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Highlights

Patient-Reported Quality of Life After Hypofractionated Versus Conventional Adjuvant Radiotherapy for Stage IIB–IIIC Breast Cancer: A Prospective 12-Month Cohort Study from Uzbekistan

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ABSTRACT:

Background: Moderately hypofractionated radiotherapy (HFRT) is standard for early breast cancer, but patient-reported evidence in higher-stage, multimodally treated patients and in capacity-constrained settings remains limited. We compared health-related quality of life (HRQoL) after HFRT and conventional fractionation in stage IIB–IIIC disease.

Methods: In this prospective, non-randomized cohort study at a national cancer centre in Uzbekistan (2020–2022), 109 women with stage IIB–IIIC breast cancer who had received neoadjuvant chemotherapy and surgery underwent 3D-conformal radiotherapy to the chest wall or breast and regional nodes with HFRT (42.56 Gy in 16 fractions; n=54) or conventionally fractionated radiotherapy (CFRT; 50 Gy in 25 fractions; n=55). The EORTC QLQ-C30 and QLQ-BR23 were completed before radiotherapy, at completion,

and at 6 and 12 months. Between-group mean differences with 95% confidence intervals (CIs) were interpreted against a 10-point minimal important difference (MID).

Results: Baseline HRQoL was similar between groups. At radiotherapy completion, emotional functioning was maintained with HFRT but declined with CFRT (84.5 vs 72.1; difference 12.4 points, 95% CI 0.7–24.1; $p=0.038$), a difference exceeding the MID that resolved by 6 months. Physical functioning, fatigue, nausea/vomiting, chest-wall discomfort, and arm symptoms did not differ at any time point. At 12 months, the 95% CIs excluded a clinically meaningful (≥ 10 -point) disadvantage of HFRT for physical and emotional functioning and for all evaluated symptom scales; global health status improved in both groups (76.3 vs 73.5; difference 2.8, 95% CI -10.9 to 16.5). Grade III acute skin reactions occurred in three patients in each group.

Conclusions: In stage IIB–IIIC breast cancer, HFRT shortened treatment by approximately 2 weeks (nine fewer fractions) without a detectable clinically meaningful HRQoL detriment at 12 months and was associated with less acute emotional burden at treatment completion. These findings extend patient-reported support for moderate hypofractionation to higher-stage, multimodally treated patients and to capacity-constrained radiotherapy services; the emotional-functioning signal is exploratory and warrants confirmation.

- Prospective patient-reported comparison of hypofractionated and conventional adjuvant radiotherapy in stage IIB–IIIC breast cancer from Central Asia.
- Women treated after multimodal therapy, including both mastectomy and breast-conserving surgery.
- 95% CIs excluded a clinically meaningful HRQoL disadvantage of hypofractionation at 12 months for all functional and symptom scales evaluated.
- Conventional fractionation was associated with a transient, clinically meaningful decline in emotional functioning at treatment completion.
- Nine fewer fractions per patient: relevant for radiotherapy capacity in resource-constrained settings.

1. INTRODUCTION

Breast cancer is the most commonly diagnosed cancer in women worldwide [1] and the leading malignancy among women in Uzbekistan, where 4,407 new cases—24.4% of all malignant neoplasms in women—were registered in 2022 [2]. Contemporary management of stage II–III breast cancer combines systemic therapy, surgery, and radiotherapy. Postoperative radiotherapy reduces locoregional recurrence and breast cancer mortality after breast-conserving surgery and, in node-positive patients, after mastectomy [3,4]. In stage IIB–IIIC disease, radiotherapy is therefore delivered at the end of a long sequential treatment pathway, when the cumulative physical and psychological burden of treatment is often substantial.

Moderately hypofractionated radiotherapy (HFRT) delivers a higher dose per fraction over a shorter overall treatment time. Randomized trials—including the Canadian trial, the UK START trials, and subsequent trials from Denmark and China—have shown that schedules of 15–16 fractions provide long-term tumour control and normal-tissue outcomes comparable to 25-fraction conventional radiotherapy [5–10], and the FAST-Forward trial has since extended this principle to a 1-week schedule [11]. Moderate hypofractionation is consequently recommended as the standard for whole-breast irradiation in international guidelines, which increasingly extend this recommendation to postmastectomy and regional nodal irradiation [12–14].

As the oncological equivalence of hypofractionation has become established, attention has shifted to how patients experience treatment. Health-related quality of life (HRQoL) is especially informative in breast cancer because patient-perceived effects reflect the cumulative burden of systemic therapy, surgery, radiotherapy, and recovery, and because clinician-graded toxicity systematically under-captures symptoms such as fatigue and emotional distress [15]. The EORTC QLQ-C30 and its breast cancer-specific module, QLQ-BR23, are the most widely used validated instruments for this purpose [16,17].

Available evidence supports the patient-reported acceptability of hypofractionation. In the START trials, hypofractionated schedules were not associated with worse patient-reported breast, arm, shoulder, or body-image outcomes [18], and subsequent studies using standardized HRQoL instruments have reported comparable longer-term outcomes across fractionation schedules [19,20]. Randomized data have also shown lower acute toxicity with hypofractionated whole-breast irradiation [21] and non-inferior locoregional control with hypofractionated postmastectomy radiotherapy in high-risk patients [22].

Three gaps nevertheless limit the applicability of this evidence. First, patient-reported data derive predominantly from early-stage or selected populations; women with stage IIB–IIIC disease who receive radiotherapy after chemotherapy and either mastectomy or breast-conserving surgery remain underrepresented [18–20,22]. Second, most studies emphasize late outcomes, so the acute window at treatment completion—when the practical burden of daily attendance is greatest—has been examined far less, even though the time patients spend receiving care is increasingly recognised as a distinct dimension of treatment burden, termed time toxicity [23]. Third, to our knowledge, prospective patient-reported data on breast hypofractionation remain scarce from Central Asia and other low- and middle-income regions, where radiotherapy capacity is limited, travel distances are long, and the time and financial costs of a 5-week course fall heavily on patients and families [24,25]. In such settings, evidence that a shorter schedule does not impair HRQoL has direct implications for service capacity as well as for individual patients.

At our centre, moderate hypofractionation was used increasingly for stage IIB–IIIC breast cancer during the COVID-19 pandemic, when reducing hospital attendance became a priority [26]. We therefore prospectively compared HRQoL after HFRT and conventionally fractionated radiotherapy (CFRT) in women with stage IIB–IIIC breast cancer receiving multimodal treatment in Uzbekistan, using the EORTC QLQ-C30 and QLQ-BR23 at four time points spanning pre-radiotherapy status, treatment completion, and 12-month recovery. Our objectives were (i) to compare functional and symptom outcomes between regimens at each time point, interpreting differences against an established minimal important difference; (ii) to estimate whether a clinically meaningful HRQoL disadvantage of HFRT could be excluded at 12 months; and (iii) to characterize the acute post-treatment window, in which any effect of treatment duration would be expected to be most apparent. We hypothesized that HFRT would not be associated with worse HRQoL at any time point.

2. MATERIALS AND METHODS

2.1. Study Design and Participants

This prospective, non-randomized comparative study was conducted in the Department of Radiotherapy of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology, Tashkent, Uzbekistan, between 2020 and 2022, and is reported in accordance with the STROBE guideline [27]. During this period, 149 women with stage IIB–IIIC invasive breast cancer completed adjuvant radiotherapy after neoadjuvant chemotherapy and surgery, receiving either HFRT ($n=74$) or CFRT ($n=75$). The present report concerns the HRQoL component of the study and includes the 109 patients who consented to complete the quality-of-life questionnaires (HFRT, $n=54$; CFRT, $n=55$; Supplementary Figure S1); radiation toxicity, its clinical predictors, and treatment costs in the full cohort were addressed as separate objectives [28].

Inclusion criteria were histologically verified invasive breast carcinoma of stage IIB–IIIC; complete radical surgery (radical mastectomy or breast-conserving surgery); age 18–75 years; Eastern Cooperative Oncology Group performance status 0–2; completion of the planned course of adjuvant radiotherapy; and, for the HRQoL analysis, informed consent to complete the questionnaires. Exclusion criteria were distant metastases; bilateral breast cancer; previous radiotherapy to the breast, chest wall, or regional nodes; severe comorbidity contraindicating radiotherapy (decompensated heart failure of NYHA class III–IV, active autoimmune disease, or systemic sclerosis); pregnancy or lactation; and medical documentation insufficient to assess the study endpoints.

In the HRQoL sample, patients were aged 31–71 years; 66 had undergone radical mastectomy and 43 breast-conserving surgery. All patients received multimodal treatment consisting of four cycles of neoadjuvant chemotherapy, surgery, three to four cycles of adjuvant chemotherapy, and endocrine therapy when indicated, followed by postoperative radiotherapy.

Treatment allocation was not randomized: the fractionation regimen was selected by a multidisciplinary tumour board taking into account disease stage, extent of surgery, and individual patient characteristics. Characteristics of the full cohort and of the HRQoL sample are summarized in Table 2, and baseline patient-reported outcomes were compared to assess comparability.

2.2. Multimodal Treatment and Radiotherapy

Radiotherapy was administered as part of multimodal breast cancer treatment following systemic therapy and surgery. All patients received postoperative external-beam radiotherapy according to either a hypofractionated or conventionally fractionated schedule.

Patients in the HFRT group received 2.66 Gy per fraction in 16 fractions, corresponding to a total dose of 42.56 Gy. Patients in the CFRT group received 2.0 Gy per fraction in 25 fractions, corresponding to a total dose of 50 Gy. The approximate overall treatment duration was 3.2 weeks for HFRT and 5.0 weeks for CFRT. The principal characteristics of the two radiotherapy regimens are summarized in Table 1.

Radiotherapy was planned on computed tomography simulation with immobilization on a breast board or vacuum mattress and delivered with three-dimensional conformal radiotherapy (3D-CRT) on an Elekta Infinity linear accelerator, using five to six tangential 6-MV photon fields with portal imaging verification. Target volumes were delineated according to the ESTRO consensus guideline [29] and comprised the chest wall (after mastectomy) or the whole breast (after breast-conserving surgery) together with the ipsilateral supraclavicular and level I–III axillary lymph nodes; the planning target volume (clinical target volume plus 5 mm) was required to be encompassed by the 95% isodose. Heart and lung doses were constrained according to QUANTEC-based institutional criteria, and for left-sided tumours a breath-hold plan was used when it reduced cardiac dose. Acute skin reactions were graded according to the RTOG/EORTC criteria [30].

Table 1. Radiotherapy fractionation schedules used in the study

<i>Characteristic</i>	HFRT (n=54)	CFRT (n=55)
<i>Treatment setting</i>	Postoperative adjuvant RT	Postoperative adjuvant RT
<i>Disease stage</i>	IIB–IIIC	IIB–IIIC
<i>Dose per fraction, Gy</i>	2.66	2.00
<i>Number of fractions</i>	16	25
<i>Total dose, Gy</i>	42.56	50.00
<i>Approximate treatment duration, weeks</i>	3.2	5.0

Radiotherapy fractionation schedules used in the two treatment groups. HFRT, hypofractionated radiotherapy; CFRT, conventionally fractionated radiotherapy; RT, radiotherapy; Gy, gray.

Because radiotherapy was delivered within a multimodal treatment pathway, patient-reported outcomes were interpreted in the context of the overall treatment and recovery process rather than as effects attributable exclusively to radiotherapy fractionation.

2.3. Health-Related Quality-of-Life Assessment

HRQoL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), version 3.0 [16], together with the breast cancer-specific EORTC QLQ-BR23 module [17], in their official Russian-language versions.

The EORTC QLQ-C30 was used to assess global health status/quality of life, functional domains, and cancer-related symptoms, whereas the QLQ-BR23 provided additional assessment of breast cancer-specific functional and symptom domains, including breast and arm symptoms. In this report, chest-wall discomfort denotes the QLQ-BR23 breast symptoms scale (pain, swelling, hypersensitivity, and skin problems in the area of the affected breast or chest wall; items 50–53), and arm symptoms denote the QLQ-BR23 arm symptoms scale (arm or shoulder pain, swelling, and difficulty raising the arm; items 47–49).

Questionnaire responses were linearly transformed to scores ranging from 0 to 100 according to the EORTC scoring manual [31]. Higher scores on the functional scales and global health status indicate better functioning or perceived health, whereas higher scores on symptom scales indicate greater symptom burden.

Questionnaires were administered before the start of postoperative radiotherapy, at completion of radiotherapy, and at 6 and 12 months after completion of treatment, during scheduled follow-up visits with the radiation oncologist. Missing questionnaire data at the 12-month assessment were limited (5% in the HFRT group and 4.5% in the CFRT group).

2.4. Study Outcomes

The principal outcomes were global health status, physical functioning, emotional functioning, fatigue, and nausea/vomiting (QLQ-C30), and chest-wall discomfort and arm symptoms (QLQ-BR23); dyspnoea was additionally described. HRQoL was a secondary objective of the parent study, and no single primary HRQoL endpoint was prespecified; all outcomes were therefore analysed as descriptive endpoints.

The principal analysis compared HRQoL outcomes between the HFRT and CFRT groups separately at each of the four predefined assessment points. Changes in HRQoL scores across the assessment period were additionally used to describe temporal patterns of patient-reported functioning and symptom burden during the 12-month follow-up.

2.5. Statistical Analysis

Continuous HRQoL variables were summarized as mean $\pm$ standard error (SE). Between-group comparisons of EORTC QLQ-C30 and QLQ-BR23 scores were performed separately at each predefined assessment point using two-sided independent-samples Student's *t*-tests; when the assumption of equal variances was not satisfied, Welch's correction with adjusted degrees of freedom was applied.

Between-group comparisons were performed at baseline, immediately after completion of radiotherapy, and at 6 and 12 months of follow-up. A two-sided *p* value <0.05 was considered statistically significant.

To support clinical interpretation, between-group mean differences (HFRT minus CFRT) were reported with 95% confidence intervals (CIs), and standardized effect sizes were expressed as Hedges' *g*, with standard deviations derived from the SEs ($SD = SE \times \sqrt{n}$). A difference of ≥ 10 points on the 0–100 scale was considered clinically meaningful, following Osoba et al. [32]. Mean differences, CIs, and effect sizes were calculated from group summary statistics; this approach was also used for global health status and arm symptoms.

In a post hoc analysis, we examined whether a clinically meaningful disadvantage of HFRT could be excluded at each post-baseline time point by determining whether the relevant 95% CI limit lay within the 10-point threshold (lower limit > -10 points for functional scales and global health status; upper limit $< +10$ points for symptom scales). This confidence-interval approach was descriptive and does not constitute a prespecified non-inferiority test.

No a priori sample size calculation was performed for the HRQoL analysis; the sample comprised all consenting eligible patients treated during the study period. In a post hoc sensitivity analysis based on the observed variability, the study had 80% power at a two-sided α of 0.05 to detect between-group differences of approximately 9–19 points for most domain–time-point combinations. Proportions were compared using Pearson's χ^2 test with Yates' correction or Fisher's exact test, as appropriate. Analyses were performed using Statistica 10.0 (StatSoft) and IBM SPSS Statistics 20.0; confidence intervals and effect sizes were calculated with SciPy (Python).

Because statistical inference was based on time-point-specific group comparisons, within-patient changes and treatment-by-time interactions were not modelled with repeated-measures or mixed-effects methods; changes across assessment points are therefore described as temporal patterns.

No adjustment for multiple comparisons was applied across the 25 pointwise comparisons. Statistically significant findings from individual comparisons were therefore interpreted as exploratory.

2.6. Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics Committee of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology (IRB No. 6/1-1444). Written informed consent was obtained from all participants before enrollment.

3. RESULTS

3.1. Study Population and Baseline Patient-Reported Outcomes

Between 2020 and 2022, 149 women completed adjuvant radiotherapy (HFRT, *n*=74; CFRT, *n*=75), of whom 109 consented to HRQoL assessment and were included in this analysis (HFRT, *n*=54; CFRT, *n*=55; Supplementary Figure S1). Patients in the HRQoL sample were aged 31–71 years (mean, 51.4 years); 66 (60.6%) had undergone radical mastectomy and 43 (39.4%)

breast-conserving surgery. In the full cohort, the distribution of surgery type was nearly identical between groups (radical mastectomy, 54.1% vs 53.3%; $p=1.00$). Characteristics of the full cohort and the HRQoL sample are shown in Table 2.

Table 2. Clinical and treatment characteristics of the study population

Characteristic	Full cohort, HFRT (n=74)	Full cohort, CFRT (n=75)	HRQoL sample (n=109)
Age, years	53.3 $\pm$ 9.3 (median 50) [†]		51.4 (range 31–71)
Clinical stage, n (%)			
IIB	48 (32) [†]		IIB–IIIC [‡]
IIIA	43 (29) [†]		
IIIB	46 (31) [†]		
IIIC	12 (8) [†]		
Histology, n (%)			
Invasive ductal carcinoma, grade 2	79 (53) [†]		—
Invasive ductal carcinoma, grade 3	70 (47) [†]		—
Surgery, n (%)			
Radical mastectomy	40 (54.1)	40 (53.3)	66 (60.6)
Breast-conserving surgery	34 (45.9)	35 (46.7)	43 (39.4)
Neoadjuvant chemotherapy (4 cycles)	All	All	All
Adjuvant chemotherapy (3–4 cycles)	—	—	All
Endocrine therapy	As indicated	As indicated	As indicated
RT target: chest wall/breast + supraclavicular and axillary nodes	All	All	All
RT technique	3D-CRT [†]	3D-CRT [†]	3D-CRT [†]

[†]Reported for the full cohort (n=149) without breakdown by group. [‡]Stage distribution by group was not available for the HRQoL sample. Surgery type in the full cohort: $p=1.00$ (Fisher's exact test). 3D-CRT, three-dimensional conformal radiotherapy; HFRT, hypofractionated radiotherapy; CFRT, conventionally fractionated radiotherapy; HRQoL, health-related quality of life; RT, radiotherapy.

At baseline, patient-reported outcomes were similar between groups, with no statistically significant differences in physical functioning, emotional functioning, global health status, fatigue, nausea/vomiting, or chest-wall discomfort (all $p>0.6$; Table 3).

Baseline patient-reported outcomes also varied descriptively according to surgical treatment. Global health status was lower among patients who had undergone radical mastectomy than among those treated with breast-conserving surgery (38.3 ± 4.1 vs 48.3 ± 4.7), while fatigue was higher (33.7 ± 3.6 vs 27.7 ± 2.4).

Table 3. Baseline patient-reported outcomes according to radiotherapy fractionation group

Outcome	HFRT (n=54)	CFRT (n=55)	<i>p</i> value
Physical functioning	75.0 $\pm$ 2.6	74.0 $\pm$ 2.2	0.770
Emotional functioning	85.2 $\pm$ 2.8	87.1 $\pm$ 3.2	0.656
Global health status	43.3 $\pm$ 4.2	45.5 $\pm$ 5.4	0.748*

Fatigue	29.7 ± 3.4	30.5 ± 4.2	0.883
Nausea/vomiting	12.8 ± 3.9	14.1 ± 4.4	0.825
Chest-wall discomfort	8.8 ± 2.3	9.2 ± 2.3	0.902

Baseline patient-reported outcomes before postoperative radiotherapy according to fractionation group. Data are presented as mean ± SE. Higher physical and emotional functioning and global health status scores indicate better functioning or health status, whereas higher symptom scores indicate greater symptom burden. HFRT, hypofractionated radiotherapy; CFRT, conventionally fractionated radiotherapy; SE, standard error. *Calculated from reported summary statistics (Welch's *t*-test).

3.2. Physical and Emotional Functioning

Physical functioning showed a modest decline immediately after radiotherapy followed by recovery during follow-up in both treatment groups (Table 4; Figure 1A). No statistically significant between-group differences in physical functioning were detected at any of the four assessment points.

Emotional functioning showed a distinct early pattern (Table 4; Figure 1B). Scores were similar at baseline (85.2 ± 2.8 vs 87.1 ± 3.2; *p*=0.656). Immediately after radiotherapy, emotional functioning was essentially unchanged in the HFRT group (84.5 ± 4.6) but had fallen by 15.0 points in the CFRT group (72.1 ± 3.7), yielding a between-group difference of 12.4 points (95% CI 0.7 to 24.1; *p*=0.038; Hedges' *g*=0.40) that exceeded the 10-point minimal important difference. The difference was no longer present at 6 months (*p*=0.633) or 12 months (*p*=0.963), by which time emotional functioning had increased in both groups.

Thus, the only statistically significant pointwise between-group difference in functional outcomes was observed for emotional functioning at treatment completion; no persistent differences were detected during follow-up.

Table 4. Physical and emotional functioning during 12-month follow-up

Domain	Assessment	HFRT	CFRT	<i>p</i> value
Physical functioning	Baseline	75.0 ± 2.6	74.0 ± 2.2	0.770
	Immediately after RT	73.0 ± 2.7	68.0 ± 3.2	0.235
	6 months	77.0 ± 3.6	73.0 ± 3.3	0.415
	12 months	81.0 ± 2.9	76.0 ± 3.1	0.241
Emotional functioning	Baseline	85.2 ± 2.8	87.1 ± 3.2	0.656
	Immediately after RT	84.5 ± 4.6	72.1 ± 3.7	0.038
	6 months	91.0 ± 2.8	88.7 ± 3.9	0.633
	12 months	93.1 ± 2.4	92.9 ± 3.6	0.963

Physical and emotional functioning assessed using the EORTC QLQ-C30 before radiotherapy, immediately after completion of radiotherapy, and at 6 and 12 months. Data are presented as mean ± SE on a 0–100 scale; higher scores indicate better functioning. Between-group *p* values were obtained using two-sided independent-samples *t*-tests, with Welch's correction where appropriate. HFRT, hypofractionated radiotherapy; CFRT, conventionally fractionated radiotherapy; RT, radiotherapy; SE, standard error.

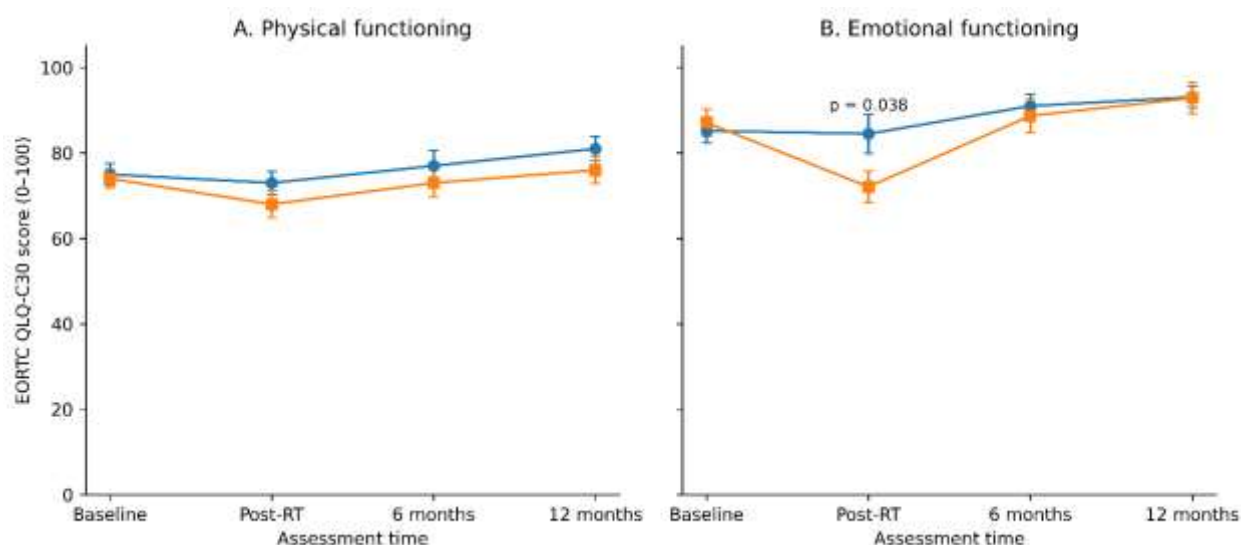


Figure 1. Patient-reported physical and emotional functioning during 12-month follow-up according to radiotherapy fractionation. (A) Physical functioning and (B) emotional functioning assessed using the EORTC QLQ-C30 before radiotherapy, immediately after radiotherapy, and at 6 and 12 months. Data are presented as mean $\pm$ SE; higher scores indicate better functioning. Emotional functioning differed significantly between groups immediately after radiotherapy ($p=0.038$). No other pointwise between-group differences were statistically significant. HFRT, hypofractionated radiotherapy; CFRT, conventionally fractionated radiotherapy; RT, radiotherapy; SE, standard error.

3.3. Symptom Burden During Follow-up

The evaluated symptom domains showed a consistent temporal pattern in both treatment groups, with worsening around completion of radiotherapy followed by improvement during follow-up (Table 5). Fatigue increased immediately after treatment and subsequently declined at 6 and 12 months (Figure 2). Similar patterns were observed for nausea/vomiting and chest-wall discomfort.

No statistically significant between-group differences were detected for fatigue, nausea/vomiting, or chest-wall discomfort at any assessment point (all $p>0.25$; Table 5; Table 6). By 12 months, scores for all three symptom domains were numerically lower than their respective baseline values in both groups.

Dyspnoea followed a similar pattern. From comparable baseline values (14.0 ± 5.5 vs 14.1 ± 5.2 ; $p=0.99$), it increased by approximately 9 points after HFRT and 10 points after CFRT and had declined to 5.2 ± 2.9 points in the overall sample at 12 months.

Table 5. Patient-reported symptom scores during 12-month follow-up

Outcome	Assessment	HFRT	CFRT	<i>p</i> value
Fatigue	Baseline	29.7 $\pm$ 3.4	30.5 $\pm$ 4.2	0.883
	Immediately after RT	38.5 $\pm$ 4.9	41.0 $\pm$ 4.0	0.694
	6 months	18.2 $\pm$ 3.7	21.4 $\pm$ 3.7	0.542
	12 months	13.2 $\pm$ 2.3	15.1 $\pm$ 3.7	0.664
Nausea/vomiting	Baseline	12.8 $\pm$ 3.9	14.1 $\pm$ 4.4	0.825
	Immediately after RT	29.2 $\pm$ 4.3	35.7 $\pm$ 3.7	0.255
	6 months	9.2 $\pm$ 2.7	11.4 $\pm$ 3.1	0.594

	12 months	7.2 ± 2.6	8.1 ± 3.8	0.846
Chest-wall discomfort	Baseline	8.8 ± 2.3	9.2 ± 2.3	0.902
	Immediately after RT	12.3 ± 2.9	13.4 ± 2.6	0.778
	6 months	3.7 ± 2.6	4.2 ± 2.3	0.886
	12 months	1.3 ± 0.4	2.0 ± 0.9	0.480

Patient-reported symptom scores before radiotherapy, immediately after completion of radiotherapy, and at 6 and 12 months. Data are presented as mean $\pm$ SE on a 0–100 scale; higher scores indicate greater symptom burden. Between-group *p* values were obtained using two-sided independent-samples *t*-tests, with Welch's correction where appropriate. HFRT, hypofractionated radiotherapy; CFRT, conventionally fractionated radiotherapy; RT, radiotherapy; SE, standard error.

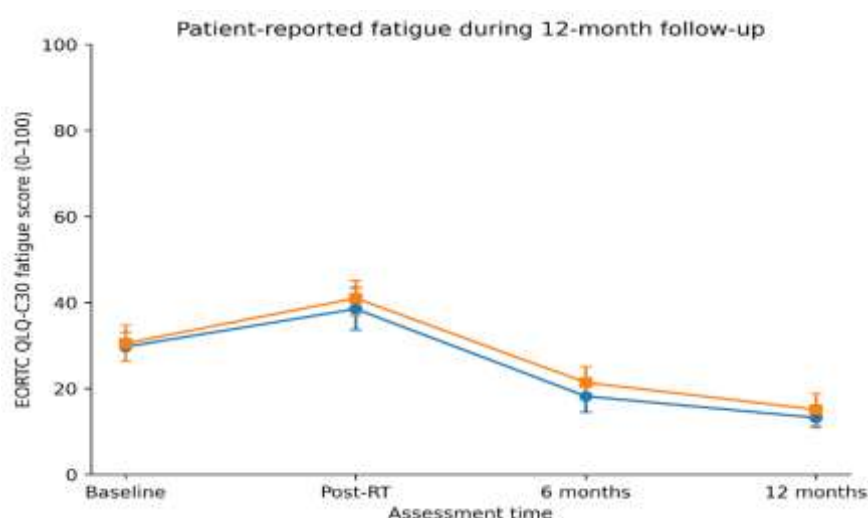


Figure 2. Patient-reported fatigue during 12-month follow-up according to radiotherapy fractionation. Fatigue was assessed using the EORTC QLQ-C30 before radiotherapy, immediately after radiotherapy, and at 6 and 12 months. Data are presented as mean $\pm$ SE; higher scores indicate greater symptom burden. No statistically significant pointwise between-group differences were detected. HFRT, hypofractionated radiotherapy; CFRT, conventionally fractionated radiotherapy; RT, radiotherapy; SE, standard error.

3.4. Arm Symptoms and Global Health Status

Arm symptoms decreased during follow-up in both groups, from 23.7 ± 3.3 at baseline to 20.1 ± 2.8 immediately after radiotherapy and 6.1 ± 1.7 at 12 months with HFRT, and from 23.6 ± 3.8 to 20.4 ± 2.6 and 6.8 ± 1.9 , respectively, with CFRT. Between-group differences were negligible at baseline ($p=0.984$), immediately after radiotherapy ($p=0.938$), and at 12 months ($p=0.783$). Restricted arm mobility after surgery occurred predominantly in patients who had undergone radical mastectomy (71%); patients received therapeutic exercise (physiotherapy) during follow-up.

Global health status decreased moderately in both groups immediately after radiotherapy and then improved substantially, from 43.3 ± 4.2 at baseline to 76.3 ± 4.9 at 12 months with HFRT and from 45.5 ± 5.4 to 73.5 ± 4.9 with CFRT, with no between-group difference at baseline ($p=0.748$) or at 12 months (difference 2.8 points; 95% CI -10.9 to 16.5 ; $p=0.687$).

Acute radiation skin reactions (RTOG/EORTC) were similarly distributed between groups: grade I–II reactions occurred in 11 of 54 patients (20.4%) receiving HFRT and 13 of 55 (23.6%) receiving CFRT ($p=0.86$), and grade III reactions in three patients in each group (5.6% and 5.5%; $p=1.00$); no grade IV reactions occurred. In the full cohort, acute pneumonitis occurred in 4 of 74 (5.4%) and 5 of 75 (6.7%) patients and pulmonary fibrosis in 3 of 74 (4.1%) and 4 of 75 (5.3%), respectively (both $p=1.00$); no late skin or subcutaneous radiation injury and no cardiac events were recorded during follow-up.

3.5. Clinically Meaningful Differences

Between-group mean differences, 95% CIs, and standardized effect sizes for all post-baseline assessments are summarized in Table 6 and Figure 3. Apart from emotional functioning at treatment completion ($g=0.40$), all standardized effects were negligible to small ($|g| \leq 0.23$). At 12 months, the 95% CIs excluded a ≥ 10 -point disadvantage of HFRT for physical functioning, emotional functioning, fatigue, nausea/vomiting, chest-wall discomfort, and arm symptoms. For global health status, the CI (-10.9 to 16.5) marginally included a clinically meaningful difference in either direction. Immediately after radiotherapy, a ≥ 10 -point disadvantage of HFRT was excluded for all domains except fatigue, for which the upper confidence limit only just reached the threshold (10.05 points).

Table 6. Between-group differences in patient-reported outcomes after radiotherapy and exclusion of a clinically meaningful disadvantage of HFRT

Outcome	Time point	Difference (95% CI) [†]	<i>g</i>	<i>p</i> value	HFRT disadvantage ≥ 10 points excluded [‡]
Physical functioning	Immediately after RT	5.0 (−3.3 to 13.3)	0.23	0.235	Yes
	6 months	4.0 (−5.7 to 13.7)	0.16	0.415	Yes
	12 months	5.0 (−3.4 to 13.4)	0.23	0.241	Yes
Emotional functioning	Immediately after RT	12.4 (0.7 to 24.1)	0.40	0.038	Yes
	6 months	2.3 (−7.2 to 11.8)	0.09	0.633	Yes
	12 months	0.2 (−8.4 to 8.8)	0.01	0.963	Yes
Global health status	12 months	2.8 (−10.9 to 16.5)	0.08	0.687	No
Fatigue	Immediately after RT	−2.5 (−15.0 to 10.0)	−0.08	0.693	No
	6 months	−3.2 (−13.6 to 7.2)	−0.12	0.542	Yes
	12 months	−1.9 (−10.6 to 6.8)	−0.08	0.664	Yes
Nausea/vomiting	Immediately after RT	−6.5 (−17.7 to 4.7)	−0.22	0.254	Yes
	6 months	−2.2 (−10.4 to 6.0)	−0.10	0.594	Yes
	12 months	−0.9 (−10.0 to 8.2)	−0.04	0.845	Yes
Chest-wall discomfort	Immediately after RT	−1.1 (−8.8 to 6.6)	−0.05	0.778	Yes
	6 months	−0.5 (−7.4 to 6.4)	−0.03	0.886	Yes
	12 months	−0.7 (−2.7 to 1.3)	−0.14	0.479	Yes
Arm symptoms	Immediately after RT	−0.3 (−7.9 to 7.3)	−0.02	0.938	Yes
	12 months	−0.7 (−5.7 to 4.3)	−0.05	0.783	Yes

†HFRT minus CFRT on the 0–100 scale; positive values favour HFRT for functional scales and global health status, whereas negative values favour HFRT for symptom scales. ‡Post hoc: lower 95% CI limit > –10 points (functional scales, global health status) or upper limit < +10 points (symptom scales). Differences, CIs, and Hedges' g were calculated from group means and SEs ($SD = SE \times \sqrt{n}$; $n=54$ and 55). HFRT, hypofractionated radiotherapy; CFRT, conventionally fractionated radiotherapy; RT, radiotherapy; CI, confidence interval.

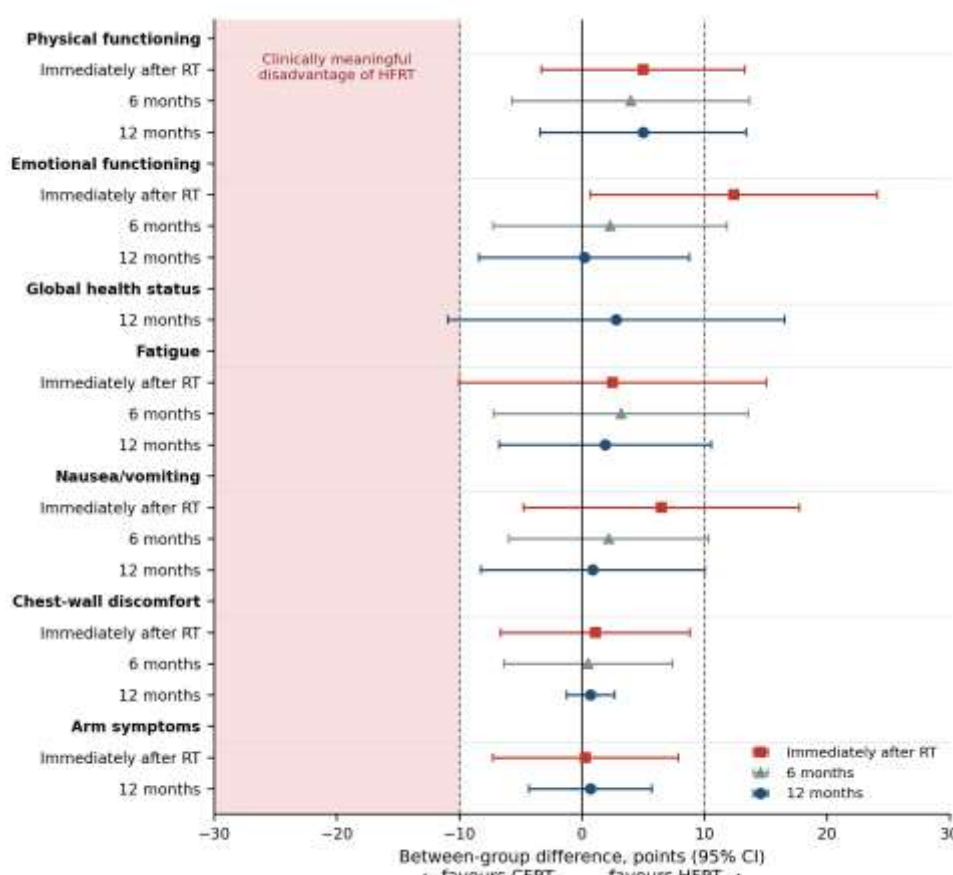


Figure 3. Between-group differences in patient-reported outcomes after radiotherapy. Points and bars show mean differences and 95% CIs, oriented so that positive values favour HFRT for all scales (symptom-scale differences sign-reversed). Dashed lines mark the 10-point minimal important difference; the shaded region indicates a clinically meaningful disadvantage of HFRT. HFRT, hypofractionated radiotherapy; CFRT, conventionally fractionated radiotherapy; RT, radiotherapy; CI, confidence interval.

4. DISCUSSION

In this prospective cohort of women with stage IIB–IIIC breast cancer treated with multimodal therapy in Uzbekistan, moderately hypofractionated adjuvant radiotherapy shortened the radiotherapy course from approximately 5.0 to 3.2 weeks without a detectable clinically meaningful detriment in patient-reported HRQoL over 12 months. Three findings extend the existing evidence. First, at 12 months the 95% CIs excluded a ≥ 10 -point disadvantage of HFRT for physical and emotional functioning, fatigue, nausea/vomiting, chest-wall discomfort, and arm symptoms, moving the interpretation beyond the mere absence of statistical significance toward a quantitative bound on potential harm. Second, the acute window at treatment completion was the only period in which the regimens diverged: emotional functioning was maintained with HFRT but declined by 15 points with CFRT, producing a between-group difference that exceeded the minimal important difference. Third, these observations derive from a higher-stage, multimodally treated population in a Central Asian health system—a population and setting that are scarcely represented in the patient-reported hypofractionation literature.

Our results are consistent with, and extend, randomized evidence. In the START trials, hypofractionation did not worsen patient-reported breast, arm, shoulder, or body-image outcomes [18], and a later study using the QLQ-C30 reported comparable HRQoL across radiotherapy regimens [19]. These data, however, came largely from early-stage patients receiving whole-breast

irradiation. In high-risk patients after mastectomy, a phase 3 trial established non-inferior locoregional control with hypofractionated postmastectomy radiotherapy [22], and an Indian postmastectomy series reported similar tolerance and quality of life with hypofractionation [20]. The present study complements these data with four-time-point patient-reported trajectories in a mixed mastectomy and breast-conserving surgery population with stage IIB–IIIC disease, in whom radiotherapy follows months of systemic therapy and surgery. The similarity of functional and symptom trajectories between regimens in this setting suggests that the cumulative burden of higher-stage treatment does not make patients more vulnerable to the higher dose per fraction of HFRT, at least within the first year.

The emotional-functioning finding merits attention because of its direction and magnitude. The between-group difference of 12.4 points exceeded the conventional 10-point threshold for a clinically meaningful change [32] and corresponded to a small-to-moderate standardized effect (Hedges' $g=0.40$). Notably, the difference arose from a decline in the CFRT group rather than an improvement with HFRT, and it coincided with the point at which the regimens differed most in cumulative treatment time—nine additional attendances over nearly two additional weeks. This pattern is consistent with the concept of time toxicity, whereby the days patients devote to receiving care constitute a burden distinct from biological toxicity [23]. Where patients may travel long distances to a limited number of radiotherapy centres, prolonged courses can additionally disrupt employment, family roles, and household finances [24,25], plausibly contributing to emotional strain as treatment is prolonged. The emotional-functioning scale of the QLQ-C30 has been validated as a measure of psychosocial function in patients with cancer [33], supporting the relevance of this domain. Nevertheless, the finding must be regarded as hypothesis-generating: it was one of 25 pointwise comparisons conducted without multiplicity adjustment, a setting in which approximately one nominally significant result would be expected by chance; the lower confidence limit (0.7 points) was close to zero; treatment allocation was not randomized; and travel burden, anxiety, and financial strain were not measured directly. Future studies should incorporate validated measures of anxiety, financial toxicity, and time spent in care to test whether shortened schedules mitigate acute psychological burden.

Both regimens showed the same temporal symptom profile: fatigue, nausea/vomiting, and chest-wall discomfort peaked at treatment completion and subsequently fell below pre-radiotherapy levels by 12 months. This identifies treatment completion as a period of heightened symptom burden that warrants proactive supportive care, irrespective of fractionation. The magnitude of the nausea/vomiting peak exceeds what would be expected from breast irradiation alone and probably reflects the residual effects of recently completed adjuvant chemotherapy, underscoring that patient-reported outcomes in this population capture the cumulative effects of multimodal treatment. Similarly, the large improvements in global health status (28–33 points) and arm symptoms over 12 months are best interpreted as recovery from chemotherapy and surgery rather than as effects of fractionation. The descriptive associations of radical mastectomy with lower baseline global health status, greater fatigue, and most arm-related symptoms (71%) point in the same direction: in stage IIB–IIIC disease, the extent of surgery appears to shape HRQoL more strongly than the fractionation schedule. Response shift—recalibration of internal standards as patients adapt to illness—may also have contributed to the large improvements and to the high emotional-functioning scores at 12 months [34].

These results have practical implications beyond the individual patient. Each patient treated with the 16-fraction schedule requires nine fewer treatment sessions than with the 25-fraction schedule, corresponding to approximately 900 linear-accelerator treatment slots per 100 patients. In an institutional analysis conducted within this study, the hypofractionated schedule shortened the average hospital stay from 35 to 21 days, reduced direct treatment costs by approximately 23% (about 5.0 million Uzbek sum per patient), and increased the estimated annual throughput of a single linear accelerator from approximately 521 to 870 patients [28]. In health systems in which radiotherapy capacity falls short of demand [24], such gains can shorten waiting times or extend access to additional patients, while also reducing patients' travel, accommodation, and productivity costs. Our findings therefore support moderate hypofractionation as the default adjuvant schedule for women with stage IIB–IIIC breast cancer, including after mastectomy, in line with randomized evidence [22] and current international recommendations [14], and provide a patient-reported rationale for evaluating shorter schedules, such as the 1-week regimen validated in FAST-Forward [11], in similar settings. Because the study was not designed as a formal non-inferiority analysis of HRQoL, the confidence-interval approach used here provides supportive rather than confirmatory evidence.

This study has limitations. First, treatment allocation was not randomized but determined by a multidisciplinary tumour board on the basis of stage, extent of surgery, and individual characteristics; despite similar baseline HRQoL and a balanced distribution of surgery type, confounding by indication cannot be excluded, and group-specific stage distribution was not available for the HRQoL sample. In addition, the HRQoL sample comprised the 73% of treated patients who consented to questionnaire completion, which may introduce selection bias. Second, the analysis was based on time-point-specific

comparisons of aggregate data rather than on mixed-effects models of individual trajectories, precluding formal tests of within-patient change and treatment-by-time interaction. Third, multiple comparisons were performed without adjustment. Fourth, the sample was not powered for HRQoL equivalence; for global health status in particular, the CI was wide, and because smaller domain-specific thresholds have been proposed for some QLQ-C30 scales [35], the 10-point criterion should be regarded as conventional rather than stringent. Fifth, although no late skin or subcutaneous injury was recorded in the full cohort, 12 months of patient-reported follow-up is too short to capture late effects—such as fibrosis, lymphoedema, and cosmetic change—that typically emerge after several years and represent the principal theoretical concern with higher doses per fraction, and cosmesis was not evaluated. Sixth, this was a single-centre study, which may limit generalizability. Strengths include the prospective design, four assessments spanning the acute and recovery phases, the use of internationally validated instruments, the low rate of missing data at 12 months, interpretation anchored in minimal important differences, and the inclusion of a higher-stage population from an under-studied region.

Randomized or propensity-adjusted studies with individual-level longitudinal modelling, longer follow-up for late toxicity and cosmesis, and direct measurement of time toxicity and financial burden are warranted to confirm and extend these findings.

5. CONCLUSIONS

In women with stage IIB–IIIC breast cancer receiving multimodal treatment, moderately hypofractionated adjuvant radiotherapy (42.56 Gy in 16 fractions) shortened the radiotherapy course by approximately 2 weeks without a detectable clinically meaningful detriment in patient-reported functioning or symptoms at 12 months compared with conventional fractionation. The only divergence between regimens occurred at treatment completion, when emotional functioning was better preserved with the shorter course—an exploratory finding consistent with a time-related burden of prolonged treatment. Treatment completion was a period of peak symptom burden with both regimens, warranting targeted supportive care. Together with its capacity advantages, these data support moderate hypofractionation as a patient-acceptable standard for higher-stage breast cancer, including in resource-constrained radiotherapy settings, pending confirmation in randomized studies with longer follow-up.

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Competing interests

The authors declare no competing interests.

Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

B.I.: Conceptualization, Methodology, Investigation, Data Curation; N.D.: Methodology, Investigation, Supervision; T.B.: Conceptualization, Supervision, Validation; N.A.: Formal Analysis, Visualization, Writing – Original Draft, Review & Editing; D.B.: Validation, Formal Analysis, Review & Editing; D.A.: Validation, Review & Editing. All authors reviewed and approved the final manuscript.

Use of AI-assisted tools

During the preparation of this manuscript, the authors used Claude (Anthropic) to assist with language editing, restructuring of the text, and calculation of confidence intervals and effect sizes from summary statistics. The authors reviewed and edited all content and take full responsibility for the publication.

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