Review Article

Radiation-induced skin changes after breast or chest wall irradiation in patients with breast cancer and skin of color: a systematic review

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ABSTRACT

Introduction: The purpose of this study is to systematically review data pertaining to breast cancer and radiation-induced skin reactions in patients with skin of color (SOC), as well as data pertaining to objective measurements of skin pigmentation in the assessment of radiation dermatitis (RD). **Methods and materials:** We conducted a systematic review utilizing MEDLINE electronic databases to identify published studies until August 2022. Key inclusion criteria included studies that described RD in breast cancer with data pertaining to skin of color and/or characterization of pigmentation changes after radiation. **Results:** We identified 17 prospective cohort studies, 7 cross-sectional studies, 5 retrospective studies and 4 randomized controlled trials. Prospective cohort and retrospective series demonstrate worse RD in African American (AA) patients using subjective physician-graded scales. There is more limited data in patients representing other non-White racial subgroups with SOC. 2 studies utilize patient reported outcomes and 15 studies utilize objective methods to characterize pigmentation change after radiation. There are no prospective and randomized studies that objectively describe pigmentation changes with radiotherapy in SOC. **Conclusions:** AA patients appear to have worse RD outcomes, though this is not uniformly observed across all studies. There are no studies that describe objective measures of RD and include baseline skin pigmentation as a variable, limiting the ability to draw uniform conclusions on the rate and impact of RD in SOC. We highlight the importance of objectively characterizing SOC and pigmentation changes before, during and after radiotherapy to understand the incidence and severity of RD in SOC.

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INTRODUCTION

Radiation dermatitis (RD) occurs in over 95% of patients after radiotherapy (RT) for breast cancer. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grades RD on a 5-point scale, with grade 1 describing erythema with intact skin and higher grades describing progressive skin changes ranging from dry to moist desquamation, ulceration and skin necrosis.[1-4] RD can negatively impact quality of life [5] and become severe enough to necessitate treatment pause, which can lead to inferior clinical outcomes.[6]

There are several respects in which the assessment and management of RD may be affected by baseline skin pigmentation. The CTCAE scale, reliant on the assessment of erythema, is more difficult to evaluate in patients with darker skin pigmentation. Further, pigmentation changes, currently omitted from the CTCAE definition of RD, have classically been considered a chronic rather than acute effect of RT. However, acute pigmentation changes can result from pheomelanin-influenced production of reactive oxygen species (ROS) after ultraviolet radiation.[7] ROS production propagates DNA damage in keratinocytes resulting in necrosis and deposition of melanin into the epidermis – a phenomenon known as postinflammatory hyperpigmentation.[7] Differences in skin structure may lead to differential acute skin effects after radiation in patients with SOC, who may be more susceptible to increased damage to melanocytes and keratinocytes, resulting in both acute and late hyperpigmentation.

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While numerous clinical trials have described toxicity for breast cancer, none have taken into account baseline pigmentation nor described changes specific to SOC.[8-10 11] We conducted a structured systematic review of studies in breast cancer patients to describe the differences in incidence and severity of RD in populations with SOC and data pertaining to skin pigmentation changes from radiotherapy.

MATERIALS AND METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA) reporting guideline (Supplemental Figure 1).

Search Strategy

We aimed to examine evidence pertaining to radiation skin toxicity in SOC. We conducted a literature search using MEDLINE electronic database (via PubMed) on November 1, 2022, March 1, 2022 and August 29, 2022. The search strategy was developed with input from research team members in dermatology and radiation oncology. Search terms included: breast cancer, radiation, dermatitis, skin toxicity, erythema, hyperpigmentation, pigmentation, skin reactions, desquamation, skin of color, Black, African, Hispanic, race, and ethnicity. The search strategy was updated on August 29, 2022 to include Asian Pacific Islander and indigenous, Fitzpatrick skin typing, skin injury, cutaneous radiation injury, hypopigmentation and colorimetry into search terms. The search was confined to peer-reviewed articles all published in English and containing an abstract. Complete search strategy is available in Supplemental table 1. Reference lists of journal articles were screened for additional citations fitting our selection criteria.

Study Selection

Abstracts were independently reviewed by author J.M.P for relevance based on title and abstract, then by full text. Inclusion criteria included original clinical investigation with clinical data pertaining to radiation skin reactions in breast cancer patients and to populations with SOC. Our definition of SOC included the following race/ethnicities: African, Asian Pacific Islander, Indigenous, and Hispanic. Given that SOC constitutes a wide range of racial and ethnic groups and is challenging to quantify based on race/ethnicity alone, we also included studies with skin color characterization by patient with patient-reported outcomes or by physician with Fitzpatrick skin type or with the use of objective instruments. We collected the following information for each study: first author, country study was conducted, year of publication, study design, description of patient population, main objective of the study, racial composition of study population, radiation technique, how RD was measured, and the main findings of the study. N.K.G and I.W.T ensured agreement for inclusion.

Quality Assessment

J.M.P and C.N independently used guidelines modified from the Oxford Centre for Evidence-based Medicine[12] for ratings of individual studies to rate the quality of evidence, with 1 being the best quality and 5 being the poorest quality.

RESULTS

Figure 1 summarizes the search strategy. The structured literature search resulted in 99 articles matching search terms published between 1994 and 2022. 33 articles were identified for inclusion. Key findings are reported in Tables 1 and 2.

A. Studies evaluating radiation dermatitis according to race/ ethnicity

5 prospective single-institution studies evaluated RD according to the cohort's racial composition. Clinicians graded RD utilizing subjective scales based on visible skin changes (Table 1).[13-17] None of these studies specifically commented on skin coloration or color change.

2 of these studies evaluated patients who exclusively underwent breast conserving surgery (BCS) and postoperative whole breast RT (WB-RT). In a study of 159 patients with a racially diverse population, there were significantly more grade 3 skin reactions ("contiguous moist desquamation and bleeding") using the CTCAE scale (Supplemental table 2) at RT completion in African American (AA) patients compared to other demographics.[13] In a larger study of 392 patients with a similarly diverse racial composition,[14] RD was graded using the Oncology Nursing Society skin toxicity scale (ONSSTS) (Supplemental table 3), a modified version of the CTCAE scale that subdivides grade 2 RD into 3 categories to capture more detailed information about the presence and severity of desquamation. There was a higher crude rate of grade 4-5 skin reactions reported in AA versus non-AA patients, but on multivariable analysis (MVA) neither race nor ethnicity predicted worse toxicity.

2 prospective studies evaluated patients who underwent predominantly WB-RT, with a smaller cohort undergoing postmastectomy radiotherapy (PMRT). In the first study of 1000 patients, investigators reported that there was a significant difference in the rate of skin toxicity by race; however, it was in patients defined as "Other" with no further classification where the largest percentage of ≥grade 3 events ONSSTS were observed.[15] Furthermore, race was not included in MVA. In the second study, investigators reported that a greater portion of AA patients developed ≥grade 4 early RD ONSSTS.[16] Race was not a significant predictor of RD on MVA. There was 1 prospective study that assessed RD in a cohort of entirely PMRT patients.[17] Using the ONSSTS, there was significantly more moist desquamation at RT completion in patients who self-identified as Black compared to non-Black patients, an association that was maintained on MVA.

5 retrospective studies evaluated RD with respect to race/ethnicity (Table 1). In a cosmetic analysis conducted among 20 AA patients and 20 White patients matched by age, follow-up, adjuvant therapy and breast size, investigators reported a lower rate of "good" to "excellent" cosmesis in AA patients compared to White patients using the Harvard criteria for cosmesis (Supplemental table 4) [18]. Furthermore, the rate of grade 2 and 3 pigmentation change was higher in AA patients compared to White patients. In another study of 265 women, MVA revealed that Black race was a significant predictor of pigmentation change and telangiectasia after RT. AA patients were also less likely than White patients to report "excellent" cosmetic results [19]. Another study of 458 patients similarly reported

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Table 1 Studies Evaluating Radiation Dermatitis According to Race and Ethnicity

Author, Country, Year	Study Design	Patient Population	Objective	Race/Ethnicity	Radiation Technique	Measure of RD	Main Findings	Q
Rodriguez-Gil et al, USA, 2014 [13]	Single institution cohort	159 patients with breast cancer who underwent BCS	Evaluate high-sensitivity CRP	• AA: 29 (18.2%) • HW: 96 (60.4%) • NHW: 29 (18.2%) • Other: 5 (3.1%)	Conventional WB-RT (45-50Gy in 1.8-2.0Gy per fraction)	NCI CTCAE: acute dermatitis week 3 and at week 6	• At week 6, more AA patients developed grade 3 RD vs. HW and NHW: 4 (13.8%) vs. 2 (2.1%) vs. 1 (3.4%), respectively ($P = .017$)	2
Wright et al, USA, 2016 [14]	Single institution cohort	392 patients with breast cancer who underwent BCS	Determine if race impacts RD in a diverse cohort of patients	• AA: 79 (20.0%) • HW: 241 (62.0%) • NHW: 59 (15%)	CF-RT (83.0%) or HF-RT (17.0%) with or without RNI	ONSSTS: week 3 and at RT completion	• More AA patients developed grade 2-3 RD vs. non-AA: 46 (58%) vs. 158 (50%), respectively ($P = .218$) • BMI, disease stage, and CF-RT significantly predicted RD, whereas race and ethnicity did not	2
Hu et al, USA, 2018 [15]	Single institution cohort	1000 patients with breast cancer who underwent BCS (90.0%) or mastectomy (10.0%)	Evaluate high-sensitivity CRP in RD	• AA: 280 (28.0%) • White: 623 (62.3%) • API: 64 (6.4%) • Other: 33 1000 (3.3%)	CF-RT (86.0%) or HF-RT (14.0%) with or without RNI	ONSSTS: at RT completion	• Race was significantly associated with grade 3+ RD ($P = .006$) • High-sensitivity CRP levels differed significantly by race and BMI but not by ethnicity • Age, menopausal status and BMI also significantly associated with grade 3+ RD	2
Lee et al, USA, 2019 [16]	Single institution cohort	416 patients with breast cancer who underwent BCS (77.2%) or mastectomy (22.8%)	Evaluate whether genetic variation in DNA damage repair genes influence RD	• AA: 86 (20.7%) • HW: 264 (63.5%) • NHW: 55 (13.2%) • Other: 11 (2.6%)	CF-RT (87.5%), or HF-RT (11.5%) with or without RNI or partial breast irradiation (1.0%)	ONSSTS: at midpoint and RT completion	• More AA patients developed RD vs. HW or NHW: 32 (37.2%) vs. 73 (27.7%) vs. 9 (16.4%), respectively ($P = .025$) • On MVA, race did not predict RD	2
Wright et al, USA, 2014 [17]	Single institution cohort	110 patients with breast cancer who underwent mastectomy	Determine if race impacts RD in a diverse cohort of patients	• Black: 26 (23.6%) • Nonblack: 84 (76.4%)	Conventional PMRT with 40-50Gy in 25 fractions with RNI (95.5%)	ONSSTS: acute dermatitis measured at week 3 and at RT completion	• More grade 4/5 RD in Black patients at RT completion vs. non-Black: 19 (73.1%) vs. 40 (47.6%), respectively ($P = .023$) • On MVA, Black patients (OR 7.47, $P = .031$) and postmenopausal status were independent risk factors for moist desquamation	2
Tuamokumo and Hafty, USA, 2003 [18]	Retrospective review	1614 women who underwent BCS	Evaluate the prognostic significance of race	• AA: 20 (50%) • White: 20 (50%) • *Subset case-control on 40 patients	Median whole breast dose 46Gy, RNI permitted, Tumor bed boost to 64Gy routine	Score 0-3 on the basis of skin pigmentation, edema and fibrosis (0=no difference, 1=mild, 2=moderate, 3=severe); Harvard criteria for cosmesis	• Cosmesis was good to excellent in 11 (55%) AA patients vs. 18 (90%) white patients ($P = .04$) • More grade 2 pigmentation change in AA patients vs. White: 14 (70%) vs. 3 (15%), respectively, ($P = .001$) • More grade 3 pigmentation change in AA patients vs. White: 2 (10%) vs. 0 (0%), respectively ($P = .001$)	3

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Table 1 (*continued*)

Author, Country, Year	Study Design	Patient Population	Objective	Race/Ethnicity	Radiation Technique	Measure of RD	Main Findings	Q
Deutsch and Flickinger, USA, 2003 [19]	Retrospective review	265 women who underwent BCS	Evaluate the cosmetic outcomes 6 months after BCS	• AA: 28 (11%) • White: 236 (89%)	Whole breast dose 50Gy in 25 fractions, 82% underwent tumor bed boost, 3% underwent RNI	Harvard criteria for cosmesis	• Cosmesis was excellent in 7 (25%) AA patients vs. 121 (51.3%) White patients ($P = .0056$) • Good to excellent cosmesis vs. fair or poor was associated with White race ($P = .0056$), smaller separation between tangential fields ($P = .01$), use of boost (p=0.0025), and no use of tamoxifen ($P = .025$)	3
Taylor et al, USA, 1995 [20]	Retrospective review	458 women who underwent BCS	Evaluate the cosmetic outcomes after BCS	• AA: 50 (11%) • White: 406 (89%)	45Gy-50.4Gy in 1.8-2Gy fractions, 32% underwent RNI	Harvard criteria for cosmesis	• Independent factors for excellent cosmetic outcome were race ($P = .002$), volume of tissue resected ($P = .001$), type of surgery ($P = .0001$), breast radiation dose ($P = .005$)	3
Vicini et al, USA, 2010 [21]	Retrospective review	662 women who underwent BCS	Analyze clinical and pathologic outcome parameters between AA and White patients	• AA: 39 (6%) • White: 660 (94%)	Median whole breast dose 45Gy, 95% underwent boost, 14% underwent RNI	RTOG toxicity grades; Harvard criteria for cosmesis	• Less excellent cosmesis ($P = 0.008$), more breast pain ($P = 0.001$) and arm edema ($P = .046$) in AA women vs. White women	3
Dzul et al, USA, 2022 [22]	Retrospective review	272 AA patients who underwent BCS	Analyze RD in AA patients	• AA: 272 (100%)	40% underwent HF-RT and 98% of those received 42.56Gy in 16 fractions; 47% underwent CF-RT (50Gy in 25 fractions)	NCI CTCAE	• BMI >40 ($P < .001$), RNI ($P = .03$) and increased breast size ($P < .001$) predicted ≥grade 2 RD • HF-RT vs. CF-RT predicted less ≥grade 2 RD ($P = .0003$) • On MVA, breast size retained significance	3
Ryan et al, USA 2007 [23]	Cross-sectional, multi-institution	656 cancer patients, 51.5% with breast cancer	Evaluate patient reported symptoms associated with radiation therapy	• AA: 33 (5%) • White: 623 (95%)	Not reported	Nationwide Symptom Inventory (patient-rated) completed pre and post radiation therapy	• More skin problems in AA than White patients: 10/18 (56%) vs. 90/393 (23%), respectively, ($P = .001$) • More severe skin reactions in AA than White patients: 1/5 (20%) vs. 12/161 (8%), respectively, (no *P*-value)	4

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Table 1 (*continued*)

Author, Country, Year	Study Design	Patient Population	Objective	Race/Ethnicity	Radiation Technique	Measure of RD	Main Findings	Q
Friese et al, USA, 2017 [24]	Cross-sectional survey study, multi-institution	1184 patients with early-stage breast cancer	Examine the frequency and severity of toxicity associated with cancer treatment	• White: 1057 (89.4%) • Black: 321 (27.1%) • Latina: 315 (26.6%) • Asian: 141 (11.9%) • Other/unknown/missing: 50 (4.2%)	75.2% underwent RT (no further data on dose/fractionation)	CTCAE (patient-rated severe toxicity at their worst during cancer treatment) completed on average 7 months after diagnosis	• Hispanic ethnicity associated with higher toxicity vs. White: odds ratio 1.3 (95% CI 1.1-1.5)	4
Hill-Kayser et al, USA, 2011 [25]	Cross-sectional, single-institution	354 breast cancer survivors	Evaluate cosmetic outcomes and complications associated with breast-conserving treatment	• Caucasian: 317 (90%) • AA: 9 (3.0%) • API: 11 (3.0%) • Hispanic/Latino: 5 (1.0%) • Mixed race: 5 (1.0%) • Other: 7 (2.0%)	63.0% underwent WB-RT and 35.0% underwent PMRT	Harvard criteria for cosmesis (patient-rated)	• No difference in excellent or good cosmetic outcomes reported in white vs. non-White patients	4
Schnur et al, USA, 2011 [26]	Cross-sectional, qualitative analysis, single institution	20 patients with stage 0-III breast cancer receiving radiotherapy	Use qualitative approach to better understand the impact of skin toxicity on quality of life	• NHW: 11 (55%) • HW: 4 (20%) • Non-Hispanic Black: 3 (15%) • Hispanic Black: 2 (10%)	100% underwent RT (no further data on dose/fractionation)	Thematic analysis of semi-structured interviews	• Generally, AA women, younger women, women not currently in a relationship, women treated during summer months and those more invested in their appearance are more distressed by skin toxicity	4
Lapen et al, USA, 2022 [27]	Cross-sectional, multi-institution	376 patients undergoing radiation therapy for primary breast cancer	Assess whether patient characteristics are associated with differences in patient-clinician symptoms assessments	• White: 239 (64%) • Asian/Indian: 40 (11%) • Black or AA: 40 (11%) • Hispanic/ Latino: 30 (8%) • Other: 11 (3%)	14% underwent PBI, 58% underwent WB-RT, and 28% underwent PMRT/WB-RT with RNI	Patient reported outcome-CTCAE and physician-graded CTCAE	• Patients who identified as Black or AA were associated with a 0.13 point decrease in discordance (95% CI -0.25 to 0.01) in matched patient-clinician assessments	4

AA= African American; API=Asian Pacific Islander; BCS=breast conserving surgery; BMI=body mass index; CF-RT=conventionally fractionated RT; CRP= C-Reactive Protein; CTCAE= Common Terminology Criteria for Adverse Events; DNA= deoxyribonucleic acid; HF-RT=hypofractionated RT; HW= Hispanic White; MVA=multivariable analysis; NHW= Non-Hispanic White; NCI= National Cancer Institute; ONSSTS=Oncology Nursing Society skin toxicity scale; PMRT=post mastectomy radiation therapy; Q= Quality; RD= Radiation Dermatitis; RNI=regional nodal irradiation; RT=radiation therapy; RTOG= radiation therapy oncology group; USA= United States of America; WB-RT=whole breast radiation therapy

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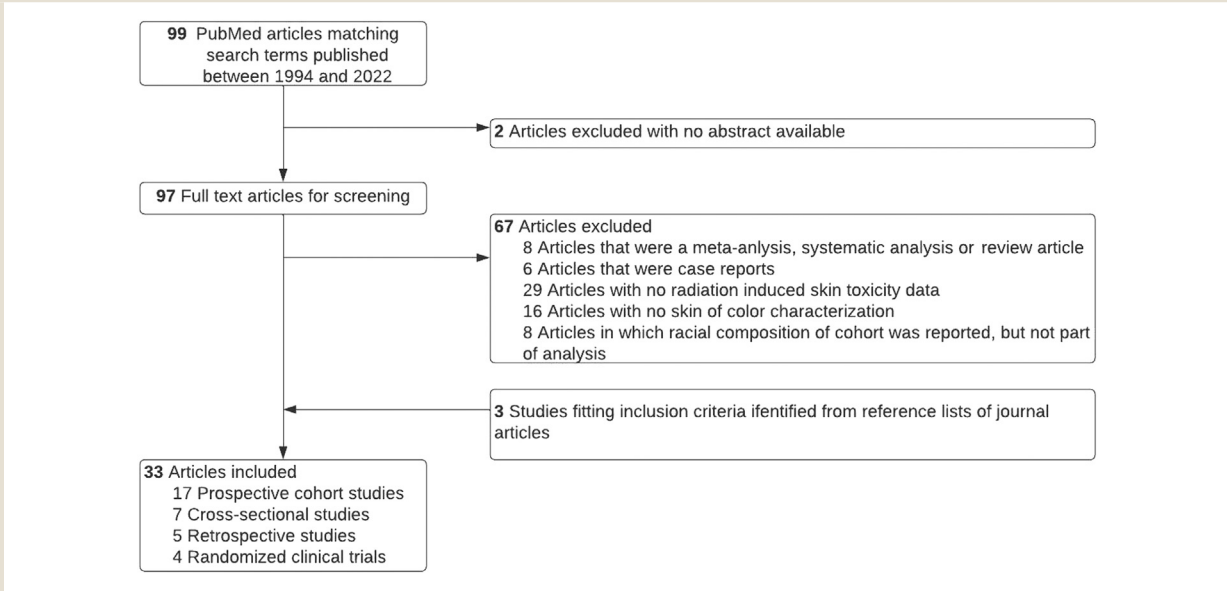
Figure 1 PRISMA Flow Diagram of Systematic Review Selection Criteria.



better cosmetic outcomes among White versus AA patients, with race significantly predicting worse cosmesis on MVA.[20] In an analysis of 662 women with breast cancer who received adjuvant WB-RT, AA patients were more likely to experience more breast pain, arm edema, and worse cosmetic results compared to White patients. Time point of RD assessment was not reported, nor were the crude rates of RD, MVA for treatment related toxicities, or cosmesis.[21] A study of 100% AA patients found only larger breast size to be a significant predictor of ≥grade 2 RD on the CTCAE scale among other clinical and treatment variables.[22]

There were 5 cross-sectional studies in which patient-reported outcomes (PRO) related to RD and cosmesis were assessed (Table 1).[23-25] In 1 study AA patients reported more severe skin problems than white patients after cancer-directed treatment (RT and/or chemotherapy),[23] but there was no further detail on the types of cutaneous issues experienced after RT. Another study reported that Hispanic ethnicity was associated with higher odds of treatment toxicity.[24] A qualitative analysis revealed that AA patients generally reported more distress from skin toxicity after RT.[26] Conversely, there was no difference in the rate of "good" to "excellent" cosmetic outcomes reported in White versus non-White patients undergoing breast or chest wall RT in a third study.[24] Finally, another cross-sectional study showed that AA patients tend to have slightly decreased discordance between patient and clinician-reported acute toxic effect outcomes, indicating that AA patients are more likely to show agreement with clinician-reports of acute toxicity, though the effect size was small.[27]

B. Studies with skin color characterization by patient

There were 2 cross-sectional survey studies in which patient-reported measures of skin color changes after breast radiotherapy were described, but there was no data on the racial composition of the cohort (Table 2).[28,29] In 1 study of 421 breast cancer survivors, 53% of patients described mild skin color darkening (described as pigment deposition) and 27% reported severe color change after RT.[28] In 21% of patients, skin problems were associated with depression or sadness. In another study of 247 breast cancer survivors, questionnaires using measures of breast cosmesis from the late effects normal tissue-subjective, objective, management, analytic (LENT-SOMA) scale (Supplemental table 5) were administered, [29] and 19% of patients reported skin color change as a late effect, but there were no significant clinical or treatment predictors of change over grade 1.

C. Studies with skin color characterization by physician

There were 4 randomized trials [30-33] where skin color was characterized before and/or after breast RT by investigators (Table 3). In a study from Iran evaluating the efficacy of a topical gel using *Nigella sativa* L. extract on preventing RD, investigators reported the Fitzpatrick scores (FS) of the patient population, invoking a skin phototype system that classifies skin by its propensity to burn. In this system, the lightest and most sun-sensitive phototype is FS I, while the darkest and least sensitive is FS VI.[34] Using the CTCAE scale, a decrease in RD severity was reported with use of the study intervention, but FS was not a variable in the analysis and was not correlated with RD severity.

The next 3 studies used objective colorimetric evaluation to characterize skin color changes according to the International Commission on Illumination classification after a study intervention. A study from Sweden and evaluated the effect of prophylactic topical steroid use during RT.[33] Erythema and pigmentation change were measured using a colorimeter at baseline and after the study intervention. There was no difference found in these parameters over the 6 year follow-up period between the patients using

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Table 2 Studies with Skin Color Characterization by Patient

Author, Country, Year	Study Design	Patient Population	Objective	Race/ethnicity or Fitzpatrick Skin Type	Radiation Technique	Measure of RD	Main Findings	Q
Chu et al, Taiwan, 2021 [28]	Cross-sectional	421 breast cancer survivors	Evaluate skin sequelae after RT	Not reported	Not reported	Patient questionnaire with 3-point scale on presence of pigment deposition among other RT-induced skin sequelae, psychological impact and QoL after RT	• 336 (79.81%) patients reported severe or mild skin color deposition (26.60% severe and 53.21% mild) • 89 (21.14%) patients reported sadness or depression due to skin problem	4
Ishiyama et al, Japan, 2006 [29]	Cross-sectional	247 early stage breast cancer survivors who were free of recurrence after BCT	Evaluate symptoms of late complications caused by RT	Not reported	CF-RT in most cases (median dose 50Gy, mean 50Gy, range: 45-54Gy)	Patient questionnaires based on the LENT/SOMA scale to quantify area of skin-color change on operated breast	• 19% of patients reported skin color change as a late effect • On MVA, shrinking in breast size >grade 1 was associated with age ($P = .020$), pain >grade 1 was associated with additional boost irradiation ($P = .015$), and firmness >grade 1 was associated with time after surgery ($P = .004$) • There were no significant clinical/ treatment predictors of patient reported skin color change >grade 1 (>1cm^2 of change)	4

Abbreviations: BCT = breast conserving therapy; LENT-SOMA= late effects of normal tissue- subjective, objective, management and analytic; MVA = multivariate analysis; QoL= quality of life; RT= radiation therapy.

potent corticosteroid cream versus a moisturizer; however, there was no specific data on the changes in these skin parameters during and immediately after RT. There was a randomized trial from France evaluating the efficacy of type of hydrogel dressing versus placebo on the topical treatment of grade 1 and 2 RD among patients with early stage breast cancer who underwent CF-RT. Colorimetric decrease of erythema was observed in both arms, however, no colorimetric differences were observed between the 2 arms on day 28.[32] The final study from Germany evaluated the difference between 2 different fractionation regimens using a reflectance spectrophotometer to evaluate RD severity.[33] Using CTCAE scale, investigators demonstrated significantly lower RD in patients following larger doses of radiation per fraction (hypofractionated-radiation therapy [HF-RT]) compared to conventionally fractionated radiation (CF-RT). There was significantly less severe objectively measured hyperpigmentation and erythema in the HF-RT arm than the CF-RT arm.

None of these randomized trials reported how baseline pigmentation affected the incidence and severity of RD.

There were 12 prospective non-randomized studies in which objective skin color changes were used to describe the incidence of RD after BCS [35-37] and neoadjuvant systemic therapy,[38] compare RD using different RT fractionations following BCS,[39,40] compare RD after BCS versus mastectomy, evaluate the use of clinical interventions for RD,[41] and establish the feasibility and accuracy for using objective and novel methods of measuring RD (Table 3).[42-45]

Most studies utilized colorimetry as the objective measure of erythema and pigmentation. These studies confirm that skin color changes with RT [36,38,41,42] and objective reddening depends on the dose received by the skin.[44] Two studies reported maximal changes 1 to 3 months post treatment completion.[35,46] In one study from Japan of 72 patients, milder objective changes in skin darkening and reddening were reported after HF-RT versus CF-RT, while the CTCAE scale for RD showed no difference between groups.[39] In another study, melanin content was measured using spectral analysis of skin with a spectrophotometer.[46] Investigators reported melanin content to be significantly higher up to 5 months post RT compared to baseline in patients who underwent CF-RT.

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Table 3 Studies with Skin Color Characterization by Physician

Author, Country, Year	Study Design	Patient Population	Objective	Race/ethnicity or Fitzpatrick Skin Type	Radiation Technique	Measure of RD	Main Findings	Q
Rafati et al, Iran, 2019 [30]	Randomized controlled trial, single-institution	62 breast cancer patients who underwent BCS (88.7%) or mastectomy (11.3%)	Evaluate the efficacy of *Nigella sativa* L. (*N. sativa*) extract on preventing RD	• FS II: 9 (14.5%) • FS III: 27 (43.5%) • FS IV: 26 (41.9%)	82.3% CF-RT and 17.7% HF-RT	CTCAE acute dermatitis evaluated every fifth RT session	• Decrease in RD severity with *N. sativa* gel vs. placebo ($P < .05$) • Moist desquamation was delayed in the *N. sativa* gel group vs. placebo (37 vs. 33 days, $P = .01$)	1
Ulff et al, Sweden, 2017 [31]	Randomized controlled trial, single-institution	60 breast cancer patients who underwent BCS (68.3%) or mastectomy (31.7%)	Evaluate the efficacy of a local potent corticosteroid during RT	• Not reported	100% underwent CF-RT	Colorimeter (DSM II ColorMeter, Cortex Technology, Hadsund, Demark)	• There were no significant differences in skin dryness, color, pigmentation or skin thickness at 6 year follow up	1
Bazire et al, France, 2015 [32]	Randomized control trial	278 breast cancer patients who underwent breast or chest wall radiotherapy	Compare the efficacy of Hydrosorb hydrogel vs. control (water based spray) in the topical treatment of grade 1 and 2 radiation dermatitis	• Not reported	100% underwent CF-RT	Colorimeter (Minolta Chroma Meter CR-400 Minolta Camera Co., Osaka, Japan)	• There was no colorimetric difference between the 2 arms on day 28 ($P = .21$) • 8 patients in the Hydrosorb arm vs. 11 patients in the placebo arm presented colorimetric regression of erythema ($P = .018$)	1
Schmeel et al, Germany, 2020 [33]	Randomized controlled trial, multi-institution	140 breast cancer patients who underwent BCS	Determine the frequency and severity of RD during HF-RT vs. CF-RT	• Caucasian: 140 (100%)	50% underwent HF-RT and 50% underwent CF-RT	Reflectance spectrophotometer (CR-10 Plus, Konica Minolta, Marunouchi, Japan) prior to first treatment, day after completion and during first follow up readings	• Spectrophotometric measurements demonstrated less erythema severity ($P = .008$) and hyperpigmentation ($P = .002$) with HF-RT vs. CF-RT	1
Yoshida et al, Japan, 2010 [35]	Prospective cohort	100 breast cancer patients	Evaluate RD after BCS	• Not reported	100% underwent CF-RT (48.4-50.0Gy); 15% underwent 9.8-10Gy boost to the tumor bed	Colorimeter (CR-13 Konica-Minolta Holdings, Inc., Tokyo, Japan) prior to RT, at completion, 1, 6 and 12 months after RT	• Objective color changes maximized at completion or 1 month post RT • 1 year post RT, skin color had returned to previous values • The lateral upper side of the breast showed the greatest changes in darkening after completion of RT	2
Yamazaki et al, Japan, 2012 [36]	Prospective cohort	87 breast cancer patients who underwent BCS	Evaluate RD after BCS	• Not reported	100% underwent CF-RT; 11.5% underwent 10Gy boost to tumor bed	Colorimeter (CR-13, Konica-Minolta Holdings, Inc., Tokyo, Japan) prior to RT, at completion and 1 month after	• RT caused changes in objective reddening and darkening ($P < .0001$) • Maximal darkening at completion of RT and 1 month post RT • Body weight and BMI correlated significantly with reddening ($P = .0012$ and 0.0017)	2

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Table 3 (*continued*)

Author, Country, Year	Study Design	Patient Population	Objective	Race/ethnicity or Fitzpatrick Skin Type	Radiation Technique	Measure of RD	Main Findings	Q
Park et al, Korea, 2022 [37]	Prospective cohort	20 breast cancer patients who underwent BCS	Objectively assess RD severity after WB-RT	• Not reported	100% underwent HF-RT with no boost	Mobile skin analysis device (API-100; Aram Huvis, Gyeonggi-do, Korey	• Red values (red-green-blue color space) for irradiated breasts increased significantly	2
Yamazaki et al, Japan, 2009 [38]	Prospective cohort	40 breast cancer patients who underwent BCS and NST and 59 patients without NST	Evaluate RD and explore the influence of NST	• Not reported	100% underwent CF-RT (48.4-50.0Gy in 1.8Gy-2Gy fractions); 27% underwent 10Gy boost to tumor bed	Colorimeter (CR-13, Konica-Minolta Holdings, Inc., Tokyo, Japan) prior to RT, at completion, 1, 6 and 12 months after RT	• Significant alterations in objective color readings when RT was added, specifically boost RT	2
Yamazaki et al, Japan, 2018 [39]	Prospective cohort	72 breast cancer patients who underwent BCS	Compare RD between HF-RT and CF-RT	• Not reported	36% underwent HF-RT and 64% underwent CF-RT	Colorimeter (CR-13, Konica-Minolta Holdings, Inc., Tokyo, Japan) prior to RT, at completion and 1 month after	• RT increased darkening and reddening gradually ($P < .0001$) • HF-RT showed milder darkening ($P = .0002$) and reddening ($P = .0001$) than CF-RT • CTCAE showed no correlation to maximal dosage, but significant alterations were observed with objective darkening and reddening	2
Tanaka et al, Japan, 2011 [40]	Prospective cohort	66 breast cancer patients who underwent BCS	Evaluate RD after APBI and compare with CF-RT	• Not reported	33% underwent APBI using open cavity implant high-dose-rate interstitial brachytherapy (36Gy in 6 fractions) and 67% underwent CF-RT	Colorimeter (CR-13, Konica-Minolta Holdings, Inc., Tokyo, Japan) prior to RT, at completion, 1, 6 and 12 months after RT	• The extent of reddening and darkening of skin were similar to those of CF-RT, although there was a slight delay in recovery due to surgical procedure with APBI	2
Partl et al, Austria, 2019 [41]	Prospective cohort	100 breast cancer patients	Compare 2 different topical products to treat RD	• FS II: 32% • FS III: 60% • FS IV: 8% *(100% Caucasian/ European descent)	100% underwent CF-RT (50.0Gy-50.4Gy) in 25-28 fractions	Digital single-lens reflex camera (Canon EOS 500D) after completion of radiotherapy	• More reddening/erythema (increase in a* values) in patients treated with a Lactokine-fluid derived from milk proteins vs. Bepanthen (mean 4.15; 95% CI: 5.97–2.33, $P < .001$)	2
Russell et al, The Netherlands, 1994 [42]	Prospective cohort	39 breast cancer patients who underwent mastectomy	Develop an accurate method for quantifying erythema	• Not reported	100% underwent HF-RT (40Gy in 16 fractions of 2.5Gy per fraction)	Colorimeter (CR-200, Minolta Camera Co., Osaka, Japan) at the start and once weekly during RT	• Validation of reflectance spectroscopy using the Minolta Chroma Meter and the L*a*b* color definition system to quantify skin redness • There was true interpatient variation in erythema in response to RT	2

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Table 3 (*continued*)

Author, Country, Year	Study Design	Patient Population	Objective	Race/ethnicity or Fitzpatrick Skin Type	Radiation Technique	Measure of RD	Main Findings	Q
Bohner et al, Germany, 2020 [43]	Prospective cohort	142 breast cancer patients who underwent BCS	Identify risk factors for RD using objective spectrophotometry	• Caucasian: 142 (100%)	50.0% underwent CF-RT and 50.0% underwent HF-RT	Reflectance spectrophotometer (CR-10 Plus, Konica Minolta, Marunouchi, Japan)	• CTCAE correlates with objective spectrophotometer	2
Momm et al, Germany, 2005 [44]	Prospective cohort	41 breast cancer patients who underwent BCS	Determine whether CTCAE correlates with spectrophotometric measurements of skin color	• Caucasian: 41 (100%)	100% underwent CF RT	Spectrophotometer (CM508i, Minolta, Ahrensburg, Germany) at baseline, at RT start, and at 20, 40 and 60Gy	• Skin redness depended on the radiation dose received by the skin • Spectrophotometric method correlated with subjective CTCAE	2
Nystrom et al, Sweden, 2007 [45]	Prospective cohort	50 breast cancer patients who underwent mastectomy	Test objective methods of measuring RD	• Not reported	100% underwent CF-RT with skin bolus to reach maximum dose in the skin	Spectrometer (Bruker FT-NIR, Matrix F) with a fiber-optic probe; Digital camera to produce average color values; Laser Doppler imaging to measure perfusion	• Erythema can be monitored with digital color photography, near infrared spectroscopy, and laser Doppler imaging	2
Yoo et al, Korea, 2021 [46]	Prospective cohort	40 breast cancer patients who underwent BCS (50%) or mastectomy (50%)	Compare RD in patients who underwent BCS or mastectomy	• Not reported	100% underwent CF-RT; 40% underwent RNI	Spectrometer (Mexameter MX 18) before RT, after the 5th, 15th, 25th RT, 1 month and 3 months after RT	• Erythema increased in the first 3 months after RT • Melanin levels were significantly higher than baseline until 5 months post RT (106.0 vs. 115.8, $P = .03$) • Erythema significantly higher after 1 month post RT in the PMRT group vs. WB-RT ($P = .04$)	2

Abbreviations: APBI= accelerated partial breast irradiation; BCS=breast conserving surgery; CF-RT=conventionally fractionated RT; CTCAE= Common Terminology Criteria for Adverse Events; FS=Fitzpatrick Skin Type; HF-RT=hypofractionated RT; NST=neoadjuvant systemic therapy; Q= Quality; RD= Radiation Dermatitis; RNI=regional nodal irradiation; RT=radiation therapy; RTOG= radiation therapy oncology group; WB-RT=whole breast radiation therapy.

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Crucially, in all of these studies, baseline pigmentation and/or race was not evaluated.

DISCUSSION

In summary, this systemic review using Medline electronic databases via Pubmed identified 15 studies that evaluated physician-rated RD according to race/ethnicity. Most of these studies demonstrated increased rates of RD in AA patients after RT. There is limited data available in patients representing other non-White racial subgroups with SOC, though there is evidence for worse treatment toxicity in patients of Hispanic ethnicity.[24] Multivariable analyses revealed race/ethnicity to be independent predictors for worse RD in populations with SOC in some but not all reports; data also suggests that AA patients are more likely to have known risk factors for worse skin toxicity, including higher BMI, disease stage and breast volume.[14,22] In several of the studies reviewed, these variables were found to be predictors of worse RD independent from race.

This systematic review has some limitations. One database (PubMed) was used as a source of the entire review of literature. Additionally, studies using race/ethnicity as a variable in the analysis of RD were limited by the potential for subjectivity in the measurement of RD. The lack of systematic measurements of RD across these studies limit the generalizability of the findings. Clinical manifestations of RD using physician-graded scales to measure erythema may not be as obvious in pigmented skin. For example, erythema may be harder to detect in darker skin due to melanin content, which may mask changes in skin perfusion until damage is more severe. Furthermore, studies that incorporated patient reported measures of skin toxicity provided limited to no further detail on the types of the cutaneous issues experienced after RT by racial or ethnic groups.

Another limitation is that these studies failed to report baseline skin pigmentation as a variable when analyzing predictors of RD severity, instead using the imperfect proxy variables of race and ethnicity. There is diverse representation in skin types across race and ethnicity and utilization of these surrogate terms may not accurately capture subgroups or multiracial populations. These studies cannot assess skin color changes that may follow RD, which although not formally included in RD grading, may have significant impact on patient quality of life and self-image. There were 2 studies that demonstrated post-RT skin darkening as a common late effect. It has been noted that in darker-skinned patients, postinflammatory hyperpigmentation occurs with greater intensity and frequency after light exposure as a result of the increased reactivity of melanocytes.[7] Furthermore, dyschromia is one of the top 5 diagnoses for patients of color in dermatology clinics based on nationally representative data.[47] Taken together, one may hypothesize that RD has further increased and insufficiently-quantified morbidity in patients with darker skin tones due to worse pigmentary alteration.

The degree towards which baseline darker skin tone serves as a risk factor for RD independent of race remains unknown, partially because the task of classifying skin pigmentation in a research setting is challenging. In dermatology, the most widely used classification system to represent skin tone is the Fitzpatrick scale, which assigns a phototype (I-VI) based on constitutive skin color and the propensity of skin to burn and/or tan.[34] Other systems classify skin color based on healing efficacy after cosmetics procedures,[48] variations in pigmentation, [48] and predicted response to insult, injury, and inflammation.[49] However, limitations for these methods include the potential for bias in conflating race and ethnicity with Fitzpatrick skin type. An objective, operator-independent system for measuring RD and baseline skin pigmentation is necessary in order to evaluate radiation skin toxicity in SOC.

There have been efforts to develop more objective metrics for assessing skin pigmentation changes after RT, though none have yet been widely adopted. The structured literature search revealed 15 prospective studies that evaluated objective measures of skin color changes during and after radiotherapy. Most of the studies using objective measures of skin color changes incorporated colorimetric methods, which demonstrate skin color changes based on the spectral properties of skin as light is delivered to the skin and reflectance is analyzed. Skin color changes in these studies were reported using l*a*b* color system, a 3 dimensional coordinate system where the l* coordinate represents perceptual light/darkness (0=black to 100=white), a* represents the color on a scale ranging from red to green, and b* represents the blue-yellow color scale. Spectrophotometers measure reflectance and transmittance for the entire electromagnetic spectrum (while colorimeters operate in only in the visible region). These instruments can estimate hemoglobin and melanin based on their known spectral properties. Skin reflectance is analyzed in the context of known absorption ranges of these skin chromophores.[46,50] Spectrophotometric methods quantify changes in pigmentation and erythema based on measured change in saturation and hue of the skin, respectively. This can potentially serve as an indicator of RD and was noted to correlate with physician-assessed RD in several of the studies reviewed.[43,44] These studies still contain limitations. All failed to evaluate the impact of race and/or baseline pigmentation on RD, as these were not included as variables in any analyses. A further limitation is that these studies were conducted in largely Caucasian populations and there was no data on the spectrum or distribution of SOC in study cohorts. At present, the impact of radiotherapy on pigmentation changes in darker skin tones is understudied.

To further evaluate the effect of skin pigmentation on the incidence and severity of RD, it becomes necessary to: (a) develop a reliable system to characterize baseline skin pigmentation that is independent of race, and (b) correlate baseline skin pigmentation with valuable metrics of RD that are relevant to SOC. Spectrophotometric analysis is primed to objectively quantify baseline skin tone and correlate skin color change with objectively measured color parameters that may indicate RD. The use of spectrophotometry offers tremendous potential to standardize a system that can characterize baseline skin pigmentation agnostic of race/ethnicity and also correlate baseline skin pigmentation and its RT-induced changes with objective metrics of RD applicable to SOC, especially in situations where subjective scales fall short. While spectrophotometers have historically not been widely adopted in the clinic due to their high cost and cumbersome use, newer commercially available compact models with Bluetooth pairing capability to modern smartphones offer rejuvenated potential to generate big data from

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small portable devices. Modern spectrophotometers can transform rapid color data into digital biomarkers, potentially identify earlier time points for changes in objective skin parameters that precede clinically visible skin changes and facilitate personalized clinical decision making in the management of RD. At New York University Grossman School of Medicine, a single-arm prospective clinical trial using the Nix Spectro 2 spectrophotometer (Nix Sensor, Ltd.) is currently investigating the changes from baseline in l*a*b* skin color readouts during and after radiotherapy in patients with breast cancer undergoing ultra-hypofractionated, hyopfractionated and conventionally fractionated radiotherapy, and further evaluating these changes within and across groups defined by baseline skin color. In this trial, baseline skin color is defined according to the individual typology angle,[51] an objective classification of constitutive skin color based on spectrophotometric measurements used in dermatological and cosmetic research that has been found to correlate with Melanin index in skin of color.[52] The expected accrual is 60 patients with enrollment currently at 60% of this goal.

With regards to establishing valid metrics of RD that are relevant to skin of color, many different physician scoring systems are in circulation, including the CTCAE, which was most commonly utilized in the studies reviewed. None have been formally validated in SOC. The recently developed Michigan scale for acute RD in breast cancer offers a valuable metric of RD that incorporates both erythema and hyperpigmentation as equivalent forms of toxicity in addition to desquamation. Both hyperpigmentation and erythema are graded on a scale of 0 to 3: mild, moderate and severe. In a rigorous validation study of 80 patients with 56.3% of Black race, overall high diagnostic accuracy and correlation with patient-reported symptoms of bother and pain was demonstrated using the scale for desquamation.[2] Higher rates of erythema and hyperpigmentation were reported with the scale based on photographic review in patients who were rated as having no RD using the CTCAE scale. Interestingly, reliability for grading erythema or hyperpigmentation between and within observers using the Michigan scale was generally lower than for dry or moist desquamation. The diagnostic accuracy was not calculated for these components due to a high rate of missing patient and physician reports. Investigators obtained colorimetric data in patients of color and reported correlation of colorimeter readings on the black-white scale with hyperpigmentation grade. However, baseline skin pigmentation was not reported and the definition of patients of color, though not specified in the manuscript was presumably based on race. We recommend further validation of the Michigan scale in skin of color using objective spectrophotometric readings to define baseline skin tone and evaluating the variation in the correlation between spectrophotometric readings and this scale according to baseline skin tone.

Inclusion of patient-rated outcomes (PROs) in research on skin toxicity is an additional crucial step to obtain valuable metrics of RD relevant to SOC. This structured literature revealed 2 cross-sectional studies in which patients reported skin color change as a late effect of RT: the first using a targeted 3-point questionnaire designed by investigators to assess skin condition, quality of life (QoL) and psychological impact of breast RT, and the second using a more common approach of adapting a preexisting physician scale for RD, such as the LENT SOMA[29], or in other cases the CTCAE[24,53] or Harvard scale[25,54] into a patient questionnaire. In an active phase III ALLIANCE study (NCT04989504) evaluating the use of Mepitel Film in reducing radiation dermatitis in patients undergoing PMRT, the patient-completed modified Radiation Induced Skin Reaction Assessment Scale (mRISRAS)[55] is the primary outcome measure. This 12 point scale specifically evaluates clinical manifestations of RD beyond skin reddening that are relevant to patients with SOC, including the presence of tenderness/pain, itchiness, burning sensation and the impact of skin reactions on day to day activities. Combinations of questionnaires including the Skindex questionnaire[56] and the Skin Toxicity Assessment Tool (STAT)[57] have been specifically developed to measure the emotional and functional impact of RD on QoL, but unlike the mRISRAS, these scales do not evaluate pain and skin symptoms concurrently. Recent data has demonstrated tremendous potential in the incorporation of electronic platforms for PROs, specifically using the PRO-CTCAE.[27] With the use of shorter courses of radiation in early stage breast cancer[58] patients are increasingly experiencing RD after radiation completion when they are not typically assessed in the clinic.[59] This has potential to amplify the disparities and underreporting of RD in patients with SOC due to scheduling and travel costs associated with additional in-person appointments. Electronic platforms enable remote symptom monitoring with high posttreatment response rates and early identification for acute symptoms.[60] Further validation is needed in patients representing racial/ ethnic groups with SOC, as well as incorporating electronic PROs that capture alterations in pigmentation in order for this to translate to a change in clinical care. Lastly, incorporating endpoints into research such as use of clinical interventions, and the type of intervention (oral versus topical) for treating RD may provide granular measurable surrogates for severe RD and more importantly, may reveal patterns and biases in the way skin toxicity is managed in SOC versus non-SOC patients.

SOC in the United States is rising as demographic composition of this country evolves and multi-racial populations grow. One way to improve health equity is to promote the inclusion of patients with SOC in clinical research, and ensuring that treatments as well as toxicities are accurately, routinely and objectively captured for all patients in a continuous format, especially as patients are undergoing shorter courses of radiation. Wider use of objective measures of skin color changes before, during and after radiotherapy will allow development of useful metrics and replicable research data, and may identify areas of improvement in the care of patients with SOC who undergo breast and chest wall radiotherapy.

CONCLUSIONS

Radiation dermatitis is a common adverse event in patients with breast cancer during and after breast and chest wall radiotherapy, with potential to negatively impact quality of life. Existing data indicates worse radiation dermatitis in African American patients, though data is limited by the lack of standardized objective methods to classify baseline skin tone and the lack of studies correlating baseline skin pigmentation agnostic of race and ethnicity with radiation dermatitis. Further data incorporating objective tools to classify skin of color and correlating these changes with valuable and objec-

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tive measures of radiation dermatitis is needed to improve care for patients with skin of color.

AUTHOR CONTRIBUTIONS

JMP designed the study, the main conceptual ideas and outline. CN, PA, DG, CA, contributed to the analysis of the results and to the writing of the manuscript. IWT and NKG contributed equally to the design and implementation of the research, the analysis of the results and to the writing of the manuscript and share senior and last authorship.

DATA SHARING STATEMENT

All data generated or analyzed during this study are included in this manuscript.

Disclosure

All authors have no competing interests to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clbc.2022.10.002.

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