The Egyptian Journal of Hospital Medicine (January 2025) Vol. 98, Page 632- 640

# Adjuvant Whole Breast Irradiation in Five Fractions versus Fifteen Fractions in Early Breast Cancer: A Randomized Comparative Prospective Phase II

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## ABSTRACT

**Background:** Adjuvant radiotherapy improves locoregional control and overall survival. The aim of this work was to identify the effectiveness and safety of a 5-fractions schedule of radiotherapy delivered in 1 week (experimental arm) compared with the 15-fractions regimen over 3 weeks (standard arm) after surgery for early breast cancer (BC).

**Patients and Methods:** This randomized comparative prospective phase II was carried out on 134 female patients aged from 18 to 80 years old, underwent breast conservation surgery or modified radical mastectomy, with early stage, (pT1–3, pN0–1, M0) BC including any histological type of invasive BC and all tumor grades (I, II, III). The standard arm (40 Gy group) (n=65) used a conventional hypofractionation protocol of 40 Gy, and the experimental arm (26 Gy group) (n=69) used ultra hypofractionation 26 Gy. All patients were subjected to usual history taking, full examination, and baseline imaging using CT scan for [chest-abdomen and pelvis], and sonomammographic and/or breast and axillary ultrasound.

**Results:** No significant variation was reported among both groups as regards death rate, locoregional failure rate, or distant recurrence. The acute skin toxicity in the form of breast edema and tender erythema were more observed with the standard arm rather than with the experimental arm with clinical significance (P =0.0001). Regularity on treatment were significantly high in 26 Gy group compared to 40 Gy group as they were regular (P= 0.0001).

**Conclusions:** Hypofractionation seems to compromise safety and efficacy same as that for the standard regimens but that longer follow-up was needed for a more complete assessment.

**Keywords:** Adjuvant Whole Breast Irradiation; Five Fractions; Fifteen Fractions; Early Breast Cancer

## INTRODUCTION

By far, breast cancer (BC) is the most prevalent form of cancer in women and the most probable cause of death among women worldwide [1].

There is a wide variation as regard symptom in breast cancer patients, numerous women with early BC exhibit no symptoms. Therefore, it is crucial to consider any new breast mass, lump, or changes in the breast after a diagnosis of breast cancer is made. It is crucial to precisely define the initial severity of the disease, as this information will influence treatment recommendations. There has been a reported increase in survival rates in recent decades, and the prognosis is typically better than that of other major cancers [2].

At present, the introduction of screening mammography has resulted in the early detection of the vast majority of breast cancers, which has led to excellent overall outcomes. This has opened up the possibility of investigating treatment approaches that will enhance patient satisfaction and convenience, such as reducing the overall duration of therapy [3].

Various therapies are chosen based on a variety of factors. Specify the clinical and pathologic characteristics of the primary tumor, tumor histology, axillary lymph node status, tumor hormone receptor, HER2 status, patient comorbid condition, age, and menopausal status [4]. BC treatment necessitates the prudent judgment and intervention of a breast surgeon, medical oncologist, and radiotherapist. BC is managed through a multidisciplinary approach that encompasses medical oncology, radiation oncology, and surgical oncology [5].

## AIM OF THE WORK

The aim of this study is to identify the effectiveness and safty of a 5-fractions schedule of curative radiotherapy delivered in 1 week (experimental arm) compaired with the 15-fractions regimen over 3 weeks (standard arm) after primary surgery for early breast cancer.

## PATIENTS AND METHODS

This randomized comparative prospective phase II was carried out on 134 female patients aged between 18 and 80 years old, underwent breast conservation surgery or modified radical mastectomy, with early stage, (pT1–3, pN0–1, M0) BC including any histological type of invasive BC and all tumor grades (I, II, III). The study was done during the period from February 2021 to October 2023.

**Exclusion criteria** were advanced stage (III or IV) BC, metastatic BC or recurrent BC, patients that have co-morbidities that contraindicate radiotherapy or previous history of radiotherapy.

### Grouping and randomization:

Randomization was done by computer-generated system. The list was concealed in sealed envelopes that were numbered and opened sequentially after obtaining patient's consent. Stratified randomization methods to reduce heterogeneity among treatment groups. Patients were randomly assigned in a 1:1 ratio to the two treatment groups and allocated using computer generated tables.The standard arm (40 Gy group) (n=65) used a conventional hypofractionation protocol of 40 Gy given on 15 fractions with 2.67 Gy per fraction, five fractions per week over 3 weeks with or



Received: 28/08/2024
Accepted: 28/10/2024

without boost according to the patient criteria, and the experimental arm (26 Gy group) (n=69) used ultra hypofractionation 26 Gy with 5.2 Gy per fraction given on 5 fractions over on week treatment, with or without boost according to patient criteria. Boost was given to eligible patients with dose 1000/4 fractions.

All patients were subjected to usual history taking, full examination, and baseline imaging using CT scan for [chest-abdomen and pelvis], and sonomammographic and/or breast and axillary ultrasound was done to scan for the tumor site.

**Radiotherapy technique**

Patients were positioned in a supine position over a breast board, with their hands above their heads and their head in a neutral position. Patients were subjected to a CT simulator that scanned them without contrast for a slice thickness of 3 mm. The scan ranged from the chin to the umbilicus.

**Target contouring and plan assessment:** Delineation of the tumor bed was advised for all patients who had undergone breast conserving surgery and were eligible for boost delivery in order to optimize target coverage. The clinical target volume (CTV) encompassed the soft tissues of the entire breast, from 5 mm below the skin surface to the deep fascia, with the exception of muscle and the underlying rib cage. A margin of 10 mm was added around the delineated CTV to account for setup error and breathing, thereby forming the planning target volume (PTV) by excluding 0.5 cm of skin surface. The Radiation Therapy (RT) Oncology Group (RTOG) contouring guidelines were followed to treat and contour eligible patients. Additionally, the guidelines were used to contour organs at risk (lung, heart, contralateral breast). To minimize the risk of irradiation to organs and optimize target volume coverage, the gantry and collimator angles were adjusted. We employed two tangential fields that were equally weighted. It was necessary to employ the field-in-field technique in order to ensure that the entire breast received a uniform dose amount. The Eclipse system (Varian) was employed to optimize the plans by utilizing 6 MV photon beams.

The ICRU83 recommendation was employed to evaluate treatment plans in the following manner: By employing the cumulative DVH to guarantee that the minimum dose to the target is 95% and the maximum dose is limited to 107% with a maximum of 3%, the standard arm received less than 107% of the prescribed dose and no more than 5% of the whole breast volume received less than 95% of the prescribed dose. The dose to the organs at risk was kept to the minimum according to the RTOG recommendation, dose constraints in standard arm for heart and ipsilateral lung and contralateral breast were V5 Gy<10%, V16 Gy<20% and V10 Gy<5%, respectively, while In the experimental arm heart V 1.5 Gy<30-35, ipsilateral lung V 8.5 Gy <15- 20%, contralateral breast V 85 cGy less than 5%, differential DVH and the colour wash used to assess dose homogeneity, the conformity index and dose gradient measure was calculated, setup error: random and systemic error was checked using EPID imaging day after day for each patient in short course group and weekly in long course group, and radiation treatment started within 8–12 weeks after breast conservative surgery or 21–30 days after systemic adjuvant chemotherapy.

**Follow up of patient:** Acute and late radiation related toxicity (skin, lung and cardiac) were assessed according to RTOG scoring system, clinical examination of the patients and with chest X-ray or CT if needed, abdomen-pelvis ultrasound or CT if needed and bilateral breast sonomammographic or ultrasound according to the availability every 3-4 month in the first 2 years, and patients who were hormonal positive continued on hormonal treatment and those with HER2 positive continued on Herceptin.

**Measure outcome**: Treatment outcome included overall survival (OS), local control, disease-free survival, early and late treatment toxicity data were collected from each patient and analyzed using appropriate statistical package

The primary endpoint was RT related toxicity. The secondary endpoints were ipsilateral breast tumor relapse whether considered local recurrence or new primary tumor, distant metastasis (DFS), and death (OS). All the related data were were collected.

***Ethical approval***

**The study received approval from the Academic and Ethical Committee of Sohag University. Each patient provided written informed consent to receive the therapy. This research was conducted in adherence to the World Medical Association's Code of Ethics (Declaration of Helsinki) pertaining to human subjects.**

***Statistical analysis***

Statistical analysis was done by SPSS v20 (IBM Inc., Armonk, NY, USA). Qualitative variables were presented as frequency and percentage (%) and were analysed utilizing the Chi-square test or Fisher's exact test when appropriate. Quantitative data were represented as mean, and standard deviation (SD). Survival analysis was done using Kaplan-Meier method and comparison among two survival curves was done using log-rank test. A two tailed P value < 0.05 was considered statistically significant.

**RESULTS**

166 patients were evaluated for eligibility in this study; 19 patients did not meet the criteria, and 13 patients declined to participate. The remaining 134 patients were randomly assigned to one of 2 groups: the 40 Gy group (n=65) or the 26 Gy group (n=69). The statistical analysis and follow-up of all allocated patients were conducted **(Figure 1)**.

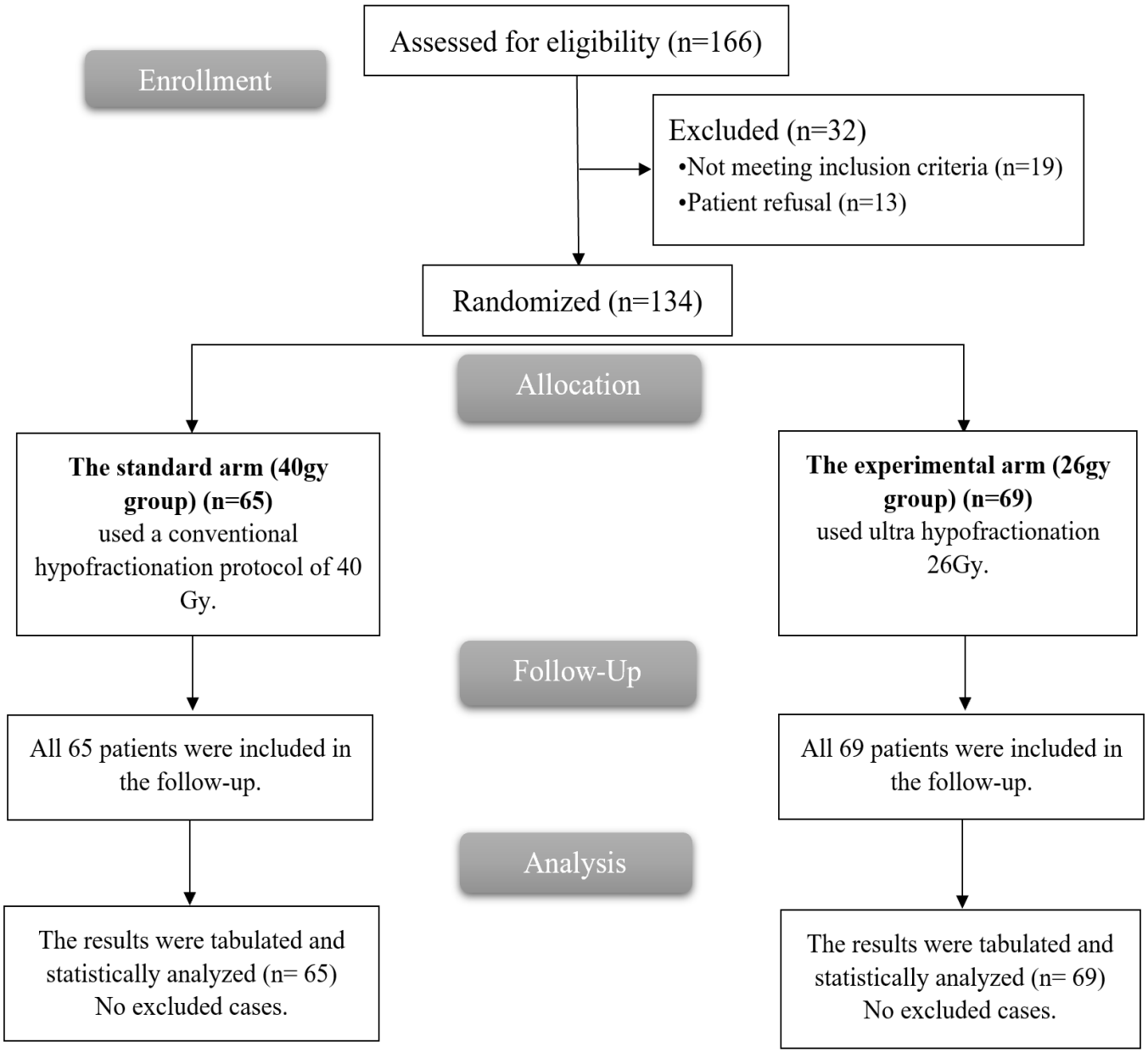



**Figure 1: CONSORT flowchart of the studied patients**

As regards age groups the median age was 54 years old, 39 (29.1%) patients were among 50-59 years. 81(59.7%) patients were in post menopause state. 68 (50.7%) of the cases were left sided disease. As regards the site of the tumor, 57(42.5%) presented with UOQ lump. The main pathology was IDC in 126(94%) cases. As regards the tumor grade, the majority 113 (84.3%) was grade 2. 126 (94%) were with no LVI. As regards the tumor stage, 100 (74.6%) were T2 staging. Regarding tumor biology, 93(69.4%) patients were positive for estrogen receptors and 97(72.4%) patients were progesterone positive. Most of the patient underwent BCS 128 (95.5%). All excised lymph nodes were negative (all patients were N0 disease). As regard chemotherapy, only 112 (83.7%) patients received chemotherapy **(Table 1)**.

**Table 1: Patient characteristics, disease characteristics, tumor biology, and treatment procedure of the studied patients**

| | | Patients (n 134) |
|---|---|---|
| **Age (years)** | **Less than 40** | 22 (16.4%) |
| | **40-49** | 34 (25.3%) |
| | **50-59** | 39 (29.1%) |
| | **60-69** | 31 (23.1%) |
| | **70 and more** | 8 (5.9%) |
| **Menopausal state** | **Pre** | 54 (40.3%) |
| | **Post** | 81 (59.7%) |
| **Disease characteristics** | | |
| **Tumor side** | **LT** | 68 (50.7%) |
| | **RT** | 66 (49.3%) |
| **Quadrant** | **UOR** | 57 (42.5%) |
| | **LOQ** | 29 (21.6%) |
| | **UIQ** | 21 (15.7%) |
| | **LIQ** | 27 (20.1%) |
| **Pathology** | **IDC** | 126 (94%) |
| | **ILC** | 7 (5.2%) |
| | **Mucinous** | 1 (0.8%) |
| **Grade** | **1** | 6 (4.4%) |
| | **2** | 113 (84.3%) |
| | **3** | 15 (11%) |
| **LVI** | | 8 (6%) |
| **Tumor stage** | **T1** | 25 (18.7%) |
| | **T2** | 100 (74.6%) |
| | **T3** | 9 (6.7%) |
| **Tumor biology** | | |
| **Estrogen receptor Positive** | | 93 (69.4%) |
| **Progesterone receptor Positive** | | 97 (72.4%) |
| **HER 2 STATUSES Positive** | | 30 (22.3) |
| **Treatment procedure** | | |
| **Surgery** | **BCS** | 128 (95.5%) |
| | **MRM** | 6 (4.5%) |
| **Chemotherapy** | | 112 (83.7%) |
| **Axillary surgery** | **Axillary evacuation** | 126 (94%) |
| | **Sentinel** | 8 (6%) |
| **The outcome** | | |
| **Death** | | 2 (1.5%) |
| **Locoregional failure** | | 0 (0%) |
| **Distant recurrence** | | 3 (2.3%) |

Data are presented as frequency (%). LT: left, RT: right, LVI: Lymphovascular invasion, BCS: Breast conservative surgery, MRM: Modified radical mastectomy.

Regularity on treatment was significantly high in 26 Gy group compared to 40 Gy group. Regarding acute skin toxicity in the form of breast edema and tender erythema, there was a significant difference between the 2 groups. While no significant difference was observed regarding age group, disease characteristics, tumor biology, treatment procedure, hormonal treatment and Herceptin, received boost, and treatment related toxicity (Late skin toxicity, acute lung toxicity, late lung toxicity, and cardiac toxicity) **(Table 2)**.

**Table 2: Comparison between 26 Gy and 40 Gy as regard age group, disease characteristics, tumor biology, treatment procedure, hormonal treatment and Herceptin, received boost, regularity on treatment, and treatment related toxicity (n=134)**

| | | 26 Gy group (n=69) | 40 Gy group (n=65) | P value |
|---|---|---|---|---|
| **Age (years)** | **Less than 40** | 7(10.1%) | 15(23%) | 0.07 |
| | **40-49** | 22(31.8%) | 12(18.4%) | |
| | **50-59** | 18(26%) | 21(32.3%) | |
| | **60-69** | 19(27.5%) | 12(18.4) | |
| | **70 and more** | 3(4.3%) | 5(6.1%) | |
| **Menopausal state** | **Pre** | 28(40.5%) | 26(40%) | 0.945 |
| | **Post** | 41(59.4%) | 39(60%) | |
| **Disease characteristics** | | | | |
| **Tumor side** | **LT** | 37(53.6%) | 31(47.6%) | 0.493 |
| | **RT** | 32(46.3%) | 34(52.3%) | |
| **Quadrant** | **UOQ** | 32 (46.3%) | 25 (38.4%) | 0.6 |
| | **LOQ** | 12 (17.3%) | 17(26.1%) | |
| | **UIQ** | 12 (17.3%) | 9 (13.8%) | |
| | **LIQ** | 13 (18.8%) | 14 (21.5%) | |
| **Pathology** | **IDC** | 66 (95.7%) | 60 (92.3%) | 0.3 |
| | **ILC** | 2 (2.8%) | 5 (7.7%) | |
| | **Mucinous** | 1 (1.4%) | 0 (0%) | |
| **Grade** | **1** | 2 (2.8%) | 3 (4.6%) | 0.4 |
| | **2** | 56 (81.1%) | 57(87.6%) | |
| | **3** | 10 (14.4%) | 5 (7.6%) | |
| **LVI** | | 4 (5.7%) | 4 (6.1%) | 0.9 |
| **Tumor stage** | **T1** | 13 (18.8%) | 12 (18.5%) | 0.5 |
| | **T2** | 53 (76.8%) | 47 (72.3%) | |
| | **T3** | 3 (4.3%) | 6 (9.2%) | |
| **Tumor biology** | | | | |
| **Estrogen receptor positive** | | 46 (66.6%) | 47 (72.3%) | 0.5 |
| **Progesterone receptor positive** | | 47 (68.1%) | 50 (77%) | 0.3 |
| **HER 2 status positive** | | 16 (23.1%) | 12 (18.4%) | 0.501 |
| **Treatment procedure** | | | | |
| **Surgery** | **BCS** | 66 (95.6%) | 62 (95.3%) | 0.9 |
| | **MRM** | 3 (4.3%) | 3 (4.6%) | |
| **Chemotherapy** | | 63 (91.3%) | 49 (75.4%) | **0.2** |
| **Type of chemotherapy** | **Taxol** | 6 (8.6%) | 4 (6.1%) | 0.8 |
| | **AC** | 19 (27.5%) | 18 (27.6%) | |
| | **T/AC** | 24(34.7%) | 21 (32.3%) | |
| | **FEC** | 11 (15.9%) | 4 (6.1%) | |
| | **FAC** | 2 (2.8%) | 1 (1.5%) | |
| | **T/FEC** | 1 (1.4%) | 1 (1.5%) | |
| **Lymph node** | **Axillary evacuation** | 63 (91.3%) | 63 (96.9%) | 0.2 |
| | **Sentinel** | 6 (8.7%) | 2 (3.1%) | |
| **Hormonal treatment and Herceptin** | | | | |
| **Patient who receives hormonal therapy** | | 51 (74%) | 51 (78.4%) | 0.54 |
| **Type of hormonal therapy** | **AI** | 31 (44.9%) | 34 (52.3%) | 0.54 |
| | **TAM/ zoladex** | 20 (28.9%) | 17 (26.1%) | |
| **Herceptin** | | 15 (21.7%) | 12 (18.4%) | 0.63 |
| **Received boost** | | 33 (47.8%) | 41 (63%) | 0.08 |
| **Regularity on treatment** | **Regular** | 69 (100%) | 54 (83%) | **0.0004*** |
| | **irregular** | 0 (0.0%) | 11 (17%) | |
| **Treatment related toxicity** | | | | |

| | | 26 Gy group (n=69) | 40 Gy group (n=65) | P value |
|---|---|---|---|---|
| **Acute skin toxicity** | **Grade 0** | 51 (73.9%) | 0 (0%) | **<0.0001*** |
| | **Grade 1** | 16 (23.1%) | 56 (86.1%) | |
| | **Grade 2** | 2 (2.8%) | 9 (13.8%) | |
| | **Grade 3** | 0 (0%) | 0 (0%) | |
| | **Grade 4** | 0 (0%) | 0 (0%) | |
| **Late skin toxicity** | **Grade 0** | 53 (76.8%) | 54 (83%) | 0.6 |
| | **Grade 1** | 12 (17.4%) | 9 (13.8%) | |
| | **Grade 2** | 4 (5.8%) | 2 (3%) | |
| | **Grade 3** | 0 (0%) | 0 (0%) | |
| | **Grade 4** | 0 (0%) | 0 (0%) | |
| **Acute lung toxicity** | **Grade 0** | 66 (95.6%) | 61 (83.8%) | 0.6 |
| | **Grade 1** | 3 (4.3%) | 4 (6.2%) | |
| **Late lung toxicity** | **Grade 0** | 63 (91.3%) | 58 (89.2%) | 0.7 |
| | **Grade 1** | 6 (8.7%) | 7 (10.7%) | |
| **Cardiac toxicity** | **Grade 0** | 67 (97.1%) | 63 (97%) | 0.95 |
| | **Grade 1** | 2 (2.9%) | 2 (3%) | |

Data are presented as frequency (%). LT: left, RT: right, LVI: Lymphovascular invasion, HER 2: Human epidermal growth factor receptor-2, BCS: Breast conservative surgery, MRM: Modified radical mastectomy. *: Significant as P value <0.05.

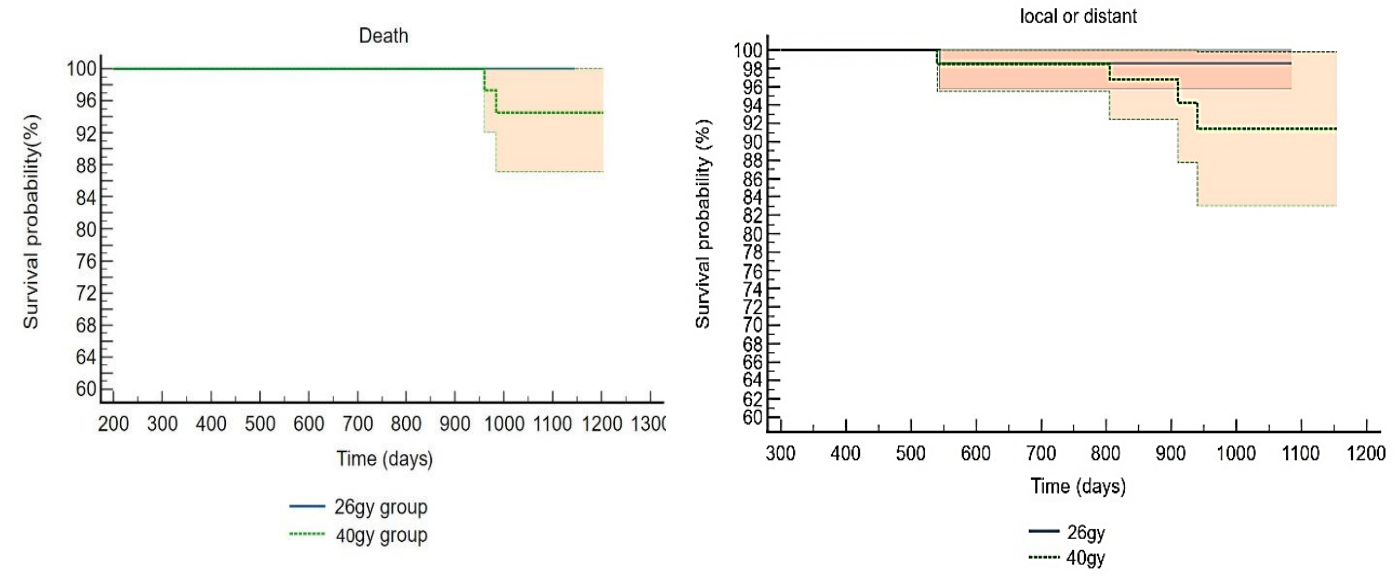
There were no significant differences among both groups regarding outcome, overall survival, and disease-free survival **(Table 3)**.

**Table 3: Comparison between 26 Gy and 40 Gy as regard outcome, overall survival, and disease-free survival (n=134)**

| | | 26 Gy (n=69) | 40 Gy (n=65) | P value |
|---|---|---|---|---|
| **Outcome** | | | | |
| **Death** | | 0 (0%) | 2 (3%) | 0.233 |
| **Locoregional failure** | | 0 (0%) | 0 (0%) | **1** |
| **Distant recurrence** | | 1 (1.5%) | 2 (3%) | 0.611 |
| **Site of distant recurrence** | **Lung** | (N=1)1 (100%) | (N=2) 1 (50%) | 1 |
| | **Bone** | 0 (0%) | (N=2) 1 (50%) | |
| **Overall survival** | **24 months** | 100% | 100% | 0.9 |
| | **At the end (32 months)** | 100% | 96.8% | |
| **Disease free survival** | **24 months** | 98.5% | 98.4% | 0.9 |
| | **At the end (32 months)** | 98.5% | 97% | |

Data are presented as frequency (%).

The mean OS rate of 26 Gy group was 1145.0 ± 0.0 days. The mean OS rate of 40 Gy group was 1191.290 ± 8.746 days. The mean DFS rate of 26 Gy group was 1077.159 ± 7.784 days. The mean DFS rate of 40 Gy group was 1126.403 ± 13.619 days. Overall disease-free survival rate and overall survival was insignificantly different among both groups **(Figure 2)**.




**A** **B**

**Figure 2: Kaplan Meier of (A) OS rate, and (B) DFS rate between the studied group**

## DISCUSSION

BC patients are typically administered postoperative radiotherapy as part of their treatment regimen. BCS followed by adjuvant radiotherapy is considered one of the most significant examples of evidence-based modern cancer care in early-stage BC [6,7]. Our investigation comprised two arms: 69 patients were assigned to the experimental 26-gy arm and 65 patients were assigned to the standard 40-Gy arm. In the FAST trial, a three-arm design was employed. The standard arm consisted of conventionally fractionated radiotherapy (50 Gy in 25 fractions over 5 weeks), while the experimental arms were 28.5 or 30 Gy in 5 once-weekly fractions of 5.7 or 6.0 Gy, respectively. In the FAST-FORWARD trial, the standard arm consisted of moderately hypofractionated accelerated radiotherapy (40 Gy in 15 fractions over 3 weeks, with 26 Gy/5 and 27/5 fractions in the experimental groups) [7].

In our study, patient eligibility was determined by factors related to patient and tumor characteristics that were associated with a relatively low risk of local tumor relapse. We selected a population that had the lowest likelihood of losing tumor control after hypofractionated radiotherapy. There was no significant difference among the two arms in terms of patient characteristics. In our study, the median age was 54, with 30% of the randomized patients being over 60 years old and 29.1% of the randomized patients falling within the 50-59 age group. The randomization of patients was well-balanced among the two groups, as there was no statistically significant difference among the age groups in either arm. This is due to the fact that age is the most significant risk factor for breast cancer[8]. The two arms of the trail were well-balanced in terms of patient characteristics. **Brunt *et al.***, 2020 trial show that eligible patients were women aged 50 years or older who had invasive early breast cancer [9], this comes in line with our trail.

**Giugliano *et al.*** demonstrated that the majority of patients with luminal BC who are enrolled in studies with hypofractionated schedules are older adults. Clinical evidence demonstrated that hypofractionation radiotherapy is the most effective treatment for older patients with early-stage, node-negative breast cancer who are treated with breast-conserving surgery without adjuvant chemotherapy or nodal irradiation [9].

The tumor stage of all randomized patients in our trail was early stage (18.7% T1, 74.6% T2, 6.7% T3), and there was no statistical significance among the two arms. Additionally, all patients had node-negative disease. Characteristics such as early-stage pathologically and node-negative illness, which are associated with a low absolute probability of local tumor relapse, were used to determine patient eligibility for the FAST trial [9]. This was consistent with the findings of our trail.

In our trail there was no difference as regard disease characteristics (tumor laterality or site, pathological type, tumor grade and tumor staging) in both groups, also there was no difference among groups as regard tumor biology. This comes in line with almost all trials of hypofractionation FAST and FAST-FORWARD trials[13,14].

There was no evidence of a differential effect based on factors such as age, grade, pathology, tumor size, nodal status, adjuvant chemotherapy, HER2 status in the FAST FORWARD experiment when comparing 26 Gy to 40 Gy [9].

In our trail the treatment time was shortened to be 5 fractions with daily fraction over one week treatment with increasing dose per fraction.

In the FAST trial, the number of fractions were 5 fractions and the treatment time was kept constant at 5

weeks [10], whereas a very accelerated course of radiotherapy was used in Fast-Forward with 5 fractions over just one week. This comes in line with our trail [9].

As by using the ultra-hypofractionation this affected the patient attendance to receive treatment more regularly than standard fractionation [11], in our trail all patients who received the 26 Gy were regular on treatment without interruption while those who received 40 Gy 11 patients (17%) showed irregularity in receiving treatment with clinical significance among both arms. This irregularity occurred due to relative longer treatment duration and the acute skin toxicity occurred during the treatment course, with p-value 0.0001.

In our trail, acute skin toxicity was more reported in the standard arm than the experimental arm with clinical significance (p value <0.0001). Grade 1 was reported in 56 patients (86.1%) in the arm who received 40 Gy, the most reported toxicity was the skin erythema, which occurred in 42 patients, while 14 patients developed dry desquamation versus 16 patients (23%) of the patients in the experimental arm who developed grade 1 in the form of skin erythema. Grade 2 was reported in 9 patients (13,8%) for 40 Gy group presented with breast edema with tender erythema and 2 patients developed patchy wet desquamation in skin folds. Management for those patients was with local bepanthen ointment and local antibiotic and this led to treatment interruption for few days, while only 2 patients (2.8%) in the experimental arm developed tender erythema and was not indicated to interrupt treatment.

In the FAST-Forward trial, breast erythema was less severe after five-fraction than 15-fraction schedules. The RTOG reported that the percentage of patients with acute grade 3 skin toxicity was 14% for 40 Gy in 15 fractions, 10% for 27 Gy in 5 fractions, and 6% for 26 Gy in 5 fractions. Additionally, the standard arm had a higher incidence of other grades of acute toxicity than the two experimental arms [12].

Also, in the FAST-FORWARD trail the erythema was less reported to 26 Gy and 27 Gy arm than for the 40 Gy. In the FAST trial, acute reactions were also less severe in both five-fraction arms (total doses 28.5 and 30 Gy) than in the 50 Gy schedule [10].

The late skin effect reported in both groups without clinical significance (p- value 0.6), in the 26 Gy group 12 patients (17.4%) for grade 1 late skin toxicity in the form of skin hyperpigmentation and 4 patients (5.8%) grade 2 toxicity developed mild degree of telangiectasia, while the 40 Gy group showed 9 patients (13.8%) as grade 1 and 2 patients (3%) as grade 2 toxicity.

In the FAST-FORWARD TRIAL for many late normal tissue effects, the 27 Gy five-fraction schedule differed statistically significantly from the 40 Gy standard. It was also slightly higher in the 26 Gy schedule, but there was no significant difference among the 26 Gy and 40 Gy. However, over time patients treated with 26 Gy had significantly higher relative risks of moderate to marked NTE than patients treated with 40 Gy ($p< 0.001$) [7]. This comes in line with our trail as there was no significant difference among both arms as regard late toxicity, perhaps a larger sample size is needed and longer time for follow up to give chance to more expected events to occur.

In our trail there was non-significant difference among the trail arms as regard lung toxicity, which showed acute lung toxicity reported in minimal number of patients, 3% for 26 Gy group and 4% for 40 Gy group. Acute lung toxicity was reported with mild symptoms of dry cough responding to usual antitussive drugs, and late lung toxicity occurred in 8% for 26 Gy group and 10% in 40 Gy group. Those patients were asymptomatic mainly and were discovered by imaging with post radiation change and fibrosis with no statistical significance among the two groups. Cardiac toxicity was also reported in 2% of patient in both groups without clinical significance, those patients were asymptomatic and showed decrease in the EF of echocardiography by more than 10%. Those patients were left sided disease and under of trastuzumab therapy. Improvement of patients was by stoppage of anti-Her2 therapy for about 2 months till restoration of cardiac function.

In the FAST trial nearly 0.9 and 1.9% of all patients were reported in the trial for ischemic heart disease and symptomatic lung fibrosis, respectively. There were non-significant changes in the incidence of ischemic heart disease or symptomatic lung fibrosis among the therapy groups in FAST and FAST-FORWARD trials [7]

The outcome of our trail shows no difference in the disease-free survival among two groups. It was 98.5% and 97% in the 26 Gy group and 40 Gy group respectively. The overall survival was 96.8 % in standard arm, death occurred in 2 patients; one of them developed kidney disease during follow up and underwent dialysis and progressed to end organ failure, and the other case was under follow up with good general condition and death cause was not related to disease events. In our trail the ultra-hypofractionation group showed 100% overall survival with no significant difference among the trail arms, this comes in line with **Giugliano *et al.*** as the overall survival was 100% after a median follow-up of 15 months, all patients were alive. No disease progression nor local recurrence were reported in patient groups **[15]**.

In our trail, following conservative breast surgery, hypofractionated radiation proved to be a great way to shorten the course of treatment. The majority of patients reported satisfactory cosmetic results from their treatments, and the patients' assessments of their own cosmetic outcomes also showed similar results. Overall, the therapy and cosmetic results went well. Also, this trail showed very good results as only a very small number of patients showed pulmonary and cardiac toxicity which was controlled and not life threatening.

Also, skin related toxicity was comparable with the standard protocols, which proves that hypofractionated radiotherapy is a good choice of treatment.

Limitations: The sample size was relatively small. Longer follow up is needed to evaluate local and distant recurrence and for detection of radiotherapy change related events especially late normal tissue effect after radiotherapy.

## CONCLUSION

In accordance with our investigation, hypofractionation appears to compromise safety and efficacy in the same manner as standard regimens; however, a more comprehensive evaluation necessitates a longer follow-up.

- **Financial support and sponsorship:** The study was fully funded by the Sohag University Hospital and the Sohag Faculty of Medicine.
- **Conflict of interest:** None.

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