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

Bhavana V. Chapman, MD, Xiudong Lei, PhD, Prithvi Patil, MS, Shikha Tripathi, MS, Krista M. Nicklaus, MS, Aaron J. Grossberg, MD, PhD, Simona F. Shaitelman, MD, EdM, Alastair M. Thompson, MD, Kelly K. Hunt, MD, Thomas A. Buchholz, MD, FASTRO, Fatima Merchant, PhD, Mia K. Markey, PhD, Benjamin D. Smith, MD, FASTRO, and Jay P. Reddy, MD, PhD

Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; Health Services Research, The University of Texas MD Anderson Cancer Center, Houston, Texas; Department of Engineering Technology, University of Houston, Houston, Texas; The University of Texas Health Science Center at Houston, Houston, Texas; Department of Plastic Surgery, The University of Texas MD Anderson Cancer Center, Houston, Texas; Department of Biomedical Engineering, The University of Texas at Austin, Austin, Texas; Department of Radiation Medicine, Oregon Health and Science University, Portland, Oregon; Breast Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; Department of Surgery, Division of Surgical Oncology, Baylor College of Medicine, Houston, Texas; Scripps MD Anderson Cancer Center, La Jolla, California; Department of Computer Science, University of Houston, Houston, Texas; and Imaging Physics, The University of Texas MD Anderson Cancer Center, Houston, Texas

Received 28 March 2020; revised 14 April 2020; accepted 16 April 2020

Sources of support: This study was supported by a grant from the Conquer Cancer Foundation (American Society for Clinical Oncology) funded by the Breast Cancer Research Foundation awarded to Dr Smith. Dr Smith is also supported by the Andrew Sabin Family Fellowship, the Cancer Prevention and Research Institute of Texas (Grant RP 160670), and the National Cancer Institute (R01CA207216 and R01CA225646). Additional funding is from R01CA203984, R01CA143190, and P30CA016672, and by the MD Anderson Cancer Center for Radiation Oncology Research.

Disclosures: Dr Smith has an equity interest in Oncora Medical, unrelated to the current project. Dr Smith and Dr Shaitelman previously received research funding from Varian Medical Systems, unrelated to the current project. Dr Shaitelman receives research funding from Elekta, but this did not support the current project. Dr Hunt is on the medical advisory board for Armada Health and Merck & Co and received research funding from Endomagnetics, Lumicell, and OncoNano, all outside the scope of the current project.

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

* Corresponding author: Jay P. Reddy, MD, PhD; E-mail: JRReddy@mdanderson.org

https://doi.org/10.1016/j.adro.2020.04.035
2452-1094/© 2020 The Authors. Published by Elsevier Inc. on behalf of American Society for Radiation Oncology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
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 \( \beta 1 (TGF\beta 1) \) status.

Methods and Materials: From 2011 to 2014, 287 women age \( \geq 40 \) 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 \( TGF\beta 1 \) 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 \( TGF\beta 1 \) 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 is a more sensitive method for measuring subtle cosmetic changes than global patient- or physician-reported assessments.

© 2020 The Authors. Published by Elsevier Inc. on behalf of American Society for Radiation Oncology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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 aesthetic 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 \( \beta 1 (TGF\beta 1) \) polymorphism status, a potential genomic marker for radiation-related fibrosis.\(^10\)

Methods and Materials

Patient cohort

Between February 2011 and February 2014, 287 women \( \geq 40 \) 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.5

**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 associated with subjective measures of cosmesis using the Radiation Therapy Oncology Group (RTOG) scale: 1 = excellent; 2 = good; 3 = fair; and 4 = poor. The Spearman correlation coefficient was used 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
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 TGF\(b\) 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). TGF$\beta$I 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](image-url) Consolidated Standards of Reporting Trials (CONSORT) diagram.
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 $0.975$ ($< 0.975, n = 57; \geq 0.975, n = 20$) for patient-reported cosmesis and $0.925$ ($< 0.925, n = 22; \geq 0.925, n = 55$) for physician-reported cosmesis. This approach yielded a volume ratio cut point of $0.928$ ($< 0.928, n = 22; \geq 0.928, n = 55$) 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.

### Table 1

| 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  | 1.01 (0.54-1.98) |
| 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  |                |

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

### Table 2

| Reported cosmetic outcome | 1-1.9 (excellent-good; n = 50) | >1.9 (fair-poor; n = 27) | Median (IQR) | $P$  |
|--------------------------|---------------------------------|--------------------------|---------------|------|
| 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.

### 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 ($P > .3$).
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. 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 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)                    |            |                |       |
| F1 C < 0.975                                       | 1          |                |       |
| F1 C ≥ 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/m²                                      | 1          |                |       |
| BMI 25-29.9 kg/m²                                   | 0.33       | 0.08-1.29      | .11   |
| BMI ≥ 30 kg/m²                                      | 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)                   |            |                |       |
| F1 C < 0.925                                       | 1          |                |       |
| F1 C ≥ 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.

Table 4  Three-dimensional photograph measures stratified by treatment arm

| 3D photograph measure                          | CF-WBI | Median (IQR) or % | HF-WBI | Median (IQR) or % | P     |
|------------------------------------------------|--------|------------------|--------|------------------|-------|
| Continuous                                      |        |                  |        |                  |       |
| F1 C                                            | 39     | 0.95 (0.92-0.98) | 38     | 0.95 (0.92-0.97) | .68   |
| F2 C                                            | 39     | 0.90 (0.85-0.95) | 38     | 0.92 (0.79-0.98) | .98   |
| F3 C                                            | 39     | 0.94 (0.90-0.96) | 38     | 0.94 (0.90-0.97) | .76   |
| F4 C                                            | 39     | 0.90 (0.87-0.95) | 38     | 0.90 (0.84-0.96) | .73   |
| F5 C                                            | 39     | 0.97 (0.95-0.98) | 38     | 0.96 (0.93-0.97) | .07   |
| F6 C                                            | 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                                    |        |                  |        |                  |       |
| F1 C < 0.975                                    | 27     | 47               | 30     | 53               |       |
| F1 C ≥ 0.975                                    | 12     | 60               | 8      | 40               | .33   |
| F1 C < 0.925                                    | 12     | 55               | 10     | 46               |       |
| F1 C ≥ 0.925                                    | 27     | 49               | 28     | 51               | .67   |
| Volume (treated/untreated) < 0.928              | 12     | 55               | 10     | 46               | .67   |
| 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.
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 ratios 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, 0.93-0.98 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. Although the oncologic equivalence of HF-WBI has been substantiated, in the United States, HF-WBI schedules are underused in eligible patients. 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. 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. 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

### 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 |  .17 |
| F1C ≥ 0.975           | 11      | 58 | 8 | 42 |  .18 |
| F1C < 0.925           | 10      | 59 | 7 | 41 |  .18 |
| F1C ≥ 0.925           | 20      | 40 | 30 | 60 |  .18 |
| Volume (treated/untreated) < 0.928 | 9 | 45 | 11 | 55 |  .98 |
| Volume (treated/untreated) ≥ 0.928 | 21    | 45 | 26 | 55 |  .98 |

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

Acknowledgments

Support provided in part by the Assessment, Intervention and Measurement (AIM) Shared Resource through a Cancer Center Support Grant (CA16672, PI: P. Pisters, MD Anderson Cancer Center) from the National Cancer Institute, National Institutes of Health, and through the Duncan Family Institute for Cancer Prevention and Risk Assessment.

Supplementary data

Supplementary material for this article can be found at https://doi.org/10.1016/j.adro.2020.04.035.

References

1. Owen JR, Ashton A, Bliss JM, et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: Long-term results of a randomised trial. Lancet Oncol. 2006;7:467-471.
2. Whelan TJ, Pignol J-P, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med. 2010;362:513-520.
3. Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results.
of two randomised controlled trials. *Lancet Oncol.* 2013;14:1086-1094.

4. Chen CM, Cano SJ, Klassen AF, et al. Measuring quality of life in oncologic breast surgery: A systematic review of patient-reported outcome measures. *Breast J.* 2010;16:587-597.

5. Kanatas A, Velikova G, Roe B, et al. Patient-reported outcomes in breast oncology: A review of validated outcome instruments. *Tumori.* 2012;98:678-688.

6. Harris JR, Levene MB, Svensson G, et al. Analysis of cosmetic results following primary radiotherapy for stages I and II carcinoma of the breast. *Int J Radiat Oncol Biol Phys.* 1979;5:257-261.

7. Cardoso MJ, Santos AC, Cardoso J, et al. Choosing observers for evaluation of aesthetic results in breast cancer conservative treatment. *Int J Radiat Oncol Biol Phys.* 2005;61:879-881.

8. Reddy JP, Lei X, Huang S-C, et al. Quantitative assessment of breast cosmetic outcome after whole-breast irradiation. *Int J Radiat Oncol Biol Phys.* 2017;97:904-902.

9. O’Connell RL, Stevens RJG, Harris PA, et al. Review of three-dimensional (3D) surface imaging for oncoplastic, reconstructive and aesthetic breast surgery. *Breast Edinb Scotl.* 2015;24:331-342.

10. Grossberg AJ, Lei X, Xu T, et al. Association of transforming growth factor β polymorphism C-509T with radiation-induced fibrosis among patients with early-stage breast cancer: A secondary analysis of a randomized clinical trial. *JAMA Oncol.* 2018;4:1751-1757.

11. Shaitelman SF, Schlembach PJ, Arzu I, et al. Acute and short-term toxic effects of conventionally fractionated vs hypofractionated whole-breast irradiation: A randomized clinical trial. *JAMA Oncol.* 2015;1:931-941.

12. Shaitelman SF, Lei X, Thompson A, et al. Three-Year Outcomes With Hypofractionated Versus Conventionally Fractionated Whole-Breast Irradiation: Results of a Randomized, Noninferiority Clinical Trial. *J Clin Oncol Off J Am Soc Clin Oncol.* 2018: JCO1800317.

13. Stanton AL, Krishnan L, Collins CA. Form or function? Part I. Subjective cosmetic and functional correlates of quality of life in women treated with breast-conserving surgical procedures and radiotherapy. *Cancer.* 2001;91:2273-2281.

14. Lee J, Kawale M, Merchant FA, et al. Validation of stereophotogrammetry of the human torso. *Breast Cancer Basic Clin Res.* 2011;5:15-25.

15. Kawale M, Lee J, Leung SY, et al. 3D symmetry measure invariant to subject pose during image acquisition. *Breast Cancer Basic Clin Res.* 2011;5:131-142.

16. Reece GP, Merchant F, Andon J, et al. 3D surface imaging of the human female torso in up right to supine positions. *Med Eng Phys.* 2015;37:375-383.

17. Li D, Cheong A, Reece GP, et al. Computation of breast ptosis from 3D surface scans of the female torso. *Comput Biol Med.* 2016;78:18-28.

18. Smith BD, Bellon JR, Blitzblau R, et al. Radiation therapy for the whole breast: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. *Prac Radiat Oncol.* 2018;8:145-152.

19. Hahn C, Kavanagh B, Bhatnagar A, et al. Choosing wisely: The American Society for Radiation Oncology’s top 5 list. *Prac Radiat Oncol.* 2014;4:349-355.

20. Bekelman JE, Sylwestrzak G, Barron J, et al. Uptake and costs of hypofractionated vs conventional whole breast irradiation after breast conserving surgery in the United States, 2008-2013. *JAMA.* 2014;312:2542-2550.

21. Jagsi R, Griffith KA, Heimburger D, et al. Choosing wisely? Patterns and correlates of the use of hypofractionated whole-breast radiation therapy in the state of Michigan. *Int J Radiat Oncol Biol Phys.* 2014;90:1010-1016.

22. Wang EH, Mougalian SS, Soulsor PR, et al. Adoption of hypofractionated whole-breast irradiation for early-stage breast cancer: A National Cancer Data Base analysis. *Int J Radiat Oncol Biol Phys.* 2014;90:993-1000.

23. Hahn EA, Segawa E, Kaiser K, et al. Health-related quality of life among women with ductal carcinoma in situ or early invasive breast cancer: Validation of the FACT-B (version 4). *Expert Rev Qual Life Cancer Care.* 2016;1:99-109.

24. Racz JM, Hong NL, Latosinsky S. In search of a gold standard scoring system for the subjective evaluation of cosmetic outcomes following breast-conserving therapy. *Breast J.* 2015;21:345-351.

25. Dahlbäck C, Ringberg A, Manjer J. Aesthetic outcome following breast-conserving surgery assessed by three evaluation modalities in relation to health-related quality of life. *BJS Br J Surg.* 2019;106:90-99.

26. Dahlbäck C, Ullmark JH, Rehn M, et al. Aesthetic result after breast-conserving therapy is associated with quality of life several years after treatment. Swedish women evaluated with BCCT.core and BREAST-Q®. *Breast Cancer Res Treat.* 2017;164:679-687.

27. Fitzal F, Krois W, Trischler H, et al. The use of a breast symmetry index for objective evaluation of breast cosmesis. *Breast Edinb Scotl.* 2017;16:429-435.

28. Cardoso MJ, Cardoso J, Amaral N, et al. Turning subjective into objective: The BCCT.core software for evaluation of cosmetic results in breast cancer conservative treatment. *Breast Edinb Scotl.* 2017;16:456-461.

29. Heil J, Dahlkamp J, Golla M, et al. Aesthetics in breast conserving therapy: Do objectively measured results match patients’ evaluations? *Ann Surg Oncol.* 2011;18:134-138.

30. Tepper OM, Unger JG, Small KH, et al. Mammmometrics: The standardization of aesthetic and reconstructive breast surgery. *Plast Reconstr Surg.* 2010;125:393-400.

31. Oliveira HP, Silva MD, Magalhães A, et al. Is kinect depth data accurate for the aesthetic evaluation after breast cancer surgeries? In: Sanches JM, Micó L, Cardoso JS, eds. *Pattern Recognition and Image Analysis. Lecture Notes in Computer Science.* Berlin, Heidelberg: Springer; 2013:261-268.

32. Pöhlmann STL, Hewes J, Williamson AI, et al. Breast volume measurement using a games console input device. In: Fujita H, Hara T, Muramatsu C, eds. *Image Analysis. Lecture Notes in Computer Science.* Cham: Springer International Publishing; 2014:666-673.

33. Salmon R, Garby M, Moore LW, et al. Interrogating a multifactorial model of breast conserving therapy with clinical data. *PLoS ONE.* 2015;10.