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Acute Skin Toxicity and Cosmetic Outcomes of Ultra-Hypofractionated Whole-Breast Radiotherapy Delivered with Intensity-Modulated Radiotherapy in Early-Stage Breast Cancer: A Phase II Single-Arm Trial

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Abstract

Background

Ultra-hypofractionated whole-breast radiotherapy (UHWBRT) is an emerging strategy for shortening the duration and burden of adjuvant radiotherapy after breast-conserving surgery. We evaluated acute skin toxicity, cosmetic outcomes, and organ-at-risk (OAR) dosimetry in early-stage breast cancer patients treated with UHWBRT delivered by intensity-modulated radiotherapy (IMRT).

Methods

In this phase II, single-arm study, 46 women aged ≥ 55 years with early-stage breast cancer (pT1-3N0) who had undergone breast-conserving surgery received 26 Gy in 5 fractions to the whole breast using IMRT with volumetric-modulated arc therapy (VMAT); 3 patients with adverse risk features received an additional sequential boost of 10 Gy in 5 fractions to the tumor bed. Acute skin toxicity was graded with the RTOG scale, and cosmesis was assessed with the 12-item Breast Cancer Treatment Outcome Scale (BCTOS-12) at baseline and 1, 6, 12, and 24 months. Oncologic outcomes were recorded over a mean follow-up of 18.6 months. Trial registration: Iranian Registry of Clinical Trials (IRCT20240112060693N1), registered on 04/06/2025.

Results

Mean age was 64.15 ± 7.03 years; 71.7% of tumors were left-sided. No patient developed grade ≥ 2 acute dermatitis; 21.7% had grade 1 dermatitis at 2 weeks. At 6 months, all patients had excellent (69.6%) or good (30.4%) cosmetic outcomes, unaffected by prior chemotherapy ($P = 0.276$). Mean heart dose (MHD) was 1.99 Gy overall (2.52 Gy for left-sided vs 0.69 Gy for right-sided tumors, $P < 0.001$), and ipsilateral lung V20 was 8.52%. Non-dermatologic complications occurred in 15.2% of patients. No local recurrence occurred, and overall survival was 100%.

Conclusions

UHWBRT (26 Gy in 5 fractions) delivered with IMRT is a safe, well-tolerated, and effective regimen for older women with early-stage breast cancer, providing excellent OAR sparing, minimal acute skin toxicity, and durable early cosmesis, while compressing treatment into one week. Confirmation in randomized and longer-term studies is warranted.

Trial registration

Iranian Registry of Clinical Trials, IRCT20240112060693N1 date of registration 04/06/2025.

1. Introduction

Breast cancer is the most common malignancy diagnosed in women worldwide and a leading cause of cancer death, with disproportionately higher mortality in less-resourced settings, largely attributable to late diagnosis and limited access to treatment infrastructure (1). Management is stage- and biology-dependent and typically multimodal, combining surgery, systemic therapy, and radiotherapy; women who undergo breast-conserving surgery require adjuvant whole-breast irradiation to achieve local control comparable to mastectomy (2).

Conventional whole-breast radiotherapy delivers 50 Gy in 25 fractions over five weeks. Randomized trials, including the UK START A and START B trials and the Danish DBCG HYPO trial, established that moderate hypofractionation (approximately 40–42.5 Gy in 15–16 fractions over three weeks) achieves local control, survival, and late toxicity equivalent to conventional fractionation, and moderate hypofractionation is now the international standard for most patients with early breast cancer (4, 5, 25, 26). More recently, ultra-hypofractionated regimens compressing treatment into a single week (5 fractions) have been investigated. The FAST and FAST-Forward trials demonstrated that 26–27 Gy in 5 fractions is non-inferior to standard fractionation for local control and late normal-tissue effects at 10 and 5 years, respectively, establishing UHWBRT as a further advance in shortening treatment duration (23, 24).

Shortening treatment from five weeks to one week reduces patient travel burden, machine occupancy, and overall healthcare costs, benefits that gained particular relevance during the COVID-19 pandemic, when many centers adopted ultra-hypofractionated schedules to limit patient visits and hospital exposure (6). However, because the dose per fraction is higher in ultra-hypofractionated regimens, there is a theoretical concern for increased acute and late toxicity to the skin and to organs at risk (OARs), particularly the heart and lungs, especially for left-sided tumors (17). Intensity-modulated radiotherapy (IMRT), including volumetric-modulated arc therapy (VMAT), enables more homogeneous dose distribution within the planning target volume (PTV) and better OAR sparing than three-dimensional conformal techniques, and has been shown to reduce acute skin toxicity in several hypofractionated cohorts (9, 10, 13).

Despite growing international experience with UHWBRT, IMRT-specific data remain comparatively limited, and evidence from Iranian and regional populations is scarce (14). We therefore conducted a prospective, phase II, single-arm study to evaluate acute skin toxicity, cosmetic outcomes, and OAR dosimetry in patients with early-stage breast cancer treated with UHWBRT (26 Gy in 5 fractions) delivered with IMRT-VMAT at a tertiary referral cancer center in Iran.

2. Materials and Methods

2.1 Study design and ethical approval

This was a prospective, single-arm, phase II clinical trial conducted at the Cancer Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences. The study was approved by the institutional research ethics committee (IR.TUMS.IKHC.REC.1402.343) and conducted in accordance with the Declaration of Helsinki. The trial was registered in the Iranian Registry of Clinical Trials (IRCT20240112060693N1; date of registration: 04/06/2025). Written informed consent was obtained from all participants before enrollment; patients were informed that this protocol, although standard practice in several countries, was investigational at our center, and that declining participation would not affect their routine care. Data were recorded without patient identifiers, with access restricted to the supervising investigators and the study coordinator.

2.2 Patients

Eligible patients were women aged ≥ 55 years with early-stage, node-negative breast cancer (pT1-3pN0) and invasive ductal carcinoma confirmed on surgical pathology, who had undergone breast-conserving surgery (lumpectomy). Of 58 patients with early-stage breast cancer initially screened, 12 (20.7%) were excluded because they declined the protocol or did not provide consent, leaving 46 patients who were allocated to and completed the UHWBRT protocol (Fig. 1).

2.3 Radiotherapy technique

All patients received whole-breast irradiation to a dose of 26 Gy in 5 fractions, delivered over one week with intensity-modulated radiotherapy using a volumetric-modulated arc therapy (VMAT) technique. Patients with adverse pathological risk factors (close or positive surgical margins, T3 stage, or aggressive tumor features at the discretion of the treating physician) received an additional sequential boost of 10 Gy in 5 fractions to the tumor bed. The boost volume was defined on the surgical clips or, when clips were not available, on the post-operative hematoma or seroma cavity; surgeons were asked to place clips at the time of lumpectomy to make this step more precise.

Patients were positioned supine on a breast board with the arm of the treated side raised above the head and held on a hand grip. The body axis was marked with a laser alignment system. To ensure reproducibility of the setup, cone-beam CT (CBCT) was performed before each of the 5 treatment fractions and used to verify the patient position before beam delivery.

Planning goals for the planning target volume (PTV) were as follows: at least 95% of the PTV volume receiving 95% of the prescribed dose, no more than 5% of the volume receiving more than 105%, no more than 2% of the volume receiving more than 107%, and no volume receiving more than 110%. All plans included a 1.5 cm skin flash over the breast surface, so that a marginal miss caused by respiratory motion during treatment would be avoided. Dose constraints for the organs at risk (heart, ipsilateral lung, contralateral breast, and brachial plexus) followed the recommendations of Bisello et al. for 5-fraction regimens (22).

2.4 Toxicity and cosmetic outcome assessment

Acute skin toxicity was graded by the treating physician using the RTOG acute skin toxicity scale (grade 0–4) at the end of treatment and at 2 weeks post-treatment. Cosmetic outcome was assessed with the 12-item Breast Cancer Treatment Outcome Scale (BCTOS-12) (20), completed at baseline and 1, 6, 12, and 24 months after treatment. Raw BCTOS-12 scores were linearly transformed to a 0–10 scale (0 = maximal deviation from the untreated breast, 10 = no change/best cosmetic result) for reporting. At 6 months, patients were additionally classified qualitatively as having excellent, good, fair, or poor cosmesis to allow comparison with previously published cohorts. Post-surgical, non-dermatologic complications recorded during follow-up (seroma, hematoma, abscess, fat necrosis, cystic collection) were also captured. Local recurrence was assessed by clinical examination every 3 months, breast ultrasonography every 6 months, and annual mammography; vital status was recorded at each visit.

2.5 Statistical analysis

Sample size was estimated from published acute skin toxicity rates with conventional three-dimensional radiotherapy (54%) versus IMRT-based hypofractionation (26%) (10) and from the toxicity/cosmesis rates reported by Sigaudi et al. for UHWBRT with IMRT (12). Assuming 80% power and a two-sided α of 0.05, a minimum of 39 patients was required; accounting for an anticipated 10–20% attrition, a target enrollment of 46–55 patients was set. Categorical outcomes were compared with reference cohorts using one-sample and two-sample proportion z-tests; because no grade ≥ 2 events occurred in our cohort, the exact binomial test was used in place of the normal approximation for these comparisons. Continuous variables (dosimetric parameters, BCTOS-12 scores) were summarized as mean ± SD or median as appropriate and compared between subgroups (e.g., tumor laterality, chemotherapy status) using the independent-samples t-test or Mann-Whitney U test, as dictated by distribution. Local recurrence and survival were intended to be analyzed with Cox proportional-hazards regression and hazard ratios; because no recurrences or deaths occurred, this model could not be fitted. Analyses were performed in SPSS (IBM Corp.); Tableau and GraphPad Prism were used for graphical presentation. A two-sided $P < 0.05$ was considered statistically significant.

3. Results

3.1 Patient flow and baseline characteristics

Of 58 women with early-stage breast cancer initially assessed, 12 (20.7%) were excluded because they declined the protocol or did not consent to enrollment. The remaining 46 patients received UHWBRT (26 Gy in 5 fractions) with IMRT and were included in the final analysis (Fig. 1). Mean age was 64.15 ± 7.03 years (range 55–78 years). Thirty-three patients (71.7%) had left-sided and 13 (28.3%) right-sided tumors. Disease stage was T1 in 26 patients (56.5%), T2 in 18 (39.1%), and T3 in 2 (4.3%). Molecular subtype was Luminal B in 22 patients (47.8%), Luminal A in 15 (32.6%), HER2-enriched in 7 (15.2%), and triple-negative in 2 (4.3%) (Fig. 2). Thirty-four patients (73.9%) received chemotherapy before radiotherapy; 12 (26.1%) did not. Mean follow-up was 18.6 months (median 18 months) (Table 1). Forty-three patients (93.5%) completed UHWBRT without a boost; 3 patients (6.5%) with close/positive

margins, T3 disease, or physician-judged high-risk features received a sequential 10-Gy/5-fraction boost to the tumor bed.

Table 1
Demographic and clinical characteristics of the study cohort.

Characteristic	Value (N = 46)
Age, years, mean ± SD (range)	64.15 ± 7.03 (55–78)
Laterality, left / right, n (%)	33 (71.7%) / 13 (28.3%)
T stage, T1 / T2 / T3, n (%)	26 (56.5%) / 18 (39.1%) / 2 (4.3%)
Molecular subtype, n (%)	
Luminal B	22 (47.8%)
Luminal A	15 (32.6%)
HER2-enriched	7 (15.2%)
Triple-negative	2 (4.3%)
Chemotherapy received / not received, n (%)	34 (73.9%) / 12 (26.1%)
Tumor bed boost received / not received, n (%)	3 (6.5%) / 43 (93.5%)
Follow-up, months, mean (median)	18.6 (18)

3.2 Dosimetric parameters

Planning achieved a mean maximum dose (Dmax) of 104.5 ± 1.8% and a mean D95 (dose covering 95% of the PTV) of 96.5 ± 1.3% of the prescription dose, indicating homogeneous target coverage. For the ipsilateral lung, mean V20 was 8.52 ± 2.74%, mean V10 was 14.89 ± 3.67%, and mean lung dose (MLD) was 4.76 ± 1.04 Gy. Mean heart dose (MHD) was 1.99 ± 1.01 Gy, and cardiac V3 and V7 were 3.91% and 3.09%, respectively. Mean maximum brachial plexus dose was 0.82 Gy. All OAR parameters remained within the safety thresholds recommended for 5-fraction regimens by Bisello et al. (22) (Table 2).

Table 2
Dosimetric parameters for the planning target volume and organs at risk (N = 46).

Dosimetric parameter	Mean	SD
PTV D95 coverage, %	96.5	1.3
Dmax, %	104.5	1.8
Ipsilateral lung V20, %	8.52	2.74
Ipsilateral lung V10, %	14.89	3.67
Mean lung dose (MLD), Gy	4.76	1.04
Mean heart dose (MHD), Gy	1.99	1.01
Heart V3, %	3.91	N/A
Heart V7, %	3.09	N/A
Brachial plexus Dmax, Gy	0.82	N/A

3.3 Cardiac dosimetry by tumor laterality

As expected, cardiac dose parameters were significantly higher for left-sided than right-sided tumors. Mean heart dose was 2.52 Gy (median 2.50 Gy) for left-sided tumors versus 0.69 Gy (median 0.50 Gy) for right-sided tumors (Mann-Whitney U test, $P < 0.001$) (Table 3, Fig. 3). Cardiac V3 and V7 were likewise significantly higher for left-sided tumors ($P < 0.001$ for both), although both remained well within internationally recommended safety margins even on the left side.

Table 3
Comparison of mean heart dose by tumor laterality.

Parameter	Left breast (n = 33)	Right breast (n = 13)	P value
Mean heart dose (MHD), Gy, mean (median)	2.52 (2.50)	0.69 (0.50)	< 0.001

3.4 Acute skin toxicity

No patient developed acute dermatitis (grade 0) during treatment (100%). At the 2-week post-treatment assessment, 36 patients (78.3%) remained free of skin reaction (grade 0) and 10 patients (21.7%) had grade 1 dermatitis; no case of grade ≥ 2 dermatitis was observed at any assessment point (0%) (Table 4). Given the absence of grade ≥ 2 events, the exact binomial test was used to compare the observed proportion with reference cohorts; the 0% rate of grade ≥ 2 toxicity was significantly lower than the 26% reported with 3D-conformal hypofractionated radiotherapy converted to IMRT by Jagsi et al. (10) and numerically lower than the 7% reported with UHWBRT-IMRT by Sigaudi et al. (12) ($P < 0.05$ for both comparisons).

Table 4
Acute skin toxicity (RTOG scale) at end of treatment and 2 weeks post-treatment.

Time point	Grade 0, n (%)	Grade 1, n (%)	Grade ≥ 2, n (%)
End of treatment	46 (100%)	0 (0%)	0 (0%)
2 weeks post-treatment	36 (78.3%)	10 (21.7%)	0 (0%)

3.5 Cosmetic outcomes

Mean BCTOS-12-derived cosmesis score (0–10 scale) was 9.19 ± 0.88 at treatment completion and remained stable throughout follow-up: 9.13 ± 0.95 at 1 month, 9.06 ± 0.97 at 6 months, 9.08 ± 1.03 at 12 months, and 9.20 ± 0.94 at 24 months, with no statistically significant change over time (Table 5). At the pre-specified 6-month landmark, cosmetic outcome was excellent (scores 9–10) in 32 patients (69.6%) and good (scores 6–8) in 14 patients (30.4%); no patient had a fair or poor outcome, for a combined excellent/good rate of 100% (Table 6). Cosmetic outcome was not adversely affected by receipt of chemotherapy: mean score was 8.97 (median 9.0) in the 34 patients who received chemotherapy versus 9.33 (median 10.0) in the 12 who did not (Mann-Whitney U test, P = 0.276).

Table 5
Cosmesis score (0–10 scale) over time.

Time point	Cosmesis score (0–10), mean ± SD
End of treatment (baseline)	9.19 ± 0.88
1 month	9.13 ± 0.95
6 months	9.06 ± 0.97
12 months	9.08 ± 1.03
24 months	9.20 ± 0.94

Table 6
Qualitative cosmetic outcome category at 6 months.

Cosmetic outcome category	n	%
Excellent (scores 9–10)	32	69.6
Good (scores 6–8)	14	30.4
Fair / poor (< 6)	0	0
Total excellent + good	46	100

3.6 Non-dermatologic complications

Non-dermatologic, post-surgical complications were recorded in 7 patients (15.2%) during follow-up: hematoma in 2, cystic collection in 2, abscess in 1, fat necrosis in 1, and seroma in 1; 39 patients (84.8%) had no complication.

3.7 Oncologic outcomes

Over a mean follow-up of 18.6 months, no local recurrence occurred (0%), and overall survival was 100%. Because no recurrence or death events occurred, a Cox proportional-hazards model and hazard ratio could not be estimated.

4. Discussion

UHWBRT has recently emerged as a new standard option for adjuvant whole-breast irradiation in early-stage breast cancer, building on the foundational moderate-hypofractionation evidence from the START and DBCG HYPO trials (4, 25, 26) and, more directly, on the FAST and FAST-Forward trials, which established that 26–30 Gy delivered in 5 once-weekly or once-daily fractions is non-inferior to conventional/moderate fractionation for local control and late normal-tissue effects at 5–10 years (23, 24). Our study extends this evidence base by evaluating the 26 Gy/5-fraction regimen (the 26 Gy arm of FAST-Forward) delivered specifically with IMRT-VMAT technique in an Iranian tertiary-referral population, an area with a comparative paucity of published IMRT-specific data (14).

The most clinically important finding of our study is the very low rate of acute skin toxicity: no patient developed grade ≥ 2 dermatitis, and only 21.7% experienced grade 1 dermatitis at 2 weeks. This compares favorably with the 26% rate of grade ≥ 2 acute skin toxicity reported by Jagsi et al. with IMRT-based hypofractionation (versus 54% with 3D-conformal technique in the same comparative cohort) (10) and with the roughly 7% rate reported by Sigaudi et al. for UHWBRT delivered with IMRT (12). Zerella et al. similarly reported lower acute skin toxicity with IMRT compared with 3D-conformal technique in a large real-world UHWBRT cohort of elderly/frail patients (13). These converging observations support the hypothesis that the dose homogeneity achievable with IMRT/VMAT mitigates the higher per-fraction dose inherent to ultra-hypofractionated schedules. Nonetheless, because our study lacked a concurrent comparator arm, the difference from historical cohorts, including our own institution's earlier moderate-hypofractionation experience (27), may be confounded by unmeasured differences in breast volume, skin/tissue characteristics, ethnicity, and surgical technique, and should be interpreted with appropriate caution.

Cosmetic outcomes were excellent and stable from treatment completion through 24 months, with 100% of patients rated excellent or good at 6 months and no significant decline in BCTOS-12-derived scores over time. This is consistent with the durable cosmesis reported after UHWBRT by Sigaudi et al. and Zerella et al. (12, 13) and supports the conclusion that increasing the dose per fraction, when paired with a conformal delivery technique such as IMRT, does not translate into early cosmetic deterioration. Notably, prior chemotherapy did not adversely affect cosmetic outcome in our cohort (P = 0.276),

suggesting that UHWBRT can reasonably be offered to patients who require adjuvant systemic therapy without compromising breast appearance.

Non-dermatologic, post-surgical complications (seroma, hematoma, abscess, fat necrosis, cystic collection) occurred in 15.2% of patients, a rate broadly consistent with expectations after breast-conserving surgery; because most comparator UHWBRT studies report skin toxicity (RTOG scale) rather than these surgical-site outcomes separately, direct comparison is limited (12, 13).

From a dosimetric standpoint, OAR sparing was excellent: mean heart dose (1.99 Gy overall) and ipsilateral lung V20 (8.52%) were well within the safety thresholds recommended for 5-fraction regimens (22). Even for left-sided tumors, mean heart dose (2.52 Gy) remained far below internationally accepted limits, consistent with prior dosimetric comparisons showing that IMRT/VMAT techniques improve OAR sparing relative to 3D-conformal planning in left-sided and bilateral breast irradiation (8, 9). This finding is reassuring given the established long-term cardiac risk associated with breast radiotherapy, particularly for left-sided disease (17).

Oncologic outcomes at this early time point were excellent, with 0% local recurrence and 100% overall survival over a mean follow-up of 18.6 months, in keeping with the short-term safety and efficacy reported in other UHWBRT cohorts, including a large Brazilian moderately-hypofractionated series (28), the Fodor et al. hypofractionated cohort (29), and comparative-effectiveness data in triple-negative breast cancer (30). However, given the radiobiological sensitivity of both tumor control and late normal-tissue effects to fraction size (α/β ratio considerations extensively discussed in the FAST-Forward analyses) (24), our short follow-up period cannot yet speak to durable local control or late toxicity, which typically manifest over several years.

4.1 Strengths and limitations

Strengths of this study include its prospective design, standardized IMRT-VMAT delivery technique, use of a validated cosmesis instrument (BCTOS-12) with structured longitudinal follow-up, and its contribution of real-world data from an Iranian tertiary-referral population, a setting under-represented in the UHWBRT literature. Several limitations should be acknowledged. First, this was a single-arm, phase II study without a concurrent control group; comparisons with historical/published cohorts are therefore unadjusted for potential confounders such as breast volume, tissue density, ethnicity, and surgical technique, and should be regarded as hypothesis-generating rather than confirmatory. Second, the mean follow-up of 18.6 months is too short to characterize late toxicity (subcutaneous fibrosis, telangiectasia, late cardiac or pulmonary effects) or to draw definitive conclusions about durable local control, particularly given the known time-course over which late radiation effects and recurrences emerge. Third, this was a single-center experience, which may limit generalizability to other populations and practice settings.

5. Conclusion

UHWBRT (26 Gy in 5 fractions) delivered with IMRT-VMAT was safe, effective, and well-tolerated in older women with early-stage breast cancer treated at our center, achieving minimal acute skin toxicity, excellent early cosmesis unaffected by chemotherapy, favorable OAR dosimetry even for left-sided tumors, and 100% short-term local control and survival, while compressing treatment into a single week. These findings support the feasibility of implementing UHWBRT with IMRT in a tertiary Iranian oncology center and add to the growing international evidence base for this approach. Longer-term follow-up and randomized comparison with conventional and moderately hypofractionated regimens are needed to confirm the durability of these outcomes.

5.1 Future directions

Planned extensions of this work include: long-term follow-up (5–10 years) of this cohort to characterize late toxicity and durable oncologic outcomes; a phase III randomized controlled trial directly comparing UHWBRT-IMRT with conventional/3D-conformal regimens; expansion of eligibility criteria to younger patients and those requiring regional nodal irradiation; a cost-effectiveness analysis of the UHWBRT-IMRT combination relative to longer conventional schedules; and incorporation of broader quality-of-life instruments (e.g., EORTC QLQ-C30 and the breast-specific QLQ-BR23 module) alongside the BCTOS-12 to more comprehensively capture patient-reported outcomes.

Declarations

Ethics approval and consent to participate:

This study was approved by the Research Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.IKHC.REC.1402.343) and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

Consent for publication:

Not applicable; no identifying patient information, images, or data are reported.

Conflicts of interest:

The authors declare that they have no competing interests.

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Author Contribution

Study concept and supervision: A.R , F.A.H.; study design and clinical input:A.R, A.M., N.M., M.A., M.B, M.L.; data acquisition, analysis, and manuscript drafting: A.R.; critical revision of the manuscript: all authors. All authors read and approved the final manuscript.

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Data Availability

Data is available from corresponding author per reasonable request

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Figures

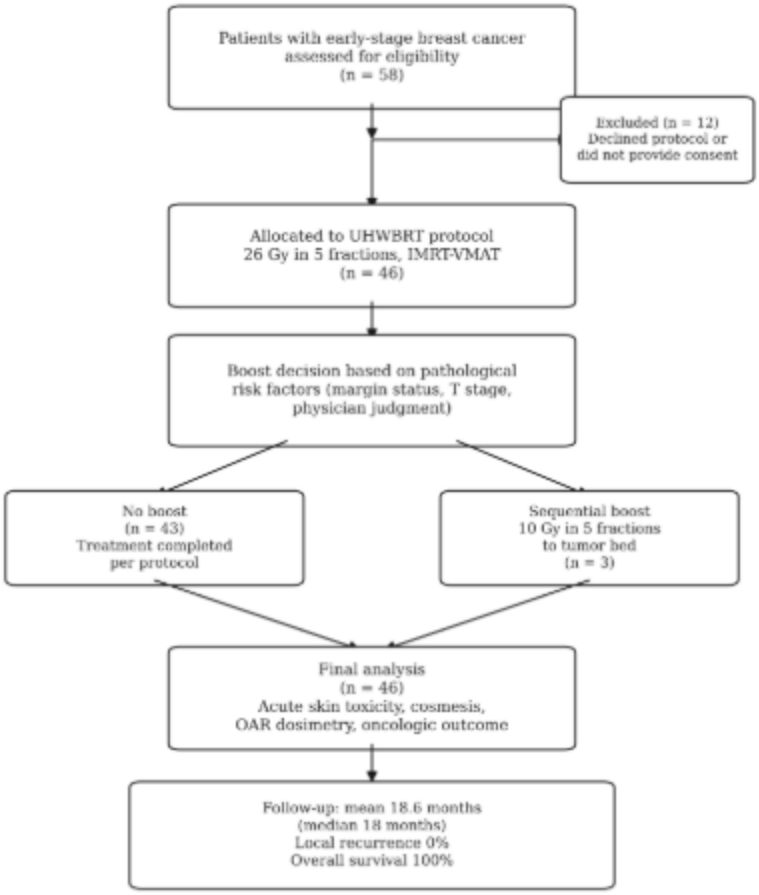


Figure 1

Study flow diagram. Of 58 patients with early-stage breast cancer screened, 12 were excluded (declined protocol/consent). Forty-six patients received UHWBRT (26 Gy/5 fractions, IMRT); 43 completed treatment without boost and 3 received a sequential 10 Gy/5-fraction boost to the tumor bed. All 46 patients were included in the final analysis (mean follow-up 18.6 months).

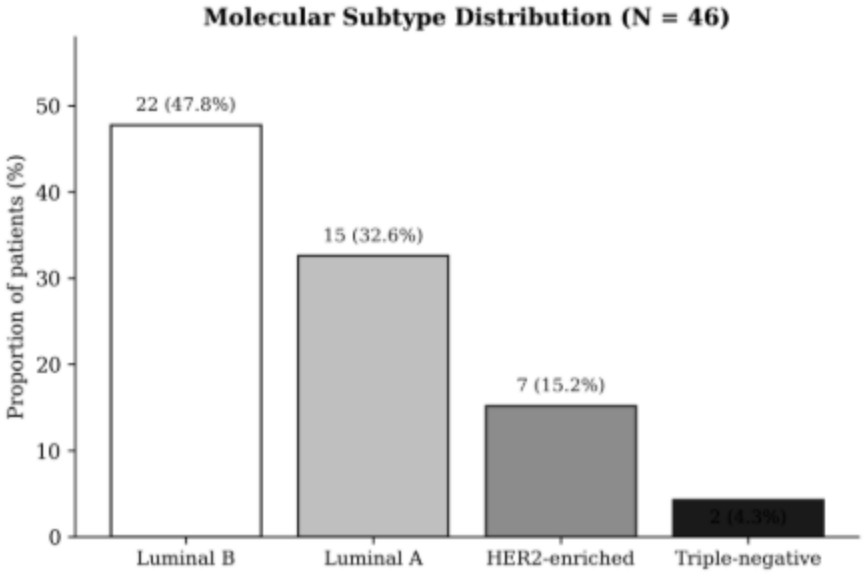


Figure 2

Molecular subtype distribution of the study cohort (N = 46).

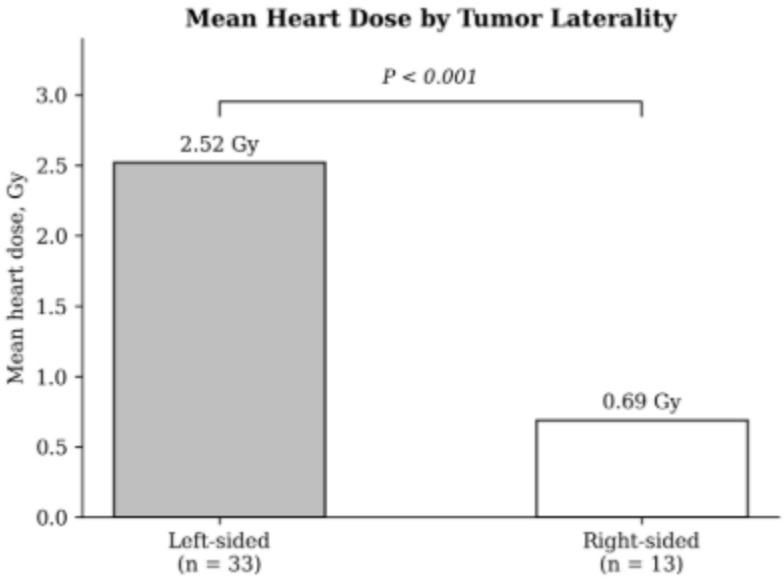


Figure 3

Mean heart dose by tumor laterality.