Original Investigation

Acute and Short-term Toxic Effects of Conventionally Fractionated vs Hypofractionated Whole-Breast Irradiation
A Randomized Clinical Trial

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IMPORTANCE The most appropriate dose fractionation for whole-breast irradiation (WBI) remains uncertain.

OBJECTIVE To assess acute and 6-month toxic effects and quality of life (QOL) with conventionally fractionated WBI (CF-WBI) vs hypofractionated WBI (HF-WBI).

DESIGN, SETTING, AND PARTICIPANTS Unblinded randomized trial of CF-WBI (n = 149; 50.00 Gy/25 fractions + boost [10.00-14.00 Gy/5-7 fractions]) vs HF-WBI (n = 138; 42.56 Gy/16 fractions + boost [10.00-12.50 Gy/4-5 fractions]) following breast-conserving surgery administered in community-based and academic cancer centers to 287 women 40 years or older with stage 0 to II breast cancer for whom WBI without addition of a third field was recommended; 76% of study participants (n = 217) were overweight or obese. Patients were enrolled from February 2011 through February 2014 and observed for a minimum of 6 months.

INTERVENTIONS Administration of CF-WBI or HF-WBI.

MAIN OUTCOMES AND MEASURES Physician-reported acute and 6-month toxic effects using National Cancer Institute Common Toxicity Criteria, and patient-reported QOL using the Functional Assessment of Cancer Therapy for Patients with Breast Cancer (FACT-B). All analyses were intention to treat, with outcomes compared using the χ^2 test, Cochran-Armitage test, and ordinal logistic regression.

RESULTS Of 287 participants, 149 were randomized to CF-WBI and 138 to HF-WBI. Treatment arms were well matched for baseline characteristics, including FACT-B total score (HF-WBI, 120.1 vs CF-WBI, 118.8; $P = .46$) and individual QOL items such as somewhat or more lack of energy (HF-WBI, 38% vs CF-WBI, 39%; $P = .86$) and somewhat or more trouble meeting family needs (HF-WBI, 10% vs CF-WBI, 14%; $P = .54$). Maximum physician-reported acute dermatitis (36% vs 69%; $P < .001$), pruritus (54% vs 81%; $P < .001$), breast pain (55% vs 74%; $P = .001$), hyperpigmentation (9% vs 20%; $P = .002$), and fatigue (9% vs 17%; $P = .02$) during irradiation were lower in patients randomized to HF-WBI. The rate of overall grade 2 or higher acute toxic effects was less with HF-WBI than with CF-WBI (47% vs 78%; $P < .001$). Six months after irradiation, physicians reported less fatigue in patients randomized to HF-WBI (0% vs 6%; $P = .01$), and patients randomized to HF-WBI reported less lack of energy (23% vs 39%; $P < .001$) and less trouble meeting family needs (3% vs 9%; $P = .01$). Multivariable regression confirmed the superiority of HF-WBI in terms of patient-reported lack of energy (odds ratio [OR], 0.39; 95% CI, 0.24-0.63) and trouble meeting family needs (OR, 0.34; 95% CI, 0.16-0.75).

CONCLUSIONS AND RELEVANCE Treatment with HF-WBI appears to yield lower rates of acute toxic effects than CF-WBI as well as less fatigue and less trouble meeting family needs 6 months after completing radiation therapy. These findings should be communicated to patients as part of shared decision making.

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To our knowledge, 4 randomized clinical trials including over 7000 women have compared conventionally fractionated (CF) whole-breast irradiation (WBI) with hypofractionated (HF) WBI.[1-3] With 10-year follow-up, these studies have shown equivalent rates of overall survival and local control between the 2 treatment regimens. In addition, the United Kingdom START A and B trials[1] reported less moderate or marked breast induration, telangiectasia, breast edema, and breast shrinkage in women randomized to HF-WBI. Nevertheless, adoption of HF-WBI in the United States has been slow, with only one-third of patients for whom HF-WBI is endorsed by the American Society for Radiation Oncology (ASTRO) actually receiving this treatment.[4-7]

The reasons underlying slow adoption of HF-WBI in the United States are likely multifactorial and reflect both scientific and pragmatic concerns.[8] Key obstacles to adoption of HF-WBI in the United States include the lingering concern that HF-WBI may actually increase toxic effects due to higher dose per fraction and questions regarding the applicability of the published trials to (1) practices that routinely use a tumor bed boost and (2) patients with higher body mass index (BMI) and larger central axis separation.[8,9]

We sought to address these obstacles to adoption of HF-WBI by incorporating detailed toxic effect and quality of life (QOL) assessments into a randomized clinical trial of HF-WBI vs CF-WBI, both followed by a tumor bed boost and inclusive of all patients regardless of BMI or central axis separation. Herein, we report physician-reported acute and 6-month toxic effects and patient-reported QOL by treatment arm.

At a Glance

- We assess acute and 6-month toxic effects and quality of life with conventionally fractionated (CF) whole-breast irradiation (WBI) vs hypofractionated (HF) WBI.
- A total of 287 women 40 years or older with stage 0 to II breast cancer following breast-conserving surgery were randomized to receive treatment with CF-WBI (50.00 Gy/25 fractions + boost) or HF-WBI (42.56 Gy/16 fractions + boost).
- Acute dermatitis, pruritus, breast pain, hyperpigmentation , and fatigue during irradiation were lower in patients randomized to HF-WBI.
- At 6 months, among HF-WBI patients, physicians reported less fatigue, and patients reported less lack of energy and less trouble meeting family needs.
- Multivariable regression confirmed an association between HF-WBI and less patient-reported lack of energy (odds ratio [OR], 0.39; 95% CI, 0.24-0.63) and trouble meeting family needs (OR, 0.34; 95% CI, 0.16-0.75).

Methods

This study was approved by the University of Texas MD Anderson Cancer Center institutional review board (study protocol provided in Supplement 1) and was independently monitored by the institution's data safety and monitoring board. Written informed consent was obtained from each participant.

Enrollment

Patients were enrolled from February 2011 through February 2014 at The University of Texas MD Anderson Cancer Center (including the main campus located in the Texas Medical Center and 4 surrounding MD Anderson regional centers); Orlando Health (formerly MD Anderson Orlando, Orlando, Florida); and Banner MD Anderson Cancer Center in Gilbert, Arizona. Women eligible for enrollment were 40 years or older with pathologically confirmed ductal carcinoma in situ or invasive breast cancer (stage Tis-T2, N0-N1a, M0) treated with breast-conserving surgery with final negative margins (defined as "no tumor on ink") and with the physician-declared intent to deliver WBI without addition of a third field to cover the regional lymph nodes. Exclusion criteria included concomitant active treatment for another malignant condition or lesion, history of prior breast cancer, bilateral breast cancer, prior overlapping irradiation, pregnancy, or lack of fluency in English or Spanish.

Randomization

Patients were randomly allocated to treatment with either HF-WBI (42.56 Gy in 16 fractions of WBI) or CF-WBI (50.00 Gy in 25 fractions of WBI). The tumor bed boost doses, if final margins were negative by 2 mm or more or if there was a negative re-excision, were 10 Gy in 4 fractions and 10 Gy in 5 fractions for HF-WBI and CF-WBI, respectively; if final margins were less than 2 mm, the tumor bed boost doses were 12.5 Gy in 5 fractions and 14.0 Gy in 7 fractions for HF-WBI and CF-WBI, respectively. The Pocock-Simon[10] randomization method of dynamic allocation was used to balance the arms of the study for postoperative physician-reported cosmetic assessment (excellent/good vs fair/poor), bra cup size (D or higher vs C or lower), receipt of chemotherapy (yes vs no), margin status (<2 mm vs ≥2 mm), and treatment location (Houston area facilities vs Banner MD Anderson vs Orlando Health).

Radiation Treatment

Patients were treated with megavoltage tangential portals and forward- or inverse-planned segmental fields to improve dose homogeneity. Dose was prescribed to a calculation point in the breast, within 2 cm of the chest wall-lung interface. Patient positioning in the supine or prone position was at the physician's discretion. Radiation oncologists were instructed to minimize the volume of tissue receiving greater than 108% of the prescription dose. Coverage of the undissected low axilla (levels I and II) was permitted if clinically indicated. The boost was delivered with either electrons or photons and could be omitted if the tumor bed volume precluded safe delivery of the boost.

Patient Assessments

Patient-reported QOL was determined using the Functional Assessment of Cancer Therapy for Patients with Breast Cancer (FACT-B), version 4, in either English or Spanish.[11-13] The FACT-B was administered prior to initiation of irradiation and 6 months after completing radiation therapy. The developer's guidelines were used for scoring the FACT-B, including handling of missing data.[14]

Physician Assessments

The treating physician assessed toxic effects using the National Cancer Institute Common Toxicity Criteria, version 4.0 (NCICTCv4.0). All patients underwent weekly toxic effects assessments during irradiation and were scheduled for assessment 6 months after completing radiation therapy. Additional toxic effects evaluations were conducted at the discretion of the treating physician and/or prompted by patient need. Acute toxic effects were defined as those occurring during irradiation or within 42 days of completion of radiation therapy; the maximum grade of each acute toxic effect is reported herein. Six-month toxic effects were defined as those documented at the 6-month follow-up visit. All toxic effects were recorded by the treating physician using templates specifying common radiation-related toxic effects and their definitions according to NCICTCv4.0.

Statistical Methods

The long-term primary outcome of this study will ultimately be the proportion of patients with an adverse patient-reported cosmetic outcome, determined using the validated Breast Cancer Treatment Outcomes Scale,[15] 3 years after completion of treatment. This outcome will be reported when all patients have completed a minimum of 3 years of follow-up. The trial was designed to enroll 288 evaluable patients, which yields 90% power with a 1-sided significance level of 0.10 to test the hypothesis that the probability of an adverse cosmetic outcome with HF-WBI is no more than 10% worse than the probability of an adverse cosmetic outcome with CF-WBI, assuming a prevalence of adverse cosmetic outcome of 35% with HF-WBI and 40% with CF-WBI and a dropout rate of 5%. Prespecified secondary outcomes, reported herein, include differences by randomization arm in physician-reported acute and 6-month toxic effects and patient-reported QOL. These secondary outcomes were considered hypothesis-generating outcomes and were thus not adjusted for multiplicity.

Differences in baseline patient, tumor, and treatment characteristics by randomization arm were assessed using the χ^2 test or the exact calculation of the Fisher exact test as appropriate. Race/ethnicity was determined via patient report and categorized by applying standard definitions in use by the US Census Bureau.[16] Differences by randomization arm in physician-reported acute and 6 month toxic effects were assessed using the Cochran-Armitage test for trend or χ^2 test as appropriate. Exploratory, post hoc subset analyses explored whether these toxic effects differed for patients in the highest quartile of BMI or central axis separation. Differences by randomization arm in FACT-B total score and component scores were assessed using the *t* test at baseline and at the 6 month assessment. Difference by randomization arm between FACT-B total and component scores at 6 months relative to baseline was also assessed via the *t* test. Given a borderline association between physical well-being and randomization arm, differences in outcome by randomization arm for each of the 7 items contributing to physical well-being were assessed using the Cochran-Armitage test for trend. Because statistically significant associations with randomization arm were noted for question 1 (Q1) ("I have a lack of energy") and question 3 (Q3) ("Because of my physical condition, I have trouble meeting the needs of my family"), ordinal logistic regression models for Q1 and Q3 were created using PROC GENMOD in SAS software, version 9.2 (SAS Institute Inc), using a multinomial distribution and cumlogit link function. We selected the following candidate variables a priori for potential inclusion in these models based on their clinical relevance: randomization arm, age, race, BMI, estrogen receptor status (negative, positive, not tested), tumor behavior (invasive vs in situ), chemotherapy receipt (none, neoadjuvant, or adjuvant), central axis separation, volume of breast tissue receiving 90% of prescription dose, volume of breast tissue receiving 105% of prescription dose, maximum point dose (D_{max}), tumor bed volume, and percentage of dose delivered with 18-MV photons. Continuous variables were divided into quartiles because we did not have any a priori hypotheses regarding specific thresholds or cut points for these variables. Candidate variables were included in the final models if associated with the outcome at $P < .20$ in bivariate analysis. Patients with missing outcome data were excluded from the relevant model. There were no missing covariable values. Sensitivity analyses tested whether type of FACT-B administration (electronic vs paper) was predictive of outcome for each model. All analyses were intention to treat with 2-sided $\alpha = .05$ and were performed using SAS software, version 9.2.

Results

Patients

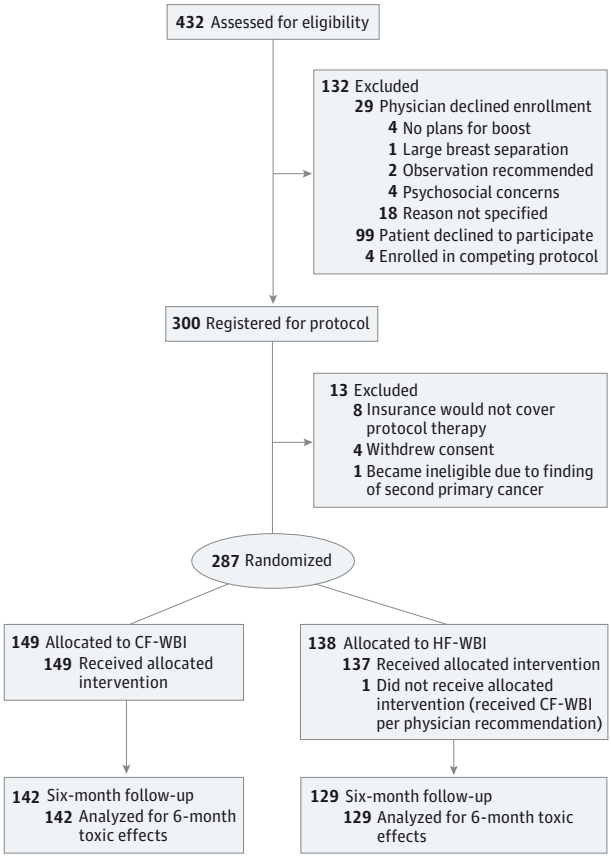
A total of 432 patients were assessed for eligibility for enrollment, of whom 300 patients were registered for protocol treatment and 287 were randomized and evaluable (**Figure**). Of 149 patients randomized to CF-WBI, all (100%) received the allocated WBI and boost doses. Of 138 patients randomized to HF-WBI, 137 (99%) received a hypofractionated schedule of WBI (n = 134, 42.56 Gy/16 fractions; n = 2, 42.40 Gy/16 fractions; n = 1, 42.52 Gy/16 fractions) and 136 (99%) received the allocated boost dose. One patient randomized to HF-WBI (1%) received conventional fractionation (46.00 Gy/23 fractions followed by a boost of 14.00 Gy/7 fractions). The median number of elapsed days over which radiation was delivered was 36 for CF-WBI (interquartile range [IQR], 35-36 days) and 22 for HF-WBI (IQR, 22-23 days). Half of the treatment plans (n = 143) involved a D_{max} of 107% of prescription dose or higher.

In total, 25% of patients (n = 72) were not non-Hispanic white; 28% (n = 80) were overweight; and 48% (n = 137) were obese, as defined by BMI.[17] Median age was 60 years (IQR, 54-66 years). Baseline patient, tumor, and treatment characteristics were well matched (see eTable 1 and eTable 2 in Supplement 2). Of those patients who received systemic therapy, type of therapy was similar between treatment arms.

Acute Toxic Effects

Overall rates of any physician-assessed grade 2 or higher and any grade 3 or higher acute toxic effects were lower with HF-WBI than with CF-WBI (47% vs 78%, $P < .001$ and 0% vs 5%, $P = .01$, respectively) (**Table 1**). For specific acute toxic effects, patients treated with HF-WBI vs CF-WBI had lower rates

Figure. Study Enrollment Flowchart



CF Indicates conventional fractionation; HF, hypofractionation; WBI, whole-breast irradiation.

of physician-assessed fatigue (grade ≥2, 9% vs 17%; $P = .02$ for trend), pruritus (grade ≥1, 54% vs 81%; $P < .001$ for trend), breast pain (grade ≥1, 55% vs 74%; $P < .001$ for trend), dermatitis (grade ≥2, 36% vs 69%; $P < .001$ for trend), and hyperpigmentation (grade ≥2, 9% vs 20%; $P = .002$ for trend). In an exploratory subset analysis, there was no difference in acute grade 2 or higher or grade 3 or higher toxic effect for patients in the highest BMI quartile ($P = .22$ for grade ≥2 [HF-WBI, 58% vs CF-WBI, 72%] and $P = .55$ for grade ≥3 [HF-WBI, 0% vs CF-WBI, 7%]) or for patients in the highest quartile of central axis separation ($P = .17$ for grade ≥2 [HF-WBI, 63% vs CF-WBI, 78%] and $P = .24$ for grade ≥3 [HF-WBI, 0% vs CF-WBI, 8%]).

Six-Month Toxic Effects

A total of 271 of 287 patients (94%) were evaluated for physician-assessed 6-month toxic effects, 142 randomized to CF-WBI (95% of CF patients) and 129 randomized to HF-WBI (94% of HF patients). Patients randomized to HF-WBI experienced less physician-rated grade 2 or higher fatigue than those in the CF-WBI group (0% vs 6%; $P = .01$ for trend). All other 6-month toxic effects were comparable between the 2 treatment arms (**Table 2**). In an exploratory subset analysis, there was no difference in 6-month grade 2 or higher or grade 3 or higher toxic effects for patients in the highest BMI quartile ($P = .86$ for grade ≥2 [HF-WBI, 41% vs CF-WBI, 43%] and $P > .99$ for grade ≥3 [HF-WBI, 0% vs CF-WBI, 2%]) or for patients in the highest quartile of central axis separation ($P = .62$ for grade ≥2 [HF-WBI, 47% vs CF-WBI, 53%] and $P > .99$ for grade ≥3 [HF-WBI, 0% vs CF-WBI, 3%]).

Patient-Reported Quality of Life

Prior to initiation of radiation therapy, 286 of 287 patients (99.7%) completed the FACT-B, 148 randomized to CF-WBI (99% of CF patients) and 138 randomized to HF-WBI (100% of HF patients). As detailed in **Table 3**, The randomization arms were well-matched for all components of the FACT-B, including total score ($P = .46$), physical well-being ($P = .63$), functional well-being ($P = .63$), and breast cancer-specific concerns ($P = .86$).

Also detailed in Table 3, at the 6-month follow up visit, 266 (93%) of 287 patients completed the FACT-B, 128 randomized to HF-WBI (93%) and 138 randomized to CF-WBI (93%). At 6 months, there was no difference by randomization arm in FACT-B total score ($P = .20$), functional well-being ($P = .10$), or breast cancer-specific concerns ($P = .82$). Although it was not statistically significant, there was improved physical well-being in patients randomized to HF-WBI vs CF-WBI at the 6-month follow-up visit (mean score, 25.5 vs 24.7; $P = .06$); there was no significant difference at 6 months relative to baseline (mean score difference, 0.28 vs 0.62; $P = .46$) (Table 3).

As detailed in eTable 3 in Supplement 2, in analyzing responses to the 7 items contributing to physical well-being, we found no difference in any item prior to irradiation ($P \geq .22$). At the 6-month follow-up, outcomes for Q1 (lack of energy) and Q3 (trouble meeting family needs) favored patients randomized to HF-WBI ($P < .001$ and $P = .01$, respectively). There was no difference by randomization arm at 6 months for the other items contributing to physical well-being. Ordinal logistic regression models confirmed the superiority of HF-WBI over CF-WBI on Q1 (lack of energy) (OR, 0.39; 95% CI, 0.24-0.63; $P < .001$) and Q3 (trouble meeting family needs) (OR, 0.34; 95% CI, 0.16-0.75; $P = .01$) (see eTable 4 in Supplement 2).

Discussion

These randomized trial data demonstrate that HF-WBI followed by a tumor bed boost, vs CF-WBI followed by a tumor bed boost, resulted in lower rates of physician-assessed acute toxic effects during radiation therapy and less physician-reported fatigue 6 months after irradiation. Patient-reported outcomes reinforced this finding, with patients randomized to HF-WBI noting less lack of energy and less trouble meeting family needs 6 months after radiation treatment. No measured adverse effects or QOL parameters were worse with HF-WBI compared with CF-WBI.

Defining the Standard of Care for WBI

Our study findings speak directly to the ongoing discussion seeking to define the most appropriate standard of care for dose fractionation in WBI. In 2011, ASTRO published an

Table 1. Physician-Reported Maximum Acute Toxic Effects[a]

Toxic Effect	Patients, No. (%) CF-WBI (n = 149)	HF-WBI (n = 138)	*P* Value[b]
Any grade ≥2 acute toxic effect			
None	33 (22)	73 (53)	<.001
Any	116 (78)	65 (47)	
Any grade ≥3 acute toxic effect			
None	141 (95)	138 (100)	.001
Any	8 (5)	0	
Fatigue			
0	23 (15)	29 (21)	.02
1	101 (68)	97 (70)	
2	20 (13)	12 (9)	
3	5 (3)	0	
Pruritus			
0	29 (20)	63 (46)	<.001
1	110 (74)	69 (50)	
2	10 (7)	6 (4)	
Breast pain			
0	39 (26)	62 (45)	.001
1	97 (65)	69 (50)	
2	13 (9)	7 (5)	
Shoulder arthralgia			
0	124 (83)	120 (87)	.46
1	24 (16)	16 (12)	
2	0	2 (1)	
3	1 (1)	0	
Dermatitis			
0	1 (1)	8 (6)	<.001
1	45 (30)	80 (58)	
2	101 (68)	50 (36)	
3	2 (1)	0	
Hyperpigmentation			
0	45 (30)	60 (44)	.002
1	74 (50)	66 (48)	
2	30 (20)	12 (9)	
Breast edema			
0	94 (63)	98 (71)	.10
1	51 (34)	39 (28)	
2	4 (3)	1 (1)	
3	0	0	
Wound complications, noninfectious			
0	147 (99)	137 (99)	.61
1	2 (1)	1 (1)	
Skin ulceration			
0	142 (95)	136 (99)	.19
1	5 (3)	1 (1)	
2	2 (1)	1 (1)	
Seroma			
0	127 (85)	109 (79)	.19
1	21 (14)	28 (20)	
2	1 (1)	1 (1)	

(continued)

Table 1. Physician-Reported Maximum Acute Toxic Effects[a] (continued)

Toxic Effect	Patients, No. (%) CF-WBI (n = 149)	HF-WBI (n = 138)	*P* Value[b]
Breast infection			
0	145 (97)	136 (99)	.46
2	4 (3)	2 (1)	
Wound infection			
0	148 (99)	137 (99)	.96
2	1 (1)	1 (1)	
Soft-tissue necrosis of the chest wall/thorax			
0	149 (100)	138 (100)	NA
Upper extremity edema			
0	141 (95)	134 (97)	.51
1	8 (5)	3 (2)	
2	0	1 (1)	
All others			
0	133 (89)	128 (93)	.20
1	12 (8)	9 (7)	
2	4 (3)	1 (1)	

Abbreviations: CF, conventionally fractionated; HF, hypofractionated; NA, not applicable; NCICTCv4.0, National Cancer Institute Common Toxicity Criteria, version 4.0; WBI, whole-breast irradiation.

[a] As defined by the NCICTCv4.0. Acute toxic effects were recorded on a weekly basis during radiation therapy using a structured template that specified these toxic effects and their definitions. Any subsequent toxic effect occurring within 42 days of treatment completion was also included in this analysis.

[b] The Cochran-Armitage test for trend used for all values except for any grade 2 or higher toxic effect (χ^2) and any grade 3 or higher toxic effect (Fisher exact test).

evidence-based guideline on fractionation for WBI.[18] The guideline concluded that the evidence suggests the equivalence of HF-WBI to CF-WBI for certain patient groups, notably those with pT1-2 N0 disease, age 50 years and older, not treated with chemotherapy, and where the radiation dose inhomogeneity could be limited to within 7% in the central axis.[18] Notably, however, the ASTRO guideline stopped short of endorsing HF-WBI as a preferred treatment strategy for such patients. Subsequently, in 2013, the ASTRO Choosing Wisely Campaign issued a stronger statement, noting "Don't initiate whole breast radiotherapy as a part of breast conservation therapy in women age ≥50 with early stage invasive breast cancer without considering shorter treatment schedules."[19]

Nevertheless, evidence suggests that there has been limited adoption of HF-WBI in the United States, in contrast to other health care systems. A recent observational cohort study from 14 commercial health care plans in the United States[4] reported that only 34.5% of appropriate candidates for HF-WBI received this treatment in 2013, similar to the rate seen in a study examining practice patterns in Michigan between 2011 and 2013.[6] In contrast, practice patterns in the United Kingdom and Canada have demonstrated much broader uptake of HF-WBI.[20-22] Limited adoption of HF-WBI in the United States has been attributed in part to concerns regarding the applicability of the available evidence to practice patterns in the United States, where use of a tumor bed boost is much more common and where higher prevalence of obesity may result in fewer patients meeting the dose homogeneity or central axis separation criteria applied in the randomized trial literature.[8,9] Within this context, results from our trial provide strong reassurance that HF-WBI with a sequential tumor bed can be safely administered with regard to acute and short-term toxic effects in a patient population where three-quarters of patients were overweight or obese and half had a D_{max} of 107% or higher.

Radiotherapy and Fatigue

Our study findings also improve the understanding of the relevance of fatigue during and after breast irradiation. Previously reported data indicate that both the severity and frequency of patient-reported fatigue increase during the course of radiotherapy, peaking during the last week of treatment and affecting over three-quarters of patients.[23,24] A recent study of 250 patients with breast cancer treated with standard fractionation breast radiotherapy in Norway found that the volume of the breast receiving 40 Gy or more was a significant predictor of increased fatigue during radiotherapy, whereas the volume of the breast receiving 5 Gy was not.[25] Finally, a chart review from the Cancer Institute of New Jersey[26] of 161 patients with breast cancer treated with CF-WBI, HF-WBI, and accelerated partial breast irradiation found mean fatigue was less with HF-WBI than with CF-WBI at the first week, midway, and 4 weeks after completion of radiation therapy.

Notably, the present study is the first to prospectively measure and report lack of energy before initiation of radiation treatment and 6 months after irradiation within the context of a randomized trial. Our novel finding of a differential effect between the treatment arms on lack of energy supports the hypothesis that HF-WBI confers a substantive benefit to patients beyond the abbreviated time to complete therapy. We hypothesize that less fatigue in the HF-WBI arm translated into less trouble meeting family needs. Strikingly, our multivariable analysis found that the negative impact of CF-WBI on both energy and ability to meet family needs was comparable to or greater than the effect of adjuvant chemotherapy on these end points. Furthermore, we found that dosimetric parameters were not associated with these patient-reported outcomes, suggesting that these complications are truly driven by the selected dose-fractionation scheme and not the volume of tissue treated or relative hot spots.

Table 2. Physician-Assessed Maximum Toxic Effects at 6 Months[a]

Toxic Effect	Patients, No. (%) CF-WBI (n = 142)	HF-WBI (n = 129)	*P* Value[b]
Combined			
Any grade ≥2			
None	96 (68)	89 (69)	.81
Any	46 (32)	40 (31)	
Any grade ≥3			
None	140 (99)	129 (100)	.18
Any	2 (1)	0	
Constitutional			
Fatigue			
0	89 (63)	94 (73)	.01
1	44 (31)	35 (27)	
2	9 (6)	0	
Dermatologic			
Skin hyperpigmentation			
0	49 (35)	54 (42)	.65
1	82 (58)	60 (47)	
2	11 (8)	15 (12)	
Skin induration			
0	121 (85)	104 (81)	.43
1	19 (13)	24 (19)	
2	2 (1)	1 (1)	
Dermatitis			
0	121 (85)	111 (86)	.73
1	20 (14)	18 (14)	
2	1 (1)	0	
Telangiectasia			
0	138 (97)	126 (98)	.60
1	3 (2)	3 (2)	
2	1 (1)	0	
Skin ulceration			
0	142 (100)	129 (100)	NA
Wound complications, noninfectious			
0	142 (100)	129 (100)	NA
Infection			
Breast infection			
0	141 (99)	128 (99)	.83
2	0	1 (1)	
3	1 (1)	0	
Wound infection			
0	142 (100)	129 (100)	NA
Lymphatics			
Upper extremity edema			
0	140 (99)	127 (98)	.92
1	2 (1)	2 (2)	
Breast edema			
0	114 (80)	97 (75)	.78
1	21 (15)	30 (23)	
2	7 (5)	2 (2)	

(continued)

Table 2. Physician-Assessed Maximum Toxic Effects at 6 Months[a] (continued)

Toxic Effect	Patients, No. (%) CF-WBI (n = 142)	HF-WBI (n = 129)	*P* Value[b]
Musculoskeletal or Soft Tissue			
Fibrosis-superficial soft tissue			
0	111 (78)	100 (78)	.89
1	30 (21)	28 (22)	
2	1 (1)	1 (1)	
Fibrosis-deep connective tissue			
0	121 (85)	104 (81)	.26
1	21 (15)	24 (19)	
2	0	1 (1)	
Seroma			
0	127 (89)	114 (88)	.80
1	14 (10)	13 (10)	
2	0	2 (2)	
Soft-tissue necrosis of the chest wall/thorax			
0	142 (100)	129 (100)	NA
Pain			
Breast pain			
0	99 (70)	92 (71)	.89
1	41 (29)	32 (25)	
2	2 (1)	5 (34)	
Other pain			
0	132 (93)	123 (95)	.49
1	9 (6)	5 (4)	
2	1 (1)	1 (1)	
Pulmonary			
Cough			
0	141 (99)	125 (97	.14
1	1 (1)	4 (3	
Dyspnea			
0	142 (100)	127 (98)	.14
1	0	2 (2)	
Pneumonitis			
0	142 (100)	129 (100)	NA
Sexual and Reproductive Function			
Nipple/areolar			
0	117 (82)	106 (82)	.93
1	21 (15)	19 (15)	
2	4 (3)	4 (3)	
Breast atrophy			
0	93 (66)	82 (64)	.72
1	33 (23)	31 (24)	
2	16 (11)	16 (12)	
Other			
All others combined			
0	136 (96)	126 (98)	.30
1	5 (4)	3 (2)	
2	1 (1)	0	

Abbreviations: CF, conventionally fractionated; HF, hypofractionated; NA, not applicable; NCICTCv4.0, National Cancer Institute Common Toxicity Criteria, version 4.0; WBI, whole-breast irradiation.

[a] As defined by the NCICTCv4.0. Acute toxic effects were recorded by the treating physician using a structured template that specified the toxic effects and their definitions.

[b] The Cochran-Armitage test for trend used for all values except for any grade 2 or higher toxic effect (χ^2) and any grade 3 or higher toxic effect (Fisher exact test).

Table 3. Mean Baseline and 6 Month FACT-B Scores by Randomization Arm

Parameter	CF-WBI		HF-WBI		*P* Value[a]
	Patients, No.	Mean (95% CI)	Patients, No.	Mean (95% CI)	
Baseline					
Physical well-being	149	24.5 (23.9 to 25.1)	138	24.7 (24.1 to 25.4)	.63
Functional well-being	148	22.2 (21.4 to 23.0)	138	22.5 (21.6 to 23.4)	.63
Emotional well-being	148	20.4 (20.0 to 20.9)	138	20.5 (19.9 to 21.0)	.92
Social well-being	149	24.4 (23.6 to 25.1)	138	25.1 (24.3 to 25.9)	.16
FACT-G total score	148	91.6 (89.7 to 93.4)	138	92.8 (90.9 to 94.8)	.35
Breast cancer concerns	149	27.2 (26.4 to 27.9)	138	27.3 (26.4 to 28.2)	.86
FACT-B total score	148	118.8 (116.4 to 121.1)	138	120.1 (117.5 to 122.6)	.46
Six-Month Follow-up					
Physical well-being	140	24.7 (24.1 to 25.3)	128	25.5 (24.9 to 26.1)	.06
Functional well-being	140	23.2 (22.5 to 24.0)	128	24.1 (23.4 to 24.9)	.10
Emotional well-being	140	21.1 (20.6 to 21.6)	128	21.3 (20.8 to 21.8)	.60
Social well-being	140	24.6 (23.9 to 25.4)	128	24.8 (24.0 to 25.6)	.74
FACT-G total score	138	93.6 (91.8 to 95.5)	128	95.7 (93.9 to 97.6)	.12
Breast cancer concerns	141	28.6 (27.8 to 29.4)	128	28.7 (27.9 to 29.5)	.82
FACT-B total score	138	122.3 (119.9 to 124.7)	128	124.5 (122.1 to 126.9)	.20
Difference Between 6-Month and Baseline Outcomes					
Physical well-being	140	0.28 (−0.40 to 0.95)	128	0.62 (0.04 to 1.19)	.46
Functional well-being	139	1.01 (0.26 to 1.76)	128	1.5 (0.69 to 2.32)	.38
Emotional well-being	139	0.67 (0.06 to 1.29)	128	0.93 (0.23 to 1.63)	.58
Social well-being	140	0.23 (−0.35 to 0.81)	128	−0.31 (−1.24 to 0.61)	.32
FACT-G total score	137	2.29 (0.58 to 4.00)	128	2.74 (0.91 to 4.56)	.73
Breast cancer concerns	141	1.50 (0.71 to 2.28)	128	1.54 (0.62 to 2.46)	.94
FACT-B total score	137	3.85 (1.74 to 5.96)	128	4.27 (2.01 to 6.53)	.79

Abbreviations: CF, conventionally fractionated; FACT-B, Functional Assessment of Cancer Therapy for Patients with Breast Cancer, version 4, in either English or Spanish.[11-13]; FACT-G, Functional Assessment of Cancer Therapy[14]; HF, hypofractionated; WBI, whole-breast irradiation.

[a] *P* value from *t* test.

The biologic mechanism underlying radiation-related fatigue is unclear. Fatigue during and acutely following CF-WBI has previously been found to be linked to higher levels of neutrophils, red blood cells, hemoglobin, and D-dimer, as well as to depression and mood disturbance prior to initiation of radiation treatment.[27-31] During irradiation, a greater decrease in platelets, albumin, and red blood cells has been seen in those patients who develop fatigue. Receipt of WBI has also been associated with alterations in amino acid homeostasis among patients experiencing fatigue, with increased urinary excretion.[30]

Limitations

This study has limitations. First, patients were not routinely assessed within 1 to 3 weeks of concluding radiation therapy, and thus acute toxic effects may have been underascertained if they did not manifest until after completion of irradiation. Second, all of the analyses reported herein were secondary and were considered hypothesis generating. Third, it was not practical to blind patients and physicians to treatment arm within the context of this trial. Fourth, long-term toxic effect data from the trial are still pending. Fifth, the dose-fractionation schema used for the CF arm of the study was 50.00 Gy in 25 fractions; however, 45 to 50 Gy at 1.8 Gy per fraction is also a commonly used method to deliver CF-WBI, and any differences in associated acute and short-term outcomes remain uncertain in their comparison with HF-WBI.

Conclusions

In this randomized clinical trial, HF-WBI resulted in substantially lower rates of acute and short-term toxic effects than CF-WBI. These findings should be communicated to patients as part of shared decision making regarding election of radiotherapy regimen and are relevant to the ongoing discussion regarding the most appropriate standard of care for WBI dose fractionation.

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