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Accelerated hypofractionated breast radiotherapy with simultaneous integrated boost: a feasibility study

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Purpose: To assess the feasibility of accelerated hypofractionated radiotherapy with simultaneous integrated boost (SIB) in patients with breast cancer.

Materials and Methods: A total of 27 patients after breast-conserving surgery were included in this study. Patients were planned on a four-dimensional computerized tomogram, and contouring was done using RTOG guidelines. The dose was 34 Gy/10#/2 week to the breast and 40 Gy/10#/2 week to the tumor bed as SIB with volumetric modulated arc technique. The primary endpoint was grade 2 acute skin toxicity. Doses to the organs-at-risk were calculated. Toxicities and cosmesis were assessed using RTOG/LENT/SOMA and HARVARD/NSABP/RTOG grading scales, respectively. Disease-free survival (DFS) and overall survival (OS) were calculated with Kaplan-Meier curves.

Results: The mean age of the patients was 42 years. Left and right breast cancers were seen in 17 (63%) and 10 (37%) patients, respectively. The mean values of ipsilateral lung V_{16} and contralateral lung V_5 were 16.01% and 3.74%, respectively. The mean heart doses from the left and right breast were 7.25 Gy and 4.37 Gy, respectively. The mean doses to the contralateral breast, oesophagus, and D_{max} to brachial plexus were 2.64 Gy, 3.69 Gy, and 26.95 Gy, respectively. The mean value of thyroid V_{25} was 19.69%. Grade 1 and 2 acute skin toxicities were observed in 9 (33%) and 5 (18.5%) patients, respectively. Grade 2 hyperpigmentation, edema, and induration were observed in 1 (3.7%), 2 (7.4%), and 4 (14.8%) patients, respectively. Mild breast pain and arm/shoulder discomfort were reported by 1 (3.4%) patient. The median follow-up was 51 months (range, 12 to 61 months). At four years, breast induration, edema, and fibrosis were observed in 1 (3.7%) patient. Cosmesis was excellent and good in 21 (78%) and 6 (22%) patients, respectively. Local recurrence and distant metastases occurred in 1 (3.7%) and 2 (7.4%) patients, respectively. DFS and OS at four years were 88% and 92%, respectively.

Conclusion: With this radiotherapy schedule, acute and late toxicity rates were acceptable with no adverse cosmesis. Local control, DFS, and OS were good.

Keywords: Breast cancer, Hypofractionation, Radiation toxicity

Introduction

Breast cancer is the most common cancer among women globally as well as in our country [1]. Radiotherapy (RT) plays an important role in breast cancer management after breast-conserving surgery (BCS) or mastectomy. In patients with BCS, whole breast irradiation (WBI) can be delivered with many techniques. These techniques include two-dimensional (2D), 3-dimensional conformal RT (3D-CRT) with or without deep inspiration breath hold, field-in-field intensity-modulated radiotherapy (FF IMRT), inverse planning IMRT, tomotherapy, image-guided radiotherapy (IGRT) and proton therapy. RT contributes by sterilizing the microscopic disease. Boost to the

primary tumor site further reduces the risk of local recurrence within 2 cm of its location [2,3]. Young patients with ductal carcinoma in situ (DCIS) histology have been reported to benefit from a boost to the primary site [4,5]. There are many techniques and modalities (photons, electrons, and brachytherapy) by which boost can be delivered. The optimal modality, timing, dose fractionation and technique of tumor bed boost have not yet been established, especially with hypofractionated RT. However, for a patient who may benefit from boost, simultaneous integrated boost (SIB) can be one of the methods for its delivery. It achieves dose conformity, homogeneity; lower toxicity rate and completes the treatment fast in one plan only leading to better patient compliance [6-8]. If boost is planned with volumetric-modulated arc therapy (VMAT), the treatment delivery is fast, and planning on four-dimensional computed tomography (4D-CT) can improve its localization and onboard imaging can increase the accuracy of dose delivery [7]. Tumor bed boost has been shown to be associated with increased acute and late toxicity [5,9]. However, it depends on the total dose, dose per fraction, volume of the boost, modality and the technique used for boost delivery. In majority of the studies SIB was delivered in 3–5 weeks and has been shown to be well tolerated [4-11]. SIB with accelerated hypofractionation can further reduce treatment duration from 3 weeks to 2 weeks.

We have published our data with a radiation schedule of 34 Gy in 10 fractions over 2 weeks with 2D technique with acceptable toxicity and local control [12,13]. Breast boost in this study was sequential, 10 Gy/5#/1 week with photons or electrons. We further wanted to reduce this treatment duration to 2 weeks only. So, we planned the current feasibility study. Equivalent doses (EQD_2) of this schedule will be 43.52 Gy_3 for the WBI and 56 Gy_3 for the tumor bed, which is quite similar to the START B trial and our past experience [14]. Here, we report dosimetry, acute and late toxicities and the cosmetic outcomes in patients with breast cancer post-BCS who were treated with accelerated hypofractionated WBI and SIB with VMAT technique over 2 weeks (10 fractions).

Materials and Methods

This prospective phase II study was conducted in the Department of Radiation Oncology, Regional Cancer Centre, PGIMER, Chandigarh from July 2016 to June 2017. Primary objective was to assess grade 2 acute skin toxicity with hypofractionated WBI with SIB completed in 10 fractions. Secondary objectives of the study were to determine dose distribution, target coverage, dose homogeneity dose conformity of the target volume, late toxicity and cosmetic outcomes.

1. Patient selection

Patients with breast cancer who had undergone BCS were included in this study. Institutional Ethics Committee of PGIMER approval was taken (No. INT/IEC/2017/127). Informed consent was taken from all the patients. The trial was registered with clinicaltrials.gov no. NCT04072718. Inclusion criteria were (1) primary cancer of breast of any histology, (2) age >18–70 years, (3) post-BCS with clear margins, healed scar, (4) Karnofsky performance status (KPS) >70, (5) regional nodal radiation when indicated (T3 tumors, positive nodes and T2 tumors with any of the two factors such as age <40 years, grade 3, estrogen receptor/progesterone receptor [ER/PR] negative and with lymphovascular invasion) and (6) no distant metastasis. Indications for the boost were age <40 years, T3 tumors, DCIS >25%, ER/PR negative, and close margins. Close margin was defined as margin <2 mm. Neoadjuvant or adjuvant chemotherapy was allowed. Adjuvant endocrine therapy was given to patients with hormone receptor positive tumors. Exclusion criteria were mastectomy, history of prior primary malignancy, prior irradiation to breast or chest, pregnancy and collagen vascular disease.

2. Radiotherapy planning

All patients were made to lie supine on a carbon fiber breast board or wing board or a T bar with ipsilateral arm abducted to 90° and face turned to the opposite side. Radiopaque markers were placed for defining the superior, inferior, medial, and lateral borders and the surgical scar. Three skin markings were placed along with the fiducials below the breast folds for the purpose of reproducibility and the location of tumor bed with respect to fiducials.

All patients underwent a normal free-breathing scan with virtual CT breast simulation. Axial cuts were taken from the mandible to the upper abdomen with a slice thickness of 3 mm. The 4D-CT images with recording of the respiratory signals were acquired, taking organ motion into account. The delineation of the tumor cavity and contouring of the organs-at-risk (OARs) was done by using RTOG guidelines. Contouring for the target volumes were done on maximum intensity projection (MIP) of the 4D-CT. The OARs contoured were heart, bilateral lungs, contralateral breast, brachial plexus, esophagus, spinal cord, left anterior descending artery (LAD) and thyroid.

The affected breast was contoured as the clinical target volume (CTV) excluding 5 mm from the skin. An additional 5 mm (0.5 cm) margin for setup error and motion was then added to CTV to form the planning target volume (PTV breast), excluding it from lungs and body by 5 mm to spare the skin. The nodal areas, when indicated according to the risk factors, were also contoured following RTOG contouring guidelines.

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3. Boost RT planning

In each patient, tumor bed was delineated using clinical, radiological (mammography/CT/ultrasound of breast), surgical (intra-operative notes, external and internal surgical scar location) findings, seroma cavity and surgical clip's location. Internal target volume (ITV) was generated by contouring tumor bed in all phases of respiratory cycles on 4D-CT based on MIP images. A margin of 5mm was added to the cavity to form PTV boost. A dose of 34 Gy/10#/2 week to the PTV breast and 40 Gy/10#/2 week to the PTV boost was delivered with IGRT using the RapidArc technique. Partial arcs were used for RT planning. Dose distribution and target coverage criteria for PTV breast and PTV boost were 98% of volume should receive >95% of dose and 2% volume should receive <107% of dose. Conformity and homogeneity indices were also calculated for each plan [15-17].

Dose constraints were calculated for this schedule by considering the radiobiological equivalence to conventional fractionation. For example, V_{20} for the lung, of the conventional fractionation (50 Gy/25#/5 week) will correspond to V_{16} of the 40 Gy (34 Gy to the breast + 8 Gy to the primary site) dose delivered in this study. Similarly for the heart and LAD D_{max} instead of V_{25} and <20 Gy, V_{18} and <15 Gy, respectively were used. Dose constraints given were ipsilateral mean lung dose (MLD) ≤9 Gy, V_{16Gy} <20% and contralateral lung V_5 <5%. Mean heart dose (MHD) ≤7 Gy, V_{18} <5% for left side and <1% for the right side. LAD D_{max} and D_{mean} to be <15 Gy and <8 Gy, respectively, from the left breast. Contralateral breast D_{mean} <3 Gy. Thyroid V_{25} and V_{30} should be <50% and <25%, respectively. D_{max} and D_{mean} for oesophagus <20 Gy and <5 Gy, respectively. D_{max} for the spinal cord and brachial plexus should be <30 Gy and <40 Gy, respectively.

Cone beam CT was done on the first three consecutive days and then orthogonal images were taken daily for set-up verification. All patients were treated in free breathing.

4. Assessments

1) Toxicities

Baseline assessment was done for all the patients. The physicians examined patients for any toxicity every week during treatment, at the treatment completion and during the follow-up visits. First follow-up was at 2 weeks of completion of radiation and then at 1 month for assessment of acute toxicity. Patients were followed every 3 months in the 1st year, every 4 months in the 2nd year, every 6 months thereafter. Toxicities were scored according to RTOG/LENT/SOMA grading scale.

Both physician and patients reported acute toxicities at 1 and 3 months of completion of radiotherapy, which consists of the highest grade/severity observed/reported for the recording purpose. Late effects are reported at 6 months and 4 years follow-up by the patient and the physician.

2) Cosmesis

Cosmetic effects were assessed in the treated breast and compared with the opposite breast and with the baseline photographic evaluation. Both objective (skin reaction, overall grade, edema, induration, subcutaneous fibrosis, tenderness, scar changes and any other skin changes/ulceration) and subjective (hyperpigmentation, change in shape, change in size, nipple changes, heaviness, pain) parameters were used. The Harvard/NSABP/RTOG scale proposed by Harris et al. [18] was used to evaluate the cosmetic parameters. Variability in both objective and subjective assessment was evaluated. Changes in terms of color, shape, size, any swelling, symmetry, texture, and position of nipple were noted in the treated breast. The assessment was done at baseline (before the start of radiation treatment), at the time of completion of treatment, at 1 month, 3 months, 6 months, 1 year and 3 years after completion of treatment. The long-term cosmetic effects were reported at 4 years. For subjective evaluation, a standard scale for assessment of cosmetic effect due to RT after BCS was used. For objective qualification, digital photography of the patient was used, before and after the treatment. Digital photo, in a front view of the patient including the sternal notch and both the breast with a light background with adequate light were taken. Two views with hands by side and hands raised above the head were taken for all the patients. A picture of the scar was also taken by the same person to avoid variability of clicked photos.

3) Clinical outcomes

Disease-free survival (DFS) and overall survival (OS) were summarized by Kaplan-Meier curves. Local recurrence was defined as recurrence in the in the involved breast, axilla, supraclavicular fossa, and internal mammary nodes. Distant metastases were defined as disease occurring in the other sites. Local recurrence and distant metastases were used to calculate DFS. Time was calculated from the date of completion of RT. OS was defined from the date of diagnosis till the last follow-up or death due to breast cancer.

5. Statistical analysis

The purpose of the trial was to reject the experimental treatment from further study if it is too toxic, and to accept it for further study if the toxicity is acceptable. The primary endpoint was grade 2 acute skin toxicity, and other toxicities were considered secondary endpoints. The study was designed as a phase II trial with the following assumptions:

(1) Grade 2 skin toxicity ≥36% was considered unacceptable, and

grade 2 skin toxicity ≤ 11% was considered acceptable. Hence the hypotheses of interest were H_0: r ≥ 36% against H_A: r ≤ 11%, where r is the proportion of patients with grade 2 skin toxicity.

(2) The type I error rate (a, probability of accepting an overly toxic treatment, a false positive outcome) was set to 5%.

(3) The type II error rate (b, probability of rejecting an acceptably toxic treatment, a false negative outcome) was set to 10%, i.e., the power is equal to 90%.

Under these assumptions, using a one-sided Fisher exact test, the design consists of treating 27 evaluable patients, and

(1) if at most five patients have grade 2 skin toxicity, the treatment was considered acceptable (5/27 = 19%),

(2) if at least six patients have grade 2 skin toxicity, the treatment was considered too toxic (6/27 = 22%).

Results

1. Patient characteristics

Between July 2016 to June 2017, 27 patients were treated. Mean age of the patients was 42 years (range, 36 to 67 years). Left and right breast cancer was seen in 17 (63%) and 10 (37%) patients, respectively. Most patients were premenopausal 22 (81%) and had T2 tumors 16 (59%). Nodes were positive in 18 (67%) patients (Table 1). Axillary clearance was till level III in 25 (92.5%) patients and median number of dissected nodes were 19. More than 50% of the patients had grade 3 disease and lymphovascular invasion. None of the patients had oncoplastic reduction. Supraclavicular fossa (SCF) was treated in 20 (74%) patients. Internal mammary nodes were treated in one patient. Chemotherapy was given as neoadjuvant and adjuvant to 4 (14.8%) and 22 (81%) patients, respectively. Hormonal therapy was received by 18 (67%) patients. Trastuzumab was received by 1 (4%) patient only.

2. Dosimetry

Mean PTV and boost volume were 1,099.58 ± 396.81 mL and 76.0 ± 41.89 mL, respectively. The mean conformity index (CI) for the PTV breast was 0.74 ± 12. The mean CI and homogeneity index (HI) for the PTV boost was 0.64 ± 0.15 and 0.09 ± 0.04, respectively. D_{max} to PTV boost was 43.2 ± 1.5 Gy. PTV breast and PTV boost $V_{107\%}$ and $V_{105\%}$ were 4.2 ± 4.6 mL and 11.8 ± 4.3 mL and 2.97 ± 8.81 mL and 8.22 ± 0.74 mL, respectively.

Ipsilateral MLD was 9.86 Gy (range, 7.12 to 13.72 Gy). Ipsilateral lung mean V_{16} and V_{10} was 16.01% (2.12%–27.42%) and 39.60% (13.6%–79.8%), respectively. Contralateral lung mean V_5 and V_2 was 3.74% (0.77%–11.33%) and 52.62% (12.31%–97.90%), respectively. MLD with and without SCF radiotherapy was 10.08 Gy (range, 7.13 to 13.72 Gy) (n = 20) and 9.22 Gy (range, 7.12 to

Table 1. Patient characteristics

Characteristic	n (%)
Comorbidities	
Yes	9 (33)
No	18 (67)
Menopausal status	
Premenopausal	22 (81)
Postmenopausal	5 (19)
Clinical tumor stage	
T1	9 (33)
T2	16 (59)
T3	2 (4)
pTumor stage	
T1	10 (37)
T2	16 (59)
T3	1 (4)
pNodal stage	
N0	9 (33)
N1	11 (41)
N2	6 (22)
N3	1 (4)
Grade	
1 & 2	13 (48)
3	14 (52)
Lymphovascular invasion	
Yes	15 (56)
No	12 (44)
DCIS	
Present	8 (30)
Absent	19 (70)
Estrogen receptor	
Positive	15 (56)
Negative	12 (44)
Progesterone receptor	
Positive	13 (48)
Negative	14 (52)
Her-2/neu	
Positive	8 (30)
Negative	19 (70)
Ki67	
≤ 14	5 (19)
> 14	22 (81)
Chemotherapy	
Yes	26 (96)
No	1 (4)
Hormones	
Yes	18 (67)
No	9 (33)
Trastuzumab	
Yes	1 (4)
No	7 (26)

DCIS, ductal carcinoma in-situ.

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11.50 Gy) (n = 7), respectively. MHD was 7.25 Gy (range, 4.31 to 10.85 Gy) from the left breast and 4.37 Gy (range, 2.32 to 7.13 Gy) from the right breast. In patients with left breast cancer (n = 17), MHD with and without SCF treatment was 7.25 Gy (n = 12) and 6.6 Gy (n = 5), respectively. Mean V_{18} and V_{15} of the heart from the left and right breast was 2.88% (0.05%–8.98%) and 0.30% (0%–1.69%); and 6.20% (0.22%–18.26%) and 1.1% (0%–3.69%), respectively. D_{max} to LAD from left breast was 14.24 Gy (8.9–27.86 Gy). Mean LAD dose from the left and right breast was 7.74 Gy (4.42–21.26 Gy) and 3.32 Gy (1.41–6.72 Gy), respectively. Mean dose to the contralateral breast was 2.64 Gy (1.53–4.16 Gy). Thyroid V_{30} and V_{25} mean were 11.83% (0%–36.90%) and 19.69% (0%–52.97%), respectively (Table 2). D_{max} and D_{mean} to the oesophagus was 15.65 Gy (4.48–32.8 Gy) and 3.69 Gy (1.55–9.02 Gy), respectively. D_{max} and D_{mean} to spinal cord and was 10.43 Gy (2.32–28.40 Gy) and 3.15 Gy (0.84–18.65 Gy), respectively. D_{max} to brachi-

Table 2. Volumes, doses to the organs-at-risk and constraints achieved

		Dose constraint	n	Mean ± SD	Constraint achieved, n (%)
Volumes	PTV breast (cm^3)			1,099.58 ± 396.81	
	Conformity index			0.74 ± 0.12	
	107%			4.20 ± 10.35	
	105%			11.80 ± 19.14	
	PTV boost (cm^3)			76.00 ± 41.89	
	Conformity index			0.64 ± 0.15	
	Homogeneity index			0.09 ± 0.04	
	107%			2.97 ± 5.43	
	105%			8.22 ± 16.65	
Organ at risk	Mean lung dose	≤ 9 Gy	27	9.86 ± 2.03	16 (59.25)
	Ipsilateral lung				
	V_{20Gy}	≤ 10%	27	8.88 ± 4.20	21 (77.78)
	V_{16Gy}	< 20%	27	16.01 ± 5.60	22 (81.48)
	V_{10Gy}	-	27	39.60 ± 15.93	-
	Contralateral lung				
	V_{5Gy}	< 5%	27	3.74 ± 3.30	22 (81.48)
	V_{2Gy}	-	27	52.62 ± 22.63	-
	Heart D_{mean}				
	Left breast	≤ 7 Gy	17	7.25 ± 2.25	10 (58.82)
	Right breast	< 3 Gy	10	4.20 ± 2.32	5 (50.00)
	Heart V_{18Gy}				
	Left breast	< 5%	17	2.88 ± 2.36	15 (88.24)
	Right breast	< 1%	10	0.33 ± 0.52	9 (90.00)
	Heart V_{15Gy}				
	Left breast	< 10%		6.20 ± 4.67	15 (88.24)
	Right breast	2%		1.10 ± 3.73	7 (70.00)
	LAD D_{max}				
	Left breast	< 15 Gy	17	14.24 ± 9.78	14 (82.35)
	LAD D_{mean}				
	Left breast	< 8 Gy	17	7.74 ± 3.86	15 (88.24)
	Right breast	< 3 Gy	10	3.32 ± 2.84	8 (80.00)
	Contralateral breast D_{mean}	< 3 Gy	27	2.64 ± 0.63	21 (77.78)
	Thyroid				
	V_{30}	< 25%	27	11.82 ± 14.57	19 (70.37)
	V_{25}	< 50%	27	19.69 ± 21.23	24 (88.89)
	Esophagus				
	D_{max}	< 20 Gy	27	15.65 ± 9.47	19 (70.37)
	D_{mean}	< 5 Gy	27	3.68 ± 1.58	23 (85.19)
	Spinal cord D_{max}	< 30 Gy	27	28.40 Gy	27 (100)
	Brachial plexus D_{max}	< 40 Gy	27	38.42 Gy	27 (100)

SD, standard deviation; PTV, planning target volume; LAD, left anterior descending artery.

al plexus was 26.95 Gy (6.72–38.42 Gy).

Dose constraints for MLD ≤9 Gy, ipsilateral lung V_{16} <20% and contralateral lung V_5 <5% were achieved in 59.25%, 81.48% and 81.48% of patients, respectively (Table 2). MHD from left breast cancer ≤7 Gy was achieved in 58.82% patients. Heart V_{18} <5% for left side and <1% for the right side were achieved in 88.24% and 90% of patients, respectively. Heart V_{15} <10% for left side and <2% for the right side were achieved in 88.24% and 70% of patients, respectively. LAD D_{max} (<15 Gy) for left breast was achieved in 82.35% patients. LAD D_{mean} <8 Gy from left breast and <3 Gy from right breast were achieved in 88.24% and 80% of patients, respectively. Contralateral breast D_{mean} <3 Gy was achieved in 77.78% of patients. Thyroid V_{30} and V_{25}, <25% and <50%, were achieved in 70.27% and 88.89% of patients, respectively. Oesophagus D_{max} (<20 Gy) and D_{mean} (<5 Gy) were achieved and 85.19% and 70.03% of patients, respectively. Average of D_{max} was higher in patients who received SCF radiation (18.66 Gy) as compared to those who did not (7.0 Gy). Spinal cord D_{mean} (<5 Gy) and D_{max} (<30 Gy) were achieved in 88.89% and 100% patients, respectively.

There was significant dose reduction to the thyroid with head position and whether SCF was treated or not (Table 3). Mean thyroid dose in patients with and without head rotation was 11.00 Gy (95% confidence interval [CI], 6.67–15.32) and 22.68 Gy (95% CI, 20.00–25.36), respectively (p < 0.0001). Similarly, mean thyroid dose with and without SCF treatment was 16.95Gy (95% CI, 13.08–20.82) and 0.67Gy (95% CI, 0.34–0.99), respectively (p < 0.0001).

3. Acute toxicity

Grade 1 and 2 acute skin toxicity was observed in 9 (33%) and 5 (18.5%) patients, respectively (Fig. 1). Acute grade 2 skin toxicity in patients with and without nodal radiotherapy was 4 (20%) and 1 (14.2%), respectively. These were dry desquamations either in axillary fold or in inframammary fold. There was no grade 3 acute skin toxicity. This rate of grade 2 acute skin toxicity met the predefined criteria of ≤5/27 for acceptable toxicity. None of the parameters such as treatment of SCF nodes, $V_{107\%}$, $V_{105\%}$, breast size and boost volume were related with acute toxicity (Table 4).

All the secondary toxicities at 1 month also met the predefined

Table 3. Thyroid dose with head position and SCF treatment

	n	Dose	95% CI	p-value
Head rotation				
Yes	23	11.00 ± 10.01	6.67–15.32	<0.0001
No	4	22.68 ± 1.68	20.00–25.36	
SCF treatment				
Yes	20	16.95 ± 0.35	13.08–20.82	<0.0001
No	7	0.67 ± 8.25	0.34–0.99	

Values are presented as mean ± standard deviation.
SCF, supraclavicular fossa; CI, confidence interval.

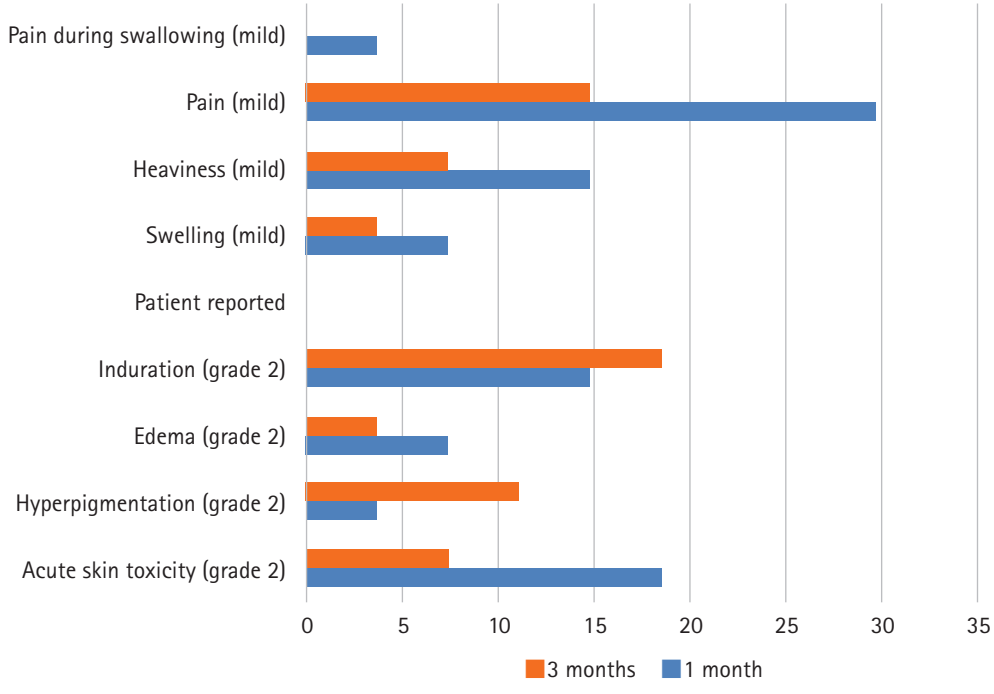

Fig. 1. Acute toxicity: patient and physician reported (rates along the X-axis).

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Table 4. Variables for acute toxicity

Variable	Acute toxicity	n	Mean ± SD	p-value (t-test)
Breast volume	Grade 0/1	22	1,257.3 ± 471.8	0.50
	Grade 2	5	1,106.4 ± 309.7	
PTV volume	Grade 0/1	22	1,126.3 ± 412.6	0.47
	Grade 1	5	982.2 ± 329.4	
Boost volume	Grade 0/1	22	81.8 ± 39.6	0.14
	Grade 2	5	51.2 ± 47.2	
$V_{107\%}$	Grade 0/1	22	12.4 ± 38.0	0.76
	Grade 2	5	7.1 ± 12.0	
$V_{105\%}$	Grade 0/1	22	29.4 ± 75.8	0.75
	Grade 2	5	17.9 ± 29.2	

SD, standard deviation; PTV, planning target volume.

criteria for acceptable toxicity. Grade 2 hyperpigmentation, edema, and induration were observed in 1 (3.7%), 2 (7%), and 4 (14.8%) patients, respectively. At 1 month, patient reported acute toxicities were mild breast swelling, heaviness, and pain in 1 (3.7%), 4 (14.8%), and 8 (29%) patients, respectively. Mild difficulty in swallowing was reported by 1 (3.7%) patient in whom internal mammary nodes were also treated. None of the patients developed acute radiation pneumonitis. D_{max} to the oesophagus in this patient was 32.8 Gy. All acute toxicities subsided by 3 months except for the induration (Fig. 1).

4. Late toxicity

Late toxicities were either grade 1 or 2 (Fig. 2). In comparison to the baseline, toxicities increased till 6 months then decreased after that. Late grade 1 and grade 2 breast induration at 4 years was observed in 4 (14.8%) and 1 (3.7%) patient, respectively. These were present at baseline also. Breast edema was seen in 2 (7.4%) patients at baseline, which reduced at 4 years to 1 (3.7%) only. Grade 1 breast fibrosis was observed in 1 (3.7%) patient at 4 years. Grade 1 arm edema was seen in 2 (7.4%) patients at baseline, which persisted in 1 (3.7%) patient till 4th year.

Patient reported outcomes were mild to moderate only. At baseline mild to moderate breast pain was reported by 2 (7.4%) patients, which became mild at 4 years. Breast heaviness was reported by 2 (7.4%) patients at baseline, which persisted till 4th year. Mild breast shrinkage was reported by 1 (3.7%) and 2 (7.4%) patients at baseline and 4 years, respectively. Mild arm/shoulder discomfort was reported by 1 (3.7%) patient only. Arm swelling at 4 years was reported by only 1 (3.7%) patient. There were no grade 3 late toxicities. There was no brachial plexopathy or rib fracture with this schedule. We did not observe any late cardiac or pulmonary toxicity.

5. Cosmesis

Physician/patient observed cosmesis was excellent and good in 21 (78%)/19 (70%) and 6 (22%)/8(30%) patients, respectively (Figs. 3, 4). None of the patients had adverse cosmesis. None of the parameters such as $V_{107\%}$, $V_{105\%}$, breast size and boost volume were related with late effects or cosmesis.

6. Outcomes

At a median follow-up of 51 months (range, 12 to 61 months), local recurrence occurred in 1 (3.7%) patient. Distant metastases were seen in 2 (7.4%) patients. Both patients with distant metastases had triple negative disease. DFS and OS at 4 years was 88% (95% CI, 77%–100%) and 92% (95% CI, 82%–100%), respectively.

Discussion and Conclusion

In this study we reported the doses to the target organ, the OARs, acute and late toxicities and the cosmesis in breast cancer patients post-BCS who were treated with accelerated hypofractionated locoregional RT schedule of 34 Gy/10#/2 week (3.4 Gy/fraction) to the whole breast and 40 Gy (4 Gy/fraction) to the tumor area with SIB with VMAT technique in 12 days. Dose constraints were achieved in most patients with low rates of acute and late toxicities. There was no adverse cosmesis. Local control and survival were good with this schedule. Since grade 2 skin toxicity occurred in 5 (18.5%) patients, this treatment seems to be acceptable according to the assumption in null hypothesis for this study.

WBI dose fractionation has changed over the years. Use of SIB with hypofractionation is investigational. In the present study we integrated boost with accelerated hypofractionation and completed treatment in 2 weeks only. With changes in hypofractionation schedules in breast cancer we have to look for OARs constraints, which can be achieved with a particular dose fractionation sched-

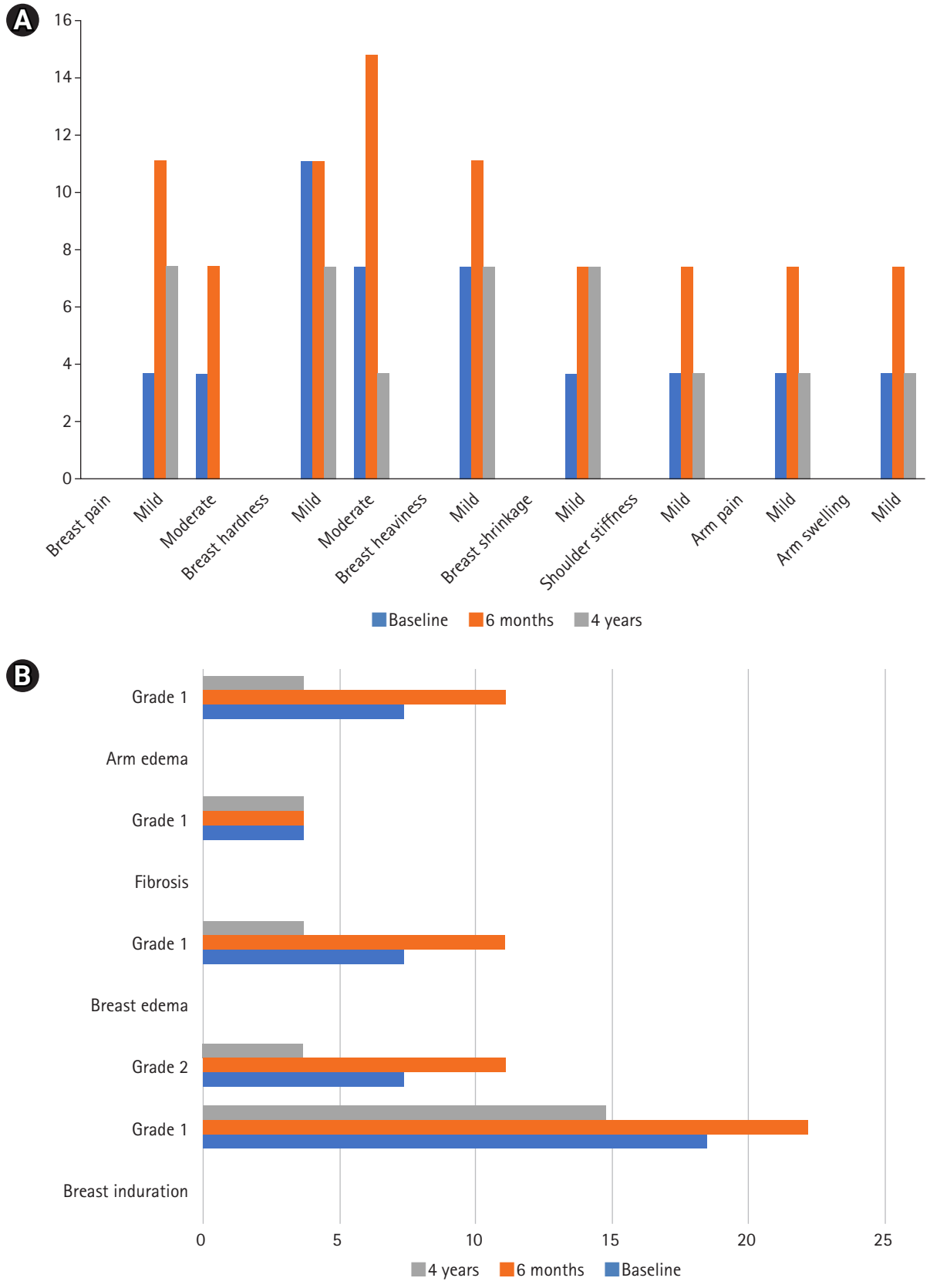

Fig. 2. Late toxicity. (A) patient reported (rates along the X-axis). (B) Physician observed (rates along the X-axis).

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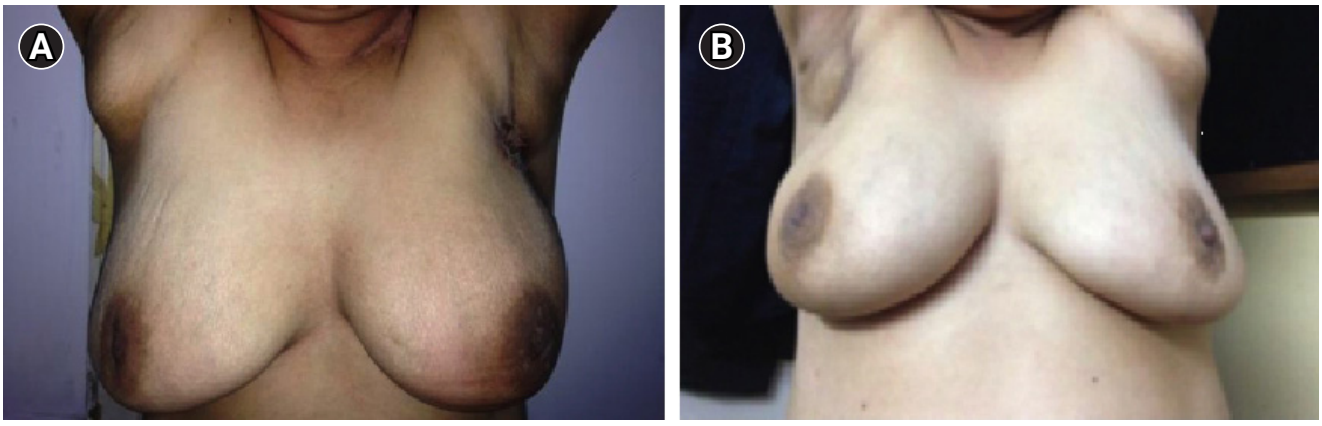

Fig. 3. Excellent cosmesis at baseline (A) and at 4 years (B).

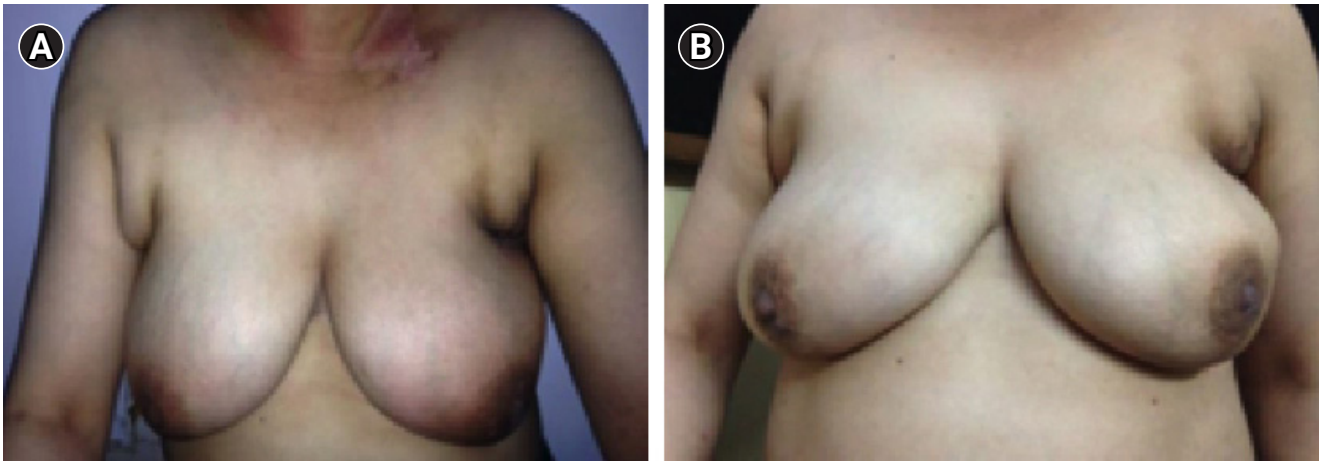

Fig. 4. Good cosmesis at baseline (A) and at 4 years (B).

ule. We modified dosimetric constraints for the lung to V_{16} and heart to V_{18}, which would be biologically equivalent to V_{20} and V_{25} that of the conventional schedule, respectively. We achieved dose constraints to the OARs such as lungs, heart (high dose volume), contralateral breast and oesophagus in >80% of patients (Table 2). MLD was slightly higher with SCF treatment (10.08 Gy vs. 9.22 Gy). There was no impact of SCF treatment on the MHD. One of the observations of our study was that dose to the thyroid could be reduced significantly with head rotation (Table 3).

Our results are quite consistent with the studies published in the literature (Table 5) in terms of acute toxicity, cosmetic outcomes, local control, DFS and OS. Acute grade 2 toxicity in the reported studies ranged from 4%–43%, and upper limit of 95% CI of our study 35%, lie well within this range. De Rose et al. [7] reported a phase II trial of hypofractionated RT with VMAT in 787 patients with early breast cancer with a dose of 40.5 Gy to whole breast and 48 Gy to the tumor bed in 15 fractions over 3 weeks with VMAT. Grade 1 and 2 acute toxicity was observed in only 51% and 9.7% patients, respectively. At a median follow-up of 45 months, grade 1 toxicity was 13.5% and 4 patients had distant relapse. Cosmetic outcomes were excellent/good in 100% patients. In our study, grade 1 acute toxicity was less than those reported by De Rose et al. [7], perhaps because of the lower total dose delivered in our study.

We did not observe any late grade 3 toxicities. In the study by Freedman et al. [8], higher grade 2 toxicity could be because of delivery of higher total dose (56 Gy). However, local control was comparable to our study. Bantema-Joppe et al. [19,20] reported cosmetic outcomes with 8.5% grade 2 fibrosis in the boost area, chest wall pain in 6.7% patients, and telangiectasia grade ≥2 in 3.7% patients at a median follow-up of 30 months. All-grade fibrosis outside the tumor bed was observed in 50% of patients. Higher fibrosis, chest wall pain and telangiectasia rate could be because of a high total dose delivered (64.4–67.2 Gy) in their study. We did not observe any telangiectasia or chest wall pain in our study. So, the present schedule may be better in terms of toxicities and cos-

Table 5. Studies with hypofractionated SIB in breast cancer

Study	n	Dose fractionation (Gy/fx)		Acute skin toxicity, Grade 2 (%)	Cosmesis, excellent/good (%)	Local control (%)
		Whole breast	SIB			
Franco et al. [6]	82	45/20	50/20	6	91	97
De Rose et al. [7]	787	40.5/15	48/15	9.7	100	99
Freedman et al. [8]	74	45/20	56/20	23	77	97
Chadha et al. [10]	74	40/15	45/15	4	NR	99
Formenti et al. [11]	91	40.5/15	48/15	8.1	96	98
Bantema-Joppe et al. [19,20]	940	50.4/28	64.4–67.2/28	NR	91.5	98.9
Krug et al. [49]	149	40/15	48/15	14.7	91	NR
Cante et al. [50,51]	465	45/20	50/20	NR	95.7	100
McDonald et al. [52]	354	45/25	59.92/28	43	96.5	97
Present study	27	34/10	40/10	18.5	100	96.5

SIB, simultaneous integrated boost; NR, not reported.

metic outcomes with comparable local control, DFS and OS.

MHD dose in the current study was 7.25 Gy, which was because of the partial arcs used for radiation planning. This MHD may not be acceptable currently because of the risk of late-term cardiac complications. In a study by Darby et al. [21], they reported that the rate of major coronary events increased by 7.4% for each 1 Gy increase in MHD. They also demonstrated a threshold MHD of 3 Gy, implying an attributable absolute increased cardiac mortality of 0.5%–0.7% for women < 50 years depending on number of cardiac risk factors. As per their observations MHD was a better predictor of coronary events than the mean LAD dose and these events started within 5-years of treatment. However, their study was from 2D era based on average anatomy and lacked individual dosimetric information hence its ramifications remain unresolved. So far, we have not observed any coronary event in our patients. Recently, we published our results at 5-year with this schedule with 2D technique. We did not encounter excess late arm/shoulder and cardiac toxicity, although 5-year may not be adequate to report cardiac toxicities [22]. MHD of 7.25 Gy in the current study was higher so the risk of coronary events in future cannot be ruled out. Earlier studies have also reported that VMAT increases MLD, MHD and dose to the opposite breast [23]. Considering this risk with partial arc VMAT, 3D-CRT with deep inspiration breath hold, inverse planned fixed field IMRT, treatment in prone position, hybrid techniques of combining tangential IMRT with VMAT and proton therapy may be more appropriate in achieving lower MHD and doses to other OARs [24-26]. IMRT has been shown to improve target coverage and reduce dose to the OARs [24]. Taylor et al. [27] in another population-based study calculated the absolute risk of mortality from lung cancer at 5 Gy MLD and ischemic heart disease at 4 Gy MHD after breast RT for smokers and non-smokers to be 4.4% and 0.3%, and 1.2% and 0.3%, respectively. However, all these doses were estimated retrospectively. In a recent study Merzenich et al. [28] reported that average MHD of 4.6 Gy for left-sided breast RT and only pre-exiting cardiac disease was associated with risk of cardiac death. While another study reported V_{25} and V_{30} to be detrimental to the heart [29]. So, it is not only the RT dose but co-morbidities and lifestyle also play a significant role in late effects on the heart in patients with breast cancer.

In our previous study with 3D-CRT in patients with left-sided breast cancer postmastectomy; MHD, LAD, proximal LAD, and distal LAD doses were 3.36 Gy, 16.06 Gy, 2.7 Gy, and 27.5 Gy, respectively. Left MLD, V_{10}, and V_{20} were 5.96 Gy, 14%, and 12.4%, respectively. Mean dose to the right lung and the opposite breast was 0.29 Gy and 0.54 Gy, respectively. V_{25} for heart was 4.25% [30]. In another study with 3D-CRT in left-sided patients with BCS, MHD in the supine and prone positions was 4.55 Gy and 2.06 Gy ($p = 0.02$), respectively. MLD in the supine and prone positions was 6.58 Gy and 0.85 Gy ($p = 0.001$), respectively [31]. All these doses are quite low as compared to the current study. Deep inspiration breath-hold (DIBH) reduces heart volume in the RT field, hence it lead to reduction in all dose parameters (mean, maximum and volume based) of the heart [32,33]. It has been shown to reduce cardiac mortality by 4.7% compared to free breathing, with normal tissue complication probability of 0.1% in patients with left-sided breast cancer [34]. Because of changes in dose fractionation (from conventional to hypofractionation) and techniques of RT for breast cancer (from 2D to 3D-CRT/FIF IMRT); dose constraints to be placed for the heart, LAD and lungs and its impact on the cardiac related morbidity and mortality still remains unclear. Although MHD has been the gold standard for prediction of late cardiac effects in the past but recent studies have suggested that reporting doses to the heart substructures such as apical part of left ventricle and LAD may be more relevant [35,36]. Hypofractionation have been reported to result in

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lower EQD_2 to the heart as compared to conventional fractionation and comparable late effects [37,38]. However, till data comes clear on these aspects, patients with left-sided breast cancer should be offered techniques, which reduce dose to the heart and lungs.

Second cancers after breast radiation are also a possibility with VMAT because of low dose to larger volume of OARs. In the present study 50% volume of the contralateral lung received 2 Gy, so it may put this OAR for second cancer. Hall and Wuu [39] in their study estimated 1% to 1.75% increase in the incidence of second cancers after 3D-CRT and IMRT at 10 years. VMAT technique was also reported to increase this risk in one study [24], where as it was comparable in another study for the contralateral breast and lung, but less risk for the ipsilateral lung because of reduced MLD with VMAT [40]. In a recent review, it was observed that VMAT increases contralateral lung V_5 by 25% as compared to other techniques [41]. In our study contralateral lung V_5 was lower as compared to other studies. This reduction in V_5 is associated with reduction in secondary cancer [40,41]. Since, ipsilateral MLD, contralateral lung V_5 and breast mean doses in our study are comparable to those observed by Zhang et al. [42], we may expect similar risk of second cancers in our patients. However, this risk may vary with distance of the organ from the sternum, patient anatomy, dose optimization, set up errors, organ motion [42] and smoking [27]. In our past series we have reported second cancers in the contralateral breast, oesophagus and lung cancers in 3.3%, 0.22% and 0.05% patients, respectively [30].

Many dosimetric studies have explored the potential benefits of integrating boost with WBI, but the majority of them are with conventional fractionation [43-47]. A multicentric study of 151 patients by Dellas et al. [48] from Germany with RT dose of 40 Gy in 16 fractions for WBI and a SIB with 0.5 Gy/fraction to the primary area, reported that SIB was feasible with hypofractionation. A few studies have integrated boost with moderate hypofractionation and treatment completed in 3–4 weeks [6-11,49-51] and 5–6 weeks in others [19,52]. Ours is the first study to report feasibility of accelerated hypofractionation with SIB in 12 days.

There are a few limitations of our study. The number of patients enrolled was less, because of the study design. Median follow-up of 51 months is modest; therefore, late toxicities and long-term clinical outcomes need to be further assessed as accelerated hypofractionation regimen with a dose of 3.4 Gy/fraction to the breast and 4 Gy/fraction to the tumor bed may lead to late radiobiological consequences, although the likely risk is less because the total dose delivered was 40 Gy with one of the optimal techniques of RT. Low doses to lungs and contralateral breast may also not favor VMAT technique but these can be further reduced by using tangential VMAT or hybrid VMAT. Lastly, it is an expensive technique and one of ASTRO Choosing Wisely Campaign initiatives is "Don't routinely use IMRT to deliver whole breast radiotherapy as part of breast conservation therapy" [53].

With high dose per fraction, we could reduce overall treatment time to 12 days only. It increased treatment compliance because of less acute toxicities. It reduced treatment cost to the patient with increased convenience by reducing the number of hospital visits. It also has potential to reduce risk of local recurrence with acceptable toxicities in the breast because of its low α/β ratio. Therefore, the implication of this study is, reduction of total treatment time from 4 weeks to 2 weeks and reduction in the waiting time for the other patients.

To conclude, this study demonstrated that accelerated hypofractionated RT with SIB boost is feasible and safe in terms of acute and late breast and arm toxicities. Radiation induced heart disease and stochastic effects might be a concern with higher MHD and low dose bath with this technique. VMAT plans may be used when conformal techniques are not able to achieve the desired dosimetric constraints. A phase III randomized controlled trial with same fractionation schedule with 2D/3D-CRT and DIBH techniques (HRBC; NCT04075058) is ongoing and has completed patient accrual.

Statement of Ethics

Institutional Ethics Committee approval was taken. Informed consent was taken from all the patients.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Research Methodology, BSY, SG, DD. Planning and treatment, BSY, SG, AG, AOS. Patient contribution, DD. Analysis, BSY, SG, AG. Manuscript writing, BSY, SG.

Data Availability Statement

Data will be provided on suitable request.

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