International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

Hypofractionated Whole-Breast Irradiation in Large-Breasted Women—Is There a Dosimetric Predictor for Acute Skin Toxicities?

Ankur K. Patel, MD, Diane C. Ling, MD, Adam H. Richman, MD, Colin E. Champ, MD, M. Saiful Huq, PhD, FAAPM, FInstP, Dwight E. Heron, MD, MBA, FACRO, FACR, and Sushil Beriwal, MD, MBA

Department of Radiation Oncology, UPMC Hillman Cancer Center, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Received Jun 4, 2018, and in revised form Jul 29, 2018. Accepted for publication Aug 14, 2018.

Summary

Underutilization of hypofractionated whole-breast irradiation in large-breasted women may be partially explained by concerns about dose heterogeneity and lack of validated dosimetric guidelines. We examined acute grade 3 dermatitis rates with hypofractionated whole-breast irradiation in large-breasted patients when our institutionally designed dosimetric guidelines are followed and evaluated predictors for skin toxicity. Whole-breast clinical target volume receiving 105% of the prescription dose (V105) >10% was a significant

Purpose: Underutilization of hypofractionated whole-breast irradiation (HF-WBI) in large-breasted women may be partially explained by concerns about dose heterogeneity. Although modern planning may mitigate this issue, validated dosimetric guidelines are lacking. Our clinical pathway mandates hypofractionation, guided by institutional dosimetric criteria for plan evaluation. We examined acute radiation dermatitis rates with HF-WBI in large-breasted patients when our guidelines are followed and evaluated factors predictive for dermatitis.

Methods and Materials: Patients with whole-breast clinical target volumes (WB-CTV) of $\geq$1000 cm^3 treated with HF-WBI were reviewed. WB-CTV V105, V107, and V110 were assessed. Our guidelines recommend limiting V105 to <10% to 15% and V110 to 0%. The highest grade of acute dermatitis was recorded. Potential clinical and dosimetric predictors of dermatitis were analyzed using logistic regression.

Results: From 2012 to 2017, 505 breasts in 502 patients were treated with HF-WBI. The median WB-CTV was 1261.3 cm^3 (interquartile range [IQR], 1115.3-1510.0). Most plans (99%) delivered 42.56 Gy in 16 fractions. A cavity boost of 10 Gy in 4 fractions was delivered in 99% of plans. Electrons were used in 69% of boost plans. Three-dimensional field-in-field technique was used in 68% of plans and inverse-planned intensity modulated radiation therapy in 32%. The median WB-CTV V105 was 9.7% (IQR, 5.6%-13.3%); the median WB-CTV V107 was 0.8% (IQR, 0.0%-2.5%). The WB-CTV V110 was 0% in 97.4% of plans (median, 0.0%; IQR, 0.0%-0.0%). Grade 1, 2, and 3 dermatitis rates were 55.0%, 40.8%, and 3.4%, respectively.

Reprint requests to: Sushil Beriwal, MD, MBA, Department of Radiation Oncology, UPMC Hillman Cancer Center, Magee-Womens Hospital of UPMC, 300 Halket St, Pittsburgh, PA 15213. Tel: (412) 641-4600; E-mail: beriwals@upmc.edu

This project was funded by the Shadyside Hospital Foundation.

Conflict of interest: S.B. is assistant medical director for radiation oncology of Via Oncology (Pittsburgh, PA). Via Oncology is an affiliated company of the University of Pittsburgh Medical Center and the University of Pittsburgh Cancer Institute and is a part of Elsevier. S.B. is also a senior editor for the *International Journal of Radiation Oncology, Biology, Physics.*

Int J Radiation Oncol Biol Phys, Vol. 103, No. 1, pp. 71–77, 2019
0360-3016/$ - see front matter
https://doi.org/10.1016/j.ijrobp.2018.08.024

predictor of grade 3 dermatitis and is a useful parameter to guide optimization of breast radiation plans.

On multivariate analysis, age >64 years ($P = .016$; odds ratio [OR] 4.0; 95% confidence interval [CI], 1.3-12.3), WB-CTV >1500 cm^3 ($P = .006$; OR, 4.3; 95% CI, 1.5-12.3), body mass index ≥34 ($P = .044$; OR, 3.9; 95% CI, 1.0-14.5), and WB-CTV V105 >10% ($P = .011$; OR, 5.3; 95% CI, 1.5-19.3) predicted for grade 3 dermatitis. **Conclusions:** With our institutional dosimetric guidelines, grade 3 dermatitis rates with HF-WBI in large-breasted women was <5%. WB-CTV V105 should be optimized to <10% to keep grade 3 dermatitis rates <2%.

Introduction

In women with early-stage breast cancer, whole-breast irradiation decreases local recurrence and breast cancer mortality after breast-conserving surgery.[1] Hypofractionated whole-breast irradiation (HF-WBI) has been shown to provide equivalent outcomes in comparison to conventionally fractionated whole-breast irradiation (CF-WBI).[2-4] Despite evidence-based consensus guidelines and long-term results from randomized trials comparing HF-WBI versus CF-WBI,[5,6] HF-WBI in the United States remains underutilized in eligible patients.[7,8] Reasons for the slow adoption of HF-WBI are multifactorial, including concerns about difficulty achieving dose homogeneity and minimizing acute skin toxicity when delivering a higher dose per fraction in large-breasted women. There is currently no consensus on appropriate parameters for dose homogeneity in hypofractionated breast radiation plans. The United Kingdom hypofractionation trials allowed for dose variation between 95% and 105%,[2,3] and the Canadian hypofractionation trial[9] allowed for dose variation of prescription dose ±7%, but neither trial evaluated for a correlation between acute skin toxicities and 3-dimensional (3D) dose distribution.

The potential for increased acute skin toxicities with HF-WBI is of particular concern in large-breasted patients because of difficulty achieving dose homogeneity, stemming from a large separation between the medial and lateral aspects of the breast. Data on acute skin toxicity with HF-WBI in large-breasted patients using modern planning techniques are limited.[10,11] The Canadian hypofractionation trial[9] excluded women with a maximum separation of breast tissue >25 cm, and women with large breasts (based on baseline photographs) encompassed only 12% to 18% of the study groups in the U.K. hypofractionation trials.[2,3] Furthermore, patients included in the aforementioned HF-WBI trials were primarily treated with 2-dimensional techniques with dose calculations performed at a point along the central axis.[2,3,9]

Although large-breasted women pose unique challenges in breast radiation planning, modern field-in-field 3-dimensional and inverse-planning intensity modulated radiation therapy (IMRT) techniques may help mitigate issues of dose heterogeneity. However, validated dosimetric criteria that predict for skin toxicities with HF-WBI using modern planning techniques are lacking.

At our integrated cancer center network, we have implemented a breast cancer clinical pathway that mandates HF-WBI in eligible patients. Furthermore, we have developed institutional guidelines on dosimetric criteria for dose homogeneity to guide breast radiation treatment planning. Herein, we report rates of acute radiation dermatitis with HF-WBI in large-breasted patients when our institutional dosimetric guidelines are followed, and we evaluate factors potentially predictive for skin toxicity.

Methods and Materials

We retrospectively analyzed a series of patients treated with HF-WBI between 2012 and 2017 at 10 sites within our network. Patients included in the analysis had a whole-breast clinical target volume (CTV) of at least 1000 cm^3. All patients had invasive breast cancer or carcinoma in situ treated with breast-conserving therapy. Surgical treatment consisted of segmental mastectomy with sentinel lymph node evaluation in women with invasive breast cancer and segmental mastectomy alone for women with carcinoma in situ. Chemotherapy and antihormonal therapy were administered at the discretion of the treating physicians. Patients treated with regional node irradiation were not eligible for HF-WBI and were not included in this study.

Radiation planning and delivery

Patients were simulated with a computed tomography scan in the supine position. Deep inspiratory breath-hold was used for simulation and treatment of left-sided breast cancers at the discretion of the treating physician. The boundaries of breast tissue and whole-breast CTV (WB-CTV) were defined clinically using standard anatomic boundaries, as suggested by the Radiation Therapy Oncology Group breast contouring atlas. WB-CTV was typically cropped 5 mm from the skin surface. For patients in whom axillary levels 1 and 2 were intentionally treated with high tangents, the WB-CTV was modified appropriately to reflect inclusion of these levels. Whole-breast planning target volume (WB-PTV) was typically defined as a 3- to 5-mm expansion of the WB-CTV, edited along anatomic boundaries. The boost CTV was defined by a 1-cm expansion on the cavity, edited to exclude muscle and

bone, and the boost planning target volume (PTV) was defined by a 3- to 5-mm expansion on the boost CTV. A hypofractionated course of radiation was defined as a definitive dose to the whole breast of ≥2.5 Gy per fraction. Our clinical pathway permits an optional tumor bed boost of 10 Gy in 4 to 5 fractions using electron or photon beam irradiation. In patients with involved sentinel lymph nodes who did not undergo an axillary lymph node dissection, level 1 and 2 axillary lymph nodes were treated with high tangential fields.

Whole-breast plans were created using 3D, forward-planned, field-in-field technique or inverse-planning tangential beam IMRT to meet institutional dosimetric criteria, limiting WB-CTV V105 to <10% to 15% and V110 to 0% and limiting hotspots in the inframammary fold and nipple-areolar complex to <105%. These constraints were applied to the whole-breast treatment alone, without the boost plan. IMRT technique was used if constraints were unable to be met using 3D technique. The coverage goal for breast PTV was D95 >95% (95% of the PTV receiving 95% of the prescribed dose), although D90 >90% was also deemed acceptable to meet homogeneity goals. When optimizing the whole-breast plan, the coverage goal for the boost PTV was D100 ≥95% (100% of the volume receiving ≥95% of the prescription dose). A representative whole-breast treatment plan is shown in Figure 1.

When delivered, lumpectomy cavity boosts were performed using either photon or electron technique. If photons were used, the target volume was the boost PTV, as described in the preceding sections. When electrons were used, a typical block margin of 2 to 2.5 cm on the cavity was used for the electron cutout.

Acute toxicity grading

Patients were evaluated on a weekly basis for acute toxicities. The highest grade of radiation dermatitis for each treated breast was prospectively recorded at each on-treatment and follow-up visit, using National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 grading criteria. Patients were offered topical skin treatments for radiation dermatitis at the discretion of the treating physician. We do not have institutional guidelines recommending specific moisturizing products or lotions for radiation dermatitis. In general, a moisturizing lotion was recommended for grade 1 to 2 dermatitis, and grade 3 dermatitis was treated with sterile petrolatum gauze dressings. Patients were typically seen for follow-up 1 month after completing treatment.

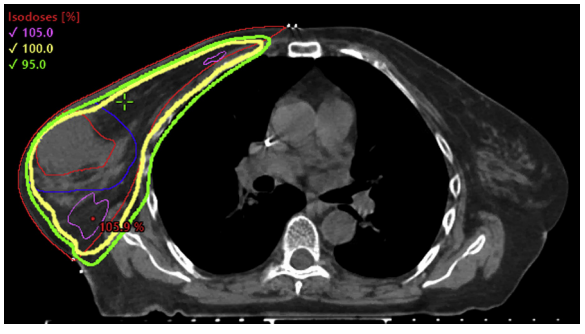

Fig. 1. Representative treatment plan showing the 95%, 100%, and 105% isodose lines. The large red contour represents the whole-breast clinical target volume. The small red contour represents the tumor cavity, and the blue contour represents the boost planning target volume. (A color version of this figure is available at https://dx.doi.org/10.1016/j.ijrobp.2018.08.024.)

Data collection and statistical analysis

Demographic characteristics; clinical and pathologic tumor characteristics; and details of radiation, chemotherapy, and antihormonal treatments were recorded for each patient. Each radiation treatment plan was accessed, and dosimetric parameters of heterogeneity (including WB-CTV V105, V107, and V110) were analyzed using a dose-volume histogram. The highest grade of acute radiation dermatitis, defined as treatment-related dermatitis occurring during or within 3 months of completing treatment, was recorded based on Common Terminology Criteria for Adverse Events v4.0 criteria (Table 1).

Data were obtained from an institutional review board–approved database of patients who were treated with HF-WBI within our network of cancer centers and had a WB-CTV of at least 1000 cm^3. Records were obtained from integrated sites through the ARIA Record-and-Verify database (Varian Medical Systems, Palo Alto, CA). Data analysis was performed with SPSS version 24 (IBM, Armonk, NY). Univariate analysis using binary logistic regression was performed to test for associations between acute skin toxicity and clinical and pathologic variables, treatment characteristics, and dosimetric parameters. Multivariate binary logistic regression using forward stepwise conditional modeling was used to examine independent associations between skin toxicity and covariates with a P value of <.10 on univariate analysis. The exception was WB-PTV, which was not included in the multivariate analysis, given the redundancy of this variable with WB-CTV. P values < .05 were considered significant. No adjustments were made for multiple testing.

Results

Patient and treatment characteristics

Overall, 2511 patients were treated with HF-WBI between 2012 and 2017 in our network. Of these, 735 (29.3%) had WB-CTV >1000 cm^3, out of which a sample of 502 patients (20.0%) with 505 treated breasts were randomly selected for inclusion in this study. Patient and treatment characteristics are displayed in Table 2. Most patients were

Table 1 CTCAE version 4.0 grading of acute radiation dermatitis

Acute radiation dermatitis grade	Definition
Grade 1	Faint erythema or dry desquamation
Grade 2	Moderate to brisk erythema, moderate edema, or patchy moist desquamation confined to the skin folds and creases
Grade 3	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion
Grade 4	Life-threatening consequences; skin necrosis or ulceration of full-thickness dermis; spontaneous bleeding from involved site; skin grafting indicated

Abbreviation: CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events, v4.0.

pathologic stage T1 (64.6%), N0 (96.4%), with estrogen receptor-positive and progesterone receptor-positive disease (86.5% and 78.5%, respectively). A dose of 42.56 Gy in daily fractions of 2.66 Gy was delivered in most (n = 500) of the plans (99.0%), but a minority (0.8%) received 40.0 Gy in 15 fractions (n = 4). One patient was planned to receive 42.56 Gy but stopped treatment prematurely after 31.92 Gy because of development of cellulitis in the treated breast that required hospitalization.

A tumor bed boost of 10 Gy in 2.5-Gy daily fractions was delivered in 99.4% of treatment plans, and electrons were used in 68.8% of boost plans. 3D planning using field-in-field technique was used in 67.5% of treatment plans, with inverse-planning IMRT used in the remaining 32.5%. IMRT was more likely to be used with WB-CTV >1500 cm^3 (P = .022).

Only 3.2% of plans intentionally covered the level 1 and 2 axillary lymph nodes. The median WB-CTV and WB-PTV volumes were 1261.30 cm^3 (interquartile range [IQR], 1115.25-1510.00) and 1472.35 cm^3 (IQR, 1259.68-1805.23), respectively. The median WB-CTV V105 was 9.67% (IQR, 5.6%-13.3%), and median WB-CTV V107 was 0.8% (IQR, 0.0%-2.5%). WB-CTV V110 was 0% in 97.4% of plans (median, 0.0%; IQR 0.0%-0.0%).

Predictors of acute radiation dermatitis

Rates of grade 1, 2, and 3 acute radiation dermatitis were 55.0%, 40.8%, and 3.4%, respectively (Table 3). No instances of grade 4 radiation dermatitis occurred. Only 1.8% of patients required a break because of treatment toxicity. On univariate analysis, the only significant predictors for grade $\geq$2 dermatitis were WB-PTV and body mass index (BMI) as a continuous variable (Table 4). There was a trend for increased grade $\geq$2 dermatitis with use of photons versus electrons for tumor bed boost (P = .079). In a multivariate model including WB-PTV, BMI, and use of photons versus electrons for tumor bed boost, only BMI remained a significant predictor for grade $\geq$2 dermatitis (P = .009; odds ratio [OR], 1.04; 95% confidence interval [CI], 1.01-1.07).

Predictors for grade 3 dermatitis on univariate analysis included age greater than the median of 64 years,

Table 2 Patient and treatment characteristics

Characteristic	n (%)*
Patients	502
Treated breasts	505
Age (y)	
Median (range)	64 (36-89)
Pathologic T stage	
T0	21 (4.2)
Tis	80 (15.8)
T1	326 (64.6)
T2	72 (14.2)
T3	4 (0.8)
Unknown	2 (0.4)
Pathologic N stage	
N0	487 (96.4)
N1	18 (3.6)
Hormone expression†	
ER+	270 (86.5)
PR+	245 (78.5)
HER2+	37 (11.8)
Unknown	193
Treatment technique	
3D	341 (67.5)
IMRT	164 (32.5)
Boost technique	
Photons	153 (31.2)
Electrons	337 (68.8)
Coverage of axilla levels 1-2	
Yes	16 (3.2)
No	489 (96.8)
Chemotherapy‡	
None	420 (83.2)
Neoadjuvant	34 (6.7)
Adjuvant	53 (10.5)
Hormonal therapy	
Yes	410 (81.2)
No	93 (18.4)
Unknown	2 (0.4)
WB-CTV median (IQR), cm^3	1261.30 (1115.25-1510.00)
V105 median (IQR)	9.67% (5.61-13.28)
V107 median (IQR)	0.82% (0.03-2.46)
V110 median (IQR)	0.00% (0.00-0.00)

Abbreviations: 3D = 3-dimensional; ER+ = estrogen receptor-positive; and *HER2* = human epidermal growth factor receptor 2; IMRT = intensity modulated radiation therapy; IQR = interquartile range; PR+ = progesterone receptor-positive; V105 = volume receiving 105% of the prescription dose; V107 = volume receiving 107% of the prescription dose; V110 = volume receiving 110% of the prescription dose; WB-CTV = whole breast clinical target volume.

* Unless indicated otherwise.

† ER, PR, and *HER2* positivity are expressed as percentage of patients whose hormonal status is known.

‡ One patient had both neoadjuvant and adjuvant chemotherapy.

Table 3 Incidence of acute radiation dermatitis by grade

Grade	Incidence (%)
Grade 1 dermatitis	55.0
Grade 2 dermatitis	40.8
Grade 3 dermatitis	3.4

BMI as a continuous variable, BMI greater than or equal to the median of 34, WB-CTV as both a continuous variable (cm^3) and a categorical variable (>1500 cm^3), WB-PTV both as a continuous variable (cm^3) and a categorical variable (>1500 cm^3), and WB-CTV V105 >10% (Table 4). Breast laterality, race, menopausal status, use of 3D over IMRT, use of high tangents to cover the level 1 and 2 axillary lymph nodes, and boost modality did not predict for grade 3 dermatitis. On multivariate analysis, age >64 years (P = .016; OR, 4.0; 95% CI, 1.3-12.3), WB-CTV >1500 cm^3 (P = .006; OR, 4.3; 95% CI, 1.5-12.3), BMI ≥34 (P = .044; OR, 3.9; 95% CI, 1.0-14.5), and WB-CTV V105 >10% (P = .011; OR, 5.3; 95% CI, 1.5-19.3) predicted for grade 3 dermatitis (Table 5). Rates of grade 3 dermatitis in patients with 0, 1, 2, 3, and 4 of the factors significant on multivariate analysis were 1.0%, 1.0%, 2.5%, 6.3%, and 40.0%, respectively.

Table 4 Predictors of acute radiation dermatitis on univariate analysis

Covariate	Grade 2-3 dermatitis		Grade 3 dermatitis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (y)				
> median 64	0.958 (0.673-1.363)	.811	2.876 (0.998-8.287)	**.050***
BMI				
Continuous	1.042 (1.012-1.072)	**.005***	1.082 (1.009-1.161)	**.028***
≥ median 34	1.405 (0.986-2.002)	.060	4.405 (1.250-15.524)	**.021***
Race				
White vs other	1.588 (0.829-3.042)	.163	0.709 (0.157-3.208)	.656
Postmenopausal (yes vs no)	0.896 (0.437-1.838)	.765	1.112 (0.143-8.663)	.919
Laterality				
Left vs right	1.084 (0.763-1.541)	.652	1.089 (0.413-2.868)	.863
3D vs IMRT	0.731 (0.503-1.063)	.101	1.585 (0.509-4.940)	.427
Boost modality (electrons vs photons)	0.709 (0.483-1.040)	.079	0.827 (0.300-2.278)	.713
Boost PTV				
Continuous (cm^3)	1.001 (0.999-1.003)	.606	1.003 (1.000-1.007)	.080
As % of WB-CTV	1.178 (0.086-16.206)	.903	3.124 (0.008-1237.65)	.709
Neoadjuvant chemotherapy (yes vs no)	0.672 (0.325-1.390)	.284	0.862 (0.111-6.700)	.887
WB-CTV				
Continuous (cm^3)	1.000 (1.000-1.001)	.170	1.001 (1.000-1.002)	**.008***
>1500 cm^3	1.162 (0.779-1.735)	.462	4.381 (1.632-11.762)	**.003***
WB-PTV				
Continuous (cm^3)	1.000 (1.000-1.001)	**.016***	1.001 (1.000-1.001)	**.028***
>1500 cm^3	1.299 (0.900-1.874)	.176	5.411 (1.534-19.089)	**.009***
WB-CTV V105				
Continuous (cm^3)	1.001 (0.999-1.002)	.527	1.005 (1.002-1.008)	**<.001***
>10%	1.146 (0.806-1.630)	.448	5.638 (1.600-19.869)	**.007***
>15%	1.165 (0.739-1.836)	.512	3.367 (1.246-9.097)	**.017***
WB-CTV V107				
Continuous (cm^3)	1.000 (0.996-1.004)	.970	1.004 (0.998-1.010)	.187
>0%	1.114 (0.731-1.699)	.616	2.234 (0.503-9.917)	.290
> median 0.82%	0.859 (0.605-1.221)	.398	2.460 (0.854-7.087)	.096
WB-CTV V110				
Continuous (cm^3)	1.003 (0.993-1.014)	.557	1.002 (0.980-1.024)	.877
>0%	0.809 (0.371-1.764)	.594	1.067 (0.136-8.349)	.951

Abbreviations: 3D = 3-dimensional; BMI = body mass index; boost PTV = boost planning target volume; CI = confidence interval; IMRT = intensity modulated radiation therapy; OR = odds ratio; V105 = volume receiving 105% of the prescription dose; V107 = volume receiving 107% of the prescription dose; V110 = volume receiving 110% of the prescription dose; WB-CTV = whole breast clinical target volume; WB-PTV = whole-breast planning target volume.

* P values < 0.05 are considered statistically significant.

Table 5 Predictors of acute grade 3 radiation dermatitis on multivariate analysis

Variable*	n (%)	Rate of grade 3 dermatitis (%)	OR (95% CI)	*P* value
Age (y)				
≤64	271 (54)	1.8		
>64	234 (46)	5.1	3.99 (1.30-12.25)	.016
BMI				
<34	239 (48)	1.3		
≥34	264 (52)	5.3	3.88 (1.04-14.52)	.044
WB-CTV (cm^3)				
≤1500	375 (74)	1.9		
>1500	234 (26)	4.3	4.33 (1.53-12.29)	.006
WB-CTV V105				
≤10%	270 (54)	1.1		
>10%	235 (46)	6.0	5.32 (1.47-19.32)	.011

Abbreviations: BMI = body mass index; CI = confidence interval; OR = odds ratio; V105 = volume receiving 105% of the prescription dose; WB-CTV = whole breast clinical target volume.

* Whole-breast planning target volume was not entered into the multivariate model given redundancy with WB-CTV. Boost planning target volume as a continuous variable and V107 greater than the median of 0.82% were entered into the multivariate analysis but dropped out of the final model.

Discussion

This report is the first to our knowledge that examines 3D dosimetric parameters predictive of acute skin toxicities with modern HF-WBI in large-breasted women, who pose unique challenges in breast radiation planning. We found that age >64 years, BMI ≥34, WB-CTV >1500 cm^3, and WB-CTV V105 >10% were significant independent predictors of acute grade 3 radiation dermatitis on multivariate analysis. Patients with all 4 of these factors had a 40.0% risk of grade 3 radiation dermatitis, compared with a risk of <5% for patients with 0 to 2 of these factors. We chose to limit our analysis to large-breasted women with a WB-CTV >1000 cm^3 because dose homogeneity is more difficult to achieve in this population due to anatomic constraints. Our results show that when our institutional guidelines on dosimetric heterogeneity are implemented, HF-WBI in large-breasted women is associated with a low rate of severe skin toxicity; the overall rate of grade 3 radiation dermatitis was less than 5%. By limiting WB-CTV V105 to <10%, grade 3 dermatitis occurred in less than 2% of patients.

Various dosimetric measures of heterogeneity that predict for acute skin toxicities with CF-WBI have been reported.[12-18] However, studies examining the correlation of dosimetric factors with acute skin toxicities in HF-WBI are sparse. Furthermore, multiple single-institution studies analyzing predictors for acute radiation dermatitis with HF-WBI evaluated cohorts of patients in which only a fraction were treated with HF-WBI. Tortorelli et al found that in women receiving whole-breast irradiation, the volume receiving 107% of the prescription dose (V107) was a significant predictor of grade 2 to 3 skin reactions on multivariate analysis; however, only 61% (n = 121) of the cohort received HF-WBI of 44 Gy in 2.75-Gy daily fractions.[17] In a cohort of patients in which 50% (n = 66) received HF-WBI, Keenan et al[14] found that V105 and V107 did not predict for grade 2 or higher acute skin toxicity, but V105 >30 cm^3 was a significant predictor on multivariate analysis. A single-institution Italian study evaluating 212 women who received 40.04 Gy in 15 daily fractions with or without a 9-Gy tumor bed boost using 3D conformal planning identified breast volume, boost administration, and surgical deficits as predictors for any grade of acute radiation dermatitis on multivariate analysis.[13] However, neither breast volume nor boost volume receiving >100%, >104%, or >107% of the prescription dose were statistically significant predictors. The aforementioned studies involved small cohorts of patients in which only a fraction were large-breasted, limiting application of the findings to obese or large-breasted women.[13,17]

Dorn et al examined a series of 80 breasts in overweight or obese women treated with 42.56 Gy in 2.66-Gy daily fractions using wedges or forward-planned field-in-field techniques.[10] No patients received a lumpectomy cavity boost. Median V105, V107, and V110 were 17.4%, 5.3%, and 0.09%, respectively, compared with 9.7%, 0.8%, and 0.0%, respectively, in our series. Focal moist desquamation occurred outside of the inframammary fold in 2.5% of patients in their study and in an unknown location in 1.3% of patients. The only characteristic associated with skin toxicity was breast volume. The authors found correlations between V105, V107, and V110 and larger breast volume, but they did not examine correlations between dosimetric parameters of heterogeneity and severity of acute radiation dermatitis.

Before our study, there were limited data supporting appropriate dosimetric parameters for HF-WBI. Our institutional guidelines for HF-WBI planning were created to guide breast radiation planning in an effort to minimize dose heterogeneity and acute skin toxicity. Breast radiation plans at our institution are recommended to limit WB-CTV V105 to <10% to 15%, V110 to 0%, and hotspots in the

inframammary fold and nipple-areolar complex to <105%. We found that optimizing the V105 to <10% limited the rate of grade 3 radiation dermatitis to 1.1% (Table 5). Therefore, the V105 is a useful parameter to guide HF-WBI planning. Indeed, the most recent American Society for Radiation Oncology evidence-based guidelines for whole-breast irradiation recommend minimizing the volume of breast tissue receiving >105% of the prescription dose.[6] Our study also should alleviate concerns about achieving dose homogeneity in large-breasted patients undergoing HF-WBI. In the era of modern radiation planning techniques, these concerns should no longer be a barrier to adopting HF-WBI in the community setting because implementing dose homogeneity guidelines similar to those used at our institution should minimize the severity of acute skin toxicity.

Limitations of our study include its retrospective design and the subjective nature of toxicity grading, which was performed individually by the treating physicians. It is possible that some of the worst acute toxicities were not captured because acute toxicities can often peak 3 to 7 days after the last radiation treatment but are significantly improved by the 1-month posttreatment visit. Because the patients at our institution were treated in the supine position, the applicability of our results to women treated in the prone position, often used for large-breasted women, is not as clear. We did not examine predictors for late radiation toxicity, given the poor reliability of retrospective chart review in determining the severity of late radiation-induced skin toxicity, which was not consistently recorded in the medical record. However, long-term results from the Canadian and U.K. hypofractionation trials have shown no worsening of late skin toxicity, cosmesis, or quality of life with HF-WBI when compared with conventional fractionation.[4,19] Furthermore, because acute skin toxicity has been shown to predict for late skin fibrosis and telangiectasias,[20] it is likely that adhering to our institutional dosimetric criteria to minimize acute severe skin toxicity will lead to low rates of late skin toxicity.

Conclusions

With implementation of our institutionally designed dosimetric guidelines, HF-WBI in large-breasted women is associated with a low grade 3 dermatitis rate of <5%. To further reduce the risk of skin toxicity in this population, WB-CTV V105 should be optimized to <10% to keep grade 3 dermatitis rates <2%.

References

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: Meta-analysis of individual patient data for 10 801 women in 17 randomised trials. *Lancet* 2011;378:1707-1716.
2. START Trialists' Group, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: A randomised trial. *Lancet Oncol* 2008;9:331-341.
3. START Trialists' Group, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: A randomised trial. *Lancet* 2008;371:1098-1107.
4. 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.
5. Smith BD, Bentzen SM, Correa CR, et al. Fractionation for whole breast irradiation: An American Society for Radiation Oncology (ASTRO) evidence-based guideline. *Int J Radiat Oncol* 2011;81:59-68.
6. 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. *Pract Radiat Oncol* 2018;8:145-152.
7. Chapman BV, Rajagopalan MS, Heron DE, et al. Clinical pathways: A catalyst for the adoption of hypofractionation for early-stage breast cancer. *Int J Radiat Oncol Biol Phys* 2015;93:854-861.
8. Jagsi R, Falchook AD, Hendrix LH, et al. Adoption of hypofractionated radiation therapy for breast cancer after publication of randomized trials. *Int J Radiat Oncol Biol Phys* 2014;90:1001-1009.
9. Whelan T, MacKenzie R, Julian J, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. *J Natl Cancer Inst* 2002;94:1143-1150.
10. Dorn PL, Corbin KS, Al-Hallaq H, et al. Feasibility and acute toxicity of hypofractionated radiation in large-breasted patients. *Int J Radiat Oncol Biol Phys* 2012;83:79-83.
11. Hannan R, Thompson RF, Chen Y, et al. Hypofractionated whole-breast radiation therapy: Does breast size matter? *Int J Radiat Oncol Biol Phys* 2012;84:894-901.
12. Chen M-F, Chen W-C, Lai C-H, et al. Predictive factors of radiation-induced skin toxicity in breast cancer patients. *BMC Cancer* 2010;10:508.
13. Ciammella P, Podgornii A, Galeandro M, et al. Toxicity and cosmetic outcome of hypofractionated whole-breast radiotherapy: Predictive clinical and dosimetric factors. *Radiat Oncol* 2014;9:97.
14. Keenan LG, Lavan N, Dunne M, et al. Modifiable risk factors for acute skin toxicity in adjuvant breast radiotherapy: Dosimetric analysis and review of the literature. [epub ahead of print]. Med Dosim. Available at: https://doi.org/10.1016/j.meddos.2018.01.004. Accessed May 9 2018.
15. Pignol J-P, Olivotto I, Rakovitch E, et al. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. *J Clin Oncol* 2008;26:2085-2092.
16. Stelzer KJ, Bailey B, Davidson M, et al. Determination of critical dosimetric parameters for breast radiation using forward-planned segmented fields for intensity modulation. *Med Dosim* 2007;32:23-32.
17. Tortorelli G, Di Murro L, Barbarino R, et al. Standard or hypofractionated radiotherapy in the postoperative treatment of breast cancer: A retrospective analysis of acute skin toxicity and dose inhomogeneities. *BMC Cancer* 2013;13:230.
18. Wright JL, Takita C, Reis IM, et al. Prospective evaluation of radiation-induced skin toxicity in a race/ethnically diverse breast cancer population. *Cancer Med* 2016;5:454-464.
19. Hopwood P, Haviland JS, Sumo G, et al. Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials. *Lancet Oncol* 2010;11:231-240.
20. Pignol J-P, Truong P, Rakovitch E, et al. Ten years results of the Canadian breast intensity modulated radiation therapy (IMRT) randomized controlled trial. *Radiother Oncol* 2016;121:414-419.