Accelerated Hypofractionated Radiotherapy With Simultaneous Integrated Boost With Volumetric Modulated Arc Technique in Patients With Breast Cancer: a Phase 2 Study.

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Research Article

Keywords: Breast cancer, accelerated hypofractionation, volumetric modulated arc technique

Posted Date: June 7th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-542950/v1

Abstract

Purpose

To assess feasibility of accelerated hypofractionated radiotherapy with simultaneous integrated boost (SIB) with volumetric modulated arc technique (VMAT) in patients with breast cancer.

Methods

Total 27 patients after breast conserving surgery (BCS) were included in this study. Patients were planned on 4-dimensional computerized tomogram (4D-CT) and contouring was done using RTOG guidelines. Dose delivered was 34 Gy/10#/2wk to the breast and 40 Gy/10#/2wk to the tumor bed as SIB with VMAT 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) was calculated with Kaplan Meier curves.

Results

Mean age of the patients was 42 years. Left and right breast cancer was seen in 17 (63%) and 10 (37%) patients, respectively. Ipsilateral lung mean V16 and contralateral lung V5 was 16.01% and 3.73%, respectively. Mean heart dose from the left and right breast was 7.25Gy and 4.37Gy, respectively. Mean dose to the contralateral breast, oesophagus and spinal cord was 2.64Gy, 3.69Gy and 3.15Gy, respectively. Thyroid V25 mean was 19.69%.

Grade 1 and 2 acute skin toxicity was 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 each. Median follow-up was 48 months (range 12-58 months). At 4 years breast induration, edema and fibrosis each 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 1(3.7%) and 2(7.4%) patients, respectively. DFS and OS at 3-years was 88% and 92%, respectively.

Conclusion

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

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 2-dimensional (2D), 3-dimensional conformal RT(3D-CRT) with or without deep inspiration breath hold, field-in-field intensity modulated RT(FF IMRT), inverse planning IMRT, tomotherapy, image guided RT(IGRT) and proton therapy. Many BCS patients may benefit from a boost to the primary site to prevent recurrences that occurs within 2cm of the primary tumor location[2]. RT contributes by sterilizing the microscopic disease thus reducing the risk of local recurrence[3,4]. 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 radiotherapy. However, for a patient who may benefit from boost, simultaneous integrated boost (SIB) can be one of the techniques for its delivery. It achieves dose conformity, homogeneity and completes the treatment fast in one plan only. If it is planned with volumetric-modulated arc therapy (VMAT), the treatment delivery is fast, and planning on 4D-CTcan improve its localization and onboard imaging can increase the accuracy of the delivery. Tumor bed boost has been shown to be associated with increased acute and late toxicity[5,6]. 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[7-11]. SIB with accelerated hypofractionation can further reduce treatment duration from 3 weeks to 2 weeks.

In this study, 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).

Methods

This prospective phase II study was conducted in the Department of Radiation Oncology, Regional Cancer Centre, XXXX, XXXX. 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.

Patient selection

Patients who had undergone BCS were included in this study. Institutional Ethics Committee approval was taken. Informed consent was taken from all the patients. The trial was registered with clinicaltrials.gov no. XXXX. Inclusion criteria were: primary cancer of breast of any histology, age >18-70 years, post BCS with clear margins, healed scar**,** Karnofsky performance status (KPS) >70, regional nodal radiation when indicated(depending on risk factors) and no distant metastasis. 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.

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 90^0 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 computerized tomogram (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 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, esophagus, spinal cord, left anterior descending artery and thyroid.

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

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 clips location. ITV was generated by contouring tumor bed in all phases of respiratory cycles on 4D-CT. All delineation was done on MIP images. A margin of 5mm was added to the cavity to form PTV BOOST SIB. A dose of 34 Gy/10#/2wk to the PTV TOTAL and 40 Gy/10#/2wk to the PTV SIB BOOST was delivered with IGRT using the RapidArc® technique. Partial arcs were used for RT planning. Dose distribution and target coverage criteria for PTV TOTAL and PTV SIB 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[12-14].

Dose constraints given were; ipsilateral mean lung dose (MLD) ≤10Gy, V16Gy < 20% and contralateral lung V5 <5%. Mean heart dose (MHD) <7Gy, V18 <5% for left side and <1% for the right side. LAD Dmax and Dmean <15Gy and <8Gy, respectively from left breast. Contralateral breast Dmean <3Gy. Thyroid V25 and V30 should be <50% and <25%, respectively. Dmax and Dmean for oesophagus 20Gy and <5Gy, respectively. Dmax for the spinal cord and brachial plexus should be <30Gy and <40Gy, respectively.

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

Assessments

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 1 month of completion of. 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 Radiation Therapy Oncology Group (RTOG) and Late Effects on Normal Tissues (LENT)/Subjective, Objective, Management and Analytic (SOMA) grading scale. Acute toxicities are reported at 1 and 3 month of completion of radiotherapy. Late effects are reported at 6 months and 4 years follow up.

Cosmesis: Cosmetic effects were assessed in the treated breast and compared with the opposite breast and also with the baseline photographic evaluation. Both objective and subjective parameters were used. The Harvard/NSABP/RTOG scale proposed by Harris et al. was used to evaluate the cosmetic parameters[15]. Variability in both objective and subjective assessment was evaluated. Changes in terms of colour, 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.

For cosmesis, both subjective (hyperpigmentation, change in shape, change in size, nipple changes, heaviness, pain) and objective (skin reaction, overall grade, edema, induration, subcutaneous fibrosis, tenderness, scar changes and any other skin changes/ulceration) response was considered. All the parameters were noticed for any change with time and graded upon accordingly.

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.

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:

- 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 ³ 36% against H_A: r £ 11%, where r is the proportion of patients with grade 2 skin toxicity
- The type I error rate (a, probability of accepting an overly toxic treatment, a false positive outcome) was set to 5%
- 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's exact test, the design consists of treating 27 evaluable patients, and

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

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

Results

Patient characteristics

Between July 2016 to June 2017, 27 patients were treated. Mean age of the patients was 42 years (range 36-67 years). Left and right breast cancer was seen in 17 (63%) and 10 (37%) patients, respectively. The majority of 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 3 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. 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.

Dosimetry

Mean PTV and boost volume were 1099.8±512.9 cc and 66.0±44.3 cc, respectively. The mean CI for the PTV and boost was 0.90±0 and 0.93±0.2, respectively. HI for the PTV and boost was 0.31±0.1 and 0.11±0.1, respectively. Dmax to PTV boost was 43.2±1.5Gy. PTV and boost V107% and V105% were 2.97±8.81cc and 0.46±0.74 cc; 3.2±4.6 cc and 0.66±0.82 cc, respectively.

Ipsilateral MLD was 9.86Gy(range 7.12Gy-13.72Gy). Ipsilateral lung mean V16 was 16.01%(2.12-27.42%) and contralateral lung mean V5 and V2 was 3.74%(0.77-11.33%) and 52.62%(12.31-97.90%), respectively. MLD with and without SCF radiotherapy was 10.08Gy(range 7.13Gy-13.72Gy) (n = 20) and 9.22Gy(range 7.12Gy-11.50Gy) (n = 7), respectively. MHD was 7.25Gy(4.31Gy-10.85Gy) from the left breast and 4.37Gy(range 2.32Gy-7.13Gy) from the right breast. In patients with left breast cancer (n =17), MHD with and without SCF treatment was 7.25Gy (n = 12) and 6.6Gy (n = 5), respectively. Mean V18 and V15 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. Dmax to LAD from left breast was 14.24Gy(8.9-27.86Gy). Mean LAD dose from the left and right breast was 7.74Gy(4.42-21.26Gy) and 3.32Gy(1.41-6.72Gy), respectively. Mean dose to the contralateral breast, oesophagus and spinal cord was 2.64Gy(1.53-4.16Gy), 3.69Gy(1.55-9.02Gy) and 3.15Gy(0.84-18.65Gy), respectively. Dmax to the oesophagus was 15.65Gy(4.48-32.8Gy). Mean of Dmax to spinal cord and brachial plexus was 10.43Gy(2.32-28.40Gy) and 26.95Gy(6.72-38.42Gy), respectively. Thyroid V25 and V30 mean were 19.69%(range 0-52.97%) and 11.83%(range 0-36.90%), respectively (Table 2).

Dose constraints for MLD ≤10Gy, ipsilateral lung V16 <20% and contralateral lung V5 <5% were achieved in 70.37%, 81.48% and 92.59% of patients, respectively (Table 2). MHD from left breast cancer <8Gy was achieved in 94.11% patients. Heart V18 <5% for left side and <1% for the right side were achieved in 88.24% and 90% of patients, respectively. LAD Dmax(<15Gy) for left breast was achieved in 82.35% patients. LAD Dmax <8Gy from left breast and <5Gy from right breast were achieved in 88.24% and 80% of patients, respectively. Contralateral breast Dmean <3Gy) was achieved in 77.78% of patients. Thyroid V25 and V30 <25% and <50%, respectively were achieved in 70.27% and 88.89% of patients, respectively. Oesophagus Dmax (<18Gy) and Dmean (<5Gy) were achieved and 85.19% and 70.03% of patients, respectively. Average of Dmax was higher in patients who received SCF radiation(18.66Gy) as compared to those who did not(7.0Gy). Spinal cord Dmean (<5Gy) and Dmax (<30Gy) 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 11.00Gy (95% CI 6.67-15.32) and 22.68Gy (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 ($p<0.0001$).

Acute Toxicity

Grade 1 and 2 acute skin toxicity was observed in 9 (33%) and 5 (18.5%) patients, respectively(Table 4). Acute grade 2 skin toxicity in patients with and without nodal radiotherapy was 1(14.2%) and 4(20%), respectively. 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.

All of the secondary toxicities at 1 month also met the predefined 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 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. Dmax to the oesophagus in this patient was 32.8Gy.

Late toxicity

Late toxicities were either grade 1 or 2(Table 5). 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 4^{th} 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 4^{th} 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(Table 5).

Cosmesis

Physician/patient observed cosmesis was excellent and good in 21(78%)/19(70%) and 6(22%)/8(30%) patients, respectively(Figures 1 and 2). None of the patients had adverse cosmesis. None of the parameters such as V107%, V105%, breast size and boost volume were related with late effects or cosmesis.

Outcomes

At a median follow-up of 48 months (range 12-58 months), local recurrence occurred in 1 (3.7%) patient. Distant metastases were seen in 2 (7.4%) patients. DFS and OS at 4 years was 88% (95% CI 77% - 100%) and 92% (95% CI 82% - 100%), respectively.

Discussion

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 loco-regional RT schedule of 34Gy/10#/2week (3.4Gy/fraction) to the whole breast and 40Gy (4Gy/fraction) to the tumor area with SIB with VMAT technique in 12 days. Dose constraints were achieved in the majority of 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 is acceptable according to the assumption in null hypothesis for this study.

WBI dose fractionation has changed over the years. We modified dosimetric constraints for the lung to V16 and heart to V18, which would be biologically equivalent to V20 and V25 of the conventional schedule, respectively. MHD dose in the current study was 7.25Gy, which may be because of the partial arcs, which were used for planning. This MHD may not be acceptable currently because of the risk of late-

term cardiac complications. In a study by Darby et al. they reported that the rate of major coronary events increased by 7.4% for each 1Gy increase in MHD. They also demonstrated a threshold MHD of 3 Gy, implying an attributable absolute increased cardiac mortality of 0.5 to 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[16]. However, their study was from 2D era based on average anatomy and lacked individual dosimetric information hence its ramifications remains unresolved. 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[17]. MHD of 7.25Gy in the current study is higher so there might be a risk of coronary events in the future. Earlier studies have also reported that VMAT increases MLD, MHD and dose to the opposite breast[18]. Considering this risk 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[19-21]. IMRT has been shown to improve target coverage and reduce dose to the OARs[19]. Taylor et al. in another population-based study calculated the absolute risk of mortality from lung cancer at 5Gy MLD and ischemic heart disease at 4Gy MHD after breast RT for smokers and non-smokers to be 0.3% and 4.4%; and 0.3% and 1.2%, respectively. However, these doses were estimated retrospectively[22]. In a recent study Merzenich et al. reported that average MHD of 4.6Gy for left-sided breast RT and only pre-exiting cardiac disease was associated with risk of cardiac death[23]. While another study reported V25 and V30 to be detrimental to the heart[24].

In our previous study with 3D-CRT in patients with left-sided breast cancer postmastectomy; MHD, LAD, proximal LAD, and distal LAD doses were 3.364 Gy, 16.06 Gy, 2.7 Gy, and 27.5 Gy, respectively. Left MLD, V10, and V20 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. V25 for heart was 4.25%[25]. 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[26]. All these doses are quite low as compared to the current study. DIBH reduces cardiac volume in the RT field, hence it lead to reduction in all dose parameters(mean, maximum and volume based) of the heart[27,28]. It has been shown to reduce cardiac mortality by 4.7% compared to free breathing with median cardiac mortality normal tissue complication probability of 0.1% in patients left-sided breast cancer[29]. Because of changes in dose fractionation (from conventional to hypofractionation) and techniques of RT for breast cancer(from 2D to 3D-CRT/FIF IMRT), it still remains unclear what dose constraints to be placed for heart, LAD and lungs; and how is it going affect the cardiac related mortality? Although MHD has been the gold standard for prediction of late cardiac effects in the past studies but recent studies have suggested that reporting doses to the heart substructures such as apical part of left ventricle and LAD may be of relevance[30,31] Hypofractionation may result in lower equivalent doses (EQD2) to the heart as compared to conventional fractionation and comparable late effects[32,33]. However, till data comes clear on these aspects, patients with left-sided breast cancer should be offered techniques, which reduces 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% of the contralateral lung received 2 Gy, so it may put this OAR for second cancer. Hall et al. in their study estimated 1% to 1.75% increase in the incidence of second cancers after 3D-CRT and IMRT at 10 years[34]. VMAT technique was also reported to increase this risk in one study[19] where as it was comparable in another for the contralateral breast and lung, but less risk in the ipsilateral lung because of reduced MLD with VMAT[35]. In a recent review, it was observed that VMAT increases contralateral lung V5 by 25% as compared to other techniques[36]. In our study contralateral lung V5 of 3.74% is still lower as compared to other studies. This reduction in V5 is associated with reduction in secondary cancer[35,36] Since, ipsilateral MLD, contralateral lung V5 and breast mean doses in our study are comparable to those observed by Zhang et al., 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[37] and smoking[22]. 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[25].

Many dosimetric studies have explored the potential benefits of integrating boost with WBI, but the majority of them are with conventional fractionation[38-42]. There are few studies where boost has been integrated with moderate hypofractionation and treatment completed in 3-4 weeks[7-11, 43-45]. and 5-6 weeks in others[47,50]. A multicentric study of 151 patients by Dellas et al. from Germany with RT dose of 40Gy in 16 fractions for WBI and a SIB with 0.5Gy/fraction to the primary area, reported that dose constraints could be achieved and SIB was feasible with hypofractionation[42].

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 schedule. In our study we achieved dose constraints to the OARs such as lungs, heart(high dose volume), contralateral breast and oesophagus in >80% of patients, except for the MLD, MHD, mean dose to contralateral breast (<3Gy) and V30 (<25%) to the thyroid that could be achieved in 70%, 59%, 77% and 70% of patients, respectively (Table 2). MLD was slightly higher with SCF treatment (10.08Gy vs 9.22Gy). 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. Dose to the thyroid was 7.84Gy and 34.73Gy($p<0.0001$) with and without head rotation, respectively (Table 3).

De Rose et al. reported a phase II trial of hypofractionated RT with VMAT in 787 patients with early breast cancer with a dose of 40.5Gy to whole breast and 48Gy 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[8]. In our study, grade 1 acute toxicity was less than those reported by De Rose et al., perhaps because of the lower total dose used in our study. We also observed only one local recurrence and two distant metastases at a median follow-up of 48 months. Both patients with distant metastases had triple negative disease. Our results are quite consistent with the

studies published in the literature (Table 6) in terms of acute toxicity, cosmetic outcomes, local control, DFS and OS. Acute grade 2 toxicity in these studies ranged from 4%-43%, and upper limit of 95% CI of our study 35%, lie well within this range. Higher grade 2 toxicity in the study by Freedman et al. could be because of delivery of higher total dose (56Gy)[9]. However, local control was comparable to our study. We did not observe any late grade 3 toxicities. At 4-years, loco-regional control and excellent/good cosmesis of 96.5% and 100% in our study are also comparable to those reported in literature (97%-100%) and (77%-100%), respectively (Table 6). Joppe et al. 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[47-50]. 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 cosmetic outcomes. In our study the treatment was completed in 12 days only with a similar toxicity profile, cosmetic outcomes and comparable local control, DFS and OS.

There are a few limitations to our study. The number of patients enrolled was less, because of the study design. Median follow-up of 48 months is modest; therefore; late toxicities and prolonged clinical outcomes need to be further assessed since we have delivered accelerated hypofractionation regimen with a dose of 3.4Gy/fraction to the breast and 4Gy/fraction to the tumor bed which may lead to late radiobiological consequences, although the likely risk is less because of the total delivered dose (40Gy) with one of the optimal techniques of RT. Low doses to lungs and contralateral breast may also not favor VMAT implementation 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”[51].

This study has shown comparable results with the previous studies(Table 6). Since the higher dose per fraction was used, the overall treatment time was reduced to only 12 days. It helped in increasing treatment compliance of the patients because of less acute toxicity. It also helped in reducing cost to the patient with increased convenience by reducing the number of hospital visits and 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 radiotherapy with SIB boost is feasible and safe in terms of acute and late breast 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 (XXXX; NCT XXXX) is on going and has completed patient accrual.

Declarations

Funding: NA

Conflicts of interest/Competing interests : none

Availability of data and material: data will be made available through suitable request

Code availability: N/A

Authors' contributions:

Research Methodology: BSY, SG, DD

Planning and treatment: BSY, SG, AG, AOS

Patient contribution: DD

Analysis: BSY, SG, AG

Manuscript writing: BSY, SG

Approval: All the authors

Ethics approval: Taken (include appropriate approvals or waivers)

Consent to participate: informed consent taken from all the patients

Consent for publication: Taken

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51. ASTRO - IMRT for whole breast radiotherapy | Choosing Wisely

Tables

Table 1. Patient characteristics

Characteristics	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)
Her2neu	
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(96)

Table 2. Doses to the organs at risk and constraints achieved (n/N)

Organ at risk	Dose constraint	N	Mean ± SD	Constraint achieved	
				n	%
Mean lung dose	≤10Gy	27	9.86 ± 1.86	19	70.37
Ipsilateral lung V20Gy	≤10%	27	8.88 ± 4.29	21	77.78
Ipsilateral lung V16Gy	<20%	27	16.01 ± 4.29	22	81.48
Ipsilateral lung V10Gy	-	27	39.60 ± 14.21	-	-
Contralateral lung V5Gy	<5%	27	3.74 ± 3.56	22	81.48
Contralateral lung V2Gy	-	27	52.62±19.21	-	-
Heart Dmean (Left breast)	<7Gy	17	7.25 ± 1.82	10	58.82
Heart V18Gy (Left breast)	<5%	17	2.88 ± 2.42	15	88.24
Heart V18Gy (Right breast)	<1%	10	0.33 ± 0.55	9	90.00
LAD Dmax (Left breast)	<15Gy	17	14.24±3.42	14	82.35
LAD Dmean (Left breast)	<8Gy	17	7.74 ± 3.77	15	88.24
LAD Dmean (Right breast)	<3Gy	10	3.32 ± 1.81	8	80.00
Contralateral breast Dmean	<3Gy	27	2.64 ±0.62	21	77.78
Thyroid V30	<25%	27	11.83± 14.85	19	70.37
Thyroid V25	<50%	27	19.69± 21.23	24	88.89
Esophagus Dmax	< 20Gy	27	15.65 ± 4.62	19	70.37
Esophagus Dmean	< 5Gy	27	3.69 ± 1.58	23	85.19
Spinal cord Dmax	< 30Gy	27	-	27	100.00
Brachial plexus Dmax	< 40Gy	27	-	27	100.00

Table 3. Thyroid mean dose with head position and ± SCF treatment

Group	n	Mean dose±SD	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	

Table 4. Acute toxicities at 1 and 3 months after radiotherapy

Toxicity	1 month		3 month	
Physician reported	n (%)	Upper limit of one-sided 95% CI	n (%)	Upper limit of one-sided 95% CI
Skin (grade 2)	5 (18.5)	35	2 (7.4)	22
Hyperpigmentation (grade 2)	1 (3.7)	16	3 (11.1)	27
Edema (grade 2)	2 (7.4)	22	1 (3.7)	16
Induration (grade 2)	4 (14.8)	31	5 (18.5)	35
Patient reported				
Swelling (mild)	2 (7.4)	22	1 (3.7)	16
Heaviness (mild)	4 (14.8)	31	2 (7.4)	22
Pain (mild)	8 (29.6)	47	4 (14.8)	31
Pain during swallowing				
Mild	1 (3.7)	16	-	-

Table 5. Late toxicities

Toxicity	Baseline		At 6 months		At 4 years	
Physcian reported	n (%)	Upper limit of one-sided 95% CI	n (%)	Upper limit of one-sided 95% CI	n (%)	Upper limit of one-sided 95% CI
Breast induration						
Grade 1	5 (18.5)	35	6 (22.2)	39	4 (14.8)	31
Grade 2	2 (7.4)	22	3 (11.1)	27	1 (3.7)	16
Breast Edema						
Grade 1	2 (7.4)	22	3 (11.1)	27	1 (3.7)	16
Fibrosis						
Grade 1	1 (3.7)	16	1 (3.7)	16	1 (3.7)	16
Arm Edema						
Grade 1	2 (7.4)	22	3 (11.1)	27	1 (3.7)	16
Patient reported						
Breast Pain						
Mild	1 (3.7)	16	3 (11.1)	27	2 (7.4)	22
Moderate	1 (3.7)	16	2 (7.4)	22	-	-
Breast hardness						
Mild	3 (11.1)	27	3 (11.1)	27	2 (7.4)	22
Moderate	2 (7.4)	22	4 (14.8)	31	1(3.7)	16
Breast heaviness						
Mild	2 (7.4)	22	3 (11.1)	27	2 (7.4)	22
Breast shrinkage						
Mild	1 (3.7)	16	2 (7.4)	22	2 (7.4)	22
Shoulder						

stiffness	1 (3.7)	16	2 (7.4)	22	1 (3.7)	16
Mild						
Arm pain						
Mild	1 (3.7)	16	2 (7.4)	22	1 (3.7)	16
Arm sweling						
Mild	1 (3.7)	16	2 (7.4)	22	1 (3.7)	16

Table 6. Studies with hypofractionated SIB in breast cancer

Study	N	Dose fractionation		Acute Skin toxicity (Grade 2)	Cosmesis (Excellent/good)	Local control
		Whole breast	SIB			
Franco et al.[7]	82	45Gy/20#	50Gy/20#	6%	91%	97%
De Rose et al.[8]	787	40.5Gy/15#	48Gy/15#	9.7%	100%	99%
Freedman et al.[9]	74	45Gy/20#	56Gy/20#	23%	77%	97%
Chadha et al.[10]	74	40Gy/15#	45Gy/15#	4%	NR	99%
Formenti et al.[11]	91	40.5Gy/15#	48Gy/15#	8.1%	96%	98%
Krug et al.[43]	149	40Gy/15#	48Gy/15#	14.7%	91%	NR
Cante et al.[44,45]	465	45Gy/20#	50Gy/20#	NR	95.7%	100%
Joppe et al.[46-48]	940	50.4Gy/28#	64.4–67.2 Gy/28#	NR	91.5%	98.9%
McDonald et al.[49]	354	45Gy/25#	59.92Gy/28#	43%	96.5%	97%
Present study	27	34Gy/10#	40Gy/10#	18.5%	100%	96.5%

Figures

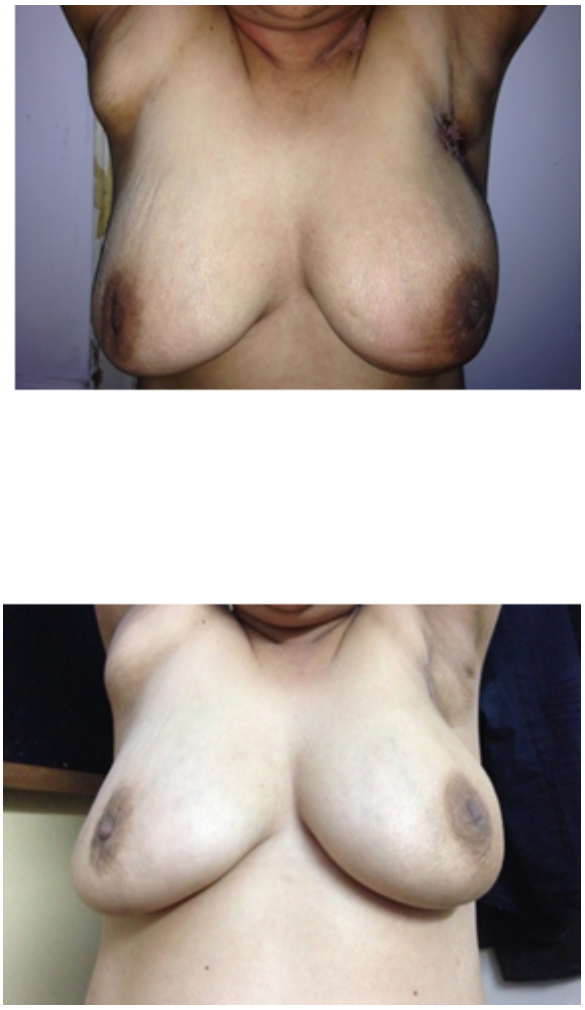
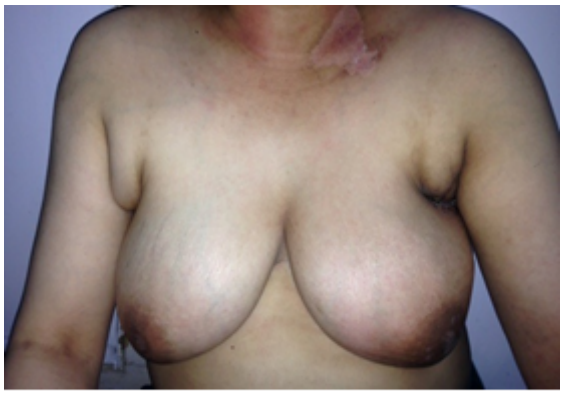


Figure 1

a. Excellent cosmesis at baseline b. Excellent cosmesis at 4 year



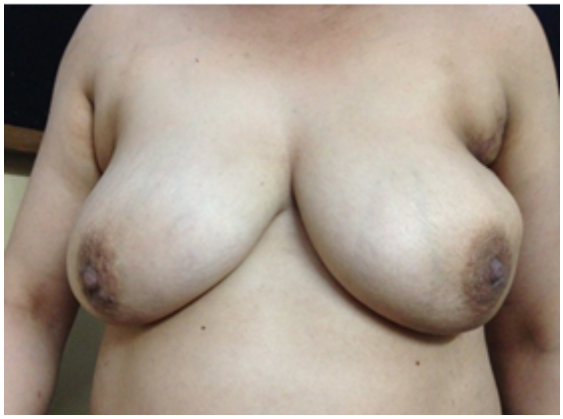


Figure 2

a. Good cosmesis at baseline b. Good cosmesis at 4 year