Preliminary results of hypofractionated radiotherapy in breast cancer in Chandigarh, India: single-centre, non-inferiority, open-label, randomised, phase 3 trial

Budhi Singh Yadav,[a,*] Divya Dahiya,[a] Manish Gupta,[b] Ankita Gupta,[c] Arun S. Oinam,[a] Siddhant Khare,[a] Santhosh Irrinki,[a] Ngangom Robert,[a] Yashwant Raj Sakaray,[a] Satish S. Nagaraj,[a] and Reena Kumari[a]

[a]Post Graduate Institute of Medical Education & Research Chandigarh (PGIMER), Chandigarh, India
[b]Regional Cancer Centre, Indira Gandhi Medical College (IGMC), Shimla, Himachal Pradesh, India
[c]Tata Memorial Centre, Mumbai, India

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Summary

Background Globally, most of the randomised trials with hypofractionation in patients with breast cancer have used 3-dimensional conformal radiotherapy technique (3D-CRT). As facilities for 3D-CRT technique may not be available in low-resource settings, there is a need to see if hypofractionation is feasible and safe with 2-dimensional (2-D) technique. In this study, we compared a 3-week radiation schedule with a 2-week schedule of hypofractionated radiotherapy in patients with breast cancer with 2-D technique.

Methods The current study was an open-label, randomised, phase 3 trial. Patients with breast cancer, stage I-III, post mastectomy or after breast conservative surgery who needed adjuvant locoregional radiotherapy were randomised in the Department of Radiotherapy & Oncology, Post Graduate Institute of Medical Education & Research (PGIMER), Chandigarh, India; to 34Gy in 10 fractions over 2 weeks (2-week arm) or 35Gy in 15 fractions over 3 weeks to the chest wall and 40Gy/15#/3wks to breast and supraclavicular fossa (3-week arm). Boost dose when indicated was 8–10Gy/2–4#/2–4 days in both the arms. Patients were planned on a 2-dimensional (2D) simulator with 2 tangential fields to breast/chest wall and incident supraclavicular fossa field. Acute toxicity was assessed using the Radiation Therapy Oncology Group (RTOG) grading scale. Assessments were carried out weekly during radiotherapy and at 4 weeks after treatment by the physician. Cosmetic outcome was assessed using the Harvard/National Surgical Adjuvant Breast and Bowel Project (NSABP)/RTOG scale. The toxicity rates between the two arms were compared using Fisher's exact tests. The trial was approved by institutional ethics committee and registered with ClinicalTrials.gov, number NCT04075058.

Findings This study included 1121 eligible patients from June 2015 to December 2020. Median follow-up was 35 months (6–84 months). Mean age was 48 years (24–75 years). The patient characteristics were comparable between the two arms except for more mastectomies in the 3-week arm and more node-positive patients in the 2-week arm. There were more oestrogen receptor-positive tumors in the 3-week arm. Acute skin toxicities were comparable between the two arms. Grade 2 and 3 skin toxicity was 100 (18%) and 82 (15%); and 16 (3%) and 12 (2%) in the 3-week and 2-week arm ($p = 0.21$), respectively. Cosmetic outcome was assessed as Excellent or Good for 89% of patients in the 3-week arm as compared to 94% in the 2-week arm ($p = 0.004$).

Interpretation The two radiation schedules were comparable in terms of acute skin toxicity. The cosmetic outcome was better with the 2-week schedule. The preliminary findings indicate 2-week radiotherapy schedule with 2-D technique was better than the 3-week schedule in patients with breast cancer. However, disease outcomes and late-term toxicities need to be further checked.

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Keywords: Breast cancer; Radiotherapy; Hypofractionation; Acute toxicity; Cosmesis

*Corresponding author. Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India.
E-mail address: yadav.budhisingh@pgimer.edu.in (B.S. Yadav).

Research in context

Evidence before this study

Hypofractionation is the delivery of greater radiation dose per fraction and completion of the treatment in lesser number of fractions. The total radiation dose is reduced but it is bioequivalent to the conventional fractionation. UK START B trial demonstrated safety and efficacy of hypofractionation in patients with early breast cancer. A study from China confirmed that postmastectomy hypofractionated radiotherapy was comparable to conventional fractionation in terms of disease outcomes and toxicity in high risk patients with breast cancer. In both the studies 3-week hypofractionation was compared with 5 week conventional fractionation. FAST Forward trial demonstrated that one-week whole breast radiotherapy was non-inferior to 3-week radiotherapy, again in low risk patients and without regional nodal irradiation. All of the above trials used 3-dimensional conformal radiotherapy technique. In low-income and middle-income countries, majority of the patients present in advanced stage of breast cancer and 3-dimensional conformal radiotherapy is not always possible due to limited resources. Hence a study was needed to see if treatment duration of hypofractionated radiotherapy can be further reduced in high risk patients with breast cancer (patients needing regional nodal irradiation) with a 2-dimensional technique.

Added value of this study

To our knowledge, this is the first large, randomised trial comparing a 3-week hypofractionated radiotherapy schedule with a 2-week schedule in high risk patients of breast cancer with 2-dimensional technique. We found that the two radiation schedules were comparable in terms of acute skin toxicity. Cosmetic outcome was better in the 2-week schedule. These findings suggest that 2-week hypofractionated radiotherapy is feasible in patients with high risk breast cancer who needs regional nodal irradiation.

Implications of all the available evidence

The results of this study suggests that a 2-week hypofractionated radiotherapy schedule can be used in high risk patients with breast cancer even with a 2-dimensional technique. It will have financial and logistic implications in limited resource settings, which will increase utilisation of hypofractionation.

Introduction

Radiotherapy plays an important role in the management of breast cancer. Over the years, radiotherapy dose fractionation has changed from conventional fraction to hypofraction. There is a continuous effort to settle this radiation dose fractionation and treatment duration phenomenon in breast cancer. In this endeavour we have published clinical outcomes of a 2-week fractionation schedule where it was observed that acute and late effects were acceptable with control rates similar to those reported in other trials with hypofractionation.[1–4] Based on these findings we started a phase 3 randomised trial to compare a 3-week radiotherapy schedule with a 2-week schedule. Here we present the acute toxicity and cosmesis data which are the secondary end points of this trial. Local recurrence and survival will be reported at 5 years follow up.

Methods

The trial was approved by an institutional ethics committee and was registered with ClinicalTrials.gov, number NCT04075058. Patients to be included in this study were pre-operatively staged according to the American Joint Committee on Cancer (AJCC) 7th edition and the Union for International Cancer Control (which uses TNM staging [tumor, node, metastasis]) as stage I-III of breast carcinoma. Enrolled patients underwent a thorough clinical examination followed by routine investigations which included complete hemogram, liver function tests and kidney function tests. Radiological investigations included: chest X-ray and ultrasound of the abdomen in early-stage patients, and bone scan and contrast-enhanced computerised tomography of chest, abdomen, and pelvis in locally advanced stage patients. Inclusion criteria were: age ≥18–75 years, female or male, invasive carcinoma of the breast, breast conservation surgery or mastectomy (reconstruction allowed but not with implant; tissue expanders with distant metal ports were allowed), axillary staging and/or dissection, complete microscopic excision of primary tumour, FagepT1-4, pN0-3, M0 disease, written informed consent and able to comply with follow up. Concurrent trastuzumab and hormone therapy was allowed.

The patient was ineligible if any of the following were met: past history of malignancy except, (i) basal cell skin cancer and cervical intraepithelial neoplasia (CIN) cervix uteri or (ii) non-breast malignancy allowed if treated with curative intent and at least 5 years disease free, contralateral breast cancer, including ductal carcinoma in situ (DCIS), irrespective of date of diagnosis, breast reconstruction using implants and concurrent cytotoxic chemotherapy (sequential neoadjuvant or adjuvant cytotoxic therapy allowed).

Randomisation

Eligible patients were randomised (1:1) by simple randomisation to 3-week or 2-week radiation schedule without stratification using a computer-generated

schedule. A radiation oncologist on the study team enrolled the patients and the research staff assigned the patients to intervention. Masking was not done because the radiation was delivered by two different schedules daily.

Radiotherapy planning

Patients were positioned supine on a breast board with ipsilateral arm abducted to 90° and planned on a fluoroscopic 2-dimensional (2D) simulator. Radiotherapy fields were standard 2 opposing tangential fields to breast/chest wall and an incident field to the supraclavicular fossa. Detailed radiotherapy planning is described in our previous publications.[1,2] Radiotherapy doses were 34Gy in 10 fractions over 2 weeks in the 2-week arm and 35Gy in 15 fractions over 3-weeks to chest wall and 40Gy in 15 fractions over 3-weeks to axilla and supraclavicular fossa in the 2-week arm. Bolus was used for postmastectomy radiation therapy (PMRT) on alternate days (i.e., in 50% of treatment) in all the patients. The dose was prescribed at 3 cm depth. A boost dose of 8–10Gy/2–4#/2–4 days was delivered in patients with intact breast in both treatment arms. Internal mammary node (IMN) irradiation was done in patients with T3-4 central and inner quadrant tumors, pN2 disease or if there was an IMN on imaging. The first three intercostals spaces were included in the radiotherapy portal. The medial border of the IMN field was midline; the lateral border was 4 cm lateral to the midline; the superior border abutted the inferior border of the supraclavicular field; and the inferior border was above the xiphoid. The field size was approximately 10 × 4 cm, a single field. Dose was prescribed at 3 cm depth. IMNs were treated with electrons or photons with 2D technique. Patients were treated on a linear accelerator or a cobalt machine.

Assessment

Acute toxicity was assessed using the RTOG grading scale. Assessments were carried out weekly during radiotherapy and at 4 weeks after treatment by MD, physician, or senior resident (radiation oncologist) in the Radiotherapy & Oncology Department, PGIMER, Chandigarh, India. The assessor was not blinded to the radiation regimen. If symptoms persisted, the patients were assessed weekly until their reaction returned to Radiation Therapy Oncology Group (RTOG) grade 1 or less. Cosmetic assessments were done using the Harvard/National Surgical Adjuvant Breast and Bowel Project (NSABP)/RTOG breast cosmesis grading scale.

Sample size

The study was designed to test the non-inferiority of the experimental radiation regimen (2-week arm) as compared with the standard radiation regimen (3-week arm) with respect to local control. The sample size for this study was calculated with the following assumptions: the 5-year local recurrence-free survival rate in this patient population with the standard radiation regimen was assumed to be 85%; a margin of non-inferiority of 5% was considered clinically meaningful; the one-sided level of statistical significance (α) was set at 5%; the power was set at 80%; and, the accrual rate was expected to be approximately 200 patients a year. With these assumptions, the number of local recurrences required was 250 and the number of patients required to be randomised was 1000. Accrual was expected to take 5 years and further follow-up was expected for up to 7 additional years before the number of events is reached. Because of uncertainty of COVID-19 pandemic during the period of study, the sample size was increased to 1139 patients.

Statistical analyses

The primary end point of the study was local control, which will be reported after 250 events occur in the trial as this is a time-to-event study design. The secondary end points included acute toxicities, cosmetic scores, and overall survival. Skin, subcutaneous toxicity and cosmetic assessments were done before treatment and then at regular follow-up visits during the study. Fisher's exact tests were used to compare categorical variables between the two radiation schedules. Descriptive statistics including median, and range were calculated for all continuous variables and were compared using nonparametric Wilcoxon rank sum tests. p values of <0.05 were considered as statistically significant.

Role of the funding source

The funding agency had no role in data collection, analysis of interpretation, trial design, patient recruitment, or any aspect pertinent to the study.

Results

From June 2015 to December 2020, 1139 patients were recruited in this study. Out of these, 18 patients were excluded: 9 did not meet the inclusion criteria, 5 refused to participate in the study and 4 could not make it because of COVID-19 pandemic and logistical reasons (Fig. 1). So, a total of 1121 patients were randomised using simple randomisation, 564 in the 3-week arm and 557 in the 2-week arm. Median follow-up was 35 months (range 6–84 months).

Patient characteristics are shown in Table 1. Mean age was 48 years (range 24–75 years). The patient characteristics were comparable between the two arms except for more mastectomies 462 (82%) in the 3-week arm as compared to 410 (74%) in the 2-week arm ($p = 0.001$). There were more node-positive patients 263 (47%) in the 2-week arm as compared to 205 (36%) in the 3-week arm ($p < 0.001$). More patients had oestrogen

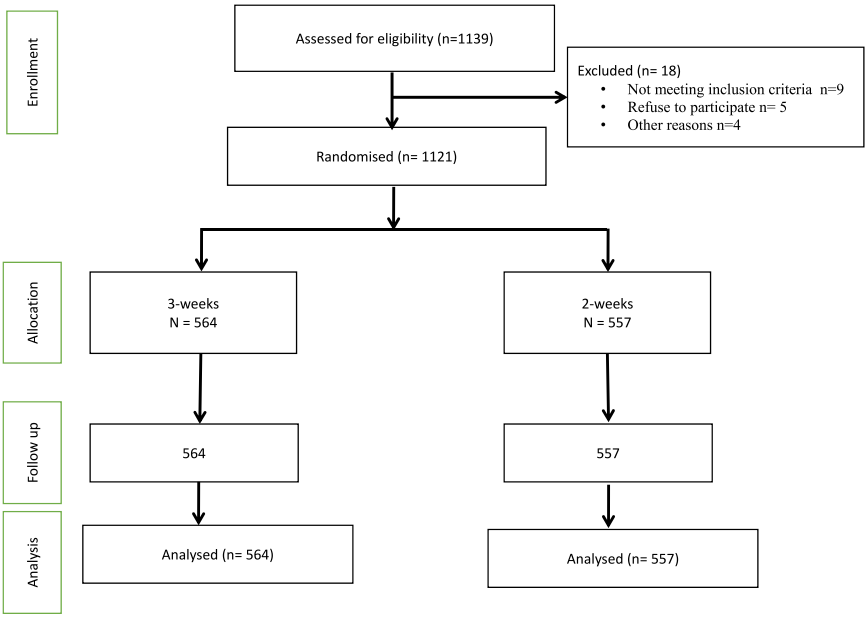

Fig. 1: **Trial profile**.

receptor-positive tumors 337 (60%) in the 3-week arm as compared to 298 (54%) in the 2-week arm (p = 0.034).

Systemic treatment was balanced between the two arms, except for more patients in the 3-week arm received hormonal therapy 357 (63%) as compared to 301 (54%) in the 2-week arm p = 0.002. This was consistent with more oestrogen-positive tumors in the 3-week arm.

Radiotherapy details were comparable between the two arms (Table 2). When the two arms were combined, breast or chest wall and supraclavicular fossa were irradiated in 85% of patients; internal mammary radiation was delivered in 42% of patients; boost was delivered in 17% of patients; and 55% of the patients were treated on a linear accelerator.

Acute skin toxicities were comparable between the two arms (Table 3). Grade 1 skin toxicity was observed in 211 (38%) and 197 (35%) patients in the 3-week and 2-week arms, respectively. Grade 2 and 3 skin toxicity was observed in 100 (18%) and 82 (15%), and 16 (3%) and 12 (2%) patients in the 3-week and 2-week arms, respectively (p = 0.21). Grade 3 skin reactions were brisk in 6 (1%) and 4 (1%) patients in the 3-week and 2-week arms, respectively, in patients who received at least one cycle of trastuzumab during radiation. Other factors for acute grade 3 skin reaction were chest wall separation >20 cm, poor scar and diabetes mellites (Table 4). Among patients with chest wall separation >20 cm, boost was associated with grade 3 acute skin toxicity in 3 patients in the 3-week arm and 2 patients in the 2-week arm. There were no statistical differences between the two arms in terms of acute toxicity. For all patients in the trial, significant factors for acute toxicity were separation >20 cm (p = 0.001), use of bolus (p = 0.016), boost ($p \leq 0.001$) and treatment with trastuzumab (p = 0.025).

None of the patients had grade 3 dysphagia. Grade 1 and 2 dysphagia was reported by 32 (6%) and 37 (7%), and 14 (2%) and 10 (2%) patients in the 3-week and 2-week arms, respectively (p = 0.59). Grade 1 and ≥ 2 arm edema was observed in 76 (13%) and 69 (12%), and 15 (3%) and 12 (2%) patients in the 3-week and 2-week arms, respectively (p = 0.73). Skin hyperpigmentation was observed in 9% of patients in each arm. Grade 3 acute radiation pneumonitis was observed in one patient in each arm (Table 3).

Cosmesis reported here was recorded at the last follow-up for each patient (Table 5). The cosmetic outcome was more often assessed as Excellent or Good in the 2-week arm 522 (94%) as compared to 501 (89%) in the 3-week arm (p = 0.004). In patients with breast conservative surgery, cosmesis was comparable between the two arms (Table 5). It was assessed as Excellent or Good in 142 (97%) and 94 (92%) in the 2-week and 3-week arms, respectively (p = 0.15). There were five patients with breast reconstruction in each arm. No adverse impact on the reconstructed breast tissue was observed in either arm.

Discussion

In this study of hypofractionated radiotherapy in patients with breast cancer, we compared two adjuvant radiation schedules of 34Gy/10#/2 weeks and 35Gy/

Characteristics	3-week (N = 564) n (%)	2-week (N = 557) n (%)
Laterality		
Right breast	282 (50)	280 (50)
Left breast	282 (50)	277 (50)
Menopausal status		
Premenopausal	251 (45)	262 (47)
Postmenopausal	313 (55)	295 (53)
Clinical tumor stage		
T1	54 (10)	52 (9)
T2	304 (54)	301 (54)
T3	95 (17)	98 (18)
T4	109 (19)	104 (19)
Tx	2	2
Clinical nodal stage		
N0	143 (25)	200 (36)
N1	273 (48)	224 (40)
N2	100 (18)	95 (17)
N3	48 (9)	38 (7)
Neoadjuvant chemotherapy		
Yes	271 (48)	268 (48)
No	293 (52)	289 (52)
Surgery		
Mastectomy	462 (82)	410 (74)
Breast conserving	102 (18)	147 (26)
Grade		
1	36 (7)	37 (7)
2	275 (50)	272 (50)
3	236 (43)	238 (44)
Unknown	17	10
Margins		
Positive	9 (2)	7 (1)
Negative	555 (98)	550 (99)
Lymphovascular invasion		
Yes	226 (40)	201 (36)
No	338 (60)	356 (64)
Ductal carcinoma in situ		
Yes	203 (36)	192 (34)
No	361 (64)	365 (66)
Pathological nodal stage		
pN0	359 (64)	294 (53)
pN1	136 (24)	150 (27)
pN2	39 (7)	72 (13)
pN3	30 (5)	41 (7)
Extracapsular extension		
Yes	65 (12)	50 (9)
No	499 (88)	507 (91)
Oestrogen receptor status		
Positive	337 (60)	298 (54)
Negative	223 (40)	256 (46)
Unknown	4	3
Progesterone receptor status		
Positive	239 (43)	227 (41)
Negative	320 (57)	323 (59)

(Table 1 continues on next column)

Characteristics	3-week (N = 564) n (%)	2-week (N = 557) n (%)
(Continued from previous column)		
Unknown	5	7
HER2-neu status		
Positive	168 (30)	139 (25)
Negative	391 (70)	410 (75)
Unknown	5	8

N: number; T: tumor stage, N: clinical nodes; pN: pathological nodes.

Table 1: **Clinical and pathological characteristics.**

40Gy/15#/3 weeks delivered with 2D technique. The two schedules resulted in comparable acute toxicity; however, cosmetic outcome was better with the 2-week schedule.

The toxicity rates reported in the present study are comparable to those reported by similar studies in the literature. A study by Wang and colleagues[4] reported grade 3 acute skin toxicity in 3% of patients with hypofractionation, which is in line with the present study of 3% in the 3-week arm and 2% in the 2-week arm. This might be because patients in both studies were treated with 2D technique. Wang and colleagues[4] used 6–9 MeV electrons and used a bolus in 40% of total prescribed doses. The current study used bolus on alternate days (i.e., in 50% of treatment) for post-mastectomy radiotherapy with photons in both arms. Acute grade 3 skin toxicity is also consistent with our phase 2 study where it was 2%.[1]

There was no grade 3 dysphagia. Only 2% of patients in each arm reported grade 2 dysphagia. Dysphasia was transient and resolved within 3 weeks of radiotherapy completion. Hyperpigmentation (grade 1 or 2) was observed in 9% patients with each radiation schedule. Acute radiation pneumonitis was reported by one patient in each arm. Both had received IMN irradiation with 6 MV photon. Pneumonitis started after 2 months of completion of radiotherapy and was controlled with tapering doses of steroids within the next three months in both patients. These patients developed low grade fever and chest pain. A disturbing symptom was dry cough in each patient; however, it was manageable with medications.

In the present study >75% patients were post mastectomy and 85% received regional nodal irradiation (RNI). Previous studies published in the English literature included 8–15% patients with mastectomy and 7–21% patients who were given RNI.[5,6] Grade 2 and 3 skin toxicity rates of 15% and 2% with the 2-week schedule are comparable to 11.7% and 2.7% in the UK FAST trial.[7] Acute skin toxicity is also comparable to those reported by the FAST Forward study: grade 2, 11% with 26Gy and 5% with 27Gy; and grade 3 in 2% patients.[8] Acute skin reactions healed in the majority of

Treatment	3wk (N = 564) n (%)	2wk (N = 557) n (%)	Fisher's exact test p-value
Adjuvant chemotherapy			
Yes	245 (43)	270 (48)	0.094
No	319 (57)	287 (52)	
Trastuzumab			
Yes	58 (35)	40 (29)	0.33
No	110 (65)	99 (71)	
Hormonal therapy			
Yes	357 (63)	301 (54)	0.002
No	207 (37)	256 (46)	
Irradiation[a]			
Breast/CW + SCF	475 (84)	478 (86)	0.50
Breast/CW only	89 (16)	79 (14)	
IMN RT[b]			
Yes	229 (41)	239 (43)	0.47
No	335 (59)	318 (57)	
Boost			
Yes	92 (16)	93 (17)	0.87
No	472 (84)	464 (83)	
Machine			
Linear accelerator	318 (56)	302 (54)	0.47
Cobalt	246 (44)	255 (46)	
CW separation			
Median	18.4 cm	17.2 cm	0.34
Range	(13–26 cm)	(12–26 cm)	
CLD Median[c]	1.9 cm	1.8 cm	0.72
Range	(1–3 cm)	(1–3 cm)	

[a]CW, chest wall; SCF, supraclavicular fossa. [b]IMN RT, Internal mammary node irradiation. [c]CLD, central lung distance.

Table 2: **Treatment details.**

patients within 3–4 weeks of their appearance. Grade 3 acute skin toxicity in all the above studies and the present study is within 2–5% although the patients' profile and radiation techniques used are different. The UK studies included early-stage patients as compared to high-risk patients in the present study and the Beijing study.[4] The UK studies used 3D techniques whereas the Beijing and the current study used 2D technique. Comparable grade 3 acute skin toxicity rates in all these trials might be because of similar EQD2. The comparable results also suggest that 2D technique may be as safe as 3D in patients with breast cancer. The volumes irradiated in the 3D technique are also contoured by defining the anatomic boundaries of the breast/chest wall using wires. These volumes may not differ much from the 2D area; however, 2D technique is simple to plan and execute and not image-dependent which further reduces the setup and treatment time in these patients. The EQ (D2) and BED for the regimen of 35 Gy in 15 fractions would be 37.5 Gy and 62 Gy, respectively. This is quite similar to the UK IMPORT LOW trial where they used 36 Gy in 15 fractions for whole-breast radiotherapy.[9] This might also be a sufficient dose for the PMRT. One can use scar boost if higher doses are indicated. We have not encountered excess recurrence rates with this schedule which we have been using since 1976.[10]

Acute grade 2 skin toxicity rates of 15–17% are also comparable to our simultaneous integrated boost study of 18.5%.[11] Boost was delivered in 17% of patients in the present study. Boost dose is also known to increase acute skin toxicity rate.[12] Therefore, based on these acute toxicity data, it appears that the 2-week schedule raises no concerns of prolonged acute skin reactions as compared to the 3-week schedule, and these toxicities were transient and manageable.

The simplicity of the 2-week schedule is that it can be practiced in a radiotherapy center even with minimal facilities. It has economic implications for the limited resource countries where the incidence of breast cancer is increasing, and facilities are limited. The planning process is simple and takes less time, so a greater number of patients can be accommodated. By using a 2-week schedule instead of a 3-week schedule, 33% more patients can be treated with the existing equipment and manpower. It will further encourage the utilisation of hypofractionation in patients with breast cancer in the limited resource countries as the waiting time for other patients for radiotherapy (RT) will be reduced.

Acute toxicities	3-week (N = 564) n (%)	2-week (N = 557) n (%)	Fisher's exact test p-value
Skin (RTOG grade)			
Grade 0	237 (42)	266 (48)	0.21
Grade 1	211 (37)	197 (35)	
Grade 2	100 (18)	82 (15)	
Grade 3	16 (3)	12 (2)	
Dysphagia			
Grade 0	518 (92)	510 (92)	0.59
Grade 1	32 (6)	37 (7)	
Grade 2	14 (2)	10 (2)	
Grade 3	0	0	
Arm edema			
Grade 0	473 (84)	476 (86)	0.73
Grade 1	76 (13)	69 (12)	
Grade ≥2	15 (3)	12 (2)	
Hyperpigmentation			
Grade 0	514 (91)	507 (91)	0.90
Grade 1	37 (7)	39 (7)	
Grade 2	13 (2)	11 (2)	
Grade 3	0	0	
Radiation pneumonitis			
None	563 (99.8)	556 (99.8)	1.00
Grade 3	1 (0.2)	1 (0.2)	

RTOG: Radiation Therapy Oncology Group.

Table 3: **Acute toxicity as per RTOG scale.**

The current study has several strengths. The study involved large and randomised data of high-risk breast cancer patients treated with simple 2D technique. We did rigorous analysis of acute toxicity and cosmesis which are comparable to the other randomised studies reported with 3D technique. Regional nodal irradiation

Factors	3-week (N = 16) n (%)	2-week (N = 12) n (%)	Fisher's Exact Test p-value
Trastuzumab	6 (38)	4 (33)	1.00
Separation >20 cm	6 (38)	5 (42)	
Poor scar	3 (19)	2 (17)	
Diabetes	1 (6)	1 (8)	

Table 4: **Factors for Grade 3 acute skin toxicity.**

Cosmesis (all patients)	**3-week N = 564 n (%)**	**2-week N = 557 n (%)**	**Fisher's Exact Test p-value**
Excellent or Good	501 (89)	522 (94)	0.004
Fair or Poor	63 (11)	35 (6)	
Cosmesis (BCS)[a]	**3-week N = 102 n (%)**	**2-week N = 147 n (%)**	**Fisher's Exact Test p-value**
Excellent or Good	94 (92)	142 (97)	0.15
Fair or Poor	8 (8)	5 (3)	
Cosmesis (mastectomy)	**3-week N = 462 n (%)**	**2-week N = 410 n (%)**	**Fisher's Exact Test p-value**
Excellent or Good	412 (89)	382 (93)	0.005
Fair or Poor	50 (11)	28 (7)	

[a]BCS: breast conserving surgery; RTOG: Radiation Therapy Oncology Group; NSABP: National Surgical Adjuvant Breast and Bowel Project.

Table 5: **Cosmetic outcome as per Harvard/NSABP/RTOG scale.**

was administered with hypofractionation. Boost dose was also delivered with hypofractionation whereas the previous UK START trials had used conventional fractionation for boost dose.[5,6]

This study has few limitations. The patients were planned on a fluoroscopic 2D simulator, and many patients (45%) were treated on a cobalt machine. Since the RT fields were tangential, there could be hot and cold spots which are likely to be missed in a 2D planning. The trial also lacks dosimetry information, but these are the limitation of the 2D planning. We have already reported the doses to the organs at risk with both radiation schedules.[13,14] It is very difficult to include internal mammary chain in a simple 3D conformal planning technique, and by anatomically marking the area we cannot be sure that the required dose has been delivered through a 2D planning technique. Although a 5% significance level for one-sided test is particularly common in non-inferiority trials but some researchers may also consider it at 2.5%.

Internal mammary chain is always a difficult area to treat with RT. The underlying cardiac doses are always a concern while doing a single direct anterior field. But the overall dose delivered is less with hypofractionation as compared to conventional fraction. There is a possibility that hypofractionation may be gentle to the heart. We have reported outcomes and toxicities with the 3-week schedule and did not encounter excess toxicities.[15] However, we have to wait for the long term results before assessing cardiac toxicities with the 2-week schedule.

In the present study, only one-third of the patients with human epidermal growth factor receptor (Her2-neu) positive disease could receive trastuzumab because of economic constraints. Also, there were few patients with breast reconstruction in this study. However, we did not observe any adverse effects with either schedule in these patients. This is a preliminary data; we need to wait for disease outcomes and late toxicities. We need to wait for local recurrence rate and survival outcomes which will be reported after completion of 5 years follow up.

The current study has demonstrated that the two radiation schedules were comparable in terms of acute skin toxicity, and that the cosmetic outcomes were better with the 2-week schedule. However, we will have to wait for local recurrence rates, overall survival outcomes, and longer-term toxicities and cosmetic results before drawing definitive conclusions about cost or benefit of the 2-week schedule versus the 3-week schedule.

Contributors

BSY and DD designed the study, analysed the data, and wrote the manuscript. BSY, DD, MG, AG, ASO, SK, SI, NR, YSR, SSN and RK contributed to the study concept. BSY, DD, MG, AG, and NR contributed to study coordination. BSY, DD, MG, AG, ASO, NR and RK contributed to data collection. BSY and DD did the statistical analysis. All authors contributed to data interpretation and approved the manuscript.

Data sharing statement

Individual patients data will be provided for methodological sound proposal for meta-analysis after signing a data sharing agreement. Data will be shared on making a suitable request to drbudhi@gmail.com. Data will be made available beginning 3 months and ending 5 years following article publication.

Declaration of interests

This study was funded by Science and Engineering Research Board (SERB), India provided to the institution (PGIMER) and BSY was the principal investigator. Authors have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lansea.2024.100392.

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