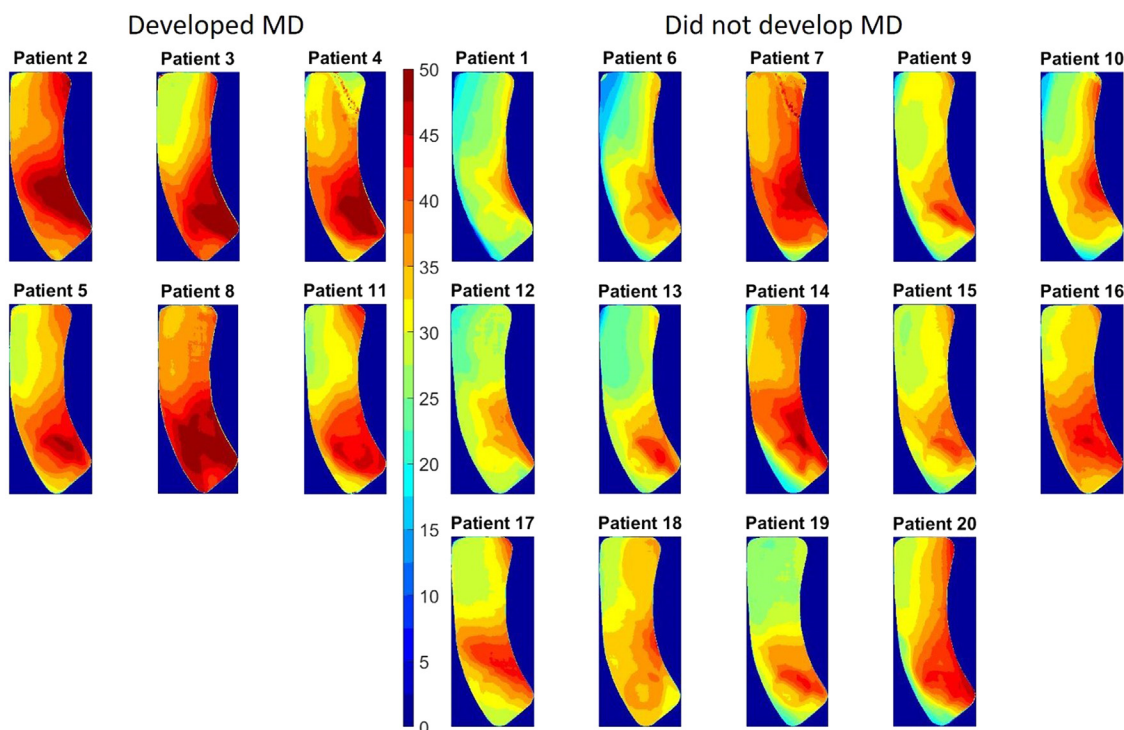Dose in this study was measured along the skin surface under the CARA device. We anticipate that the dose area

Figure 3 The average of the 3 dose maps acquired for each patient. Each color map is the pixel-by-pixel average of the 3 dose maps for that patient given as equivalent total doses in 2-Gy fractions with $\alpha/\beta = 11$ Gy. The 6 patients on the left of the color bar were assessed by staff and in the patient-reported outcome as positive for moist desquamation on the inferior breast skin where the dose was measured.
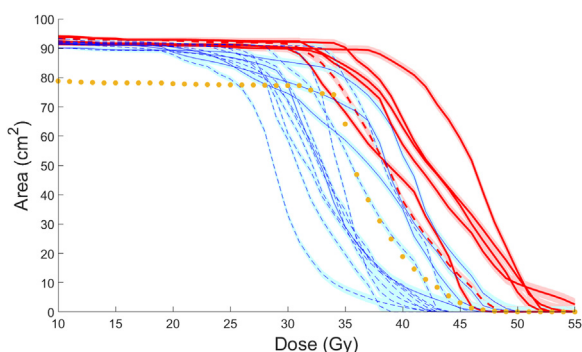

Figure 4 Cumulative dose-area histogram data, from the inferior portion of the breast surface, for all patients. The horizontal axis represents dose as equivalent total doses in 2-Gy fractions with $\alpha/\beta = 11$ Gy, and the vertical axis is the area on the average dose map that received the corresponding dose or more. Film uncertainties of 3.7% are plotted as a shaded region around each line. Thicker red lines indicate the patient developed moist desquamation on the inferior breast surface and blue lines indicate the patient did not. Solid lines show patients with a prescribed dose of 50 Gy/25 fractions, and dotted lines show patients with a prescribed dose of 42.5 Gy/16 fractions. The orange circles indicate the maximum dose from the lateral portion of the breast surface across all patients for comparison.

metrics identified in the study would be translatable to treatments without breast support or with other forms of breast support, when accurate skin dose information is available. These results should also translate to prone setup in breast RT, which is a very effective approach to eliminating IMFs and reducing skin reactions for patients with large or pendulous breasts.[23]

With the basal layer of skin at a depth of <0.1 mm and with skin at the interface of air and tissue, predicting dose to the skin in the treatment planning system comes with challenges. Defining a skin structure model within the treatment planning system to calculate dose to the skin can be done by creating a rind on the body structure with a volume, or it can be calculated through scripting to pull off dose at points along the surface. These techniques will be subject to the limited spatial resolution of the treatment planning system. Translating the results from this study into a practical treatment planning procedure is the subject of ongoing investigation.

Mapping the measured skin dose-area data to the location where MD was observed was a key factor in this study. The 2-dimensional maps of in vivo measured surface dose, paired with skin reaction assessments, form a unique data set. GafChromic film for breast skin dosimetry has been used in brachytherapy studies,[24] but the current study is the first in vivo demonstration in the external beam clinical setting. Most studies present

Table 3 A comparison of results for staff assessments alone and a Boolean AND of staff and PRO

$EQD2_{11}$ dose (Gy)	P value		Median area (cm^2) staff assessment	Median area (cm^2) staff AND PRO
30	<.0001	MD	90.4	91.0
		No MD	74.6	76.1
32	<.0001	MD	89.2	89.5
		No MD	58.3	59.7
34	<.0001	MD	85.0	85.6
		No MD	40.5	40.9
36	<.0001	MD	79.7	80.7
		No MD	24.5	24.9
38	<.0001	MD	72.8	74.0
		No MD	14.3	14.5
40	.0001	MD	57.1	60.1
		No MD	8.3	8.5
42	.0003	MD	46.6	49.0
		No MD	2.8	3.1
44	.0046	MD	35.7	38.8
		No MD	0.0	0.0
46	.0082	MD	27.0	28.5
		No MD	0.0	0.0
48	.0094	MD	15.6	17.3
		No MD	0.0	0.0
50+	.1002	MD	6.7	8.2
		No MD	0.0	0.0

Abbreviations: $EQD2_{11}$ = equivalent total doses in 2-Gy fractions with α/β = 11 Gy;
MD = moist desquamation; PRO = patient-reported outcomes.
The *t* test *P* values on the staff AND PRO for cases of MD versus no MD are reported.

Figure 5 These box plots contain the cumulative measured dose-area histogram data from the inferior breast surface for all patients. The black boxes represent the 6 patients who developed MD on the inferior breast surface, and the green boxes represent the 14 patients who did not develop MD in this region. Each box spreads from the 25th to 75th percentiles of the cumulative area corresponding to each dose for those patient groups. A line is drawn at the median area for each dose level, and the whiskers extend to encompass the outlying data points. The red Xs are located to split the difference between the 25th percentile of patients who developed MD and the 75th percentile of patients who did not. *Abbreviation:* MD = moist desquamation.

surface dose for anthropomorphic phantoms.[10,25,26] Studies have established some correlation between calculated dose-volume statistics for the breast target volume and adverse skin reactions in external beam breast RT.[4,27-30] However, these studies do not provide any insight into tolerance doses for skin. Point measurements of skin dose are not sufficient to establish effective skin dose-area metrics.[31] Predictive models for grade 3 skin toxicity based on calculations of skin dose in breast RT have been put forward,[32] but these are not specific to MD, and skin dose calculations in the conventional treatment planning setting are limited in accuracy.[33,34]

A limitation of the study was the inability to measure dose along the inframammary crease, the line where the breast meets the chest. Some patients did experience small patches of MD along the crease, but these areas were not
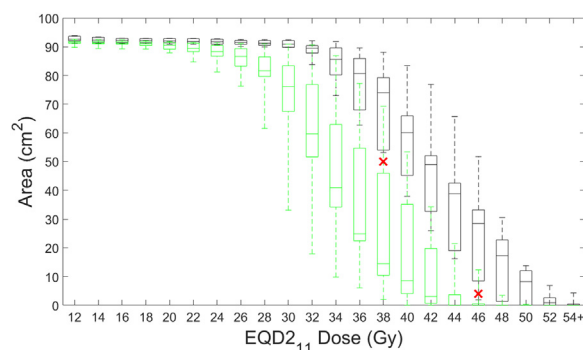
included in the dose-area analysis. Additionally, boost doses were sequentially delivered and thus were not included in the reported doses here. There were no boost doses delivered to the region of the breast in contact with

Table 4 $EQD2_{11}$ and prescription isodose levels with dose-area data limits that split the difference between the 25th percentile of patients who developed MD and the 75th percentile of patients who did not, to prevent MD

$EQD2_{11}$ dose (Gy)	Isodose level		Area (cm^2)
	50 Gy/25 fractions	42.5 Gy/16 fractions	
30	64%	71%	87
32	67%	75%	82
34	71%	79%	72
36	75%	83%	61
38	79%	87%	50
40	82%	91%	40
42	86%	95%	26
44	89%	99%	11
46	93%	103%	4
48	97%	106%	1

Abbreviations: $EQD2_{11}$ = equivalent total doses in 2-Gy fractions with α/β = 11 Gy;
MD = moist desquamation.

the CARA device because patients with boosts to the inframammary area were excluded from this study. The small number of patients in this pilot study was a limitation that is being addressed in an ongoing clinical trial.[35] Another limitation in this study is that we were unable to measure or account for differences in sweating or rubbing in the inframammary area during or after RT.

Future directions

Recent studies have demonstrated potential methods to reduce skin toxicity. Mepitel film and bacterial decolonization have significantly reduced the occurrence of radiation dermatitis in breast patients.[14,15] It is predicted that these interventions can be used in parallel with a physical support like CARA. The V1.0 device prototype used in this study had an effective water equivalent thickness of 0.95 ± 0.02 mm. A 50% reduction in equivalent thickness of the CARA carbon-fiber support has been achieved subsequent to this study, and a new prototype is in use in an ongoing prospective trial (ClinicalTrials.gov Identifier: NCT04257396).[35] An estimated reduction of ≥10% in skin dose under this new, lighter version is expected.

The ongoing trial also includes the 26 Gy/5 fraction dose prescription from the FAST-Forward Trial[22] and assesses MD for patients receiving CARA versus current standard of care to expand on the findings of this study.[35]

The results from this study lend insight into how skin dose tolerances vary with irradiated area, but dose-area alone does not describe the actual distribution of dose across the skin. Contiguous and multiple separate regions of skin having the same total area are not distinguishable using the metrics investigated here, and more complex metrics are currently under consideration.

Conclusion

This is the first study to report a relationship between measured skin dose-area metrics and the development of MD in external beam breast RT, combining detailed skin assessments and location-specific in vivo dose-area information. The conclusions apply to both the 50 Gy/25 and 42.50 Gy/16 fraction regimens through the use of $EQD2_{11}$. Dose constraints such as a maximum point dose ≤46 Gy and ≥38 Gy to ≤50 cm^2 are suggested for future evaluation to prevent MD. This prospective study was based on a small 20-patient sample, and it would be valuable to see these results validated in a larger patient population.

Disclosures

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