Three-Year Outcomes With Hypofractionated Versus Conventionally Fractionated Whole-Breast Irradiation: Results of a Randomized, Noninferiority Clinical Trial

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A B S T R A C T

Purpose

The adoption of hypofractionated whole-breast irradiation (HF-WBI) remains low, in part because of concerns regarding its safety when used with a tumor bed boost or in patients who have received chemotherapy or have large breast size. To address this, we conducted a randomized, multicenter trial to compare conventionally fractionated whole-breast irradiation (CF-WBI; 50 Gy/25 fx + 10 to 14 Gy/5 to 7 fx) with HF-WBI (42.56 Gy/16 fx + 10 to 12.5 Gy/4 to 5 fx).

Patients and Methods

From 2011 to 2014, 287 women with stage 0 to II breast cancer were randomly assigned to CF-WBI or HF-WBI, stratified by chemotherapy, margin status, cosmesis, and breast size. The trial was designed to test the hypothesis that HF-WBI is not inferior to CF-WBI with regard to the proportion of patients with adverse cosmetic outcome 3 years after radiation, assessed using the Breast Cancer Treatment Outcomes Scale. Secondary outcomes included photographically assessed cosmesis scored by a three-physician panel and local recurrence-free survival. Analyses were intention to treat.

Results

A total of 286 patients received the protocol-specified radiation dose, 30% received chemotherapy, and 36.9% had large breast size. Baseline characteristics were well balanced. Median follow-up was 4.1 years. Three-year adverse cosmetic outcome was 5.4% lower with HF-WBI ($P_{\text{noninferiority}} = .002$; absolute risks were 8.2% [$n = 8$] with HF-WBI v 13.6% [$n = 15$] with CF-WBI). For those treated with chemotherapy, adverse cosmetic outcome was higher by 4.1% (90% upper confidence limit, 15.0%) with HF-WBI than with CF-WBI; for large breast size, adverse cosmetic outcome was 18.6% lower (90% upper confidence limit, -8.0%) with HF-WBI. Poor or fair photographically assessed cosmesis was noted in 28.8% of CF-WBI patients and 35.4% of HF-WBI patients ($P = .31$). Three-year local recurrence-free survival was 99% with both HF-WBI and CF-WBI ($P = .37$).

Conclusion

Three years after WBI followed by a tumor bed boost, outcomes with hypofractionation and conventional fractionation are similar. Tumor bed boost, chemotherapy, and larger breast size do not seem to be strong contraindications to HF-WBI.

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INTRODUCTION

Four large, randomized trials have been published comparing hypofractionated whole-breast irradiation (HF-WBI) with conventionally fractionated whole-breast irradiation (CF-WBI).¹⁻³ With a 10-year follow-up on greater than 7,000 patients with early-stage invasive breast cancer, these trials have demonstrated equivalency in both local

control and overall survival (OS). These trials variably allowed delivery of a tumor bed boost, primarily included women who did not receive current-era chemotherapy, and in certain cases restricted enrollment of women with large breast size. Because of questions about the appropriateness of HF-WBI, in 2011 the American Society for Therapeutic Radiology and Oncology (ASTRO) published an evidence-based guideline⁴

ASSOCIATED CONTENT

Appendix
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that endorsed the equivalency of HF-WBI and CF-WBI for patients meeting these criteria: ≥ 50 years of age, pT1-2 N0, not treated with chemotherapy, and central axis dose homogeneity of $\pm 7\%$.

Since 2013, the ASTRO Choosing Wisely Campaign has endorsed considering HF-WBI for such women,⁵ but adoption has been slow in the United States.⁶⁻⁹ Reticence to embrace HF-WBI has included concerns about the effect of this treatment regimen on cosmesis, particularly when used with a tumor bed boost or in patients who receive chemotherapy or with larger breast size.

To address these concerns, we conducted a randomized, phase III noninferiority clinical trial to test the hypothesis that HF-WBI followed by a tumor bed boost is not inferior to CF-WBI followed by a tumor bed boost with respect to the proportion of patients with adverse patient-reported cosmetic outcome 3 years after completing radiation. We specifically sought to include patients for whom controversy remains about the cosmetic effect of HF-WBI, including those treated with neoadjuvant or adjuvant chemotherapy and those with large breast size. We also included women with ductal carcinoma in situ (DCIS) given limited data supporting HF-WBI for this diagnosis.

PATIENTS AND METHODS

Patients

Between February 2011 and February 2014, patients were enrolled in an institutional review board–approved protocol at MD Anderson Cancer Center Main Campus and four surrounding community-based centers, Orlando Health (formerly MD Anderson Orlando, Orlando, FL), and Banner MD Anderson Cancer Center (Gilbert, AZ). Eligibility criteria have been described¹⁰ and included women ≥ 40 years of age with stage Tis-T2N0-N1M0 breast cancer who underwent margin-negative segmental mastectomy. Patients who received regional nodal irradiation via a third field; those with a history of breast cancer, concurrent bilateral breast cancer, prior radiation to potential areas of overlap, or lack of fluency in English or Spanish; and those who were pregnant were not eligible. For this analysis, the database was locked in May 2017.

Random Assignment

Patients were randomly assigned to treatment with CF-WBI (50.00 Gy in 25 fractions) or HF-WBI (42.56 Gy in 16 fractions). Boost dose fractionation varied by treatment arm and margin status. If final margins were negative by 2 mm or more, the dose was 10.0 Gy in five fractions for CF-WBI and 10.0 Gy in four fractions for HF-WBI; if final margins were less than 2 mm, the dose was 14.0 Gy in seven fractions for CF-WBI and 12.5 Gy in five fractions for HF-WBI. Random assignment was stratified by baseline (postoperative, preradiation) physician-assessed cosmesis (excellent or good *v* fair or poor); bra cup size ($\geq$ D cup *v* $\leq$ C cup); receipt of chemotherapy (yes *v* no); margin status (< 2 mm *v* ≥ 2 mm); and treatment location (Houston area *v* Banner MD Anderson *v* Orlando Health).

Radiation Treatment

Radiation was delivered with tangential portals primarily using forward planning to improve dose homogeneity. Radiation dose was prescribed to a calculation point in the breast, typically within 2 cm of the chest wall–lung interface. Radiation was delivered in either the supine or the prone position, at physician discretion. The volume of breast tissue receiving greater than or equal to 108% of the prescription dose was specified to be less than or equal to 1 mL. Coverage of the undissected low axilla (levels 1 and 2) was allowed if indicated. The tumor bed boost was

delivered using either photons or electrons and could be omitted if tumor bed size precluded safe delivery.

Patient-Reported Outcomes

The Breast Cancer Treatment Outcomes Scale (BCTOS) was used to evaluate patient-reported cosmetic outcome, functional status, and breast pain.¹¹ Each BCTOS subscale (cosmetic, functional status, and breast pain) is calculated by computing the arithmetic mean of the answers to each item relevant to a given subscale. The score is a continuous variable ranging from 1 to 4, with 1 indicating no difference between the treated and untreated breast, 2 indicating a slight difference, 3 indicating a moderate difference, and 4 indicating a large difference. For this analysis, each BCTOS outcome was dichotomized at a cut point of greater than or equal to 2.5, reflecting an average difference of moderate or greater. Quality of life was assessed using the Functional Assessment of Cancer Therapy–Breast Treatment Outcome Index (FACT-B TOI), version 4. The FACT-B TOI includes a summary assessment of physical well-being, functional well-being, and breast cancer subscales, with a cumulative score range of 0 to 92. Body image was assessed using the Body Image Scale (BIS).¹²⁻¹⁴ The 10-item BIS is scored in a range of 1 to 4, with a smaller value indicating a better outcome.

Oncologic and Physician-Assessed Outcomes

Physician-assessed cosmetic outcome was evaluated using the Radiation Therapy Oncology Group/Harvard Scale and was scored as excellent, good, fair, or poor.¹⁵ Cosmetic outcome was assessed by the treating physician on the basis of clinical assessment. Cosmetic outcome was also assessed by a three-physician panel blinded to treatment arm. This panel was composed of two breast radiation oncologists (B.D.S. and S.F.S.) and one breast surgical oncologist (A.T.). Before conducting the scoring, the panel reviewed representative photos of each possible cosmetic outcome and discussed the criteria for assessment, which was based on material generated to support photographic scoring for the RAPID trial (ClinicalTrials.gov identifier: NCT00282035).¹⁶ The panel evaluated a total of five photographs per patient (right lateral, right anterior oblique, en face, left anterior oblique, and left lateral) taken at baseline and at 3 years. Scoring was by consensus.

Treating physician–assessed toxicities were recorded for 22 discrete items using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 4) in the domains of constitutional, dermatologic, infection, lymphatic, musculoskeletal or soft tissue, pain, pulmonary, and sexual or reproductive function during follow-up visits, graded on a scale of 0 to 5. Pathologically confirmed local (defined as ipsilateral breast) recurrence, regional recurrence, contralateral breast cancer, and distant metastasis, and OS were also collected prospectively.

Statistical Methods

Differences in baseline patient characteristics, treatment, patient-reported outcomes, and cosmetic outcomes were evaluated using Pearson's χ^2 , Fisher's exact test, and the Wilcoxon rank sum test as appropriate. The primary outcome of this study was defined as the proportion of patients with an adverse patient-reported cosmetic outcome, defined as a BCTOS cosmesis score of 2.5 or more at the 3-year follow-up visit. The null hypothesis specified that the proportion of patients with an adverse cosmetic outcome who received HF-WBI would be at least 10% greater than those who received CF-WBI. The trial was designed initially to enroll a total of 200 evaluable patients, yielding 80% power with a one-sided significance level of 0.10 to test the hypothesis that the probability of an adverse cosmetic outcome with HF-WBI would be greater than or equal to 10% worse than the probability with CF-WBI, assuming a prevalence of adverse cosmetic outcome of 35% with HF-WBI and 40% with CF-WBI. A one-sided *P* value $< .10$ was used to reject the null hypothesis to claim overall noninferiority and was evaluated using a χ^2 test stratified by the baseline cosmetic outcome, bra cup size, receipt of chemotherapy, and

margin status. After enrolling 135 patients, accrual was increased to 288 patients to increase the power to 90%, assuming a dropout rate of 5%. Interim outcomes were not evaluated before choosing to increase accrual.

For each stratification factor, strata-specific effect sizes of the primary outcome were measured with the accompanying 90% upper confidence limit (UCL). For declaration of noninferiority, the upper limit of the one-sided 90% CI needed to be less than 10%.

Associations between the random assignment arm with BCTOS functional status and breast pain, treating physician cosmesis, physician panel cosmesis, and National Cancer Institute CTCAE toxicities were evaluated using Pearson's χ^2 or Fisher's exact test as appropriate. Associations of treatment arm with BIS and FACT-B TOI were evaluated using Wilcoxon rank sum test.

OS, local recurrence-free survival, distant metastasis-free survival and contralateral breast cancer-free survival were calculated from the date of diagnosis to the date of death or cancer-related event using the Kaplan-

Meier method, with differences by treatment arm compared using the log-rank test. A P value $< .05$ was considered statistically significant in detecting a difference in secondary outcomes between the two arms. All analyses were intention to treat and were conducted using SAS, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline Features

Of the 287 patients, 149 were randomly assigned to CF-WBI and all (100%) received the protocol-specified WBI and boost doses; 138 patients were randomly assigned to HF-WBI, and 137 (99.3%) received the allocated WBI dose and 136 (99%) received

Fig 1. Consort diagram. BCTOS, Breast Cancer Treatment Outcomes Scale; BIS, Body Image Scale; CF-WBI, conventionally fractionated whole-breast irradiation; CT, computed tomography; HF-WBI, hypo-fractionated whole-breast irradiation; MD, physician; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

Table 1. Baseline Patient, Tumor, and Treatment Characteristics

Characteristic	CF-WBI (n = 149)		HF-WBI (n = 138)		Total	
	No.	%	No.	%	No.	%
Patient characteristics						
Age at diagnosis, years						
40-49	13	8.7	19	13.8	32	11.1
50-59	55	36.9	46	33.3	101	35.2
60-69	59	39.6	51	37.0	110	38.3
≥ 70	22	14.8	22	15.9	44	15.3
Ethnicity						
White non-Hispanic	116	77.9	99	71.7	215	74.9
Hispanic	16	10.7	20	14.5	36	12.5
Black non-Hispanic	15	10.1	17	12.3	32	11.1
Asian non-Hispanic	2	1.3	2	1.4	4	1.4
Menopausal status						
Premenopausal	9	6.0	13	9.4	22	7.7
Perimenopausal	8	5.4	3	2.2	11	3.8
Postmenopausal	132	88.6	122	88.4	254	88.5
Bra cup size						
A	13	8.7	7	5.1	20	7
B	31	20.8	34	24.6	65	22.6
C	50	33.6	46	33.3	96	33.4
D-EE	55	36.9	51	37.0	106	36.9
BMI, kg/m ²						
< 25	38	25.5	42	30.4	80	27.9
25-29	40	26.8	40	29.0	80	27.9
≥ 30	71	47.7	56	40.6	127	44.3
Physician-assessed cosmesis						
Excellent or good	135	90.5	131	94.8	266	92.7
Fair or poor	14	9.4	7	5.2	21	7.3
Tumor characteristics						
Tumor histology						
Invasive carcinoma	110	73.8	114	82.6	224	78
DCIS	39	26.2	24	17.4	63	22
Tumor grade						
1	40	26.8	34	24.6	74	25.8
2	70	47.0	73	52.9	143	49.8
3	39	26.2	30	21.7	69	24
Unclassified*	0	0.0	1	0.7	1	0.3
Margin status						
Negative, ≥ 2 mm	133	89.3	121	87.7	254	88.5
Close, < 2 mm	16	10.7	17	12.3	33	11.5
Quadrant						
Central	16	10.7	27	19.6	43	15
Lower inner	9	6.0	7	5.1	16	5.6
Lower outer	22	14.8	17	12.3	39	13.6
Upper inner	22	14.8	15	10.9	37	12.9
Upper outer	80	53.7	72	52.2	152	53
Estrogen receptor status						
Positive	130	87.2	118	85.5	248	86.4
Negative	18	12.1	16	11.6	34	11.8
Not tested	1	0.7	4	2.9	5	1.7
Progesterone receptor status						
Positive	112	75.2	102	73.9	214	74.6
Negative	36	24.2	32	23.2	68	23.7
Not tested	1	0.7	4	2.9	5	1.7
HER2-neu status						
Positive	12	8.1	11	8.0	23	8
Negative	102	68.5	103	74.6	205	71.4
Not tested	35	23.5	24	17.4	59	20.6
Pathologic stage among invasive patients without neoadjuvant therapy (n = 196)						
pT1mic-pT1a	16	17.0	12	11.8	28	14.3
pT1b	24	25.5	23	22.5	47	24.0
pT1c	43	45.7	48	47.1	91	46.4
pT2	11	11.7	19	18.6	30	15.3
pN0	79	84.0	89	87.3	168	85.7
pN1mic	14	14.9	6	5.9	20	10.2
pN1a	1	1.1	7	6.9	8	4.1

(continued on following page)

Table 1. Baseline Patient, Tumor, and Treatment Characteristics (continued)

Characteristic	CF-WBI (n = 149)		HF-WBI (n = 138)		Total	
	No.	%	No.	%	No.	%
Clinical and pathologic stage among invasive patients with neoadjuvant therapy (n = 28)						
cT1c	2	12.5	2	16.7	4	14.3
cT2	14	87.5	10	83.3	24	85.7
cN0	13	81.3	11	91.7	24	85.7
cN1a	3	18.8	1	8.3	4	14.3
pT0	7	43.8	5	41.7	12	42.9
pTis	1	6.3	2	16.7	3	10.7
pT1a	2	12.5	0	0.0	2	7.1
pT1b	0	0.0	0	0.0	0	0.0
pT1c	4	25.0	3	25.0	7	25.0
pT2	2	12.5	2	16.7	4	14.3
pN0	16	100.0	12	100.0	28	100
Treatment characteristics						
Chemotherapy						
None	106	71.1	96	69.6	202	70.4
Neoadjuvant	16	10.7	12	8.7	28	9.8
Adjuvant	27	18.1	30	21.7	57	19.9
Anthracycline-based chemotherapy						
Yes	32	21.5	30	21.7	62	21.6
No	117	78.5	108	78.3	225	78.4
Taxane-based chemotherapy						
Yes	39	26.2	39	28.3	78	27.2
No	110	73.8	99	71.7	209	72.8
Herceptin-based therapy						
Yes	10	6.7	9	6.5	19	6.6
No	139	93.3	129	93.5	268	93.4
Treatment location						
Houston area	141	94.6	132	95.7	273	95.1
Banner MD Anderson	4	2.7	0	0.0	4	1.7
Orlando Health	4	2.7	6	4.3	10	3.5
Dmax quartile, % of prescription dose						
≤ 107.00	73	49.0	72	52.2	145	50.5
>107.00	76	51.0	66	47.8	142	49.5
Central axis separation quartile, cm						
< 25.00	104	69.8	95	68.8	199	69.3
≥ 25.00	45	30.2	43	31.2	88	30.7
Met 2011 ASTRO consensus guidelines for hypofractionation						
No	124	83.2	113	81.9	237	82.6
Yes	25	16.8	25	18.1	50	17.4

NOTE. Estrogen receptor positive: ≥ 1% of cells stained for estrogen receptor; progesterone receptor positive: ≥ 1% of cells stained for progesterone receptor; HER2-neu positive: ≥ 3 by immunohistochemistry or gene amplification by fluorescence in situ hybridization. To meet 2011 ASTRO criteria, patients must meet all the following: ≥ 50 years of age, no chemotherapy, Dmax ≤ 107.00%, and stage T1 to T2 N0.

Abbreviations: ASTRO, American Society for Therapeutic Radiology and Oncology; BMI, body mass index; CF-WBI, conventionally fractionated whole-breast irradiation; DCIS, ductal carcinoma in situ; Dmax, maximum dose; HER2, human epidermal growth factor receptor 2; HF-WBI, hypofractionated whole-breast irradiation.

*This patient's cancer was diagnosed on core biopsy but grade could not be assigned. There was no residual disease in the lumpectomy specimen.

the allocated boost dose. At the 3-year follow-up, 213 returned for follow-up (74.2%) and 207 (72.1%) completed the BCTOS cosmetic assessment, of whom 110 were randomly assigned to CF-WBI and 97 to HF-WBI (Fig 1). Median follow-up time was 4.1 years (range, 0.2 to 6.0 years).

Baseline patient and tumor characteristics were well balanced between the two treatment arms and have been described previously.¹⁰ In brief, most patients were ≥ 50 years of age and white non-Hispanic (Table 1). A total of 92.6% of patients had an excellent or good baseline (postoperative, preradiation) cosmesis, which was well balanced by treatment arm. One hundred six patients (36.9%) had a bra cup size of D or larger; 127 (44.3%) were obese; and 85 (29.6%) received chemotherapy, 57 (19.9%) in the adjuvant setting and 28 (9.8%) in the neoadjuvant setting. All

patients treated with chemotherapy received a taxane-based and/or anthracycline-based regimen, and 22.4% (n = 19) received trastuzumab. Of note, 237 of the enrolled patients (82.6%) did not meet the 2011 ASTRO guideline criteria for patients in whom evidence supported equivalence of HF-WBI to CF-WBI.

Patient-Reported Outcomes

Baseline BCTOS cosmetic, functional status, and breast pain scores and BIS and FACT-B TOI were not significantly different by treatment arm (Table 2). The proportion of patients with the primary outcome, adverse patient-reported cosmesis at 3 years, was 8.2% (n = 8) with HF-WBI versus 13.6% (n = 15) with CF-WBI ($P = .002$ for noninferiority), yielding a difference of −5.4%

Table 2. Primary and Secondary Cosmetic and Quality-of-Life Outcomes

Outcome	Baseline					3-Year				
	HF-WBI		CF-WBI		P	HF-WBI		CF-WBI		P
	No.	%	No.	%		No.	%	No.	%	
Primary outcome										
BCTOS cosmesis					.26*					.22
< 2.5	128	96.2	142	98.6		89	91.8	95	86.4	
≥ 2.5	5	3.8	2	1.4		8	8.2	15	13.6	
Secondary outcomes										
BCTOS functional status					.48*					.45*
< 2.5	130	96.3	145	98.0		98	98.0	106	95.5	
≥ 2.5	5	3.7	3	2.0		2	2.0	5	4.5	
BCTOS breast pain					.33					.66
< 2.5	127	94.8	136	91.9		91	91.0	99	89.2	
≥ 2.5	7	5.2	12	8.1		9	9.0	12	10.8	
Treating physician–assessed cosmesis					.16					.40
Good or excellent	131	94.9	135	90.6		71	73.2	86	78.2	
Poor or fair	7	5.1	14	9.4		26	26.8	24	21.8	
Panel physician–assessed cosmesis					.08					.31
Good or excellent	107	79.9	126	87.5		62	64.6	79	71.2	
Poor or fair	27	20.1	18	12.5		34	35.4	32	28.8	
FACT-B TOI†	138	74.5	148	74.0	.72‡	100	77.9	111	77.6	.84‡
BIS†	133	1.3	140	1.3	.98‡	97	1.3	106	1.3	.41‡

NOTE. P values from χ^2 test unless indicated otherwise.

Abbreviations: BCTOS, Breast Cancer Treatment Outcome Scale; BIS, Body Image Scale; CF-WBI, conventionally fractionated whole-breast irradiation; FACT-B TOI, Functional Assessment of Cancer Therapy–Breast Treatment Outcome Index; HF-WBI, hypofractionated whole-breast irradiation.

*Fisher's exact test.

†Data are presented as No. and mean score.

‡Wilcoxon rank sum test.

favoring HF-WBI (the noninferiority margin is +10%) with a 90% UCL of +0.1%. Strata-specific analyses are presented in [Figure 2](#). For patients treated with chemotherapy, adverse cosmetic outcome was +4.1% higher with HF-WBI than with CF-WBI, and thus, noninferiority of HF-WBI in this patient subgroup ($n = 71$) was inconclusive. For patients with poor or fair preradiation cosmesis ($n = 17$) and those with close margins less than 2 mm ($n = 25$), the estimated differences of adverse cosmetic outcomes between HF-WBI and CF-WBI were below +10% (+8.6% and +0.6%, respectively); however, smaller sample sizes limited the power to establish noninferiority in these subgroups, with their UCL greater than 10%. For patients with large breast size, adverse cosmetic outcome was 18.6% lower (90% UCL, −8.0%) with HF-WBI. Strata-specific treatment center location was not evaluated because of the relatively few patients ($n = 14$) not treated in Houston.

Regarding secondary outcomes, there was no difference in 3-year patient-reported adverse functional status (2.0% with HF-WBI ν 4.5% with CF-WBI, $P = .45$) or breast pain (9.0% with HF-WBI ν 10.8% with CF-WBI, $P = .66$; [Table 2](#)). There was also no significant difference by treatment arm in 3-year mean FACT-B TOI score (77.90 with HF-WBI ν 77.64 with CF-WBI, $P = .84$) or mean BIS (1.33 with HF-WBI ν 1.28 with CF-WBI, $P = .41$).

Physician-Assessed Toxic Effects

There was no difference in 3-year poor or fair cosmesis as assessed by the treating physician (26.8% with HF-WBI ν 21.8% with CF-WBI, $P = .40$) or the three-physician panel (35.4% with HF-WBI ν 28.8% with CF-WBI, $P = .31$; [Table 2](#), Appendix [Fig A1](#), online only). At 3 years, a total of 205 patients had a physician-

assessed CTCAE-based toxicity evaluation. Overall, rates of any grade greater than or equal to 2 toxicity were 19.6% with HF-WBI versus 18.5% with CF-WBI ($P = .84$) and rates of grade greater than or equal to 3 toxicity were 0.0% with HF-WBI versus 0.9% with CF-WBI ($P = 1.00$; Appendix [Table A1](#), online only).

Tumor Control Outcomes

There were a total of three deaths, four local recurrences (three in the CF-WBI arm), zero regional recurrences, three distant recurrences, and six contralateral breast cancers. None of the patients with DCIS in the HF-WBI arm experienced a local recurrence. Three-year OS was 100% for HF-WBI and 100% for CF-WBI ($P = .68$; [Table 3](#)). Local, distant, and contralateral breast cancer-free survival at 3 years was similarly high for both arms of the study ([Table 3](#)).

DISCUSSION

In this prospective, randomized, noninferiority trial, we found that HF-WBI with a sequential tumor bed boost was not inferior to CF-WBI with a sequential tumor bed boost with respect to the proportion of patients with an adverse patient-reported cosmetic outcome 3 years after completing WBI. Specifically, 5.4% fewer patients treated with HF-WBI than with CF-WBI experienced an adverse patient-reported cosmetic outcome. This finding meaningfully extends the evidence base supporting extending HF-WBI to a broader patient population, considering that 82.6% of patients included in this trial did not actually meet the 2011 ASTRO

Fig 2. Forest plot. Strata-specific analyses. The x-axis indicates the absolute difference in the percentage of patients with adverse cosmetic outcome (the primary outcome) among those treated with hypofractionated whole-breast irradiation (HF-WBI) minus those treated with conventionally fractionated whole-breast irradiation (CF-WBI). For example, the overall primary outcome was 8.2% with HF-WBI and 13.6% with CF-WBI, for a difference of 8.2% – 13.6% = –5.4%, which is shown as the gold diamond for the overall effect size. The vertical line at 10% indicates the noninferiority margin, and the gold horizontal bars indicate the 90% upper confidence limit (UCL) for each difference. The top two rows of the graph refer to the baseline (postoperative, preradiation) physician-assessed cosmesis, which was one of the stratification factors. CF, conventional fractionation; HF, hypofractionation.

guideline criteria for patients in whom evidence supported equivalence of HF-WBI to CF-WBI. The findings are also relevant to informing patients, because, to our knowledge, this is the only randomized trial evaluating WBI in which the primary outcome is patient reported. Furthermore, to our knowledge, this is the only trial evaluating WBI dose fractionation in which a tumor bed boost was used uniformly. The collective findings thus lend additional evidence to support the conclusion of the 2018 ASTRO guideline on WBI that HF-WBI should be the preferred dose fractionation for patients receiving WBI without the addition of a third field.¹⁷

Furthermore, our unique study design permits the assessment of HF-WBI outcomes in patients for whom the appropriateness of HF-WBI remains controversial (eg, patients treated with current-era chemotherapy regimens or with larger breast size).^{4,18-20} All patients treated with chemotherapy in this study received an anthracycline- or taxane-based regimen, and among these patients, the proportion with an adverse cosmetic outcome was 4.1% higher with HF-WBI than with CF-WBI, although it was below the 10% noninferiority margin, with a 90% UCL of 15.0%. This finding, likely the result of having a moderate sample size, shows that the

Table 3. Three-, 4-, and 5-Year Oncologic Outcomes Overall and by Random Assignment Arm (n = 287)

Outcome	3-Year Estimate (95% CI)	4-Year Estimate (95% CI)	5-Year Estimate (95% CI)
Overall survival			
All (n = 287)	1	1 (0.97 to 1.00)	0.99 (0.94 to 1.00)
CF-WBI (n = 149)	1	1 (0.97 to 1.00)	0.98 (0.89 to 1.00)
HF-WBI (n = 138)	1	0.99 (0.93 to 1.00)	0.99 (0.93 to 1.00)
Local recurrence-free survival			
All (n = 287)	0.99 (0.97 to 1.00)	0.98 (0.96 to 0.99)	0.98 (0.96 to 0.99)
CF-WBI (n = 149)	0.99 (0.95 to 1.00)	0.98 (0.93 to 0.99)	0.98 (0.93 to 0.99)
HF-WBI (n = 138)	0.99 (0.95 to 1.00)	0.99 (0.95 to 1.00)	0.99 (0.95 to 1.00)
Distant recurrence-free survival			
All (n = 287)	0.99 (0.97 to 1.00)	0.99 (0.97 to 1.00)	0.99 (0.97 to 1.00)
CF-WBI (n = 149)	0.99 (0.95 to 1.00)	0.99 (0.95 to 1.00)	0.99 (0.95 to 1.00)
HF-WBI (n = 138)	0.99 (0.95 to 1.00)	0.99 (0.95 to 1.00)	0.99 (0.95 to 1.00)
Contralateral breast cancer-free survival			
All (n = 287)	0.98 (0.95 to 0.99)	0.98 (0.95 to 0.99)	0.98 (0.95 to 0.99)
CF-WBI (n = 149)	0.96 (0.92 to 0.99)	0.96 (0.92 to 0.99)	0.96 (0.92 to 0.99)
HF-WBI (n = 138)	0.99 (0.95 to 1.00)	0.99 (0.95 to 1.00)	0.99 (0.95 to 1.00)

Abbreviations: CF-WBI, conventionally fractionated whole-breast irradiation; HF-WBI, hypofractionated whole-breast irradiation.

trial was inconclusive regarding noninferiority in this strata-specific subgroup. Conversely, our finding that adverse cosmetic outcome was 18.6% lower with HF-WBI than with CF-WBI among patients with D cup or larger breasts offers strong reassurance that HF-WBI should not compromise cosmetic outcome among large-breasted patients. Such data may facilitate shared decision making regarding the choice to proceed with HF-WBI for patients with large breasts. Additional study of current-era chemotherapy combined with HF-WBI could be beneficial to decrease the uncertainty surrounding cosmetic outcome.

Another novel aspect of this study is that, to our knowledge, it was the first randomized trial comparing HF-WBI with CF-WBI that included patients with DCIS. Twenty-two percent of patients ($n = 63$) in this trial had DCIS, and no recurrences were noted in the HF-WBI arm. Although the follow-up time remains relatively short, the findings support the updated ASTRO consensus guidelines, which indicate that HF-WBI may be used for patients with DCIS.¹⁷ Earlier phase II trials and population-based studies similarly supported the oncologic efficacy²¹⁻²⁴ and acceptable toxicity^{23,25,26} of HF-WBI for DCIS. Currently, there is an ongoing multicenter phase III trial by the Trans-Tasman Radiation Oncology Group examining fractionation of radiation in the setting of DCIS, which should definitively address the appropriateness of HF-WBI for DCIS ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00470236) identifier: NCT00470236).

Our trial differed significantly from prior published trials with regard to radiation treatment planning, in that all patients underwent computed tomography–based treatment planning with three-dimensional dose compensation. With this planning approach, we chose not to impose a simple central axis dose homogeneity limit as was used in the previous studies and instead specified a whole breast goal of V108 less than or equal to 1 mL. Within this context, it is worth noting that 50% of treatment plans ($n = 143$) had a maximum dose (Dmax) greater than 107.00% of the prescription dose.¹⁰ Considering that the overall risk of adverse patient-reported cosmetic outcome was only 11.1% (23), our findings support V108 less than or equal to 1 mL as a reasonable planning constraint for WBI.

Adoption of HF-WBI in the United States has lagged behind the publication of level I evidence supporting this treatment. Long-term follow-up data from four multi-institutional randomized trials evaluating CF-WBI and HF-WBI were published between the years 2006 and 2013.¹⁻³ Despite the ASTRO 2011 guideline and the subsequent Choosing Wisely Campaign,⁵ an examination of 2,309 patients with breast cancer treated with whole-breast radiation in Michigan between 2011 and 2014 revealed that only 25% (578) were treated with HF-WBI.²⁷ A retrospective, observational cohort study of administrative claims data from 14 commercial health plans revealed that among patients endorsed for HF-WBI by the ASTRO guidelines, usage of HF-WBI increased from 10.6% in 2008 to 34.5% in 2013.⁸ The usage of HF-WBI has been shown to increase after delineation of discrete clinical pathways outlining when its use is appropriate in clinical practice.²⁸ To our knowledge, this is the first trial to compare CF-WBI with HF-WBI specifically in the United States population, which may differ from prior trials with regard to the frequent use of a boost and the high prevalence of overweight and obesity (73.9% in this study).

To our surprise, only 74% of patients ($n = 213$) returned for the 3-year follow-up assessment. We found that many patients either lost their insurance coverage or transitioned to policies that did not contract with the practice where they received radiation, contributing to this limitation. This trend highlights the challenges of conducting community-based studies requiring long-term follow-up within today's health care environment. Nevertheless, because the study was designed initially to accrue only 200 patients, the follow-up remained adequate to test the noninferiority hypothesis with approximately 80% power, as designed initially. Second, it was not practical to blind patients or treating physicians to treatment arm, although the three-physician panel that scored 3-year photographs was blinded to treatment arm. Third, there are ranges of acceptable dose fractionation regimens for both HF-WBI and CF-WBI, and variations therein that could be associated with distinct cosmetic outcomes remain uncertain. Fourth, follow-up is still relatively short at 3 years. Although cosmetic outcome could potentially worsen with longer follow-up, there is no evidence in the literature to suggest that degradation of cosmetic outcome over time varies by treatment arm.¹⁻³

This randomized, prospective clinical trial found that HF-WBI followed by a sequential tumor bed boost was not inferior to CF-WBI followed by a sequential tumor bed boost with respect to adverse patient-reported cosmetic outcome 3 years after radiation. Receipt of chemotherapy, breast cup size, margin status, and postoperative cosmetic outcome did not interact with treatment arm, suggesting that the noninferiority of HF-WBI is likely to extend across these clinically relevant subgroups.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Three-Year Outcomes With Hypofractionated Versus Conventionally Fractionated Whole-Breast Irradiation: Results of a Randomized, Noninferiority Clinical Trial

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Appendix

Fig A1. Representative photographs for 3-year end points rated by the physician panel.

Table A1. Physician-Assessed Toxicities 3 Years After Whole-Breast Irradiation (NCI CTCAE, version 4.0)

Toxicity	CF-WBI (n = 108)		HF-WBI (n = 97)		P*
	No.	%	No.	%	
Constitutional					
Fatigue					.41
0	93	86.1	89	91.8	
1	12	11.1	7	7.2	
2	3	2.8	1	1.0	
3	0	0.0	0	0.0	
Dermatology and skin					
Hyperpigmentation					.93
0	85	78.7	75	77.3	
1	22	20.4	21	21.6	
2	1	0.9	1	1.0	
Skin induration					.76
0	103	95.4	91	93.8	
1	5	4.6	6	6.2	
2	0	0.0	0	0.0	
3	0	0.0	0	0.0	
4	0	0.0	0	0.0	
5	0	0.0	0	0.0	
Dermatitis					.18
0	106	98.1	91	93.8	
1	2	1.9	5	5.2	
2	0	0.0	1	1.0	
3	0	0.0	0	0.0	
4	0	0.0	0	0.0	
5	0	0.0	0	0.0	
Telangiectasias					.28
0	104	96.3	89	91.8	
1	4	3.7	7	7.2	
2	0	0.0	1	1.0	
Skin ulceration					.
0	108	100.0	97	100.0	
1	0	0.0	0	0.0	
2	0	0.0	0	0.0	
3	0	0.0	0	0.0	
4	0	0.0	0	0.0	
5	0	0.0	0	0.0	
Wound complications, noninfectious					.
0	108	100.0	97	100.0	
1	0	0.0	0	0.0	
2	0	0.0	0	0.0	
3	0	0.0	0	0.0	
4	0	0.0	0	0.0	
5	0	0.0	0	0.0	
Infection					
Breast infection					1.00
0	107	99.1	97	100.0	
2	1	0.9	0	0.0	
3	0	0.0	0	0.0	
4	0	0.0	0	0.0	
5	0	0.0	0	0.0	
Wound infection					.
0	108	100.0	97	100.0	
2	0	0.0	0	0.0	
3	0	0.0	0	0.0	
4	0	0.0	0	0.0	
5	0	0.0	0	0.0	
Lymphatics					
Upper-extremity edema					.10
0	108	100.0	94	96.9	
1	0	0.0	2	2.1	
2	0	0.0	1	1.0	
3	0	0.0	0	0.0	

(continued on following page)

Three-Year Outcomes With HF-WBI Versus CF-WBI

Table A1. Physician-Assessed Toxicities 3 Years After Whole-Breast Irradiation (NCI CTCAE, version 4.0) (continued)

Toxicity	CF-WBI (n = 108)		HF-WBI (n = 97)		P*
	No.	%	No.	%	
Breast edema					.07
0	104	96.3	86	88.7	
1	4	3.7	10	10.3	
2	0	0.0	1	1.0	
3	0	0.0	0	0.0	
Upper-extremity or breast edema					.05
0	104	96.3	85	87.6	
1	4	3.7	10	10.3	
2	0	0	2	2.1	
3	0	0	0	0	
Musculoskeletal or soft tissue					.67
Fibrosis: superficial soft tissue					
0	80	74.1	74	76.3	
1	27	25.0	21	21.6	
2	1	0.9	2	2.1	
3	0	0.0	0	0.0	
4	0	0.0	0	0.0	
5	0	0.0	0	0.0	
Fibrosis: deep connective tissue					.93
0	92	85.2	83	84.7	
1	16	14.8	14	14.3	
2	0	0.0	1	1.0	
3	0	0.0	0	0.0	
4	0	0.0	0	0.0	
5	0	0.0	0	0.0	
Seroma					.58
0	101	93.5	89	91.8	
1	6	5.6	8	8.2	
2	1	0.9	0	0.0	
3	0	0.0	0	0.0	
Soft-tissue necrosis of the chest wall or thorax					
0	108	100.0	97	100.0	
2	0	0.0	0	0.0	
3	0	0.0	0	0.0	
4	0	0.0	0	0.0	
5	0	0.0	0	0.0	
Pain					
Breast pain					.51
0	93	86.1	88	90.7	
1	14	13.0	9	9.3	
2	1	0.9	0	0.0	
3	0	0.0	0	0.0	
Other pain					1.00
0	106	98.1	97	100.0	
1	1	0.9	0	0.0	
2	0	0.0	0	0.0	
3	1	0.9	0	0.0	
Pulmonary					
Cough					.10
0	108	100.0	94	96.9	
1	0	0.0	3	3.1	
2	0	0.0	0	0.0	
3	0	0.0	0	0.0	
Dyspnea					.62
0	105	97.2	96	99.0	
1	3	2.8	1	1.0	
2	0	0.0	0	0.0	
3	0	0.0	0	0.0	
4	0	0.0	0	0.0	
5	0	0.0	0	0.0	

(continued on following page)

Table A1. Physician-Assessed Toxicities 3 Years After Whole-Breast Irradiation (NCI CTCAE, version 4.0) (continued)

Toxicity	CF-WBI (n = 108)		HF-WBI (n = 97)		P*
	No.	%	No.	%	
Pneumonitis					
0	108	100.0	97	100.0	
1	0	0.0	0	0.0	
2	0	0.0	0	0.0	
3	0	0.0	0	0.0	
4	0	0.0	0	0.0	
5	0	0.0	0	0.0	
Sexual or reproductive function					
Nipple or areolar					.058
0	95	88.0	85	87.6	
1	12	11.1	6	6.2	
2	1	0.9	6	6.2	
Breast atrophy					.38
0	68	63.0	68	70.1	
1	29	26.9	18	18.6	
2	11	10.2	11	11.3	
3	0	0.0	0	0.0	
Other					
All others combined					.75
0	101	93.5	93	95.9	
1	6	5.6	3	3.1	
2	1	0.9	1	1.0	
3	0	0.0	0	0.0	
4	0	0.0	0	0.0	
5	0	0.0	0	0.0	
Any grade $\geq$ 2 toxicity					.84
None	88	81.5	78	80.4	
Any	20	18.5	19	19.6	
Any grade $\geq$ 3 toxicity					1.00
None	107	99.1	97	100.0	
Any	1	0.9	0	0.0	

NOTE. These toxicities were recorded by the treating physician using a structured template that specified these toxicities and their definitions.

Abbreviations: CF-WBI, conventionally fractionated whole-breast irradiation; HF-WBI, hypofractionated whole-breast irradiation; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

*P values from Cochran-Armitage test for trend.