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Scientific Article

Quantitative 3-Dimensional Photographic Assessment of Breast Cosmesis After Whole Breast Irradiation for Early Stage Breast Cancer: A Secondary Analysis of a Randomized Clinical Trial

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Abstract

Purpose: Our purpose was to use 3-dimensional (3D) surface photography to quantitatively measure breast cosmesis within the framework of a randomized clinical trial of conventionally fractionated (CF) and hypofractionated (HF) whole breast irradiation (WBI); to identify how 3D measurements are associated with patient- and physician-reported cosmesis; and to determine whether objective measures of breast symmetry varied by WBI treatment arm or transforming growth factor β 1 (*TGFβ1*) status.

Methods and Materials: From 2011 to 2014, 287 women age ≥40 with ductal carcinoma in situ or early-stage invasive breast cancer were enrolled in a multicenter trial and randomized to HF-WBI or CF-WBI with a boost. Three-dimensional surface photography was performed at 3 years posttreatment. Patient-reported cosmetic outcomes were recorded with the Breast Cancer Treatment Outcome Scale. Physician-reported cosmetic outcomes were assessed by the Radiation Therapy Oncology Group scale. Volume ratios and 6 quantitative measures of breast symmetry, termed F1-6C, were calculated using the breast contour and fiducial points assessed on 3D surface images. Associations between all metrics, patient- and physician-reported cosmesis, treatment arm, and *TGFβ1* genotype were performed using the Kruskal-Wallis test and multivariable logistic regression models.

Results: Among 77 (39 CF-WBI and 38 HF-WBI) evaluable patients, both patient- and physician-reported cosmetic outcomes were significantly associated with the F1C vertical symmetry measure (both $P < .05$). Higher dichotomized F1C and volumetric symmetry measures were associated with improved patient- and physician-reported cosmesis on multivariable logistic regression (both $P \leq .05$). There were no statistically significant differences in vertical symmetry or volume measures between treatment arms. Increased F6C horizontal symmetry was observed in the CF-WBI arm ($P = .05$). Patients with the *TGFβ1* C-509T variant allele had lower F2C vertical symmetry measures ($P = .02$).

Conclusions: Quantitative 3D image-derived measures revealed comparable cosmetic outcomes with HF-WBI compared with CF-WBI. Our findings suggest that 3D surface imaging may be a more sensitive method for measuring subtle cosmetic changes than global patient- or physician-reported assessments.

Introduction

Longitudinal results from 4 seminal randomized clinical trials conducted in the United Kingdom and Canada have demonstrated equivalent local control and overall survival between hypofractionated whole-breast irradiation (HF-WBI) and conventionally fractionated whole-breast irradiation (CF-WBI).[1-3] Although oncologic outcomes from various breast conserving therapies (BCT) can be objectively measured, there is no standard, objective method to evaluate cosmetic outcome to date. Physician panel- and patient-reported assessments comprise the mainstay of esthetic assessment and are, unfortunately, subject to notable inter- and intraobserver heterogeneity.[2-7]

We have previously shown that quantitative measures of breast symmetry derived from 2-dimensional (2D) photographs significantly correlate with both patient- and physician-reported cosmetic outcomes at 1 year post-WBI.[8] This study was performed within the context of a randomized, noninferiority clinical trial comparing CF- and HF-WBI. Similar or improved symmetry for several 2D measurements was noted in the HF-WBI arm compared with CF-WBI, suggesting that the collection and analysis of objective measures of breast cosmesis may be useful in future comparative effectiveness studies. Despite this, measures derived from 2D photographs have limitations in fully characterizing breast cosmesis; most notably, they do not account for breast volume changes, which may occur after WBI or over time and influence cosmetic outcome. Furthermore, our initial study lacked long-term follow-up and relied on measures and cosmetic assessments collected at 1-year post-WBI.

We sought to address these limitations by employing modern 3-dimensional (3D) surface photography, a novel clinical and research tool employed in oncoplastic, reconstructive, and esthetic breast surgery but not yet routinely applied to oncologic care.[9] 3D measures are particularly advantageous in that both curvilinear and volumetric measurements can be generated. Our goal in the present study was to evaluate cosmetic outcome after BCT by generating clinically relevant quantitative parameters derived from 3D photographs from patients enrolled in this clinical trial (ClinicalTrials.gov identifier: NCT01266642) and to compare these measurements with patient- and physician-reported cosmetic evaluation at 3 years after completion of treatment. Additionally, we sought to evaluate whether 3D measurements of cosmesis varied by radiation treatment arm or by transforming growth factor β 1(*TGFβ1*) polymorphism status, a potential genomic marker for radiation-related fibrosis.[10]

Methods and Materials

Patient cohort

Between February 2011 and February 2014, 287 women ≥40 years with stage Tis-T2N0-N1M0 breast

cancer who underwent margin-negative segmental mastectomy were enrolled in an institutional review board–approved protocol at The University of Texas MD Anderson Cancer Center. Eligibility criteria have been previously described.[11] Patients were randomized to treatment with CF-WBI (50 Gy in 25 fractions with a 10-14 Gy boost in 5-7 fractions) or HF-WBI (42.56 Gy in 16 fractions with a 10-12.5 Gy boost in 4-5 fractions). Details regarding patient and tumor characteristics and 3-year cosmetic and survival outcomes were recently reported.[12]

Patient- and physician-reported cosmesis

The Breast Cancer Treatment Outcome Scale (BCTOS) was administered during the 3-year follow-up visit to evaluate patient-reported cosmetic outcome.[13] The BCTOS ranges from 1 to 4: 1 = no difference between the treated and untreated breast; 2 = slight difference; 3 = moderate difference; and 4 = large difference. The BCTOS cosmetic subscale was calculated by computing the arithmetic means of the 7 items used to assess cosmetic outcome. A panel of 3 breast cancer physicians (B.D.S., S.F.S., and A.M.T.) blinded to treatment arm evaluated photographic cosmetic outcome using a series of 5 photos per patient and scored cosmesis using the Radiation Therapy Oncology Group (RTOG) scale: 1 = excellent; 2 = good; 3 = fair; and 4 = poor.[6]

Quantitative measure of cosmesis derived from 3-dimensional photographs

This study enrolled patients at 7 different treatment sites; at 1 site (The University of Texas MD Anderson Cancer Center main campus), the 3dMDtorso System (3dMD LLC, Atlanta, GA) was available and was used to acquire 3D photographs at the 3-year follow-up visit. Patients were photographed in the supine position from the low neck to the upper abdomen, with arms at side, unclothed, and with all jewelry removed. Two investigators (P.P. and S.T.) blinded to treatment arm calculated the 6 curvilinear and 1 volume qualitative measurements from measurements using the breast contour derived from 3D photographs using customized software developed at the University of Houston.[14-16] Fiducial points were manually annotated on the 3D images to compute the quantitative measures: F1C = vertical distance from the nipple to sternal notch; F2C = vertical distance from the nipple to the lowest visible point of the breast mound; F3C = horizontal distance from the nipple to the midline point; F4C = horizontal distance from the nipple to the lateral most extent of the breast mound; F5C = vertical distance from the sternal notch to the lowest visible point of the breast mound, obtained by adding the curvilinear distances between sternal notch to each nipple and nipple to lowest visible point of each breast mound; and F6C = horizontal distance from midline to the lateral most extent of the breast mound. The lowest visible point was defined as the inferiormost point along the inferiormost visible contour of the breast in a woman in a frontal standing or lateral position.[17] The midline point was defined as the point midway between the 2 medial points where the inframammary fold ends medially in both left and right breasts. The 6 curvilinear measurements were calculated relative to the contralateral, untreated breast and reported on a scale of 0 to 1, with values closer to 1 indicating better symmetry with the contralateral breast. Volume ratios were also reported as the calculated volume of the treated to untreated breast as rendered by 3D photography. The fiducial points and formulas used to calculate these measures are depicted in Figure 1.

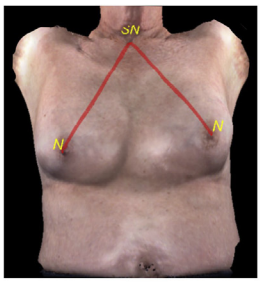
TGFβ1 genotyping

A total of 217 of 287 randomized patients consented and underwent venipuncture to evaluate *TGFβ1* status. DNA extraction and polymerase chain reaction methods have been previously described.[10] The presence of at least one C-to-T single-nucleotide polymorphism at the first major transcription start site, position −509, of the *TGFβ1* gene, was defined as a genomic marker for breast fibrosis risk.

Statistical methodology

Using the X^2 test, we compared clinicopathologic variables from the 77 patients who underwent 3D surface imaging at 3 years and the remaining 210 patients included in the randomized clinical trial who did not undergo follow-up 3D surface imaging. Variables included age, race, menopausal status, bra cup size, body mass index (BMI), tumor histology, tumor grade, margin status, tumor location (quadrant), estrogen receptor status, progesterone receptor status, and HER2-neu status. The BCTOS patient-reported (1-1.9 vs >1.9) and the RTOG physician-reported (1-2 vs 3-4) cosmetic outcomes were dichotomized to reflect "good" to "excellent" cosmesis versus "fair" to "poor." The Spearman correlation coefficient was used to evaluate the relationship between patient- and physician-reported cosmetic outcomes. Univariate associations between F1-6C and volume measurements and patient- and physician-reported cosmetic outcomes were assessed using the nonparametric Kruskal-Wallis test. Recursive partitioning analysis was used to identify clinically relevant binary cut points of 3D photograph-derived quantitative continuous measurements associated with subjective measures of cosmetic outcomes (RPART package of R). Logistic regression was used to evaluate the association of binary

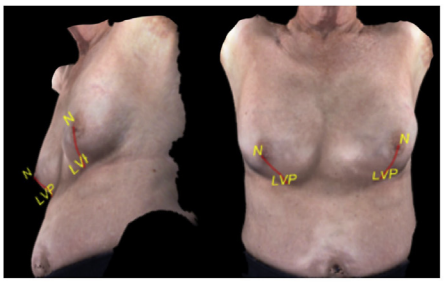
A



B

$$\text{F1C} = \left(\frac{N_L - SN}{N_R - SN}\right) \text{ if } N_L - SN > N_R - SN \text{ or}$$
$$\text{F1C} = \left(\frac{N_R - SN}{N_L - SN}\right) \text{ if } N_R - SN > N_L - SN$$

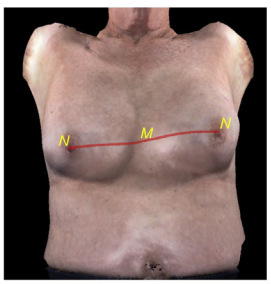
C



D

$$\text{F2C} = \left(\frac{N_L - LVP_L}{N_R - LVP_R}\right) \text{ if } N_L - LVP_L > N_R - LVP_R \text{ or}$$
$$\text{F2C} = \left(\frac{N_R - LVP_R}{N_L - LVP_L}\right) \text{ if } N_R - LVP_R > N_L - LVP_L$$

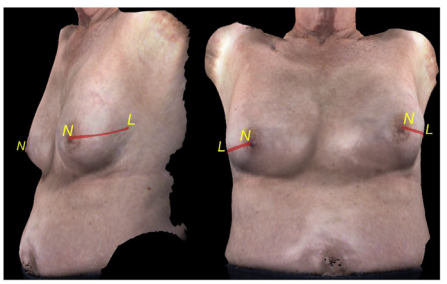
E



F

$$\text{F3C} = \left(\frac{N_L - M}{N_R - M}\right) \text{ if } N_L - M > N_R - M \text{ or}$$
$$\text{F3C} = \left(\frac{N_R - M}{N_L - M}\right) \text{ if } N_R - M > N_L - M$$

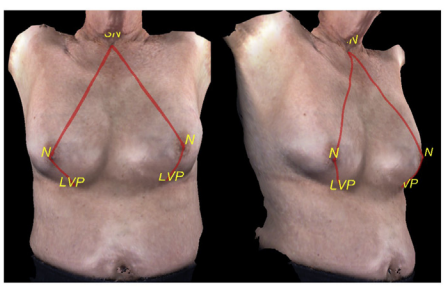
G



H

$$\text{F4C} = \left(\frac{N_L - L_L}{N_R - L_R}\right) \text{ if } N_L - L_L > N_R - L_R \text{ or}$$
$$\text{F4C} = \left(\frac{N_R - L_R}{N_L - L_L}\right) \text{ if } N_R - L_R > N_L - L_L$$

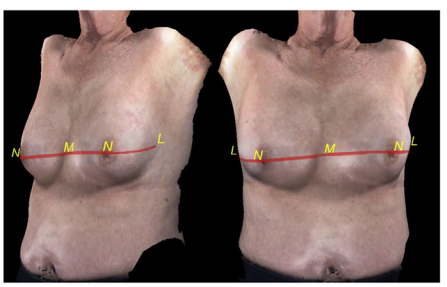
I



J

$$\text{F5C} = \left(\frac{LVP_L - SN}{LVP_R - SN}\right) \text{ if } LVP_L - SN > LVP_R - SN \text{ or}$$
$$\text{F5C} = \left(\frac{LVP_R - SN}{LVP_L - SN}\right) \text{ if } LVP_R - SN > LVP_L - SN$$

K



L

$$\text{F6C} = \left(\frac{L_L - M}{L_R - M}\right) \text{ if } L_L - M > L_R - M \text{ or}$$
$$\text{F6C} = \left(\frac{L_R - M}{L_L - M}\right) \text{ if } L_R - M > L_L - M$$

Figure 1 (A) F1C is the ratio of the vertical distance from each nipple (N) to the sternal notch (SN) along the breast mound contour. (B) Formula for the F1C calculation. (C) F2C is the ratio of the vertical distance from each N to the lowest visible point (LVP) of each breast mound. (D) Formula for the F2C calculation. (E) F3C is the ratio of the horizontal distance from each N to midline (M). (F) Formula for the F3C calculation. (G) F4C is the ratio of the horizontal distance from each N to the most lateral extent (L) of each breast mound. (H) Formula for the F4C calculation. (I) F5C is the ratio of the vertical distance from the SN to the LVP of each breast mound. The distance from SN to LVP is obtained by adding the curvilinear distances between SN to each N and N to LVP of each breast mound. (J) Formula for the F5C calculation. (K) F6C is the ratio of the horizontal distance from M to the most L of each breast mound. The distance from M to LVP is obtained by adding the curvilinear distances between M to each N and N to LVP of each breast mound. (L) Formula for the F6C calculation.

quantitative measures, F1C-F6C, and volume ratios, based on cut points with patient- and physician-reported cosmetic outcomes. Association of 3D measures with treatment arm and *TGFβ1* status was analyzed using the Kruskal-Wallis test for continuous variables and the X^2 test for categorical variables. The association of baseline patient-reported (or physician-reported) cosmesis, age, BMI, bra cup size, and T stage with 3-year patient-reported (or physician-reported) cosmesis was tested using univariate logistic regression models.

Three-dimensional measures and covariates with P values $< .15$ from univariate analysis were included in final multivariable logistic regression models. P values $\leq .05$ were considered to be statistically significant. All tests were 2-sided. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC) and R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline features and 3-year patient- and physician-reported cosmetic outcomes

Of the 287 randomized patients, 140 and 138 patients were allocated to CF-WBI and HF-WBI, respectively (Fig 2). Within this group, 39 patients in the CF-WBI arm and 38 patients in the HF-WBI arm returned to the MD Anderson Cancer Center Main campus facility for 3-year follow-up, at which time 3D photographs were obtained and patient- and physician-reported cosmetic outcomes were recorded. Comparison between 77 patients with 3D surface imaging and 210 patients without 3D surface imaging revealed that the patients who did not undergo 3D surface imaging at 3 years tended to be of non-Hispanic white race ($P < .001$) and had lower grade tumor ($P = .05$; Table E1). *TGFβ1* testing was performed in 87% of patients in each arm (34/39 of CF-WBI patients and HF-WBI 33/38 patients).

At 3 years, the patient-reported BCTOS score ranged from 1 to 3.43, with a median score of 1.71 (Table 1). Sixty-five percent of patients reported "good" to "excellent" cosmesis (BCTOS 1-1.9), whereas 35% of patients reported "poor" to "fair" cosmesis (BCTOS > 1.9). The physician panel found "excellent," "good," "fair," and "poor," cosmesis in 25%, 45%, 25%, and 5% of patients, respectively. Patient- and physician-reported cosmetic outcomes significantly correlated (Spearman coefficient $= 0.31$, $P = .008$).

Correlation between 3D measurements and patient- and physician-reported cosmesis

Table 1 illustrates the median and ranges for the 6 curvilinear and volume measurements obtained from 3D photos. Table 2 shows 3D measures stratified by patient- and physician-reported cosmesis. F1C, the vertical measure from the nipple to sternal notch, significantly correlated with both patient- and physician-reported

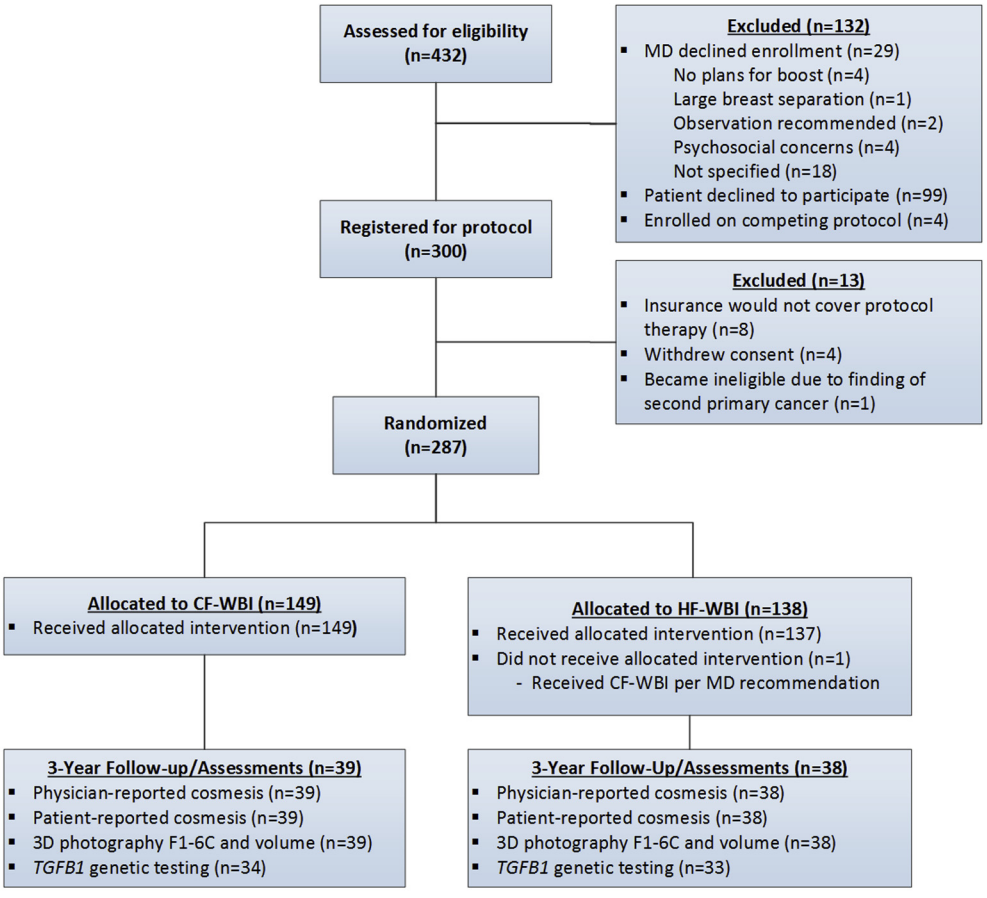


Figure 2 Consolidated Standards of Reporting Trials (CONSORT) diagram.

Table 1 Summary of patient- and physician-reported cosmetic outcomes and 3D photo measures

Reported cosmetic outcome	n	%	Median (range)
Patient-reported (BCTOS)	77	100	1.71 (1.00-3.43)
1-1.9 (excellent-good)	50	65	
>1.9 (fair-poor)	27	35	
Physician-reported (RTOG)	77	100	2 (1-4)
1 (excellent)	19	25	
2 (good)	35	45	
3 (fair)	19	25	
4 (poor)	4	5	
3D photograph measures	77	100	
F1C	77	100	0.95 (0.79-1.00)
F2C	77	100	0.92 (0.69-1.00)
F3C	77	100	0.94 (0.38-1.00)
F4C	77	100	0.91 (0.61-1.00)
F5C	77	100	0.96 (0.85-1.00)
F6C	77	100	0.95 (0.60-1.00)
Volume (treated/untreated)	77	100	1.01 (0.54-1.98)

Abbreviations: 3D = 3-dimensional; BCTOS = Breast Cancer Treatment Outcomes Scale; RTOG = Radiation Therapy Oncology Group.

cosmesis ($P = .03$ and $P = .02$). The ratio of the volume of the treated to untreated breast significantly correlated with physician-reported cosmesis ($P = .03$) but not patient-reported cosmesis.

A recursive partitioning method was applied to define clinically relevant cut points for continuous outcomes for F1C and volume ratio measurements, the quantitative variables most strongly correlated with subjective cosmetic evaluation. For F1C, this approach resulted in cut points of 0.975 (<0.975, n = 57; ≥0.975, n = 20) for patient-reported cosmesis and 0.925 (<0.925, n = 22; ≥0.925, n = 55) for physician-reported cosmesis. This approach yielded a volume ratio cut point of 0.928 (<0.928, n = 22; ≥0.928, n = 55) to discriminate patient- and physician-reported cosmesis. On multivariable analysis, F1C and volume ratios with the aforementioned cut points continued to be significantly associated with improved patient- and physician-reported cosmetic outcomes at 3 years after adjusting for baseline covariates ($P \leq .05$ for all; Table 3). For patient-reported cosmetic outcome, BMI and bra cup size had a $P < .15$ and thus were retained in the multivariable model; however, neither of these variables reached statistical significance ($P \geq .11$ for BMI; $P = .14$ for bra cup size). For physician-reported cosmetic outcome, baseline physician-reported cosmesis fair/poor, versus good/excellent, was associated with worse 3-year physician-reported cosmesis ($P = .008$) on multivariable analysis.

Comparison of 3D measures by randomization arms

The median and ranges for F1-6C and volume measurements stratified by randomization arm are depicted in Table 4. Of these values, the F6C measure indicating the horizontal distance from midline to the most lateral extent of the breast mound was the only quantitative measure that significantly varied between treatment arms and was higher in the CF-WBI group ($P = .05$). F1C and volume ratio evaluated as continuous or dichotomized variables at previously defined cut points were not significantly different by treatment arm ($P > .3$).

Table 2 Three-dimensional photograph measures stratified by patient- and physician-reported cosmetic outcomes

Reported cosmetic outcome	Median (IQR)		*P*
Patient-reported (BCTOS)	1-1.9 (excellent-good; n = 50)	>1.9 (fair-poor; n = 27)	
F1C	0.96 (0.93-0.98)	0.93 (0.90-0.96)	.03
F2C	0.91 (0.83-0.96)	0.92 (0.82-0.96)	.72
F3C	0.94 (0.91-0.97)	0.93 (0.88-0.96)	.45
F4C	0.9 (0.85-0.96)	0.91 (0.86-0.95)	.85
F5C	0.96 (0.94-0.98)	0.96 (0.95-0.98)	.86
F6C	0.95 (0.92-0.98)	0.95 (0.90-0.98)	.90
Volume (treated/untreated)	1.05 (0.94-1.30)	0.96 (0.82-1.13)	.11
Physician-reported (RTOG)	1-2 (excellent-good; n = 54)	3-4 (fair-poor; n = 23)	
F1C	0.96 (0.93-0.98)	0.92 (0.88-0.97)	.02
F2C	0.92 (0.83-0.96)	0.88 (0.82-0.95)	.58
F3C	0.94 (0.91-0.96)	0.94 (0.86-0.98)	.74
F4C	0.90 (0.85-0.95)	0.9 (0.84-0.97)	.76
F5C	0.96 (0.94-0.98)	0.96 (0.94-0.98)	.44
F6C	0.96 (0.93-0.98)	0.94 (0.90-0.98)	.56
Volume (treated/untreated)	1.05 (0.94-1.22)	0.94 (0.78-1.11)	.03

Abbreviations: 3D = 3-dimensional; BCTOS = Breast Cancer Treatment Outcomes Scale; IQR = interquartile range; RTOG = Radiation Therapy Oncology Group.

Table 3 Multivariable logistic model for cumulative probability of improved patient- and physician-reported cosmetic outcomes with covariate adjustment

Reported cosmetic outcome	Odds ratio	95% CI	*P*
3-year patient-reported (BCTOS)			
F1C < 0.975	1		
F1C ≥ 0.975	9.33	1.83-47.6	.007
Volume (treated/untreated) < 0.928	1		
Volume (treated/untreated) ≥ 0.928	3.58	1.05-12.13	.041
BMI < 25 kg/m^2	1		
BMI 25-29.9 kg/m^2	0.33	0.08-1.29	.11
BMI ≥ 30 kg/m^2	1.01	0.24-4.30	.99
Bra cup size A-C	1		
Bra cup size D-E	0.38	0.11-1.38	.14
3-year physician-reported (RTOG)			
F1C < 0.925	1		
F1C ≥ 0.925	6.63	1.85-23.7	.004
Volume (treated/untreated) < 0.928	1		
Volume (treated/untreated) ≥ 0.928	3.56	1.0-12.97	.05
Baseline physician-reported (RTOG) cosmesis good/excellent	1		
Baseline physician-reported (RTOG) cosmesis fair/poor	0.07	0.01-0.49	.008

Abbreviations: BCTOS = Breast Cancer Treatment Outcomes Scale; BMI = body mass index; CI = confidence interval; RTOG = Radiation Therapy Oncology Group.

Comparison of 3D measures by *TGFβ1* status

We have previously reported that presence of the C509T TC/TT variant allele in the *TGFβ1* promoter region is associated with Common Terminology Criteria for Adverse Events v4.0 grade ≥ 2 breast fibrosis and breast atrophy at 3 years post-WBI in this clinical trial cohort.[10] We sought to determine whether the aforementioned 3D measures of breast cosmesis were associated with the presence of the C509T variant. The median and ranges for F1-6C and volume measurements stratified by *TGFβ1* status are depicted in Table 5. Of these values, only F2C, a measure of the vertical distance from the nipple to the lowest visible point of the breast mound, was significantly different when stratifying by *TGFβ1* status and lower in patients harboring the C509T TC/TT variant allele ($P = .02$).

Discussion

We identified quantitative measures of breast symmetry derived from 3D photographs that correlated with

Table 4 Three-dimensional photograph measures stratified by treatment arm

3D photograph measure	CF-WBI		HF-WBI		*P*
	n	Median (IQR) or %	n	Median (IQR) or %	
Continuous					
F1C	39	0.95 (0.92-0.98)	38	0.95 (0.92-0.97)	.68
F2C	39	0.90 (0.85-0.95)	38	0.92 (0.79-0.98)	.98
F3C	39	0.94 (0.90-0.96)	38	0.94 (0.90-0.97)	.76
F4C	39	0.90 (0.87-0.95)	38	0.90 (0.84-0.96)	.73
F5C	39	0.97 (0.95-0.98)	38	0.96 (0.93-0.97)	.07
F6C	39	0.96 (0.93-0.99)	38	0.94 (0.91-0.97)	.05
Volume (treated/untreated)	39	0.98 (0.91-1.14)	38	1.05 (0.90-1.28)	.39
Dichotomized					
F1C < 0.975	27	47	30	53	
F1C ≥ 0.975	12	60	8	40	.33
F1C < 0.925	12	55	10	46	
F1C ≥ 0.925	27	49	28	51	.67
Volume (treated/untreated) < 0.928	12	55	10	46	
Volume (treated/untreated) ≥ 0.928	27	49	28	51	.67

Abbreviations: 3D = 3-dimensional; CF-WBI = conventionally fractionated whole-breast irradiation; HF-WBI = hypofractionated whole-breast irradiation; IQR = interquartile range.

Table 5 Three-dimensional photograph measures stratified by *TGFβ1* status

3D photograph measure	C509T CC		C509T TC/TT		*P*
	n	Median (IQR) or %	n	Median (IQR) or %	
Continuous					
F1C	30	0.95 (0.92-0.98)	37	0.96 (0.93-0.97)	.90
F2C	30	0.94 (0.85-0.98)	37	0.88 (0.81-0.93)	.02
F3C	30	0.95 (0.92-0.98)	37	0.95 (0.90-0.97)	.71
F4C	30	0.91 (0.86-0.96)	37	0.89 (0.84-0.94)	.21
F5C	30	0.96 (0.93-0.98)	37	0.97 (0.95-0.98)	.14
F6C	30	0.95 (0.93-0.98)	37	0.95 (0.90-0.98)	.41
Volume (treated/untreated)	30	1.08 (0.81-1.15)	37	0.97 (0.91-1.10)	.89
Dichotomized					
F1C < 0.975	19	40	29	60	
F1C ≥ 0.975	11	58	8	42	.17
F1C < 0.925	10	59	7	41	
F1C ≥ 0.925	20	40	30	60	.18
Volume (treated/untreated) < 0.928	9	45	11	55	
Volume (treated/untreated) ≥ 0.928	21	45	26	55	.98

Abbreviations: 3D = 3-dimensional; IQR = interquartile range; *TGFβ1* = transforming growth factor β 1.

patient- and physician-reported cosmesis at 3 years post-treatment as part of a prospective, randomized clinical trial comparing CF-WBI and HF-WBI. Higher values of F1C, a measure of the vertical distance of the nipples relative to the sternal notch, were associated with improved cosmetic outcome. Three-dimensional photography allowed for volume ratios of the treated to untreated breast to be calculated; these volume measurements correlated with physician panel assessment of cosmesis. Although on univariate analysis there was no significant association between volume ratios and patient-reported cosmesis, on multivariable analysis higher dichotomized volume ratios were associated with improved patient-reported cosmesis. Clinically relevant cut points determined by recursive partitioning methodology demonstrated there was no significant difference in dichotomized F1C or volume ratio measurements between treatment arms. F6C, a horizontal measure of the curvilinear distance from midline to the lateral most part of the breast mound, was the only continuous 3D measurement that was significantly different between treatment arms and, in this cohort, demonstrated only slightly improved symmetry in the CF-WBI arm (median, 0.96; interquartile range, 0.93-0.99 vs median, 0.94; interquartile range, 0.91-0.97; $P = .05$). Finally, median values of F2C, a vertical measurement of nipple position relative to the lowest visible point of the breast mound, were higher among patients with at least 1 copy of the C-509C allele compared with patients homozygous for the C-509T allele. This finding suggests a relationship between increased genetic susceptibility to fibrosis and atrophy and decreased symmetry, which merits further study. However, F6C and F2C were not detected as clinically relevant measures of breast symmetry by patients or physicians. To our knowledge, this is the first study to compare breast cosmesis in a randomized trial of 2 different fractionation regimens using a novel 3D photography instrument in addition to a genomic factor. Our results provide further evidence that the cosmetic outcome after HF-WBI is comparable to that after CF-WBI.

Conclusions

HF-WBI is considered standard of care for early-stage invasive breast cancer and ductal carcinoma in situ and is supported by American Society for Radiation Oncology consensus guidelines and Choosing Wisely recommendations from the American Society for Radiation Oncology.[18,19] Although the oncologic equivalence of HF-WBI has been substantiated, in the United States, HF-WBI schedules are underused in eligible patients.[20-22] Reticence to adopt HF-WBI is likely, in part, due to concerns about the cosmetic outcome of an accelerated schedule and the absence of a reliable and standardized method of evaluating post-BCT cosmesis.[23,24] Findings from this study using 3D photography can help identify quantitative parameters that are important to both patients and their providers. The vertical position of the nipples was found to correlate with patient- and physician-reported cosmesis both in our prior 2D photography study, assessed 1 year after completing radiation, and in the present study, assessed 3 years after completing radiation, highlighting the durable importance of evaluating this metric over time.[8] Initial breast and tumor size, location and extent of resection, oncoplastic rearrangement, subsequent mammoplasty/mastopexy, and radiation-related fibrosis can all affect volume and vertical nipple symmetry. However, differences in other

curvilinear measures calculated from 3D photographs may be too subtle to be detected by global subjective scales. Based on our findings, future efforts could be undertaken to develop techniques to optimize volumetric and vertical nipple symmetry, and, in turn, patient satisfaction with breast cosmesis, which has been validated as an integral component of long-term quality of life after BCT.[25,26] As more women transition to survivorship after being cured of their early stage breast cancer, improving quality of life after cancer treatment becomes paramount.

Recent instruments including the Breast Analyzing Tool and the Breast Cancer Conservative Treatment cosmetic result software (BCCT.core) have been developed where digital photographs are used to evaluate the size, shape, color, and scar appearance of the treated breast compared with the untreated breast.[27,28] These tools were shown to be fairly concordant with subjective physician-reported cosmesis per the 4-point RTOG scale established by Harris et al and patient-reported cosmesis per the BCTOS.[6,29] However, the clinical relevance of these objective measurements of cosmesis are yet to be determined.

Three-dimensional surface imaging has been used for decades in engineering industries, but has only recently been used in medicine. The term "mammometrics" was coined to describe the use of fixed planes and fiducial points to perform objective breast measurements.[30] By standardizing these measures, breast volume, shape, and symmetry can be compared with the contralateral breast or to evaluate changes in the ipsilateral breast over time. The accuracy of 3D-derived mammometrics has been validated with manual measurements and gold standard water molds.[31,32] Although early 3D cameras were bulky, modern equipment is more portable and cost effective. As a result, clinical applications for 3D photography are broadening beyond surgical planning. Three-dimensional photography can be used to objectively evaluate breast cosmesis in multi-institutional clinical trials and to determine which patients are appropriate candidates for BCT.[33] Overall, 3D photography has the potential to serve as an additional tool to guide physician recommendations, visually inform patients, and become a key component of shared decision making.

This study has limitations that must be acknowledged. Notably, 3D photographs were not obtained before surgery and before WBI. Baseline asymmetry and changes after breast conserving surgery and/or oncoplastic rearrangement could have also contributed to differences between treated and untreated breasts. Although patient and tumor characteristics were balanced between randomization arms, we do not have initial 3D measurements before radiation therapy to definitively state that there was no difference in clinically relevant measures, for example, F1C and volume ratios. Perhaps other measures would have been identified as relevant based on subjective evaluation if baseline photos were available for pre- and posttreatment assessment of breast symmetry. Additionally, late toxicities related to breast fibrosis and changes in shape and volume may continue to evolve beyond the 3-year time point. Future studies can be designed to incorporate 3D technology in the pretreatment phase as well as longitudinal time points to capture significant parameters associated with breast symmetry at early and later time points. Lastly, because the camera was housed at our main center, only 27% (77/287) of patients randomized in the multicenter trial underwent 3D photographic assessment at 3 years after completion of radiation therapy. Nonetheless, 3D surface images from this subset of patients generated valuable insight into quantitative measures that correlate with subjective reports of breast cosmesis after BCT.

In conclusion, vertical measurements of nipple location and breast volumes derived from 3D photographs were associated with patient- and/or physician-reported cosmesis at 3 years. Overall, breast cosmesis as determined by objective measures in women treated with HF-WBI was comparable to those treated with CF-WBI, further supporting subjective cosmetic evaluations reported by others previously. Three-dimensional measures of breast symmetry can be applied in future clinical trials to objectively assess cosmetic outcome and to guide shared decision making for selection of breast conserving therapies.

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Supplementary data

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