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Oral curcumin for radiation dermatitis: A URCC NCORP study of 686 breast cancer patients

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Abstract

Purpose—Despite advances in medical technology, radiation dermatitis occurs in 95% of patients receiving radiation therapy (RT) for cancer. Currently, there is no standard and effective treatment for the prevention or control of radiation dermatitis. The goal of the study was to determine the efficacy of oral curcumin, one of the biologically active components in turmeric, at reducing radiation dermatitis severity (RDS) at the end of RT, using the RDS scale, compared to placebo.

Methods—This was a multisite, randomized, double-blinded, placebo-controlled trial of 686 breast cancer patients. Patients took four 500 mg capsules of placebo or curcumin three times daily throughout their prescribed course of RT until one week post-RT.

Results—A total of 686 patients were included in the final analyses (87.5% white females, mean age = 58). Linear mixed model analyses demonstrated that curcumin did not reduce radiation dermatitis severity at the end of RT compared to placebo (B (95% CI) =0.044 (−0.101, 0.188), p=0.552). Fewer curcumin patients with RDS > 3.0 suggested a trend toward reduced severity

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(7.4% vs. 12.9%, p=0.082). Patient-reported changes in pain, symptoms, and quality of life were not statistically significant between arms.

Conclusions—Oral curcumin did not significantly reduce radiation dermatitis severity compared to placebo. The skin rating variation and broad eligibility criteria could not account for the undetectable therapeutic effect. An objective measure for radiation dermatitis severity and further exploration for an effective treatment for radiation dermatitis is warranted.

Keywords

radiation therapy; dermatitis; curcumin; cancer; skin

INTRODUCTION

Ionizing radiation is a widely accepted form of cancer treatment. Approximately half of all women diagnosed with breast cancer receive radiation therapy (RT) [41]. Conventional fractionation RT involves 1.8–2.0 Gy per session for 25 to 35 sessions [2]. In recent years, Canadian, or short-course, fractionation, has become more popular and involves 2.2–3.0 Gy per session for 16 to 20 sessions [7, 13]. Despite advances in medical technology, radiation-induced skin reactions remain a problem. Intensity modulated RT (IMRT) should reduce the prevalence of moist desquamation by providing a more uniform radiation dose; however it is not the standard RT for breast cancer [9].

Radiation dermatitis is one of the most common side effects experienced by patients with breast cancer, head and neck cancer, lung cancer, or sarcoma, occurring in approximately 95% of patients [5, 22, 37]. The skin reactions range in severity from mild erythema to moist desquamation. Approximately, 10% of patients experience moist desquamation and ulceration [5, 22, 37]. Radiation dermatitis severity varies by individual and is influenced by genetic factors, body area, as well as type and dose of radiation [5, 22, 37]. Important consequences of radiation dermatitis include impaired quality of life and premature RT interruption, which in turn, may impair local control of disease [20, 36]. Currently, there is no effective treatment for the prevention or control of radiation dermatitis.

Curcumin is one of the most widely studied nutraceuticals with over 10,000 publications in PubMed and over 120 clinical trials (www.clinicaltrials.gov) [17]. Curcumin is an active polyphenolic constituent of turmeric (*Curcuma longa*). [17]. Turmeric contains 2% to 6% curcumin along with 60 other compounds that have antibiotic, anti-tumor, anti-inflammatory, and antioxidant properties [35]. Curcumin and turmeric have been used to treat acne, eczema, wound healing, and wrinkled skin [16, 24, 34, 44]. Modern research supports curcumin's antioxidant, anti-inflammatory, anti-cancer, anti-microbial, anti-proliferative, and pro-apoptotic properties [14, 17, 25, 26, 28]. In 2006, Okunieff *et al* published that oral curcumin reduced acute and chronic cutaneous radiation toxicity in mice [32]. In 2013, we published a clinical trial of 30 breast cancer patients showing that 6.0 grams of oral curcumin daily during RT reduced the severity of radiation dermatitis and presence of moist desquamation compared to placebo [38]. This study was a confirmatory, multi-site, randomized, double-blinded, placebo-controlled clinical trial of 686 breast cancer patients to assess the efficacy of oral curcumin to reduce radiation dermatitis severity.

MATERIAL AND METHODS

Patients and Study Design

Eligible patients were adult females (≥18 years of age) diagnosed with non-inflammatory breast cancer or carcinoma *in situ*, able to read and understand English, and prescribed conventional or Canadian (i.e., short course) fractionated RT without concurrent chemotherapy. Eligible patients included those who had: lumpectomy or mastectomy, breast reconstruction, implants, expanders, chemotherapy prior to RT, hormone treatment, and/or Herceptin. Exclusion criteria included: previous RT to the chest or breast area, partial breast irradiations, anticoagulant therapy, epidermal growth factor receptor inhibitor (EGFRI) therapy, history of radiosensitivity disorder or collagen vascular disease, unhealed surgical wounds, and/or breast infections in the RT area.

This study was a phase 2, randomized, double-blind, placebo-controlled trial conducted in 21 private practice oncology groups via the National Community Oncology Research Program (NCORP) Research Base (a legacy NCI Community Clinical Oncology Program (CCOP) Research Base) and NCORP affiliates nationwide. The study was conducted under FDA IND 75,444 for Curcumin C3 Complex®, approved by the University of Rochester Institutional Review Board and NCI Division of Cancer Prevention Office, and registered on ClinicalTrials.gov Identifier: NCT01246973. Written informed consent was obtained from each patient. Stratification included NCORP site and RT regimen (conventional vs. Canadian). Within each site, a computer-generated random numbers table with block size of four was used to randomly assign patients to curcumin or placebo in the ratio of 1:1. The primary objective was to determine if oral curcumin reduced the severity of radiation dermatitis in breast cancer patients during RT. Secondarily, we examined effects of curcumin on moist desquamation, pain at RT site, skin-related quality of life, and severity of adverse symptoms.

Study Medication

Sabinsa Corporation (Payson, UT) manufactured the curcumin (Curcumin C3 Complex®) and placebo capsules. The curcumin product was an opaque gelatin capsule filled with yellow-colored granular powder consisting of 500mg of curcuminoids (450mg curcumin, 40mg dimethoxy curcumin, 10mg bisdemethoxy curcumin). The placebo product was the same capsule filled with yellow-colored granular powder consisting of dicalcium phosphate and a suitable food grade dye. Patients were dispensed one 84-count bottle of capsules (i.e., 7 day supply of capsules) each week throughout their course of RT. All patients took four capsules of curcumin or placebo three times daily with food (i.e., 6.0 g daily dose) throughout their prescribed course of RT plus one week post-RT. Compliance was measured by weekly pill counts prior to dispensing the new bottle of capsules.

Study Procedures and Measures

Eligibility screening and informed consent were performed prior to the start of RT. All patients started their study medication on Day 1 of RT and continued until one week Post-RT. “Standard care” for radiation dermatitis was allowed in all study arms. Patients were assessed at baseline, weekly after every fifth RT session, at the end of RT (EndRT), and one week after RT (Post-RT). Patient assessments involved a clinical skin rating, digital imaging of the skin changes, and the completion of three self-report questionnaires. The treating radiation oncologist or trained study personnel performed the clinical skin ratings using the Radiation Dermatitis Severity (RDS) scale [5, 37, 38]. The RDS scale is a 0 to 4 scale, with 0.5 increments, that evaluates radiation-induced color and texture changes in skin. The primary outcome measure was the RDS score at EndRT. Secondary outcome measures included the presence of moist desquamation at the EndRT, pain at RT site (McGill Pain Questionnaire-Short Form (SF-MPQ), skin-related quality of life (Skindex-29), and adverse symptoms (Symptom Inventory (SI)) [6, 38]. The SF-MPQ evaluated the severity and type of pain (i.e., sensory, affective, or perceived pain) experienced by the patient at the RT site. The SF-MPQ contains 11 sensory pain items, 4 affective pain items, and 1 perceived pain item [38]. The sensory and affective pain items are rated on a 4-point scale anchored by 0 ("none") and 4 ("severe") with maximum subscales scores of 44 and 16, respectively. The perceived pain item is rated on a 6-point scale anchored by 0 ("not present") and 5 ("excruciating"). The maximum total SF-MPQ score is 66. The Skindex-29 questionnaire measures the effects of a skin condition or disease on the patient's quality of life [6]. In this study, the Skindex-29 evaluated how radiation dermatitis altered a patient's quality of life. The questionnaire contains 30 items for health-related quality of life: emotions (10 items), symptoms (7 items), and functioning (12 items). Patients rate how often a certain statement describes them using a 5-point analog scale (e.g., never, rarely, sometimes, often, all the time). The maximum composite Skindex-29 score is 145 with maximum subscale scores of 50 for emotion, 35 for symptoms, and 60 for functioning. The SI is a 17-item questionnaire, adapted from the MD Anderson Symptom Inventory, used to monitor the severity of various side effects of RT and/or study medication [38]. Patients rate the severity of symptoms (pain at RT site, other pain, nausea, vomiting, distress, memory, appetite, diarrhea, skin problems, sleep difficulties, fatigue, mood, breathing, urination, walking, relationships, activity, and quality of life) using an 11-point scale anchored by 0 ("not present") and 10 ("as bad as you can imagine").

Radiation Dermatitis Severity Ratings from Digital Images—Coordinators at each site took digital images (i.e., photos) of the radiation-induced skin changes using a Canon Powershot SD1300 IS Digital ELPH camera. The photos were uploaded onto a secure, study-specific server at the NCORP Research Base. Using the photos from the End RT visit, two reviewers (one Dermatologist and one Radiation Oncologist) rated radiation dermatitis severity (RDS scale) and the presence of moist desquamation. Both reviewers were blinded to the treatment arms and in-person RDS scores. The reviewers' Photo RDS values were averaged for final analysis.

Statistical Analyses—Our published pilot trial showed a 0.65 decrease in RDS in the curcumin arm with an upper 95% confidence bound of 1.1 on the standard deviation of 0.81 [38]. The upper confidence bound was used to infer that a sample of 254 patients per arm would have 80% power to detect a 10% difference (a change in mean RDS score of 0.3) at significance level of 0.05. Primary analysis included all randomized subjects who completed baseline (N=686) and all other analyses included completed cases (N=578) (Figure 1). A linear mixed model (LMM) was used to estimate the effect of the intervention on RDS at

EndRT. Site was entered as a random effect, with Arm and RT regimen as fixed effects. Restricted Maximum Likelihood estimation was used, and the Kenward-Roger method was used for the F tests [27]. Under the plausible assumption that the missing value mechanism was missing at random (MAR), we performed multiple imputation (MI) to assess the magnitude of any biases due to missingness [31]. Chi-square tests were used to compare proportions of patients with moist desquamation between each group. LMMs adjusting for baseline were used to evaluate differences in pain at the RT site (MPQ-SF), quality of life (Skindex-29), and other symptoms (SI) between arms. Forest plots were used to visualize differences in mean change in severity (i.e., End RT-baseline) of pain descriptors (MPQ-SF) and adverse symptoms (SI). In addition, comparative trajectories of MPQ-SF over time (weeks) were assessed using LMMs and the addition of Week, and Week*Arm, and Week*Arm*Stratification interaction. Due to skewness, the MPQ-SF values were log transformed. LMM was also performed on the photo RDS ratings and results were compared between the blinded reviewer ratings and the in-person ratings.

RESULTS

Patient characteristics

From February 2011 to February 2012, a total of 695 patients with breast cancer were enrolled and randomized into one of two arms (Figure 1). Of these 695 patients, nine patients withdrew prior to baseline and 686 patients continued forward with study medication during RT. Of the 686 patients, 108 (15.7%) withdrew from the study and 578 patients completed the study. Reasons for non-completion included: unspecified reasons (63; 58.3%), diarrhea/nausea/vomiting (17; 15.7%), capsule size (6; 5.6%), and allergic reaction (5; 4.6%) (Figure 1). The only reported adverse event involved Grade 2 abdominal pain and vaginal infection, which was considered “unrelated” to study drug. Baseline characteristics did not differ between arms, except for ER/PR (estrogen receptor/progesterone receptor) status and chemotherapy prior to RT (Table 1). The curcumin arm had fewer patients with ER-tumors and patients who had chemotherapy prior to RT (Table 1). Overall, the majority of patients were white females (87.5%), with a mean age of 58 years, prescribed conventional fractionation RT (89.1%). The total prescribed radiation dosage, maximum radiation skin dosage, and total radiation treatment sessions were similar across treatment arms (Table 1). Compliance did not differ between arms (96 % compliance = curcumin; vs. 97% compliance = placebo; p=0.251).

Severity of radiation dermatitis

The most common locations for worst radiation dermatitis were the axillary region (placebo = 44.2% and curcumin = 40.4%) and the inframammary fold (placebo = 44.6% and curcumin = 42.6%). Of the 63 patients with moist desquamation, the inframammary fold was the most common location (placebo = 49.2% and curcumin = 42.8%). The primary analysis showed no significant difference in mean RDS score at EndRT between curcumin and placebo (B (95%CI) = 0.044 (−0.101, 0.188), p=0.552). Site and RT regimen had highly significant effects (p<0.001). In Figure 2a, boxplots show similar mean RDS scores across treatment arms. The mosaic plot in Figure 2b shows a smaller proportion of RDS > 3.0 in the curcumin arm, suggesting a trend toward reduced severity (7.4% (21/283) vs. 12.9%

(38/295), p=0.082, monte-carlo estimate). The presence of moist desquamation (Figure 2c) did not differ between arms (9.54% vs. 12.20%, OR (95% CI) = 0.763 (0.432–1.305, p=0.324). No significant differences were observed for RDS scores (B (95% CI) = 0.109 (−0.226, 0.109, p=0.489) and moist desquamation (16.7% vs. 14.8%, OR (95% CI) = 1.15 (0.716–1.842), p=0.565) at 1 Week Post-RT. RDS scores ≥ 3.5 denote the presence of moist desquamation; however, no correlation was observed between RDS ≥ 3.5 and moist desquamation (Pearson r (95% CI) = 0.316 (0.056, 0.069), p=0.062). Only 23.2% of patients with reported moist desquamation had an RDS score ≥ 3.5; whereas 69.6% of patients with reported moist desquamation had RDS scores 2.0, 2.5 or 3.0. These results suggest no beneficial curcumin effect, as well as inconsistencies with RDS ratings and reporting of moist desquamation.

An exploratory aim of this study was to evaluate the ability of blinded reviewers to rate radiation dermatitis severity from digital photos. Unfortunately, poor image quality led to a low number of RDS ratings by blinded reviewers (N=519). The photo RDS values tended to be higher with less NCORP variation than the corresponding site RDS values. The photo ratings did not show any treatment arm effect for RDS (B (95% CI) = 0.036 (−0.086, 0.158), p=0.563) or moist desquamation (15.29% vs. 16.67%; OR (95% CI) = 0.897 (0.554, 1.449); p = 0.656).

Patient-reported Pain, Quality of Life, and Symptoms

The SF-MPQ was used to assess pain at the RT site. The LMMs revealed no significant differences in change of total, sensory, affective, or perceived pain from baseline to End RT between arms (Table 2). Additionally, change of pain descriptors did not differ between arms (Figure 3). Longitudinal analyses did not reveal any significant trajectory differences between treatment arms. However, RT regimen did influence the longitudinal patterns of affective pain. Over time, affective pain increased with Canadian fractionation, but decreased with conventional fractionation. Furthermore, skin-related quality of life (Skindex-29) did not differ between arms at End RT (Table 2). Similarly, mean change in symptom severity, as measured by the SI, did not differ between arms (Figure 3). Overall, patient-reported symptoms and quality of life did not differ between curcumin and placebo arms.

DISCUSSION

Despite a better understanding of the biological mediators of radiation skin toxicity, an effective therapy has yet to be added to skin management guidelines. For over ten years, the guidelines for management of skin during radiation recommend “washing with mild soap and lukewarm water”, use of unscented, lanolin-free, water-based moisturizers, and avoidance of sun exposure [5, 37]. Standard care for management of radiation dermatitis varies greatly across cancer centers nationwide. We surveyed our 21 sites on standard care for radiation dermatitis and none of the sites matched with each other. The list included: aloe vera, Aquaphor, udder cream, Radiaplex®, corticosteroid creams, lidocaine cream, Silvadine®, and antibiotic ointment. Topical agents are distributed to patients without supportive evidence of therapeutic benefit [5, 11, 30]. Many studies have evaluated the use of topical corticosteroids with mixed results [5, 39]. Prophylactic steroid cream (0.1% mometasone fuorate) and barrier film spray (3M Cavilon Barrier Film) was shown to improve tolerance of radiotherapy in patients due to its ability to minimize inflammation and protect skin barrier [42]. Recently, Ulff *et al* demonstrated that betamethasone-17-valerate cream, a potent corticosteroid, was effective at preventing and reducing radiation dermatitis in breast cancer patients [43]. However, the concern of skin integrity and adverse reactions from prolonged treatment of local steroids has hindered its mainstream use. Di Franco *et al* showed that prophylactic topical hyaluronate and steroid therapy combined with an Ixor® oral therapy (consisting of Resveratrol, Lycopene, Vitamin C, and Anthocyanins) effectively reduced the number of patients with high-grade radiation-induced skin toxicity [9]. Some studies have shown increased wound healing with curcumin when combined with other compounds, such as ginger and aloe vera [4, 12]. Undoubtedly, further studies are warranted for an effective treatment for radiation dermatitis.

Our previous study showed oral curcumin reduced the severity of radiation dermatitis and moist desquamation in breast cancer patients. In contrast, the current study did not show a significant difference between curcumin and placebo. There were several factors that introduced variation that may have masked a beneficial effect. The eligibility criteria were more inclusive in this current trial compared to the previous trial. Eligible patients included those with breast reconstructions prior to RT and two different RT fractionation regimens. We did stratify for RT regimen, but not breast reconstruction. Skin on a reconstructed breast reacts differently than skin on an unaltered breast. After breast reconstruction, the skin is more likely to burn due to its inability to dissipate heat [8]. The complication risks from RT differ between autologous tissue reconstructions and implant/expander reconstructions [40, 41]. We could not use breast reconstruction as a factor in the statistical analyses due to lack of documentation of which patients had reconstructions prior to RT. Overall, oral curcumin did not demonstrate a detectable benefit for radiation dermatitis.

Skin rater variation was the most contributing factor to our inconclusive results. First, two RDS scores (i.e., 3.5 or 4.0) signify the presence of moist desquamation; however, close to 70% of patients with moist desquamation were given RDS scores of 2.0, 2.5 and 3.0, suggesting inconsistencies in the RDS scale utilization. Secondly, the number of raters performing skin assessments at each site was not limited to one rater per patient. Ideally, one skin rater should assess one patient throughout the course of the study. However, sites did not meet this ideal scenario. Inter-rater variation was evaluated because the number of skin raters per patient per site was not recorded. For years, radiation dermatitis severity assessments have utilized various subjective scales, including RDS, RTOG (Radiation Therapy Oncology Group), and CTC (Common Toxicity Criteria) [5, 37]. Our RDS manual containing pictures and descriptions was not enough training to minimize rating variation across sites. Addition of a secondary subjective measure, such as the RTOG scale, would not have reduced rating variation. Our study controlled for rater variation through the use of blinded reviewers and digital photos. Unfortunately, insufficient numbers of quality images lead to insignificant findings. However, our study did demonstrate the ability to document radiation-induced skin changes during RT using digital images. The photo RDS values had less variation than the in-person RDS values. Limiting the number of raters and extensive rater training may have minimized the variation across sites.

Clearly, there is substantial need for an objective and/or quantitative measure for radiation dermatitis severity. Gonzalez Sanchis *et al* showed that real-time laser Doppler flowmetry (LDF), which measure cutaneous microcirculation, is an accurate, objective measure for radiation dermatitis severity [15]. The microcirculation index significantly increased from baseline to end of RT and the skin changes were classified more objectively using LDF compared to CTC scale [15]. Additionally, Esteva *et al* demonstrated the importance of capturing skin reactions by digital photography [10]. Esteva et al developed a computational method in which a computer, using a single convolutional neural network (CNN), can be trained to classify and diagnose skin lesions using a large dataset of digital images [10]. The study showed that the CNN performed on par with 21 board-certified dermatologists on biopsy-proven clinical images. This computational method has not been applied to radiation dermatitis; however Zenda *et al* has developed a picture atlas for grading of radiation dermatitis for head-and-neck cancer patients [45]. LDF, digital images, and computer-aided technology are promising solutions to the inconsistency and subjectivity of measuring radiation dermatitis severity in clinical trials.

For over a decade, curcumin has been evaluated for therapeutic potential due to its antioxidant, anti-inflammatory, and anti-cancer properties. A systematic review concluded that there is evidence that curcumin may benefit skin health, but further clinical studies are required to evaluate efficacy and mechanism [44]. Recently, the clinical efficacy of curcumin has been questioned due to its variable results in molecular drug screens [3, 18]. However, 44 published clinical trials have shown therapeutic effect [18]. Curcumin is limited by its hydrophobic nature, poor water solubility, low bioavailability, and chemical instability. New advances in pharmaceutical strategies, such as nanoencapsulation, may overcome these limitations [1, 18, 21, 23]. Additionally, the isolation of curcumin from the other constituents in turmeric may reduce its therapeutic potential. Curcumin's demonstrated therapeutic benefit and increased bioavailability when used as an adjunct drug in therapy supports this argument [1, 4, 18, 21, 23, 33]. A future trial exploring turmeric or a combined nutraceutical therapy for radiation dermatitis may yield positive results.

In conclusion, oral curcumin did not reduce radiation dermatitis severity compared to placebo. High compliance rate and minimal adverse symptoms suggest that the oral curcumin dose was well tolerated by patients. One critical finding from this study is the need for an objective and/or quantitative measure for radiation dermatitis. A blood or skin biomarker predictive of skin's response to radiation therapy would be ideal; however LDF technology is also promising and quantitative. All the limitations could be addressed in a subsequent trial with a more stringent study design. Investigation of turmeric or combined nutraceutical therapy for radiation dermatitis should be considered.

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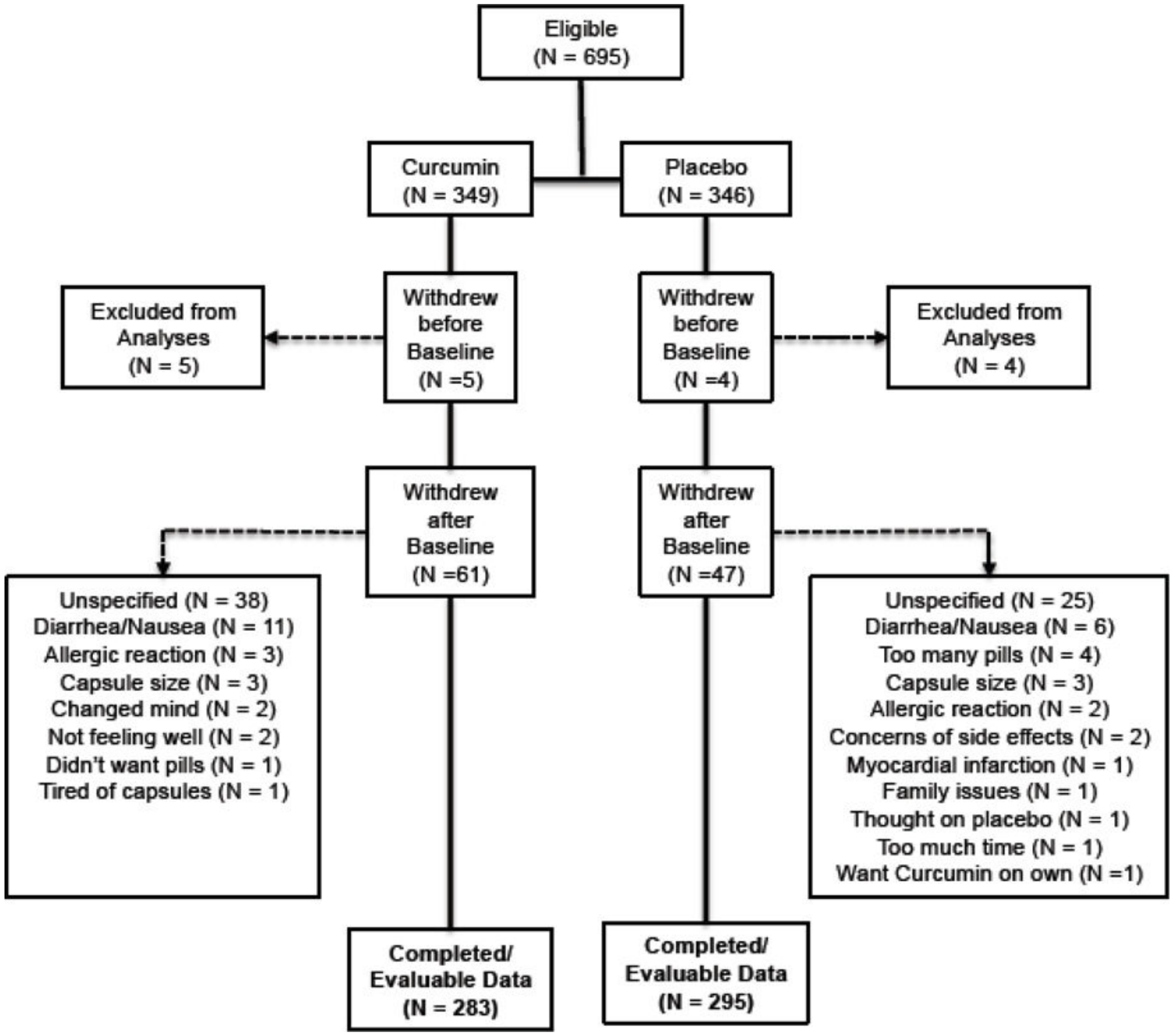

Figure 1. Consort Diagram

This diagram documents the patient flow of the randomized patients in the trial.

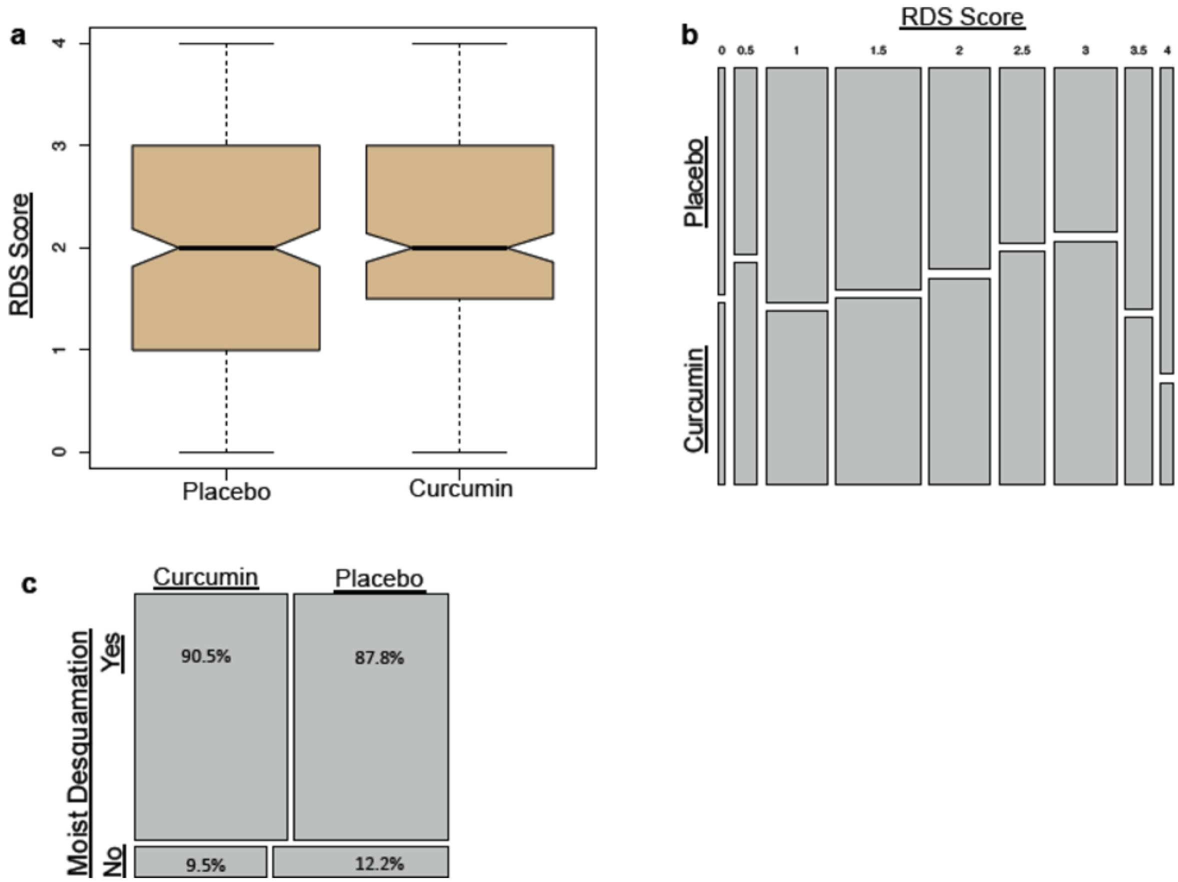

Figure 2. Radiation dermatitis severity (RDS) and moist desquamation did not differ between treatment arms

Panel a: Boxplots portray the mean RDS scores at End RT by treatment arm. The mean and range did not differ between treatment arms. Panel b: The mosaic plot shows fewer patients in the curcumin arm with RDS > 3.0. Panel c: The mosaic plots shows similar proportions of patients with moist desquamation in each treatment arm.

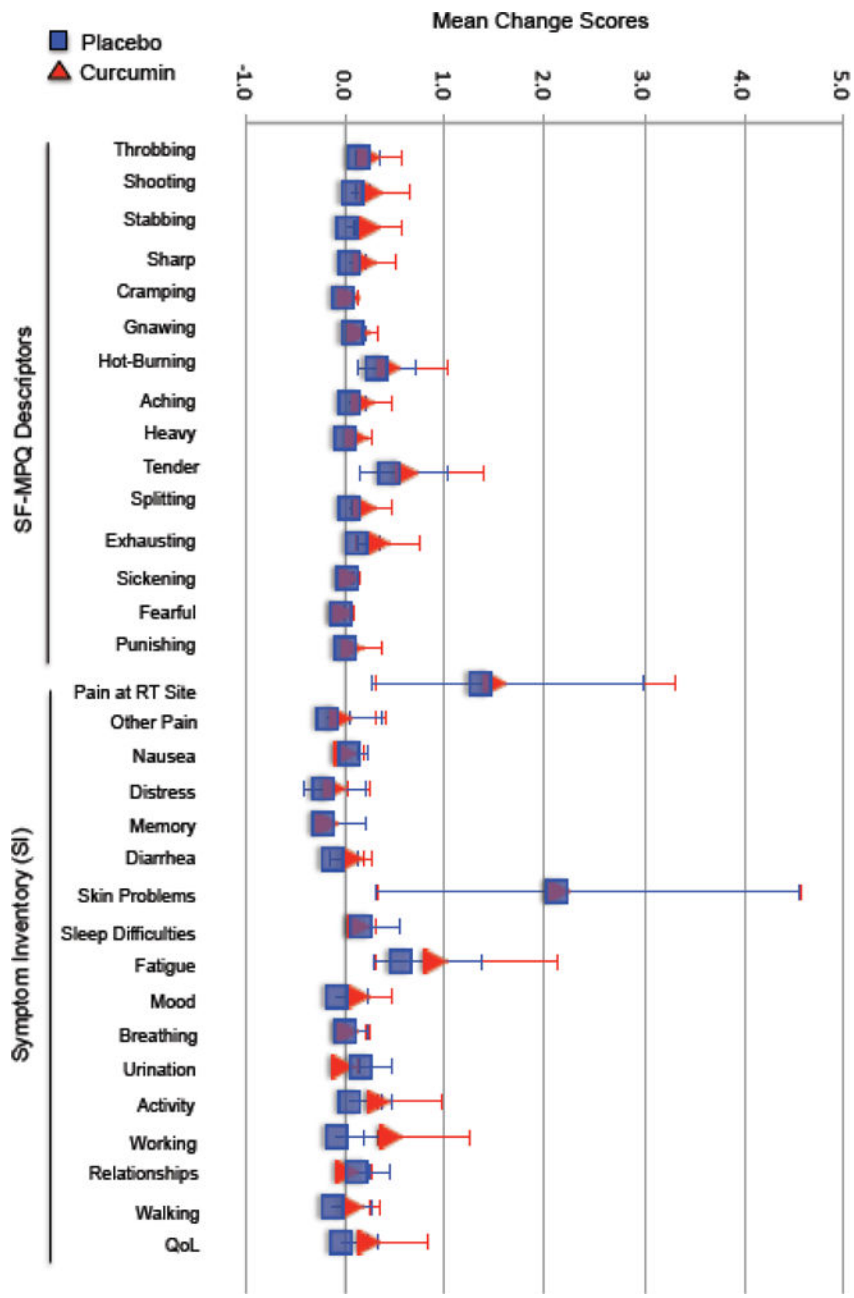

Figure 3. Mean change scores for SI symptoms and SF-MPQ pain descriptors

The forest plot presents the mean severity change scores for pain descriptors on the SF-MPQ and the symptoms on the SI. Red triangles are curcumin and blue squares are placebo. Errors bars are 95% confidence intervals. QoL = quality of life.

Table 1

Patient Demographics

	All N = 686	Curcumin N = 344 (50.1%)	Placebo N = 342 (49.9%)
Age			
Mean (SE)	57.6 (0.4)	57.6 (0.6)	57.7 (0.5)
Race			
White/Caucasian	600 (87.5%)	307 (89.2%)	293 (85.7%)
Black/African American	59 (8.6%)	29 (8.4%)	30 (8.8%)
Multiracial	27 (3.9%)	8 (2.3%)	19 (5.6%)
Ethnicity			
Hispanic	13 (1.6%)	6 (1.7%)	7 (2.0%)
Non-Hispanic	672 (98%)	264 (76.7%)	237 (69.3%)
Unknown	1 (0.1%)	1 (0.3%)	0 (0.0%)
BMI			
Mean (SE)	29.8 (0.3)	29.5 (0.4)	30.0 (0.4)
Tumor Location			
Right	340 (49.6%)	169 (49.1%)	171 (50.0%)
Left	333 (48.5%)	169 (49.1%)	164 (48.0%)
Bilateral	13 (1.9%)	6 (1.7%)	7 (2.0%)
Tumor Stage			
0	97 (17.4%)	48 (14.0%)	49 (14.3%)
I	235 (42.2%)	125 (36.3%)	110 (32.2%)
II	141 (25.3%)	69 (20.0%)	72 (21.1%)
III	75 (13.5%)	36 (10.5%)	39 (11.4%)
IV	6 (1.1%)	4 (1.2%)	2 (0.6%)
More than One Stage	3 (0.4%)	1 (0.3%)	2 (0.6%)
ER/PR Status *			
ER^+/PR^+	501 (73.6%)	264 (76.7%)	237 (69.3%)
ER^+/PR^-	9 (1.3%)	6 (1.7%)	3 (0.9%)
ER^-/PR^+	68 (10.0%)	27 (7.8%)	41 (12.0%)
ER^-/PR^-	102 (15.0%)	42 (12.2%)	60 (17.5%)
ER^+/PR^+ & ER^-/PR^-	1 (0.1%)	1 (0.3%)	0 (0.0%)
Her2/Neu Status			
Positive	89 (14.8%)	40 (11.6%)	49 (14.3%)
Negative	512 (85.2%)	262 (76.2%)	250 (73.1%)
Previous Chemotherapy **			
Yes	283 (41.3%)	128 (37.2%)	155 (45.3%)
No	396 (57.7%)	212 (61.6%)	184 (53.8%)

	All N = 686	Curcumin N = 344 (50.1%)	Placebo N = 342 (49.9%)
Radiation Therapy Stratification			
Conventional Fractionation	611 (89.1%)	307 (89.2%)	304 (88.9%)
Canadian Fractionation	75 (10.9%)	37 (10.8%)	38 (11.1%)
Mean Radiation Dose (Gy)			
Prescribed Whole Breast Dose (SE)	48.34 (0.14)	48.43 (0.19)	48.24 (0.19)
Whole Breast Maximum Skin Dose (SE)	51.10 (0.26)	51.20 (0.37)	51.02 (0.37)
Total RT Sessions (SE)	29.89 (0.23)	30.18 (0.32)	29.61 (0.32)
Expected RT Skin Problem			
Yes	407 (59.3%)	192 (55.8%)	215 (62.9%)
No	277 (40.4%)	150 (43.6%	127 (37.1%)
Expected RT Pain			
Yes	148 (21.6%)	73 (21.2%)	75 (21.9%)
No	535 (78.0%)	269 (78.2%)	266 (77.8%)

[*] Curcumin arm had significantly fewer patients with ER- tumors (p=0.033).

[**] Curcumin arm had significantly fewer patients with previous chemotherapy (p=0.040).

Table 2

LMM results for SF-MPQ & Skindex-29

	Effect Estimate (B)	95% CI	p-value
MPQ-SF Scales			
Sensory	0.007	−0.023, 0.034	0.714
Affective	0.034	−0.003, 0.071	0.068
Perceived Pain	0.012	−0.021, 0.045	0.481
Total MPQ-SF	0.791	−0.572, 2.154	0.255
Skindex-29 Scales			
Emotion	0.911	−0.361, 0.021	0.286
Symptom	0.654	−2.310, 3.617	0.665
Composite	0.741	−0.394, 0.021	0.407
Worry	0.281	−2.910, 3.473	0.863