Advances in Radiation Oncology (2025) **10**, 101756

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Tolerance of Adjuvant Ultrahypofractionated Whole-Breast Radiation Therapy Employing Moderately Hypofractionated Sequential Boost: A Single Institution Analysis

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Received 18 May 2024; accepted 28 February 2025

Purpose: This analysis evaluates early and intermediate treatment tolerance in a prospective observational cohort study of patients who underwent adjuvant ultrahypofractionated whole-breast radiation therapy (uhWBRT), with or without moderately hypofractionated sequential boost, following breast-conserving surgery.

Methods and Materials: uhWBRT was introduced in our department in March 2020. Data from 436 patients with breast tumors not requiring lymphatic irradiation were analyzed, including 376 with invasive carcinomas (pT1-pT3) and 60 with ductal carcinoma in situ. The mean age was 62 years (range, 26-85). Acute reactions (Common Terminology Criteria for Adverse Events v4.03) were assessed at radiation therapy completion and after 2 to 3 weeks. Late effects and patient-reported outcomes (Late Effects in Normal Tissues−Subjective, Objective, Management and Analytic and Harvard for Cosmesis) were evaluated at 6 months after radiation therapy and annually thereafter. The prescribed uhWBRT dose was 26 Gy in 5 daily fractions. A sequential boost of 10.0 to 12.5 Gy in 4 to 5 daily fractions was administered to 338 patients (77.5%), while 98 (22.5%) did not receive a boost.

Results: Acute toxicity grades 0, 1, and 2 were observed in 29.8%, 59.9%, and 10.3% of patients, respectively, at radiation therapy completion and 52.1%, 40.8%, and 7.2% of patients at 2 to 3 weeks after radiation therapy. Grade 2 late effects were identified in 5.3%, 2.0%, 1.8%, 1.1%, and 0%, and grade 3 late effects were identified in 1.5%, 2.3%, 0.9%, 0%, and 0% of patients at 6 months, 1 years, 2 years, 3 years, and 4 years. Patient-reported outcomes for cosmesis were rated as good or excellent in 97.7% of patients. After a mean follow-up of 18 months (median 14, range, 0-48), 1 local failure, 2 nodal failures, and 9 distant relapses were detected. Three deaths were reported, all nontumor-related.

Conclusions: Early and intermediate results indicate that the treatment schedules, including the moderately hypofractionated boost, are safe and well tolerated, with acute toxicity rates comparable to those in the FAST-Forward trial. Although our study follow up is relatively short, our findings indicate that uhWBRT, with or without a moderately hypofractionated boost, is safe and well tolerated.

Sources of support: This work had no specific funding.
Research data are not available at this time.

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https://doi.org/10.1016/j.adro.2025.101756

Introduction

Moderate and, more recently, ultrahypofractionation for adjuvant whole-breast radiation therapy has increasingly become a standard of care in recent years, particularly following the publication of the 5-year FAST-Forward trial results, which compared 26 or 27 Gy in 5 fractions with 40 Gy in 15 fractions.[1] Ultrahypofractionation is now a standard of care in many clinics worldwide.[2-5] Despite its economic benefits and convenience for patients, the adoption of the 5-fraction schedule has faced significant criticism and has not yet achieved widespread implementation.[6,7]

At our clinic, as in many others globally, the onset of the COVID-19 pandemic in 2020 triggered the implementation of shorter fractionation regimens.[8,9] Consequently, we introduced ultrahypofractionated whole-breast radiation therapy (uhWBRT) in March 2020, following the FAST-Forward protocol for patients who were ineligible for accelerated partial breast irradiation and did not require lymphatic pathway irradiation.[1,10,11] For those requiring a boost, standard institutional guidelines for delivering a moderately hypofractionated sequential boost of 10 to 12.5 Gy were maintained.

In this prospective observational cohort study, we assessed the tolerance and outcomes of patients receiving a whole-breast irradiation schedule of 26 Gy delivered in 5 daily fractions, with or without a moderately hypofractionated sequential boost of 10 or 12.5 Gy in 4 or 5 daily fractions of 2.5 Gy to the resection cavity.

Methods and Materials

In March 2020, we introduced uhWBRT as the standard treatment for whole-breast irradiation in patients without indications for lymphatic pathway irradiation. A prospective observational cohort study was conducted to evaluate acute and late adverse effects, treatment outcomes, and subjective patient-reported outcomes (PROMs) associated with uhWBRT. This analysis focuses on the acute and intermediate-term adverse effects, as well as the available PROMs data from this study.

Patients

According to the institutional breast cancer treatment protocol, uhWBRT was offered to patients with invasive breast carcinoma and/or ductal carcinoma in situ (DCIS), classified as pT1-3, pN0-1, and M0, with no or microscopic residual tumor (R0-R1 [According to definitions of negative margins after breast-conservation therapy from the 2014 SSO/ASTRO Margins Guideline for Stage I/II Invasive cancers[12] and the 2016 SSO/ASTRO/ASCO Guideline for DCIS.[13]]) and negative or microscopic positive resection margins, irrespective of tumor grade. Patients with or without confirmed lymphatic or vascular invasion were eligible. All patients had undergone prior breast-conserving surgery with axillary staging and/or dissection. Patients were not eligible if they met the institutional criteria for accelerated partial breast irradiation or had an indication for lymphatic pathway irradiation.[10,11] Neoadjuvant or adjuvant systemic therapy was administered when indicated.

Treatment

The whole-breast radiation therapy regimen was based on the test arm of the FAST-Forward trial.[1] A total dose of 26 Gy in 5 daily fractions of 5.2 Gy was delivered to the whole breast. A sequential moderately hypofractionated boost, consisting of 4 to 5 fractions of 2.5 Gy, was indicated for selected patients. Boost indications included patients aged ≤35 years or, regardless of age, the presence of any of the following factors: grade 3 invasive carcinoma, high-grade DCIS, estrogen receptor-negative tumors, human epidermal growth factor receptor 2-positive tumors, DCIS with R0 and surgical margins <2 mm or R1,[1] or evidence of lymphatic or vascular invasion. Additional indications were determined through risk factor evaluation using nomograms based on the predictive model for ipsilateral breast tumor recurrence after surgery, as described by Corso et al.[14]

Radiation therapy was started 6 to 12 weeks postsurgery in patients who did not receive adjuvant chemotherapy and 4 to 8 weeks after completing adjuvant chemotherapy in those who did. A subset of prospective cohort patients with multicentric tumors, multifocal tumors with more than 2 deposits, an uncertain boost cavity, or a boost volume exceeding one-quarter of the breast volume received an alternative fractionation scheme (28 Gy in 5 fractions delivered twice per week without a boost) and were excluded from this analysis.

Radiation therapy planning and treatment delivery

Planning computed tomography (CT) scans were performed with patients positioned supine, arms raised, covering the region from the mid-neck to at least 5 cm below the breast, and including full lung volume, with a slice thickness of 5 mm. CT data were acquired using a Canon Aquilion LB CT scanner (Canon Medical Systems Corporation). For left-sided breast treatments or medially located tumor beds, an additional deep inspiration breath

hold CT was acquired for cooperative patients, and the CT scan with the most favorable heart-chest wall separation was selected for planning.

The whole-breast clinical target volume was delineated in accordance with European Society for Radiotherapy and Oncology guidelines.[15] A 5-mm margin was added to create the planning target volume (PTV). The boost volume was delineated using surgical clips placed during a lumpectomy, if available, supplemented by visible postoperative changes, surgical reports, and preoperative imaging, with no additional clinical expansion. A clinical target volume-to-PTV margin of 5 mm was added, as per institutional standards. The boost PTV generally was not to exceed one breast quadrant.

Dose limits for the whole-breast PTV were adopted from the FAST-Forward protocol as follows:[16]

- >95% of the volume should receive at least 95% of the prescribed dose
- <5% of the volume should receive ≥105% of the prescribed dose
- <2% of the volume should receive ≥107% of the prescribed dose
- global dose maximum should be <110% of the prescribed dose

Dose constraints for healthy tissues and organs included:

- Ipsilateral lung: <15% of lung volume receiving ≥12 Gy
- Contralateral lung: Dmax < 3%
- Contralateral breast: dose exposure should be as low as possible
- Heart: maximum point dose (Dmax) <10 Gy, <5% of volume receiving ≥7.0 Gy, <30% of volume receiving ≥1.5 Gy
- Chest wall: Dmax ≤ 27 Gy

Plans were created using the Eclipse treatment planning system (version 15.6, Varian Medical Systems). Three-dimensional conformal radiation therapy with static fields (3D-CRT) was the preferred planning technique; intensity modulated radiation therapy or volumetric-modulated arc therapy techniques were used only in exceptional cases. Volumetric, contour-based 3-dimensional planning was employed for all patients, similar to the "Volume-based planning" described in the FAST-Forward Planning Pack.[17] Notably, our smaller 5-mm clinical target volume -to-PTV margin (with daily image guidance) differed from the 10-mm margin used in FAST-Forward and likely helped in meeting the specified dose constraints and coverage requirements.

All patients were irradiated on a linear accelerator with daily image guidance, using kV-kV 2D-3D matching or Cone Beam Computed Tomography 3D-3D matching for online position corrections.

Patient data collection and follow up

Data were collected at baseline (prior to radiation therapy), at radiation therapy completion (end of treatment), 2 to 3 weeks after radiation therapy completion (for early side effects), at 6 and 12 months, and annually thereafter. At baseline, any postsurgical changes were documented separately to distinguish them from subsequent radiation therapy-induced effects. Objective and subjective side effects and cosmetic outcomes were scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03 for acute toxicity[18] and the Late Effects in Normal Tissues −Subjective, Objective, Management and Analytic scale for late effects.[19] Early effects evaluated included skin erythema, desquamation, edema, bleeding, and necrosis/ulceration. Late effects, defined as occurring >3 months after radiation therapy, included breast retraction/atrophy, edema of the irradiated breast tissue, skin changes (telangiectasia, hyperpigmentation/hypopigmentation), radiogenic fibrosis (palpatory and subjective indications), lymphedema of the ipsilateral arm, and any need for treatment of a skin/tissue condition. Subjective data were collected using standardized patient surveys, including self-assessment questionnaires (Late Effects in Normal Tissues−Subjective, Objective, Management and Analytic PROMs). Pain and its intensity, skin sensation changes, and cosmetic outcomes were evaluated. Cosmetic outcomes were evaluated by both patients and examiners using the Harvard/NSABP/RTOG Breast Cosmesis Grading Scale.[20] Comparisons were made between the treated and contralateral breast. Photographic documentation of the breast was performed at each visit. Regular oncologic follow up was carried out by referring physicians, surgeons, and gynecologists in accordance with standard protocols.

Statistics

Descriptive statistical methods were used to summarize the data and outcomes. Risk ratios, confidence intervals, and *P* values were calculated using contingency tables, normal distribution confidence intervals, and the t-test. The statistical significance of differences in numerical parameters in the patient groups with different outcomes was assessed using the Wilcoxon rank-sum statistic. A *P* value threshold of .05 was used to determine statistical significance for rejecting the null hypothesis. Because this was an observational, nonrandomized study, comparisons between boost and no-boost groups should be interpreted with caution. Treatment allocation depended on clinical judgment and specific risk factors, introducing potential selection bias and confounding.

Ethics approval and Informed Consent

Ethical approval was obtained from the Regional Ethics Committee (approval number 2024-00139). Written informed consent was obtained from all subjects prior to the study. All patients included in this analysis initially confirmed their consent to further follow up and the anonymous use of their clinical data (general informed consent of the hospital).

Results

Data from 436 consecutive patients treated with the uhWBRT regimen in our department between March 2020 and October 2023 were included in this prospective analysis. Data were collected until April 29, 2024. Table 1[21] summarizes the tumor- and therapy-related characteristics of the patient cohort, while Table E1 provides selected characteristics stratified by whether or not patients received a boost.

Radiation therapy

The mean duration of the treatment course was 11 ± 3 calendar days (median, 12; IQR, 11-13). Among patients who received 26 Gy whole-breast dose with a sequential boost, the mean duration was 12 ± 2 calendar days (median, 13; IQR, 11-13), whereas those without a boost had a mean duration of 8 ± 3 calendar days (median, 7; IQR, 5-7). There was no statistically significant difference in the irradiated whole-breast volume between the boost and nonboost groups (mean, 587 ± 309 vs 537 ± 333; $P = .184$).

The mean boost PTV constituted 16% ± 6% (median, 15%; IRQ, 12%-19%) of the total breast volume (Table 1). In 314 patients (92.8% of those receiving a boost), the boost PTV was one-quarter or less of the total breast volume, whereas in 24 patients (7.2%), it exceeded one-quarter of the breast volume.

Treatment was delivered predominantly using 3-dimensional conformal radiation therapy with static fields ($n = 430$; 98.6%), with intensity modulated radiation therapy in 5 patients (1.2%) and volumetric-modulated arc therapy in 1 patient (0.2%).

Follow-up

The mean follow-up duration was 18 ± 12 months (range, 0-48), with a median of 14 months (IQR, 8-27). As of April 29, 2024, follow-up data were available for 390 patients (89%) at 2 weeks, 384 (89%) at 6 months, 290 (67%) at 1 year, 161 (37%) at 2 years, 66 (15%) at 3 years, and 8 (2%) at 4 years. Overall, 911 follow-up assessments took place at 6 months or later, and 395 patients had at least one follow-up assessment at or beyond the 6-month mark. Of 436 patients, 10 (2%), 84 (19%), 185 (42%), 315 (72%), and 393 (90%) patients had follow-up data at 4 years, 3 years, 2 years, 1 year, and 6 months, respectively, by the end of April 2024.

Tumor control

During the observation period, one local recurrence (at 34 months), 2 nodal failures (at 7 and 35 months), and 9 distant relapses (mean, 20 months; range, 8-39) were diagnosed. One patient developed Paget disease with histologically confirmed DCIS in the same breast at 35 months. To date, 3 nontumor-related deaths have been reported.

Objective evaluation of early reactions

No grade 3 or higher acute reactions were observed. Baseline skin changes or mild erythema at before radiation therapy assessment were attributed to a recent surgery. At the completion of therapy, 29.6% of patients ($n = 128$) had grade 0 reactions, which increased to 51.8% ($n = 202$) at 2 to 3 weeks posttreatment (Fig. 1, Table E2). The cumulative incidence of acute grade 2 reactions was 13.8% (95% CI, 10.5%-17.0%). Erythema was the most frequent finding, with grade 1 erythema observed in up to 68% of patients at treatment completion, declining to about 44% at 2 to 3 weeks. Desquamation, if present, remained almost exclusively grade 1 and resolved quickly. No significant difference was noted in the cumulative incidence of acute grade 2 reactions between the boost and nonboost groups (RR = 0.992; $P = .866$; 95% CI, 0.906-1.087).

Subjective late effects/PROMs

Figure 2 shows the frequency and severity of self-reported pain before and after radiation therapy over time. Prior to treatment, 22.3% of patients reported pain, with 4.1% ($n = 18$) experiencing endurable pain. Endurable pain was reported in 4.4% of all follow-up assessments. Among patients reporting pain, 11.9% ($n = 17$) required analgesics after 6 months, 3.8% ($n = 3$) after 1 year, 6.3% ($n = 1$) after 2 years, and none at 3 or 4 years. No significant effect of the boost was observed on the presence of endurable pain (RR = 1.006; $P = .957$; 95% CI, 0.807-1.254) or more frequent than rare pain (RR = 1.033; $P = .456$; 95% CI, 0.948-1.127).

The mean/median age of the patients who reported having pain at any follow up, whether sometimes or more frequently, was 59/57 years (SD, ±14; IQR, 50-73),

Table 1 Therapy- and tumor-related characteristics of the patient cohort

Characteristics	Value	Percentage if not indicated differently
Number of patients		436 (100.0%)
Age [y.o.]	Median [IQR]	63 [54-72]
	Mean ± SD	62.3 ± 11.6
	Range	26-85
Side of primary tumor	Left	224 (51.4%)
	Right	212 (48.6%)
Histology	DCIS	60 (13.7%)
	Infiltrating ductal carcinoma	279 (64.0%)
	Infiltrating lobular carcinoma	97 (22.3%)
Grading carcinoma	G1	44 (11.6%)
	G2	216 (57.6%)
	G3	116 (30.8%)
Grading DCIS	DCIS high grade	48 (79.5%)
	DCIS intermediate grade	5 (7.7%)
	DCIS low grade	7 (12.8%)
Pathologic tumor size, cm	Median [IQR]	1.5 [1.1-2.2]
	Mean ± SD	1.7 ± 1.0
Pathologic T stage	DCIS	60 (13.7%)
	T1	7 (1.6%)
	T1a	12 (2.8%)
	T1b	66 (15.1%)
	T1c	193 (44.3%)
	T2	96 (22.0%)
	T3	2 (0.5%)
Maximal extent of axillary staging	Sentinel node biopsy	408 (93.6%)
	Axillary clearance	15 (3.4%)
	Not performed (DCIS)	13 (3.0%)
Pathologic node status	Positive	80 (18.3%)
	Negative	343 (78.7%)
	Not known	13 (3.0%)
Pathologic N stage	N0	343 (78.6%)
	N0(i+)	15 (3.5%)
	N1	5 (1.3%)
	N1a	18 (4.0%)
	N1mi	42 (9.5%)
	NX (DCIS)	13 (3.0%)
Resection margin	R0	430 (98.6%)
	R1	6 (1.4%)
Oncoplastic surgery	Yes	142 (32.6%)
	No	294 (67.4%)

(*continued on next page*)

Table 1 (*Continued*)

Characteristics	Value	Percentage if not indicated differently
Clips tumor bed	0	20 (4.6%)
	2-3	53 (12.3%)
	4-6	347 (79.6%)
	7-13	15 (3.5%)
Estrogen receptors	Positive (>1%)	398 (91.2%)
	Negative	38 (8.8%)
Progesterone receptors	Positive (>1%)	351 (80.5%)
	Negative	85 (19.5%)
Her-2/new	Positive	42 (9.6%)
	Negative	394 (90.4%)
Ki-67[21]	>30%	67 (15.3%)
	≤ 30%	369 (84.7%)
Lymphovascular invasion	Yes	60 (13.8%)
	No	376 (86.2%)
Neoadjuvant chemotherapy	Yes	6 (1.5%)
	No	430 (98.5%)
Adjuvant chemotherapy	Yes	117 (26.9%)
	No	319 (73.1%)
Adjuvant hormonotherapy	Yes	337 (77.4%)
	No	99 (22.6%)
Irradiated whole-breast volume, cm^3	Median [IQR]	514 [343-748]
	Mean ± SD	576 ± 315
	103-541 cm^3	234 (53.7%)
	541-977 cm^3	155 (35.6%)
	977-1414 cm^3	39 (9.0%)
	1414-1850 cm^3	5 (1.2%)
	1850-2286 cm^3	2 (0.5%)
Boost planning target volume, cm^3	Median [IQR]	103 [73-130]
	Mean ± SD	106 ± 45
Deep inspiration breath hold for left-sided breast	Yes	179 (79.9%)
	No*	45 (20.1%)
26 Gy ultrahypofractionated whole-breast radiation therapy plus sequential boost	Yes	338 (77.5%)
	No	98 (22.5%)
Dose boost	10.0 Gy in 4F	326 (96.4%)
	12.5 Gy in 5F	12 (3.6%)

Abbreviation: DCIS = ductal carcinoma in situ.
*Mainly aged patients >75 y.

compared with 63/63 years (SD, ±11; IQR, 55-72) for those reporting rare or no pain (t-test P = .038). Those reporting endurable or intensive pain were significantly younger (mean/median, 57/53; SD, ±12; IQR, 49-67) than those with minimal pain (62/63; SD, ±12; IQR, 54-72; t-test P = .006).

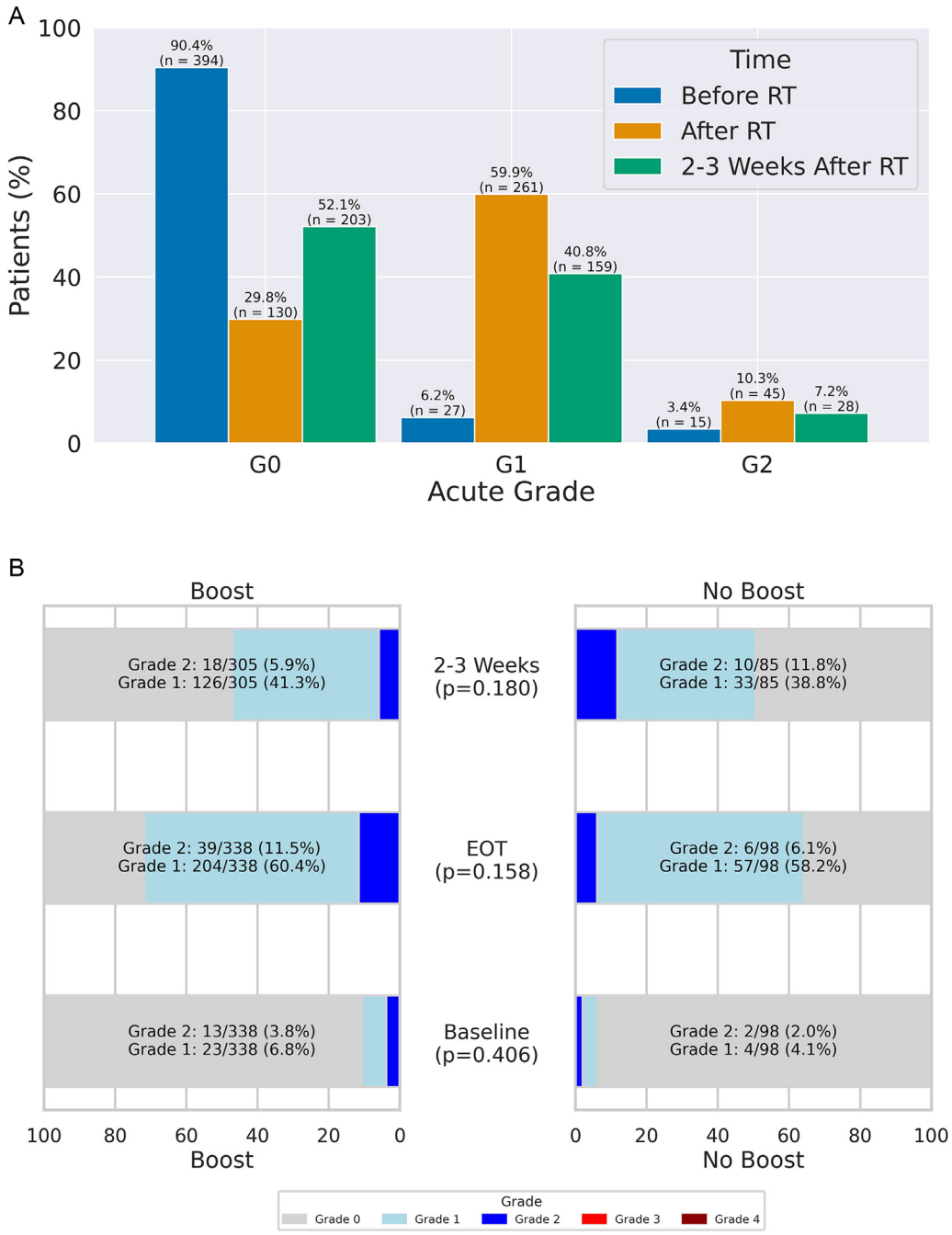

Figure 1 Acute reactions before, on completion, and 2 to 3 weeks after ultrahypofractionated whole-breast radiation therapy (A) all patients (B) split by the presence or absence of a boost.

Objective evaluation of late effects

Figure 3 and Table E3 display the frequency of objective late effects over time among patients with at least a 6-month follow-up assessment. Overall, grade 2 or higher (G2+) effects were observed in 7.3% (95% CI, 4.7%-9.8%) of patients at 6 months, 3.4% (95% CI, 1.3%-5.5%) at 1 year, and 2.5% (95% CI, 0.1%-4.9%) at 2-years. No G2+ toxicity was noted at the 3 or 4-year year follow-ups (n = 66 and n = 8, respectively). In total, G2+ effects were observed in 8.1% of patients with at least 6 months of follow up (95% CI, 5.4%-10.8%), which corresponds to 4.6% per the total number of follow-up assessments. Grade 3 toxicity was rare (<2%) at 6 months and 1 year, mainly

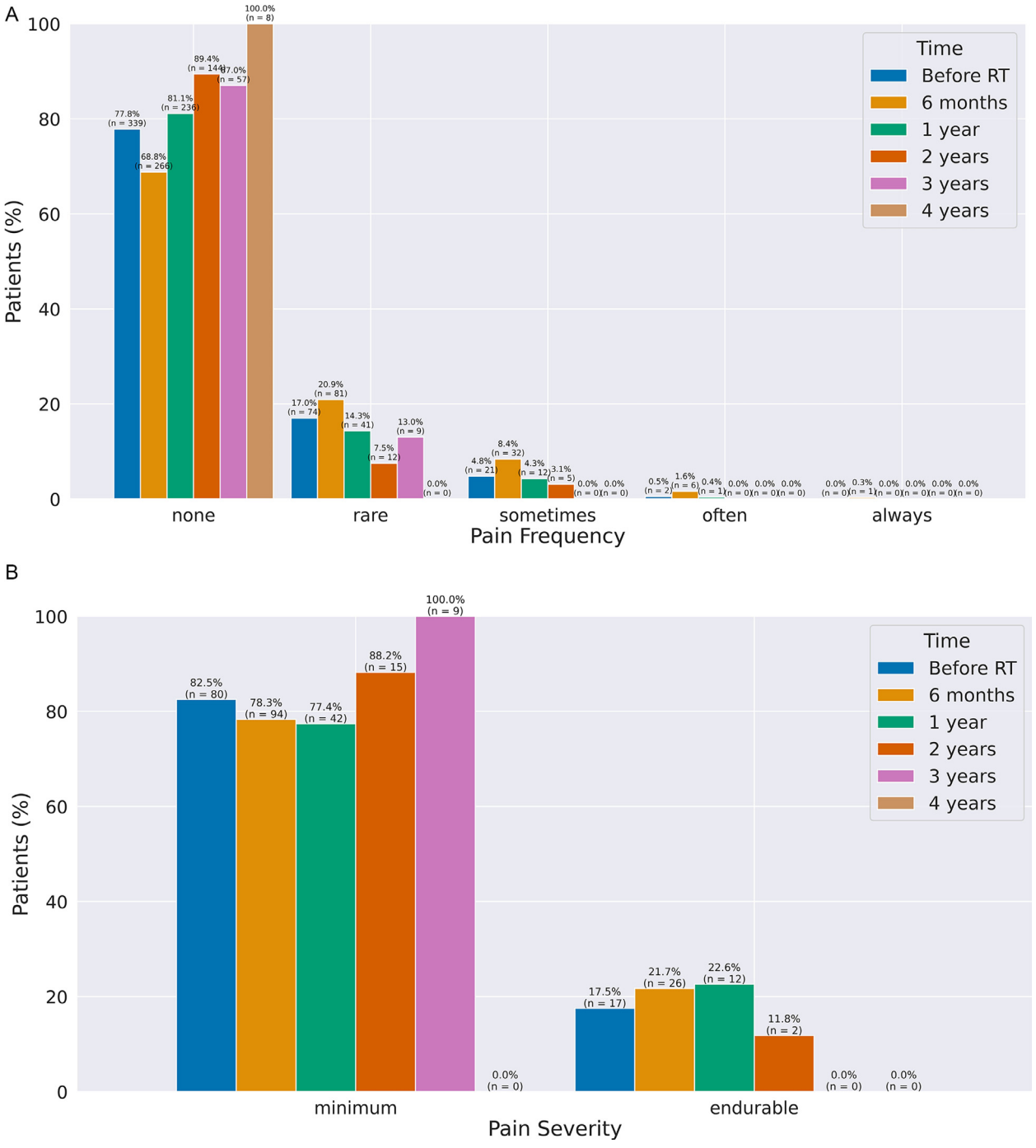

Figure 2 Breast pain (A) and its severity (B) before radiation therapy after 6, 12, and 24 months.

manifesting as edema requiring physiotherapy, with no events beyond 2 years. Retraction and atrophy and radiogenic fibrosis generally remained grade 1 or lower, often improving over time. Pigmentation changes and telangiectasia were likewise uncommon and, when present, were mild (grade 1). One patient (no boost) experienced grade 3 after radiation fibrosis at 6 months and 1 year, which fully resolved by the 2-year follow-up. The same patient had grade 3 retraction and atrophy (>40%-75%) at 1-year follow-up, which improved to grade 1 (>10%-25%) by 2 years. With a mean follow-up of 18 months, there was no statistically significant difference in the presence of G2 + effects between patients who received a boost and those who did not (RR = 0.971; P = .456; 95% CI, 0.899-1.049).

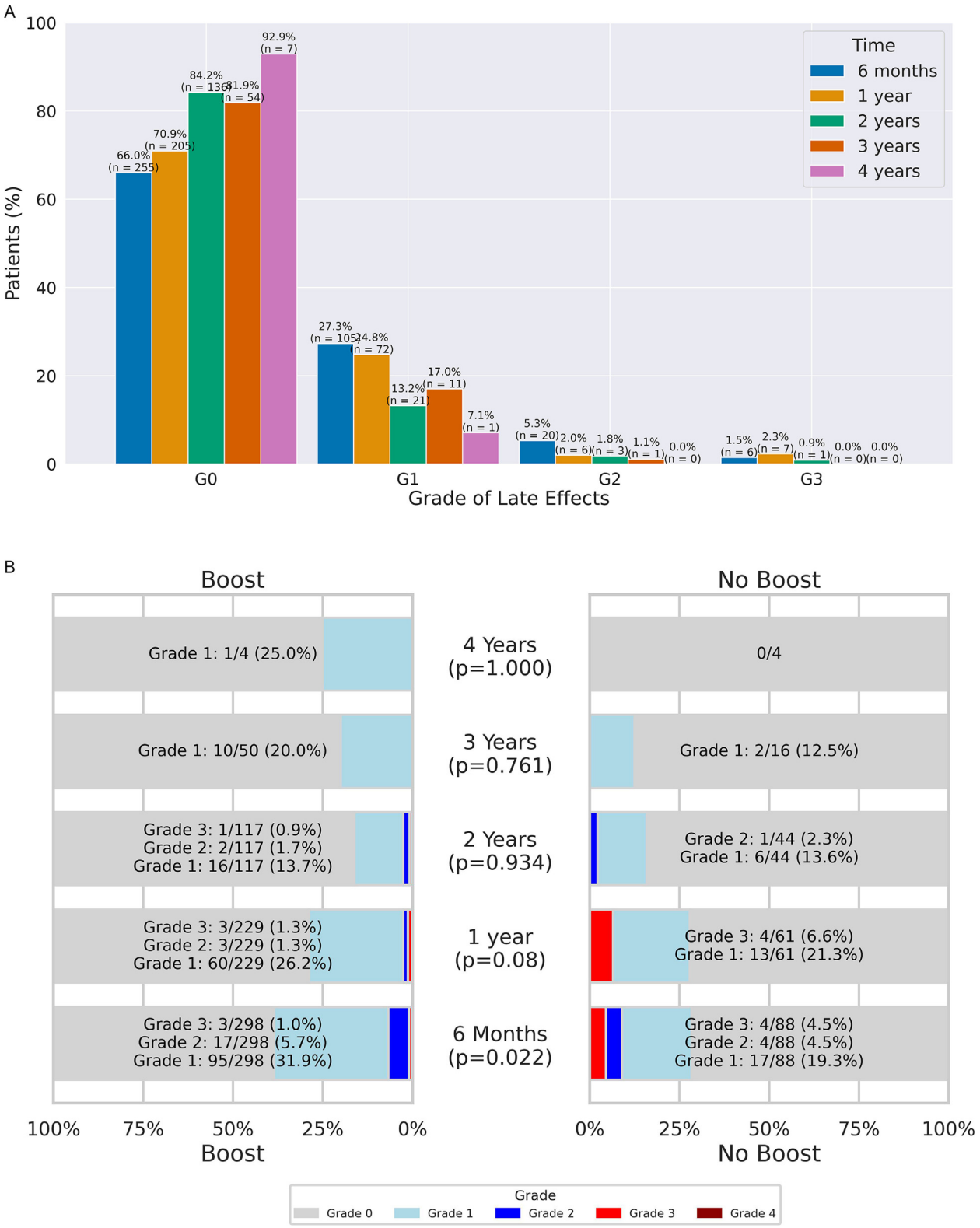

Figure 3 The frequency distribution of objective late effects (A) all patients (B) split by the presence or absence of a boost.

Cosmetic result

Based on PROMs, 97.6% (n = 375), 97.8% (n = 284), 100% (n = 161), 100% (n = 66), and 100% (n = 8) of patients rated their cosmetic result as "good" or "very good" at 6 months, 1 year, 2 years, 3 years, and 4 years, respectively (Fig. 4). Overall, 2.0% (n = 8) of patients with at least one follow-up assessment described a "fair" cosmetic appearance, and 0.3% (n = 1) of patients reported a "poor" appearance at any point. Therefore, 97.7% (n = 386) of patients rated their outcomes as "good" or "excellent." No significant difference in fair cosmetic outcomes was observed between the boost and no boost groups (RR = 1.016; P = .29; 95% CI, 0.987-1.046).

Discussion

We observed very mild acute toxicity and minimal short-term adverse effects following uhWBRT, both with and without a moderately hypofractionated boost to the resection cavity. Although our PROMs assessment period was limited, PROMs were excellent.

Several trials are currently investigating ultrahypofractionation compared with both moderate hypofractionation and conventional fractionation for whole-breast irradiation in the adjuvant radiation therapy settings for breast cancer. In all these trials, the resection cavity boost is delivered using either conventional fractionation or a simultaneous integrated boost approach. However, variations in radiation therapy techniques, target volumes, and disease stages among these studies limit comparability with our results.

For example, the HYPORT adjuvant study (N = 2100) compares 26 Gy in 5 fractions over 1 week with 40 Gy in 15 fractions over 3 weeks, but 70% of patients in this trial received lymphatic drainage irradiation, which was not part of our protocol.[5,22] Similarly, the HRBC study (N = 1121) recruited only high-risk cases requiring nodal radiation therapy, administering 34 Gy in 10 fractions over 2 weeks versus 40 Gy in 15 fractions over 3 weeks, using 2-dimensional planning.[22] Its continuation, the HYPART study (N = 1018), is evaluating 26 Gy in 5 fractions over 1 week versus 34 Gy in 10 fractions over 2 weeks, again restricted to patients with high-risk diseases requiring lymphatic drainage irradiation and using 2-dimensional planning.[23] Given these differences, the comparability of our results primarily relies on data from the experimental arms of the FAST-Forward study evaluating uhWBRT[1,24] and the MC1635 study[25] assessing uhWBRT with or without a simultaneous integrated boost (Table 2).

The FAST-Forward trial evaluated uhWBRT schedules of 26 and 27 Gy in 5 fractions, compared with a moderately hypofractionated schedule of 40 Gy in 15 fractions, followed by a conventionally fractionated boost. In FAST-Forward, 24.7% of patients received a tumor bed boost, whereas 77.9% of our patients underwent boost treatment. This disparity likely reflects broader criteria for boost administration in our protocol. Although the FAST-Forward study primarily recommended a boost for patients under 50 years with grade 3 tumors and/or lymphovascular invasion and for those aged 50 to 59 years with additional adverse prognostic factors, our study included

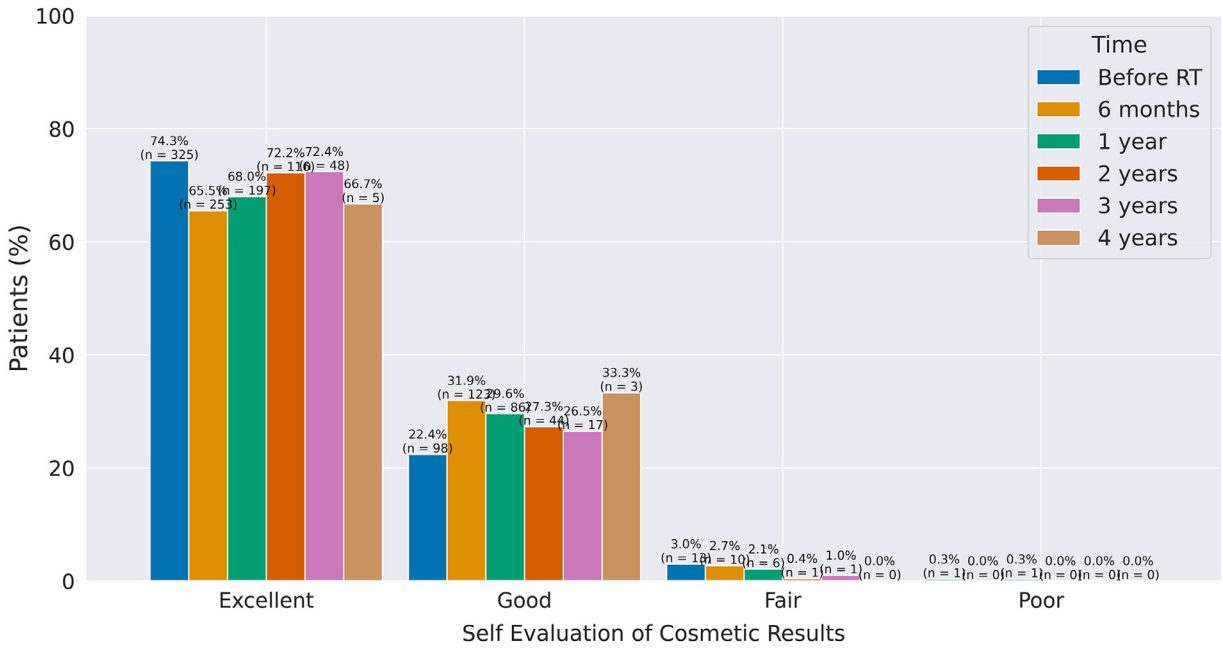

Figure 4 Cosmetic self-evaluation before radiation therapy and during follow-up assessments.

Table 2 Parameters and outcomes of FAST-Forward, MC1635 ultrahypofractionated whole-breast radiation therapy (uhWBRT) studies, and present analysis

Parameter	Study		
	FAST FORWARD, 2016, 2020[1,24]	MC1635, 2024[25]	Present analysis, 2024
Study type	Prospective randomized phase 3	Prospective randomized phase 3	Single arm single institution
Accrual	11/2011-06/2014	02/2018-02/2020	03/2020-10/2023
Number of patients	Total 4096 1361: 40 Gy/15Fx, 1368: 26 Gy/5Fx, and 1367: 27 Gy/15Fx	Total 107 54: 40 Gy/15Fx and53: 25 Gy/5Fx	436
Median follow-up, months	71.5	42.8	14
Lymphatic RT inclusion	0%	0%	0%
uhRT Fractionation	26 or 27 Gy/5Fx/1 W	26 or 27 Gy/5Fx/1 W*	26 Gy/5Fx/1 W
Boost	24.7% conventional fractionation, sequential	43.4% simultaneous integrated boost-uhWBRT 30Gy/5Fx/1 W	77.9%, moderately hypofractionated
Acute reactions ≥ G2 in uhWBRT patients	33/49% G2/3, 26/27Gy 8.9/5.8% G3 26/27Gy	3.7% G2, 0% G3	Cumulative: 13.8% G2, 0% G3
Late effects ≥ G2 in uhWBRT patients	12.2%/15.9% G2+ 26/27Gy (Per total number of follow-up assessments)	Not reported	Cumulative: 8.1% G2+, 2.8% G3 G2+ Per total number of follow-up assessments: 4.6%
High cosmetics satisfaction in uhWBRT patients†	70%/63.6% 26/27 Gy	93.3%	97.7%
Moderate (endurable) or marked (intensive) breast pain	Baseline: 9.0%/7.1% 26/27 Gy Per total number of follow-up assessments: 16.1%/16.5% 26/27 Gy	Not Reported	Baseline: 4.4% Per total number of follow-up assessments: 4.4%
Locoregional Relapse	2.1%/2.6% 26/27Gy at 71.5 mo median follow-up	0% at 42.8 mo median follow-up	1 nodal failure at 14 mo median follow-up

Abbreviation: RT = Radiotherapy; uhRT = ultrahypofractionated Radiotherapy.
*51% treated with spot-scanned proton therapy.
†Absence of moderate/marked changes or good/excellent cosmetics.

estrogen receptor-negative status, human epidermal growth factor receptor 2-positive tumors, and close resection margins (<2 mm) among the indications for boost. Moreover, unlike FAST-Forward, which did not recommend a boost for patients aged 60 years or older, our study considered a boost in older patients who had high-risk features. Variability in boost practices is further illustrated by the Danish Breast Cancer Group Hypo trial, where boost rates ranged from 14% in Denmark to 84% in Germany and only 3% in Norway.[26]

The FAST-Forward trial reported grade 2 and grade 3 acute toxicity rates of 27.2% and 5.8%, respectively, in the 26 Gy arm, and 39.2% and 9.8%, respectively, in the 27 Gy arm. In comparison, our study found a lower grade 2 acute toxicity rate of 13.8% and no grade 3 toxicity. These findings suggest that our moderately fractionated boost regimen of 10.0 to 12.5 Gy in 4 to 5 fractions does not lead to greater acute toxicity than the conventional boost regimen used in FAST-Forward.

The MC1635 trial examined ultrahypofractionated versus moderately hypofractionated whole-breast radiation therapy with simultaneous integrated boost following breast-conserving surgery. Its ultrahypofractionation arm showed lower acute toxicity compared with our results. Notably, a substantial proportion of patients (51% in the uhWBRT arm) received spot-scanned proton therapy, which may have contributed to a more favorable toxicity profile. In the MC1635 trial, acute toxicity was reported at the end of treatment, whereas in the FAST-Forward trial, it was evaluated at any point from the start of radiation therapy to 4 weeks posttreatment. Our protocol accessed acute toxicity both at the end of treatment and 2 to 3 weeks after radiation therapy, a time frame that may capture acute or subacute reactions potentially overlooked in the trials evaluating toxicity earlier or later.

Despite the limited follow-up period—only 15% (n = 66) of patients reached 3 years follow-up—the 4.6% rate of G2+ late effects per follow-up assessment among patients with at least 6 months of follow-up aligns with the FAST-Forward trial, which reported G2+ late effects rates of 12.2% and 15.9% in its 26 and 27 Gy arms, respectively, with a median follow-up of 71.5 months.

Our findings on cosmetic outcomes are also favorable compared with the FAST-Forward and MC1635 studies. With only 2.3% of patients reporting fair or poor outcomes to date, our results suggest that this treatment regimen does not lead to worse cosmetic deterioration in the short term.

In FAST-Forward, moderate-to-marked pain was reported at baseline in 9.0% and 7.1% in the 26 and 27 Gy arms, respectively, increasing to 16.1% and 16.5% per assessment at follow-up. In our study, 4.4% reported endurable pain at both baseline and per follow-up assessment. Additionally, we identified age as a statistically significant factor in both the frequency and severity of pain, emphasizing the importance of age-specific considerations in managing radiation therapy-related pain. Longer-term follow-up is necessary to fully assess and compare these outcomes.

Limitations/deficits of the work

The observation period was too short to allow a statistically and clinically significant evaluation of long-term healthy tissue effects and oncological outcomes. Moreover, the higher proportion of patients receiving a boost compared with those who did not may introduce bias in interpreting the findings. Because this study is observational rather than randomized, potential selection bias and other confounding factors warrant a cautious interpretation of the results.

Conclusion

Our early and intermediate results indicate that the applied schedules, including the moderately hypofractionated boost, are safe and well tolerated, with acute toxicity rates comparable to those reported in the FAST-Forward trial. Although our study follow-up is relatively short, our findings indicate that uhWBRT, with or without a moderately hypofractionated boost, is safe and well tolerated.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Olga Unterkirhere was responsible for statistical analysis.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2025.101756.

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