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Hypofractionated vs Conventionally Fractionated Postmastectomy Radiation After Implant-Based Reconstruction
A Randomized Clinical Trial

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IMPORTANCE Postmastectomy radiation therapy (PMRT) improves local-regional disease control and patient survival. Hypofractionation (HF) regimens have comparable efficacy and complication rates with improved quality of life compared with conventional fractionation (CF) schedules. However, the use of HF after mastectomy in patients undergoing breast reconstruction has not been prospectively examined.

OBJECTIVE To compare HF and CF PMRT outcomes after implant-based reconstruction.

DESIGN, SETTING, AND PARTICIPANTS This randomized clinical trial assessed patients 18 years or older undergoing mastectomy and immediate expander or implant reconstruction for breast cancer (Tis, TX, or T1-3) and unilateral PMRT from March 8, 2018, to November 3, 2021 (median [range] follow-up, 40.4 [15.4-63.0] months), at 16 US cancer centers or hospitals. Analyses were conducted between September and December 2023.

INTERVENTIONS Patients were randomized 1:1 to HF or CF PMRT. Chest wall doses were 4256 cGy for 16 fractions for HF and 5000 cGy for 25 fractions for CF. Chest wall toxic effects were defined as a grade 3 or higher adverse event.

MAIN OUTCOMES AND MEASURES The primary outcome was the change in physical well-being (PWB) domain of the Functional Assessment of Cancer Therapy–Breast (FACT-B) quality-of-life assessment tool at 6 months after starting PMRT, controlling for age. Secondary outcomes included toxic effects and cancer recurrence.

RESULTS Of 400 women (201 in the CF arm and 199 in the HF arm; median [range] age, 47 [23-79] years), 330 patients had PWB scores at baseline and at 6 months. There was no difference in the change in PWB between the study arms (estimate, 0.13; 95% CI, −0.86 to 1.11; $P = .80$), but there was a significant interaction between age group and study arm ($P = .03$ for interaction). Patients younger than 45 years had higher 6-month absolute PWB scores if treated with HF rather than CF regimens (23.6 [95% CI, 22.7-24.6] vs 22.0 [95% CI, 20.7-23.3]; $P = .047$) and reported being less bothered by adverse effects (mean [SD], 3.0 [0.9] in the HF arm and 2.6 [1.2] in the CF arm; $P = .02$) or nausea (mean [SD], 3.8 [0.4] in the HF arm and 3.6 [0.8] in the CF arm; $P = .04$). In the as-treated cohort, there were 23 distant (11 in the HF arm and 12 in the CF arm) and 2 local-regional (1 in the HF arm and 1 in the CF arm) recurrences. Chest wall toxic effects occurred in 39 patients (20 in the HF arm and 19 in the CF arm) at a median (IQR) of 7.2 (1.8-12.9) months. Fractionation was not associated with chest wall toxic effects on multivariate analysis (HF arm: hazard ratio, 1.02; 95% CI, 0.52-2.00; $P = .95$). Fewer patients undergoing HF vs CF regimens had a treatment break (5 [2.7%] vs 15 [7.7%]; $P = .03$) or required unpaid time off from work (17 [8.5%] vs 34 [16.9%]; $P = .02$).

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, the HF regimen did not significantly improve change in PWB compared with the CF regimen. These data add to the increasing experience with HF PMRT in patients with implant-based reconstruction.

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Visual Abstract

Supplemental content

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Breast cancer is the most common malignant neoplasm among women globally.[1] Approximately 40% of patients in the US undergo mastectomy,[2] with most undergoing breast reconstruction.[3-5] Breast reconstruction options include autologous tissue, an implant, or a combination of these approaches. There are psychological benefits to immediate reconstruction (performed at the time of mastectomy) rather than delayed reconstruction (performed months later).[6] The most common immediate reconstruction techniques use either a temporary tissue expander (TE) followed by later placement of a permanent implant (PI) or immediate (direct) placement of a PI.[4,7]

Many patients benefit from postmastectomy radiation therapy (PMRT) to the ipsilateral chest wall with or without regional lymph nodes to improve local-regional control and survival.[8-10] Hypofractionated (HF) regimens using smaller numbers of treatment sessions but a higher daily dose show comparable oncologic efficacy and complication rates[11,12] with improved quality of life (QOL) compared with conventional fractionation (CF) schedules and are now the preferred approach after breast-conserving surgery.[13] However, few studies have examined HF after mastectomy, with a lack of prospective data on HF after mastectomy in patients undergoing breast reconstruction.

A single, prospective randomized clinical trial comparing HF and CF schedules for PMRT found no difference in local-regional recurrence or disease-free or overall survival, but this trial specifically excluded patients undergoing immediate reconstruction.[14] Several retrospective studies of patients having implant-based reconstruction suggest comparability of HF to CF.[15,16] Although the efficacy of HF with regard to tumor control in breast cancer has been established, the effects of shorter schedules on reconstruction outcomes remain unclear. Implant-based reconstructions are at risk for complications, including infection, capsular contracture, malposition, and rupture, which may be exacerbated by PMRT.[17-19] Therefore, we designed the prospective, randomized Study of Radiation Fractionation on Patient Outcomes After Breast Reconstruction (FABREC) to compare HF and CF PMRT for this population undergoing immediate implant-based reconstruction. We hypothesized that, compared with baseline, there would be improvement in physical well-being for those treated with HF relative to CF.

Key Points

Question What are the outcomes of hypofractionated (16 treatments) postmastectomy radiation therapy in the setting of implant-based reconstruction compared with conventionally fractionated (25 treatments) radiation therapy?

Findings In this multi-institutional randomized clinical trial of 400 patients, there was no statistically significant increase in change in physical well-being at 6 months (primary study outcome) with hypofractionation. However, among younger patients (aged <45 years), the hypofractionation group had higher physical well-being scores and were less bothered by treatment-related adverse effects compared with those randomized to conventional fractionation at 6 months.

Meaning This study's finding that hypofractionation did not result in significantly improved physical well-being at 6 months adds to the growing body of data on hypofractionated postmastectomy radiation therapy.

Methods

Study Design and Participants

The FABREC trial recruited patients from 16 institutions in the US between March 8, 2018, and November 3, 2021, and was reported following the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The ethics committees of all participating institutions and the lead site (Dana-Farber Cancer Institute) approved the protocol (see the trial protocol in Supplement 1). Patients provided written informed consent and were enrolled by the treating radiation oncologist.

Patients 18 years or older who underwent mastectomy and immediate implant-based reconstruction with placement of a TE or PI and were to receive PMRT for clinical or pathologic stage 0 to III breast cancer were eligible. Patients with T4 disease, prior ipsilateral breast radiation therapy, uncontrolled intercurrent illness, or bilateral radiation therapy were excluded, as were those with other prior malignant tumors, unless disease free for 5 years or more or deemed to be at low risk for recurrence. Systemic therapy was recorded, and chemotherapy concurrent with PMRT was not allowed. Concurrent trastuzumab was permitted. Local-regional recurrence event rate monitoring was used to compare against stopping criterion for safety.

Randomization and Masking

Patients were allocated (1:1) to the HF or CF regimen with a computer-generated random sequence and an interactive web-based system using stratified permuted-block randomization. Randomization was stratified by treatment center and age (<45 vs ≥45 years). The assigned treatment could not be masked due to the different durations. Study staff did not have access to the randomization sequence and thus did not know group assignments until interventions were designated.

Treatment

Patients randomized to the CF group received 5000 cGy (25 fractions) to the chest wall, with or without the internal mammary nodes, and discretionary irradiation of 4600 to 5000 cGy in 23 to 25 fractions to the supraclavicular lymph nodes, with or without axillary lymph nodes. Patients randomized to the HF group received 4256 cGy (16 fractions) to the chest wall with or without internal mammary nodes or supraclavicular nodal irradiation (3990 cGy, 15 fractions). Treatment was given daily on weekdays (excluding holidays) using either 3-dimensional conformal or intensity-modulated radiation techniques and field arrangements in accordance with institutional policy using photon energies of 6 MV or higher (proton irradiation was not permitted). Tissue-equivalent bolus (to increase the skin dose) over the mastectomy scar or entire chest wall was prescribed at physician discretion. A boost dose to the scar or other areas was not allowed. Radiation therapy planning included the goal

of achieving an even dose (homogeneity) throughout the target area. Institutional guidelines for prescription points, normalization conventions, and target and normal-tissue dose-volume goals were used, with the requirement that the maximum dose in the chest wall and nodal fields be no greater than 110% of the prescribed dose. Patients in the HF arm were treated with the CF regimen if inhomogeneity constraints could not be met.

Outcomes

Patients completed questionnaires that included Functional Assessment of Cancer Therapy–Breast (FACT-B), version 4[20,21] at baseline (before radiation therapy initiation) and 6, 12, and 18 months after radiation therapy initiation and completed measures of treatment burden at 6 months (eAppendix in Supplement 2). The primary study outcome was change in physical well-being (PWB) derived from the PWB domain of FACT-B at 6 months with prespecified stratification by age (<45 years vs ≥45 years). The PWB of FACT-B was selected to be the most important outcome from a prior study of similar patients, where younger patients had worse PWB scores.[22] The 6-month time point from start of radiation therapy was selected as a compromise between capturing QOL differences resulting from shorter therapy and including recovery from short-term radiation adverse effects.

Serious adverse events were defined by the Common Terminology Criteria for Adverse Events, version 4[23] and reported at time of occurrence. Reportable events included the following: brachial plexopathy (grades 1-3), chest wall pain (grade 3), lymphedema (grade 3), myocardial infarction (grades 3-5), pneumonitis (grades 1-5), treatment-related secondary malignant tumor (grades 3-5), death (grade 5), or any unexpected event (grade 3 or 4) with a possible, probable, or definite attribution to PMRT.

Chest wall toxic effects were defined as any grade 3 or higher adverse event in the ipsilateral chest wall area after PMRT began (infection, delayed wound healing, TE or implant removal, or unplanned surgical intervention), including 3 patients with a qualifying adverse event during PMRT (after 1, 3, and 7 fractions, respectively). Patients who underwent bilateral mastectomy and reconstruction who had contralateral chest wall toxic effects were followed up for ipsilateral events.

Statistical Analysis

The primary population for analysis was the as-randomized population (N = 400), based on the intention-to-treat principle, excluding patients for whom baseline data were not available. The as-treated population (n = 385) included all randomized patients for whom baseline and radiation therapy information was known but excluded 1 patient who received a radiation boost. The 3 patients initially assigned to the HF group who were converted to the CF group due to homogeneity constraints were included in the HF arm for the as-treated population analyses. Patients were censored at the time of study withdrawal or development of any recurrence.

A difference of 2.8 in PWB scores was informed by the survey study[22] and expected correlation in scores between the time points. A change in PWB score of 2.0 or greater has been defined as clinically meaningful in a study of patients with lung cancer receiving radiation therapy.[24] The study sample size (N = 400) was determined to be sufficiently powered to detect the between-group difference in change in PWB scores and the interaction between treatment group and age group (<45 and ≥45 years). This was expected to have greater than 99% power (2-sided α = .05) for a marginal treatment difference of 2.8 in PWB scores and adequate power to accommodate nonresponse. The power for the interaction test was 80% when the expected treatment differences for the younger and older groups were 4.0 and 2.0, respectively, with an expected SD for change in PWB scores of 3.5.

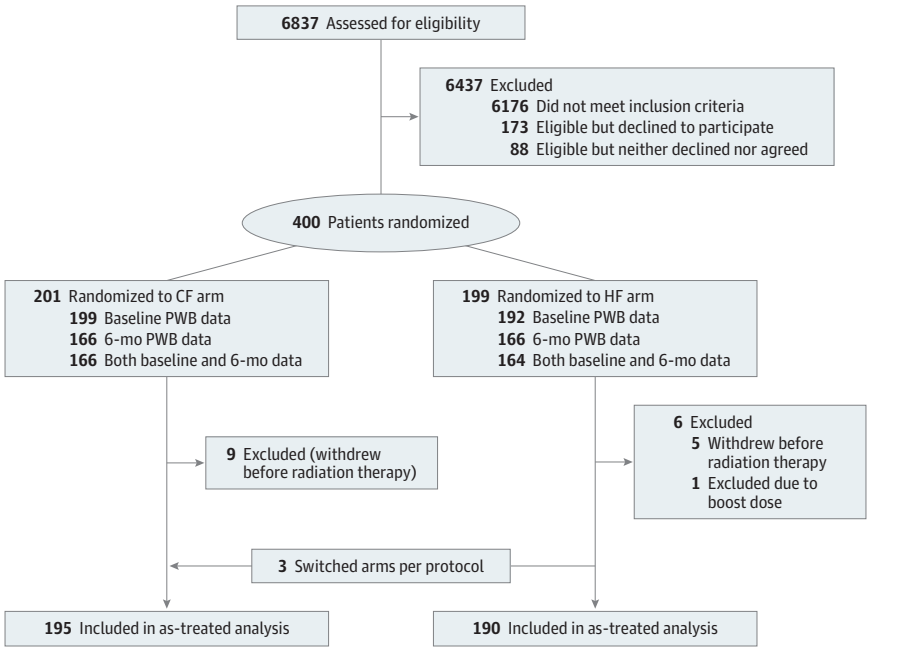
Analysis of covariance was performed for change in PWB scores from baseline to 6 months, with age group and study arm as covariates. Likert responses for the analyses of individual questions were made categorical. We further analyzed this change by performing an analysis of covariance that included an interaction between age group and study arm. Patients for whom missing data comprised more than 50% of the FACT-B were excluded from FACT-B analyses. For the PWB score analyses, patients with missing data for greater than 50% were excluded. When missing data comprised less than or equal to 50% of the scale, the missing item was imputed by taking the mean of the completed items. The QOL scores were compared using 2-sample *t* tests.

Kaplan-Meier estimates of time to occurrence of chest wall toxic effects were stratified by treatment arm and compared using the log-rank test. Cox proportional hazards regression models were used to assess the bivariate associations between individual variables and study treatment toxic effects. We did not consider treatment center as a variable due to the small numbers of patients with toxic effects relative to the numbers of centers. We developed a multivariable Cox proportional hazards regression model that included variables determined to be statistically significant in the univariable Cox proportional hazards regression model, plus forced inclusion of treatment arm, patient age, and interval from surgery to PMRT. The final multivariable Cox proportional hazards regression model included treatment arm, age, and surgery-to-PMRT interval, plus those variables that remained significant using backward elimination. Statistical significance was defined as $P < .05$ in a 2-sided test. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc). Due to the multiple comparisons and introduction of possible type I errors, secondary analyses should be considered exploratory. Analyses were conducted between September and December 2023.

Results

Among the 400 total women, the median age was 47 (range, 23-79) years; self-reported race included Asian (33 [8.2%]), Black or African-American (14 [3.5%]), White (318 [79.5%]), and other (35 [8.8%]), including American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, more than 1 race, or any other race not listed. A total of 201 were assigned to the

Figure 1. Study Flow Diagram



CF indicates conventionally fractionated; HF, hypofractionated; PWB, physical well-being.

CF arm and 199 to the HF arm (**Figure 1**). Detailed characteristics of the cohort were well balanced between both arms (**Table 1**; eTable 1 in Supplement 2). A total of 166 patients (82.6%) in the CF cohort and 164 (82.4%) in the HF cohort had both baseline and 6-month PWB scores (Figure 1). There was no significant difference in change in PWB scores at 6 months between the 2 treatment arms as randomized (CF arm: mean difference, 0.05; 95% CI, −0.63 to 0.74; HF arm: mean difference, 0.18; 95% CI, −0.53 to 0.88; *P* = .81). Patients for whom PWB data were available at both time points (n = 330) did not differ with respect to age and treatment arm from those patients for whom these data were not available. In a model of change in PWB scores (primary study outcome) at 6 months controlling for age group, an improvement of 0.13 with the HF regimen was not significant (95% CI, −0.86 to 1.11; *P* = .80) (**Table 2**). However, the interaction between age and study arm was significant in the interaction model (*P* = .03 for interaction) (Table 2). There was a significant improvement in the difference in scores at 6 months for bothered by nausea (mean [SD], 0.16 [0.68] in the HF arm and −0.16 [0.73] in the CF arm; *P* = .01) and feeling ill (mean [SD], 0.19 [0.87] in the HF arm and −0.12 [0.77] in the CF arm; *P* = .03) among patients younger than 45 years in the HF cohort vs those randomized to the CF arm (eFigure 1 in Supplement 2).

At 6 months after PMRT initiation, the total PWB score for patients younger than 45 years in the HF arm was higher than that for patients in the CF arm (23.6 [95% CI, 22.7-24.6] vs 22.0 [95% CI, 20.7-23.3], *P* = .047) (eFigure 2 in Supplement 2). Younger patients treated with the HF regimen less frequently reported being bothered by nausea (mean [SD], 3.8 [0.4] vs 3.6 [0.8]; *P* = .04) and bothered by adverse effects of treatment (mean [SD], 3.0 [0.9] vs 2.6 [1.2]; *P* = .02) than younger patients treated with the CF regimen at the 6-month time point (eFigure 2 in Supplement 2).

The median follow-up for assessment of toxic effects in the as-treated population was 40.4 months (range, 15.4-63.0 months). A total of 316 patients (79.0%) were irradiated to a TE and the remainder to a PI; 225 patients (58.0%) had prepectoral placement of the reconstruction, with the remainder being subpectoral (eTable 2 in Supplement 2). The median (IQR) time from surgery to PMRT was 2.7 (1.8-5.2) months for CF and 2.4 (1.8-4.9i) months for HF (*P* = .63). Postoperative infections requiring antibiotics developed in 24 patients (6.2%) (13 in the CF arm and 11 in the HF arm). Patients receiving the HF regimen were less likely to have an unplanned treatment break, defined as weekdays without treatment not due to holidays or machine issues (5 [2.7%] in the HF arm vs 15 [7.7%] in the CF arm, *P* = .03). The mean (SD) total break time (for those having a break) was 2.8 (2.0) days for the HF arm and 3.3 (2.8) days for the CF arm, with most breaks being less than 4 days. Fewer patients in the HF arm required unpaid time off from work (17 [8.5%] in the HF arm vs 34 [16.9%] in the CF arm, *P* = .02), with the mean (SD) number of such hours per patient reduced to 14.8 (43.3) hours from 39.8 (82.8) in the CF cohort (*P* = .01).

There were 4 deaths (2 in the HF arm and 2 in the CF arm), all following distant recurrence of breast cancer; 23 distant recurrences (11 in the HF arm and 12 in the CF arm); and 2 local-regional recurrences (1 in each arm). One patient in the CF arm and 3 in the HF arm developed grade 1 or 2 pneumonitis 1.6 to 3.6 months after starting PMRT. Chest wall toxic effects occurred in 39 patients (20 in the HF arm and 19 in the CF arm, *P* = .80) at a median (IQR) time of 7.2 (1.8-12.9) months (**Figure 2**). The median (IQR) time to observed chest wall toxic

Table 1. Cohort Characteristics

Characteristic	No. (%)	
	Conventional therapy (n = 201)	Hypofractionated therapy (n = 199)
Patient characteristics		
Age, y		
<40	41 (21.4)	42 (21.7)
40-50	90 (46.9)	84 (43.3)
51-60	42 (21.9)	49 (25.3)
≥60	19 (9.9)	19 (9.8)
Missing, No.	9	5
Race		
Asian	12 (6.0)	21 (10.6)
Black or African American	8 (4.0)	6 (3.0)
White	161 (80.1)	157 (78.9)
Other[a]	20 (10.0)	15 (7.5)
Ethnicity		
Non-Hispanic	174 (86.6)	180 (90.5)
Hispanic or Latino	27 (13.4)	19 (9.5)
Educational level		
No college	29 (14.5)	20 (10.3)
Some college	42 (21.0)	32 (16.4)
College graduate	57 (28.5)	63 (32.3)
Some graduate or graduate degree	72 (36.0)	80 (41.0)
Missing, No.	1	4
BMI		
<20	11 (5.5)	18 (9.1)
20.0-24.9	75 (37.5)	79 (39.9)
25.0-29.9	60 (30.0)	55 (27.8)
30.0-34.9	34 (17.0)	30 (15.2)
≥35.0	20 (10.0)	16 (8.1)
Missing, No.	1	1
Smoking status		
Never smoked	140 (69.7)	147 (73.9)
Current or former smoker	61 (30.4)	52 (26.1)
Prior infection		
No	187 (93.0)	188 (94.5)
Yes	14 (7.0)	11 (5.5)
Cancer characteristics		
Laterality		
Right	93 (46.5)	113 (56.8)
Left	107 (53.5)	86 (43.2)
Missing	1	0
Hormone receptor positive		
Positive	174 (86.7)	162 (81.4)
Negative	27 (13.4)	37 (18.6)
ERBB2 status		
Equivocal	11 (5.5)	11 (5.5)
Negative	149 (74.9)	146 (73.3)
Positive	39 (19.6)	42 (21.1)
Unknown	2	0

(continued)

Table 1. Cohort Characteristics (continued)

Characteristic	No. (%)	
	Conventional therapy (n = 201)	Hypofractionated therapy (n = 199)
Histology		
Both	14 (7.0)	25 (12.6)
Invasive ductal	147 (73.1)	139 (69.9)
Invasive lobular	32 (15.9)	29 (14.5)
Other	8 (4.0)	6 (3.1)
Grade		
Poorly differentiated	78 (38.8)	82 (41.2)
Moderately differentiated	96 (47.7)	95 (47.7)
Well differentiated	26 (12.9)	20 (10.1)
NA	1 (0.5)	2 (1.0)
Tumor size		
≤2	114 (61.3)	99 (55.0)
>2-≤5	49 (26.3)	60 (33.3)
>5	23 (12.4)	21 (11.7)
Missing	15	19
Lymphatic vessel invasion		
Negative	126 (63.3)	118 (59.9)
Other	73 (36.7)	79 (40.1)
Missing	2	2
Total No. of positive nodes		
0	52 (26.8)	56 (29.2)
1	76 (39.2)	65 (33.9)
2	32 (16.5)	33 (17.2)
≥3	34 (17.5)	38 (19.8)
Missing	7	7
Treatment characteristics		
Surgery		
Axillary node dissection		
No	112 (55.7)	99 (49.8)
Yes	89 (44.3)	100 (50.3)
No. of axillary nodes removed, median (range)	9.0 (0-27)	8.5 (0-36)
Location of device		
Prepectoral	118 (59.9)	115 (57.7)
Subpectoral	79 (40.1)	84 (42.2)
NA or unknown	4	0
Device irradiated		
Expander	156 (77.6)	160 (80.4)
Implant	45 (22.4)	39 (19.6)
Systemic therapy		
Neoadjuvant chemotherapy		
Yes	134 (66.7)	137 (68.8)
No	67 (33.3)	62 (31.2)
Unknown	0	0
Neoadjuvant endocrine therapy		
Yes	39 (19.4)	46 (23.2)
No	162 (80.6)	152 (76.8)
Unknown	0	1

(continued)

Table 1. Cohort Characteristics (continued)

Characteristic	No. (%)	
	Conventional therapy (n = 201)	Hypofractionated therapy (n = 199)
Radiation therapy		
Chest wall and nodes	160 (87.4)	170 (90.0)
Chest wall alone	23 (12.6)	19 (10.1)
Missing due to study withdrawal	9	5
Technique		
IMRT	78 (41.0)	82 (42.9)
Three-dimensional conformal	112 (59.0)	109 (57.1)
Missing	2	3
Time from surgery to radiation therapy, median (IQR), mo	2.7 (1.8-5.3)	2.4 (1.8-4.9)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IMRT, intensity-modulated radiation therapy; NA, not applicable.

[a] Other includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, more than 1 race, and any other race not listed.

Table 2. Models for the Primary Outcome Adjusted for Patient Age

Variable	Estimate (SE) [95% CI]	*P* value
Model controlling for age		
CF therapy	1.0 [Reference]	NA
HF therapy	0.13 (0.50) [−0.86 to 1.11]	.80
Age group, y		
<45	1.0 [Reference]	NA
≥45	−0.21 (0.51) [−1.21 to 0.80]	.68
Subgroup analysis of age		
Age <45 y		
CF therapy	1.0 [Reference]	NA
HF therapy	1.46 (0.83) [−0.18 to 3.11]	.08
Age >45 y		
CF therapy	1.0 [Reference]	NA
HF therapy	−0.73 (0.62) [−1.95 to 0.49]	.24
Model with age interaction		
CF therapy	1.0 [Reference]	NA
HF therapy	1.46 (0.80) [−0.10 to 3.03]	.07
Age group, y		
<45	1.0 [Reference]	NA
≥45	0.87 (0.71) [−0.54 to 2.27]	.23
Study arm and age interaction		.03[a]
<45 y and CF therapy	−0.32 (0.45) [−1.20 to 0.56]	.47
<45 y and HF therapy	0.40 (0.45) [−0.49 to 1.30]	.38
≥45 y and CF therapy	1.00 (0.57) [−0.13 to 2.13]	.08
≥45 y and HF therapy	−0.46 (0.55) [−1.55 to 0.62]	.40

Abbreviations: CF, conventionally fractionated; HF, hypofractionated; NA, not applicable.

[a] *P* value for interaction.

effects was 3.5 (1.9-11.9) and 7.6 (1.6-15.6) months after PMRT initiation in the HF and CF arms, respectively (*P* = .65).

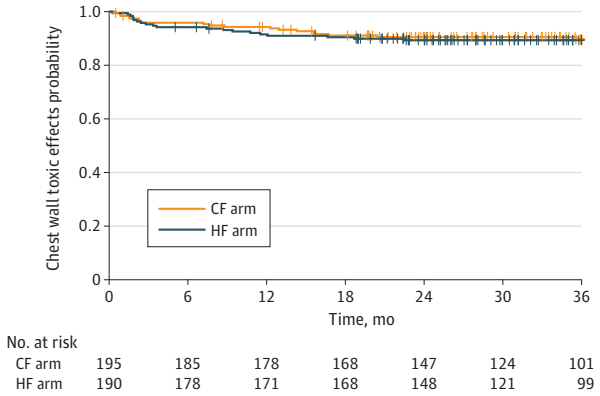
In univariable Cox proportional hazards regression analyses, variables associated with developing chest wall toxic effects included higher body mass index (hazard ratio [HR], 1.02; 95% CI, 1.00-1.03; *P* = .003), having a postoperative infection (HR, 3.14; 95% CI, 1.32-7.50; *P* = .01), undergoing axillary dissection (HR, 2.07; 95% CI, 1.08-3.98; *P* = .03), the number of nodes removed (per node: HR, 1.05; 95% CI, 1.01-1.10; *P* = .01), irradiation of a TE vs PI (HR, 3.32; 95% CI, 1.02-10.80; *P* = .04), and preoperative endocrine therapy (HR, 2.99; 95% CI, 1.59-5.64; *P* = .001) (eTable 3 in Supplement 2). Only infection (HR, 3.19; 95% CI, 1.18-8.65; *P* = .02), irradiation of a TE (HR, 4.44; 95% CI, 1.05-18.75; *P* = .04), receipt of neoadjuvant endocrine therapy (HR, 2.80; 95% CI, 1.42-5.50; *P* = .003), and the number of nodes removed (per node: HR, 1.06; 95% CI, 1.02-1.10; *P* = .008) remained significant in the multivariable Cox proportional hazards regression model (**Table 3**). Fractionation schedule was not significantly associated with chest wall toxic effects (HF arm: HR, 1.02; 95% CI, 0.52-2.00; *P* = .95).

Discussion

The use of PMRT improves local-regional control and breast cancer–specific survival rates for patients with breast cancer at elevated risk of local-regional recurrence.[8-10,25] However, it has been unclear how to best integrate PMRT with immediate breast reconstruction surgery to minimize the risk of complications. In this large, multicenter, prospective randomized clinical trial, we found no significant improvement in change in PWB scores with hypofractionation and no difference in recurrence or toxic effects between HF and CF PMRT in patients having mastectomy with immediate implant-based reconstruction.

Although the primary outcome, change in PWB scores at 6 months stratified by age, was not improved with the HF regimen, the timing of giving patients their baseline surveys was not specified relative to randomization; hence, some patients were aware of their treatment assignment when they received that survey. Patients randomized to the HF arm reported more energy at baseline than those randomized to the CF arm, which may have also contributed to better baseline FACT-B scores of younger patients who were randomized to the HF arm. Higher baseline scores may have limited the opportunity to fully assess the degree of improvement at the 6-month time point. Still, although the change in PWB was not significant for the entire population, younger patients randomized to the HF arm had better total PWB scores at 6 months compared with those randomized to the CF arm, which may indicate that HF has more targeted benefits in younger populations. Moreover, younger patients had less bother from nausea and from other treatment adverse effects with the HF vs the CF regimen. Although statistical benefit in QOL may not necessarily be clinically significant,[24] our findings were consistent with the magnitude of benefit with HF at 6 months in a prior study of breast-conserving surgery,[13] despite our patient population having more extensive surgery (on average) and systemic treatment. In addition, perhaps the 6-month time point after PMRT initiation was too late to capture the full benefit of decreased irradiation duration. Nevertheless, longer-term QOL is important to understand the full impact of a given treatment.

Figure 2. Kaplan-Meier Plot for Freedom From Chest Wall Toxic Effects by Treatment Arm



CF indicates conventionally fractionated; HF, hypofractionated.

Table 3. Multivariable Cox Proportional Hazards Regression Model for Chest Wall Toxic Effects

Variable	HR (95% CI)	*P* value
Treatment arm		
CF treatment	1.0 [Reference]	NA
HF treatment	1.02 (0.52-2.00)	.95
Age, y		
<40	1.0 [Reference]	NA
40-50	1.65 (0.65-4.17)	.29
51-60	1.32 (0.46-3.78)	.60
≥60	0.89 (0.18-4.45)	.88
Time from surgery to PMRT, mo	0.99 (0.84-1.17)	.92
Postoperative infection		
No	1.0 [Reference]	NA
Yes	3.19 (1.18-8.65)	.02
Device irradiated		
Permanent implant	1.0 [Reference]	NA
Expander	4.44 (1.05-18.75)	.04
Neoadjuvant endocrine therapy		
No	1.0 [Reference]	NA
Yes	2.8 (1.42-5.5)	.003
No. of nodes removed (continuous)	1.06 (1.02-1.1)	.008

Abbreviations: CF, conventionally fractionated; HF, hypofractionated; HR, hazard ratio; NA, not applicable; PMRT, postmastectomy radiation therapy.

The absolute risk of chest wall toxic effects was lower in both arms than that previously reported for patients with implant-based reconstruction undergoing PMRT. This finding may perhaps reflect improvements in surgical technique and improved radiation dose homogeneity with current techniques. We found higher complication rates after irradiation of TE than PI, similar to some[26-29] but not all studies.[30] We also found a significantly increased risk of chest wall toxic effects with neoadjuvant endocrine therapy. Most patients received radiotherapy and endocrine therapy concurrently in our study, raising the question of whether concurrent endocrine therapy and radiotherapy increases toxic effects in this specific patient population, although it does not appear to be a risk factor in the overall breast radiation population.[31,32] Neoadjuvant endocrine therapy was perhaps used more frequently in our patients than in most studies because of the COVID-19 pandemic, as a method to delay surgery when hospitals were overwhelmed.

We also found that HF therapy decreased the number of unplanned treatment breaks. Unplanned radiation treatment interruptions have been associated with worse cancer outcomes.[33] Although most treatment breaks in our study were less than 4 days, a recent analysis demonstrated inferior outcomes among patients with triple-negative breast cancer who had as few as 2 to 5 days of interruption.[34] The shorter duration of treatment may also have economic implications for patients because fewer patients receiving HF therapy (compared with CF therapy) required unpaid time off from work.

Limitations

We recognize several limitations of our study. Although it included a broad spectrum of patients who typically receive PMRT and the treatment arms were well balanced and randomized, the trial had a limited number of events. Although capsular contracture is common for such patients, we did not include this outcome due to concerns regarding the subjectivity of evaluation and the difficulty of achieving interobserver consistency, particularly because this is not routinely assessed by radiation oncologists. Our median follow-up exceeded the median time to development of chest wall toxic effects, although follow-up time was modest with regard to the course of recurrence. Other studies of HF therapy suggest that a substantial increase in local-regional failure rates at later time points is unlikely. The COVID-19 pandemic may have caused some deviation from usual practice patterns and certainly resulted in slower accrual than expected, which may have introduced subtle changes in outcome.

Conclusions

Patients surveyed after CF PMRT and implant-based immediate reconstruction[22] underscore the potential effect of shorter treatment duration on well-being and clinical experience. The results of this randomized clinical trial reveal that the primary outcome of change in PWB scores was not significantly improved with hypofractionation. The overall toxicity profile and oncologic outcomes of HF PMRT were comparable to those of CF PMRT. Hypofractionated therapy was associated with significantly higher QOL domains at 6 months among younger patients, fewer treatment breaks, and less disruption to employment. These data add to the increasing experience with HF PMRT after immediate implant-based reconstruction for breast cancer. Future reports will include other patient-reported and outcomes data with longer follow-up.

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