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Original Research Paper

Accelerated hypo-fractionated Whole Breast Radiotherapy by 3-Dimensional conformal field-in-field approach for simultaneous integration of boost: do we have an optimal planning solution that fits most?

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ABSTRACT:

Background: Compliance to Whole Breast(WB) Radiotherapy(RT) may be improved by shortening treatment duration using accelerated hypofractionated schedules. The current study evaluates clinical feasibility of hypofractionated WBRT with Simultaneous Integrated Boost (SIB) by 3Dimensional Conformal Radiotherapy(3DCRT) Field-in-Field (FIF) technique in terms of dosimetric acceptability, acute toxicities and cosmesis at 6 months. **Materials and Methods**: Female patients with early breast cancer were recruited post breast conserving surgery. WBRT was planned using 3DCRT -FIF technique with static multi-leaf collimators and 6 Mega Voltage(MV) photons. 40 Gray(Gy)/15 fractions at 2.67 Gy/fraction with SIB to tumor bed of 48Gy in 15 fractions at 3.2 Gy/fraction was delivered. Acute skin toxicity and cosmesis were documented. **Results**: Mean age of patients was 48 $\pm$ 2 years. 5/11 patients with right and 6/11 with left breast cancer. Mean Planning Target Volume (PTV)-WB V38(95%) = 94.98 $\pm$ 3.92 %. Dmax = 51.04 $\pm$ 0.99Gy (106%) was confined within boost volume. No isolated hot spots > 48 Gy were found in the breast outside boost volume. Conformity Index(CI) was 1.31$\pm$ 0.2, within the acceptable range of >0.95 and < 2.0. PTV-boost 45.6Gy(95%) = 98.34% $\pm$ 1.79%. Dose to Organs at Risk were within the acceptable limits. Assessment by Harvard Breast cosmesis criteria revealed grade 2 score for all patients except one patient whose score consistently remained grade 3 after surgery. **Conclusion**: WBRT with SIB by 3DCRT-FIF allows us to achieve acceptable dosimetric parameters, good cosmetic outcome and good patient compliance. This may be adapted in centres which lack advanced radiation facilities.

Key words: Whole Breast Radiotherapy, 3DCRT, Field-in-Field, Simultaneous Integrated Boost

INTRODUCTION:

Breast conservation therapy (BCT) for early breast cancers involves Breast conservation Surgery (BCS) followed by delivery of Whole Breast Radiotherapy (WBRT) with/without boost to the tumour bed. WBRT using conventional fractionation of 50Gy/25 Fractions stretches over 5 weeks followed by two weeks of boost RT by conventional fractionation. Such a protracted course of RT has often been deemed burdensome to patients with respect to travel time, distance, cost involved and loss of productivity. As a result, nearly 35% of patients who are eligible for BCS undergo mastectomy [1]. Only 65-80% of patients who undergo BCS receive adjuvant WBRT [2]. Compliance to radiotherapy may be improved if treatment duration can be safely shortened. Radiobiological superiority and clinical non-inferiority has been demonstrated for hypofractionated schedules vs conventional RT with respect to local recurrence free survival, breast cancer specific survival and overall survival [3-8]. Advanced RT techniques such as Intensity Modulated Radiotherapy (IMRT), Volumetric Modulated Arc therapy (VMAT) and Helical Tomotherapy (HT) have been suggested for adjuvant radiotherapy to the whole breast for better sparing of organs at risk. However, these remain largely expensive, not universally available and labour intensive in terms of requirement of experienced personnel and meticulous quality checks. The delivery of sequential boost by conventional fractionation extends the treatment time by 1-2weeks. It also compounds the cost of treatment by nearly 60% [9,10]. Patterns of practice data suggest underutilization of boost in combination with hypofractionated WBRT. This has led to evolution of several guidelines from several radiation oncology groups supporting use of boost radiation in specific subgroup of patients.

However, the role of hypofractionation for the boost phase, as well as the sequence for delivery of boost RT has been less commonly explored. By simultaneously integrating the boost (SIB) phase along with hypofractionated WBRT, the total treatment time can potentially be reduced to 3 weeks. Three-Dimensional conformal Radiotherapy(3DCRT) is still considered the safe standard which is most commonly available and being practised widely. 3DCRT with field in field technique [FIF] for whole breast radiotherapy along with SIB to tumor bed, has been demonstrated to be dosimetrically comparable to IMRT and VMAT plans, in terms of Planning target volume (PTV) coverage and safe in terms of doses delivered to organs at risk (OARs) like heart and lung [11]. The contralateral lung received 2.12 +/- 2.18 Gy with IMRT vs. 0.595 +/- 0.89 Gy with 3DCRT (p=0.008) [11]. There is a twofold reduction in monitor units delivered as well as the overall treatment time. Thus, harnessing the radio-biological benefit of hypofractionation with lower alpha/beta values of 3-4 for breast cancer [7,8] , we can integrate the tumor bed boost into the whole breast radiation treatment. The current study intends to evaluate the clinical feasibility of delivery of hypofractionated breast conserving radiotherapy with SIB by 3DCRT- FIF technique in terms of dosimetric acceptability, acute toxicities and cosmesis at 6 months. The implications of the results would be a simpler, more cost-effective and widely available technique to execute the current standard of care in resource constrained countries.

METHODOLOGY:

The current study was carried out in Department of Radiation Oncology of a Regional Cancer Centre in India during the period of 2019-2020 with 2020. Female patients between age 18 - 70 years with ECOG performance status 0-2 who have been diagnosed with early breast cancer (T1-2, N0-2) and undergone breast conserving surgery with axillary lymph node dissection were prospectively recruited for the current study. Patients aged > 70 years, tumor size > 4cm, those who have a prior history of receiving radiation to the thorax, those with pre-existing cardiac or respiratory co-morbidities were excluded. Ethical clearance was obtained from the institutional ethics committee; Informed consent was obtained from all patients prior to enrolment. Pulmonary and cardiac function were evaluated at baseline. Patients were simulated in the supine position with arms above the head. A radio-opaque marker was used to delineate the palpable breast tissue superiorly, inferiorly, medially and laterally as well as the lumpectomy scar. The scan extended from the mandible cranially to the 2nd lumbar vertebra with 0.5cm CT slices. Target Volume delineation was done according to the guidelines recommended by the European Organisation for Research and Treatment of Cancer (EORTC) [12]. The Boost Clinical Target Volume (CTV) was contoured using all clinical and radiological information available at the time of contouring, editing out the lungs, ribs and muscles as the tumour is not expected to infiltrate these structures based on given information. Surgical clips which were placed intraoperatively, aided the delineation of tumour bed. 10mm concentric expansion was used to generate the Boost Planning target volume (PTV-Boost). The Planning Target Volume for Whole Breast (PTV-WB) as well as the PTV-Boost were further cropped from the skin by 3mm [12,13]. 3DCRT-FIF technique with static multi-leaf collimators (MLC) was used for forward planning using 6MV photons. The FIF-3DCRT treatment plans were constructed with multileaf collimator (MLC) shielding and gantry angles of beams adjusted to provide optimal avoidance of OAR volumes. The PTV-Boost plans were similarly constructed, and manual optimization was performed by adjusting beam weight and MLC settings so as to encompass the 95% isodose and minimize hotspots of >107%. Treatment fields were designed with gantry angles ranged from 330° to 150° for left-sided tumors and from 50° to 200° for right-sided targets. An additional beam margin of 5 mm was used beyond whole breast PTV. WBRT of 40Gy in 15 fractions at 2.67 Gy/fraction (Biological Equivalent Dose (BED)-70.60Gy and 2 Gy Equivalent dose EQD_2- 44.92Gy) with SIB to tumor bed of 48Gy in 15 fractions at 3.2 Gy/fraction (BED- 91.88Gy and EQD_2-58.47Gy) was planned. The optimization objectives followed were as enlisted in Table 1. Portal images were obtained on the first three days of treatment and approved if appropriate for treatment. Following this, weekly imaging was performed to ascertain the accuracy of the treatment fields. During treatment, all patients were assessed for acute skin toxicity based on National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) V.5.0 [14]. Pulmonary and cardiac function were evaluated at baseline and compared, post treatment six months. Cosmesis was objectively evaluated using Harvard breast cosmesis scale [15].

Statistical analysis:

Results of variables with normal distribution were studied by Mean $\pm$ Standard Deviation (SD) and dosimetric parameters were expressed with Median $\pm$ Interquartile Range (IQR).

RESULTS:

The mean age of the patients was 48 years $\pm$ 2 years. Out of 11 patients, 5 patients had right breast cancer and six patients had left breast cancer. All patients had normal baseline pulmonary and cardiac functions which were evaluated by pulmonary function test and electrocardiogram and echocardiogram respectively. Stage wise distribution of the patients are as follows: pT1 = 5 patients, T2 = 6 patients; N0= 7 patients,

N1=1 patient , N2 = 3 patients;6/11 patients were positive for Estrogen-Progesterone receptor and 3/11 patients exhibited Her2neu over-expression.

The mean doses of the accepted plans have been elaborated in Table No. 2. Use of 3DCRT FIF technique allowed to attain a mean PTV-WB V38Gy(95%) of 94.98 ± 3.92 % . Volume of whole breast receiving more than 44 Gy was 30.71 ± 7.9 % which was within the acceptable 50% cut off. A Dmax of 51.04 ± 0.99Gy (106%) confined within the boost volume was observed. No isolated hot spots > 48 Gy were found in the breast outside the boost volume. Conformity Index(CI) which is defined as the ' ratio of the volume covered by 95% isodose line and the volume of the PTV- WB, was 1.31± 0.2. This was within the acceptable range of more than 0.95 and less than 2.0 The coverage of PTV-Boost 45.6Gy(95%) was 98.34% ± 1.79%. Although homogeneity was maintained avoiding 110% and 115 % hotspots, the conformity was slightly compromised towards the periphery of the boost volume The OAR doses have been reported in table 3. which were within the acceptable limits. All patients completed treatment with a maximum of grade 2 acute toxicity. Assessment of cosmesis by Harvard Breast cosmesis criteria revealed a grade 2 score for all patients except one patient whose score consistently remained grade 3 after surgery.

DISCUSSION:

Comparison of hypofractionated WBRT schedules with the conventional WBRT schedules under the Cochrane systematic review have revealed non inferior local recurrence free survival rates (HR 0.94 (95% Confidence Interval (CI) = 0.77 to 1.15)) and Breast Cancer specific survival rates (Hazard Ration (HR) 0.91 (95% CI 0.78 to 1.6)). The cosmetic outcomes (RR 0.90 (0.81 to 1.01)) and late subcutaneous toxicity (RR 0.93 (0.83 to 1.05)) have also been comparable between the two fractionation schedules [7]. Studies have suggested an Alpha/Beta ratio of 3-4 to be used for Breast tissue [7,8] which has allowed us to harness the radiobiological benefit of hypofractionation schedules. The hypofractionation approach used in the current study yielded EQD2 of 44.92 Gy to the whole breast and an EQD2 of 58.47 Gy to the boost volume, assuming an α/β ratio of 3.5Gy [16] Additionally, cost-effectiveness analyses have demonstrated a 33% reduction in costs with adoption of hypofractionated schedules for breast cancer RT in comparison with conventional fractionation, with respect to transportation costs, productivity cost and favourable quality adjusted life years for the patients [10,21]. The shorter treatment time has also provided logistic benefit to hospital resources by reducing patient waiting lists and better utilization of RT resources to treat larger number of patients [22]. One drawback of most hypofractionation WBRT studies is the lack of consensus regarding the applicability of boost. Use of boost RT has been implicated in poor long term cosmesis [17] and adding to the cost of RT [10]. Therefore, radiation boost had been reserved for patients whose potential benefits outweighed their toxicities. The EORTC Boost vs no boost study [18] has clearly demonstrated the higher absolute risk reduction of local recurrence with delivery of boost (≤ 40 years: 11.6%; 41-50 years: 5.9%; 51-60 years : 2.9% and > 60 years : 3 %). Thus, ASTRO [19] has now recommended that use of boost phase should be independent of the whole breast fractionation scheme. Age ≤ 50 years, high tumor grade in patients above 50 years and positive margins are the absolute indications. Tumor >3 cm, extensive intraductal component, Lympho-vascular invasion, nodal involvement, triple negative disease, or residual disease after neoadjuvant chemotherapy have evolved as other relative indications as per recommendations by The Groupe Européen de Curiethérapie (GEC) and the European Society for Radiotherapy & Oncology (ESTRO) working group [20]. There is a paucity of evidence regarding the integration of boost with the WBRT. While few mono-institutional studies have reported their outcomes for integration of Boost RT with the WBRT, only few studies have evaluated the regimen in a prospective manner. Mondal et al[23] have delivered 48 Gy/15 Fr to tumour bed by SIB along with WBRT of 40.5Gy/15 fractions over three weeks using the VMAT in their single arm clinical feasibility study. They have obtained a PTV-WB V95 of 96.84% and PTV- boost V95 of 97.91%. Use of 3DCRT FIF technique in the current study allowed to attain a similar mean PTV-WB V38Gy(95%) of 94.98 ± 3.92 % with the boost cavity coverage of 98.34% ± 1.79% to PTV-Boost 45.6Gy(95%). This is also comparable to the dosimetric parameters attained by Moorthy et al (24) who have used a similar hypo-fractionated SIB-boost schedule. They have demonstrated comparable coverage of PTV-WB 95% by both 3DCRT and IMRT techniques (98.3% vs 99.7 %; p=0.13). 3DCRT plans were however, significantly favourable with respect to lower monitor units (180 vs 1441; $p < 0.01$) and integral doses (145210 Gy-Cm^3 vs 197428 Gy-Cm^3; $p < 0.01$).

The high dose volumes of 110% and 115% of the whole breast were well within the acceptable cut offs as suggested in the other protocols [12]. Dosimetric comparison of Breast conserving radiotherapy with SIB using 3DCRT, IMRT and VMAT has revealed that 3DCRT FIF with SIB offers an acceptable and feasible alternative with respect to target and OARs, in comparison with more advanced technologies [10,23-28]. The ipsilateral mean lung dose in the current study was

10.1 Gy and V20 = 20.25% which was comparable to Cante et al [29] (10.94 ± 7.77 Gy), Mondal et al [23] (Dmean 13.92Gy and V20 = 21.53 %) and much lesser than those obtained by Moorthy et al [24] (SIB-3DCRT – 20.29 Gy vs SIB- IMRT -16.51 Gy). The mean heart dose obtained for left sided tumors in the current study was 6.47 Gy ; Cante et al (2.46 ± 1.08 Gy)); Mondal et al (6.22 Gy). The contralateral breast Dmax, however , was on the higher side in the current study (19.87 Gy) as well as Mondal et al (35.51 Gy) [23]. This had to be permitted in view of point dose and the dose to 5% of breast volume being within acceptable limits. Comparison of sequential boost RT versus SIB has demonstrated that SIB allows the volume of whole breast, excluding the boost volume receiving > 95% of prescribed to be lesser, with better conformity [26-28]. These studies have used a conventional fractionation regimen with 1.8-2 Gy per fraction for WBRT. The RTOG 1005 [12] is a phase III prospective trial intending to compare conventional WBRT with sequential boost with a accelerated hypofractionation WBRT with SIB to the tumor bed; the results of this study are awaited. A comparative account of the dose volume parameters achieved in the current study with the various plans in the RTOG 1005 interim report has been described in Fig1 and Fig 2.

Clinical outcomes:

Chadda et al [30] observed a maximum of Grade 2 Acute dermal toxicity with 40.5Gy/15 fr (2.7 Gy/Fr) WBRT along with 0.3 Gy/Fr SIB to the tumor bed to a dose of 45Gy/15 Fr. Formenti et al [31] used the same fractionation regimen and observed 67 % reversible Grade 1-2 skin toxicity. Cante et al [29] used a WBRT of 45Gy/20 fr at 2.25 Gy/Fr with a concomitant boost of 0.25 Gy/Fr everyday, delivered over 4 weeks. Cosmetic outcomes were scored as excellent/good in 87.8% of patients and fair/poor in 12.2% in their 10 years follow up reports. > G2 fibrosis was observed in 7% of the patients and telangectasia was seen in 5% of the patients, at the 10 years follow up. The retrospective series by McDonald et al [32] has also demonstrated <1% grade 3 toxicity with good to excellent global cosmetic outcome in 96.5%. All the above studies demonstrated > 95% rates of 5 yr OS, DFS and and local control rates. The cosmetic outcomes of the current study are comparable with above mentioned studies; with the maximum acute radiation toxicity detected in the current study being grade 2 (8/11 patients) which reversed by 1-6 months follow up (Fig 3) . Similar toxicity pattern was reported by VMAT based SIB studies by de Rose et al [33] and Mondal et al [23] where none of the patients experienced grade 3 toxicity. Physician reported cosmetic scoring by Harvard Breast cosmesis grading scale was fair to good at 6 months in most patient, similar to the satisfactory grades reported by Mondal et al [23]. Cosmesis, however, requires a long term follow up. Few drawbacks with the current study were the small sample size used and the relatively short follow up. As this was a clinical feasibility study, the same protocol will be used for an expanded sample size with longer follow up for the future.

CONCLUSION:

Whole breast radiotherapy with concurrent boost to the tumor bed by 3DCRT FIF technique is a clinically feasible option to achieve acceptable dosimetric parameters and good cosmetic outcome. It is well tolerated by the patients with good compliance. This may be well adapted in centres which lack facilities for IMRT.

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List of Abbreviations

BCT	Breast Conservation Therapy
BCS	Breast Conservation Surgery
WBRT	Whole Breast Radiotherapy
IMRT	Intensity Modulated Radiotherapy
VMAT	Volumetric Modulated Arc therapy
HT	Helical Tomotherapy
SIB	Simultaneous Integration of Boost
3DCRT	Three-Dimensional conformal Radiotherapy
FIF	Field-in-field
OAR	Organs at Risk
CTV	Clinical Target Volume
PTV	Planning Target Volume
WB	Whole Breast
MV	Megavoltage
Gy	Gray
EORTC	European Organisation for Research and Treatment of Cancer
ASTRO	American Society for Radiation Oncology
GEC - ESTRO	The Groupe Européen de Curiethérapie and the European SocieTy for Radiotherapy & Oncology
RTOG	Radiation Therapy Oncology Group (RTOG)
MLC	Multi Leaf Collimator
BED	Biological Equivalent Dose
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
SD	Standard Deviation
IQR	Interquartile Range
95%CI	95% Confidence Interval
HR	Hazard Ratio
CI	Conformity Index
HI	Homogenity Index
EQD_2	2 Gy Equivalent dose

Tables:

OPTIMISATION OBJECTIVES		
Target/ organ	Type	constraint
PTV-WB	V95	>95%
	V110	<50%
PTV-Boost	V95	>95%
	Dmax	<115%
	V110	<5%
Ipsilateral lung	V20	<15%
	V16	< 20%
	V8	< 35%
	V4	< 50%
Contralateral lung	V4	<10%
Heart(Left Breast)	V16	< 5%
	V8	<30%
	Dmean	< 3.2 Gy
Contralateral breast	Dmax	<2.5Gy

Table 1. Optimization Objectives

Whole Breast	**WB PTV 38Gy (%) (95%)**	94.98 $\pm$ 3.92
	PTV 36 Gy (%) (90%)	97.45 $\pm$ 3.23
	44Gy (%) (110%)	30.71 $\pm$ 7.90
	Conformity Index	1.31 $\pm$ 0.20
	Homogenity Index	0.35 $\pm$ 0.19
Boost volume (LC)	**Boost PTV 45.6 Gy (%) (95%)**	98.34 $\pm$ 1.79
	Boost PTV 43.2Gy (%) (90%)	99.63 $\pm$ 0.55
	52.80 Gy (110.%)	**0**
	55.20Gy (115.%)	**0**
	Homogenity Index	0.08 $\pm$ 0.03

Table 2. Objectives achieved

C/L Breast	**Dmax (Gy)**	**19.87**
	D5%(Gy)	**6.23**
I/L Lung	**V20 (%)**	**20.25**

	V16 (%)	**22.26**
	V8(%)	**29.43**
	V4(%)	**44.02**
	Dmean (Gy)	**10.10**
	D50% (Gy)	**3.69**
C/L Lung	**V4 (%)**	**0.21**
	Dmean (Gy)	**0.43**
Heart	**V20 (%)**	**6.88**
	V16(%)	**6.95**
	V8 (%)	**10.12**
	Dmean (Gy)	**4.16**
	Heart Dmean Left breast (Gy)	**6.47**
	Heart Dmean Right breast (Gy)	**1.38**

Table 3. Doses achieved for the OARs

Pt No.	RT week 1	RT week 2	RT week 3	post RT 4 weeks
1	1	1	2	1
2	1	1	2	1
3	1	1	2	1
4	1	1	2	1
5	1	1	2	1
6	1	1	2	1
7	1	1	2	1
8	1	1	1	1
9	1	1	1	1
10	1	1	1	1
11	1	1	2	1

Table 4. RTOG Acute Radiation Dermatitis Grading

Pt No.	prior to RT	week 1	week 2	week 3	1 months	6 months
1	2	2	2	2	2	2
2	2	2	2	2	2	2
3	2	2	2	2	2	2
4	2	2	2	2	2	2
5	2	2	2	2	2	2
6	3	3	3	3	3	3
7	2	2	2	2	2	2
8	2	2	2	2	2	2
9	2	2	2	2	2	2
10	2	2	2	2	2	2
11	2	2	2	2	2	2

Table 5. Harvard Cosmesis Grading Scores

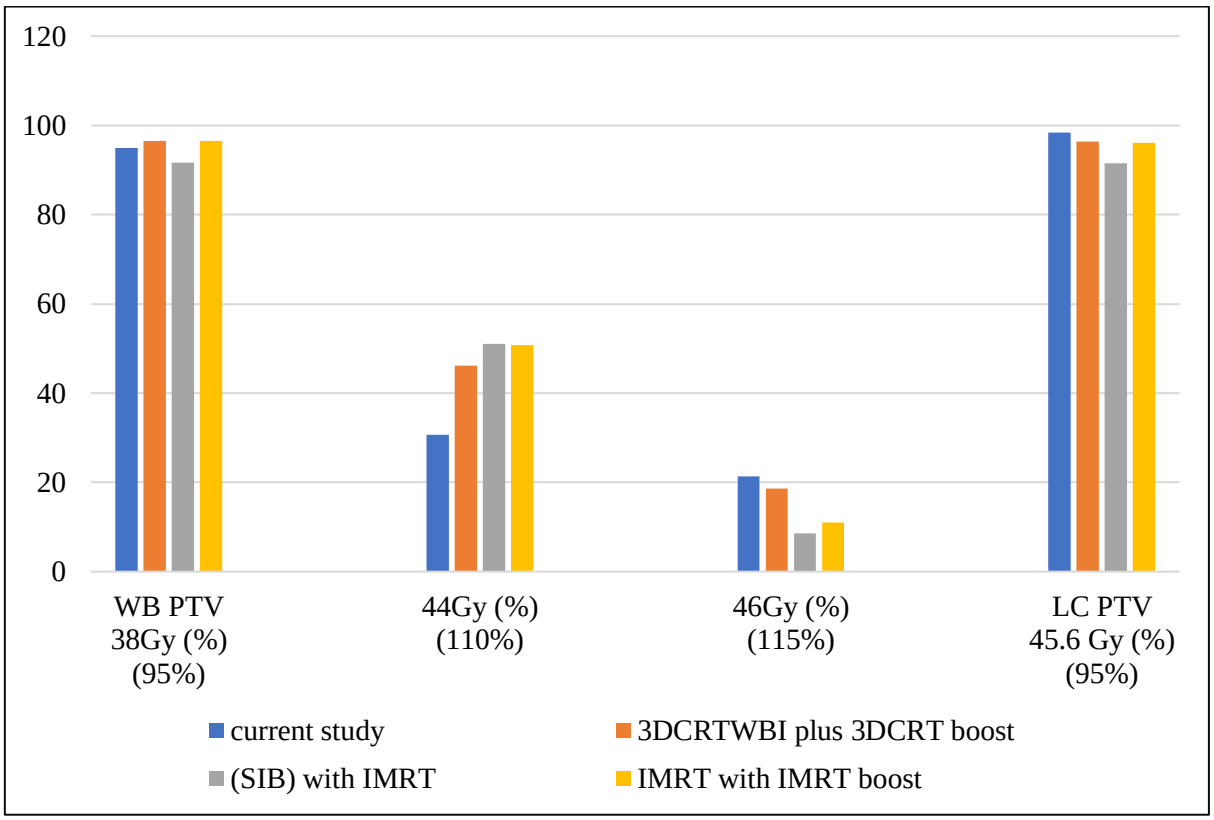

Fig 1. A Comparative account of Dose Volume parameters of target between the current study and the various arms of RTOG 1005

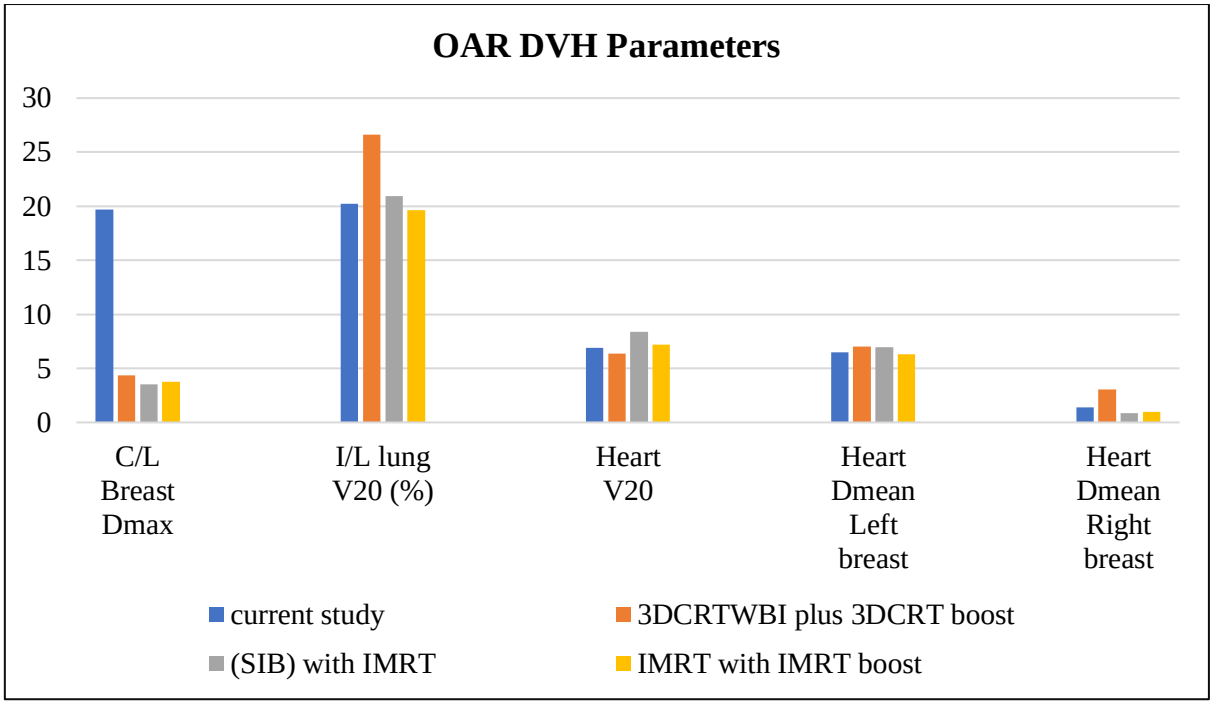

Fig. 2: A Comparative account of Dose Volume parameters of OAR between the current study and the various arms of RTOG 1005

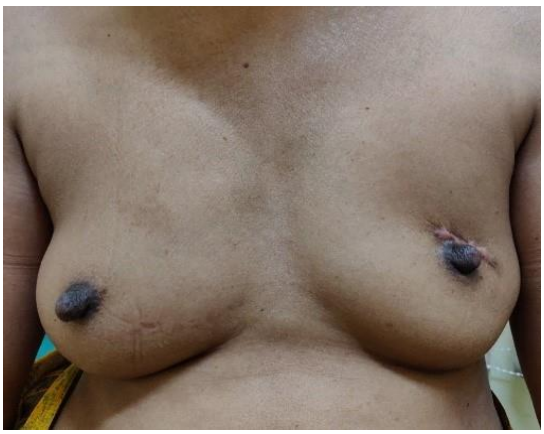

Fig 3a: Post-surgery, prior to commencement of Radiotherapy

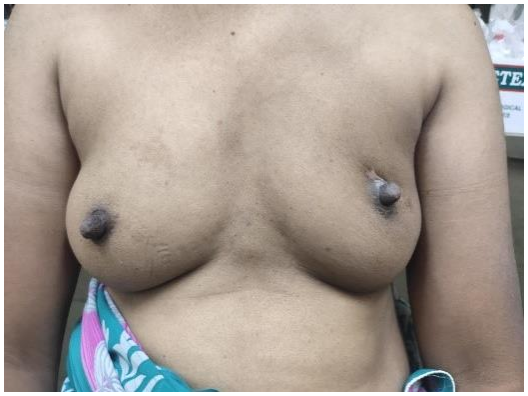

Fig 3b: Six months post completion of Radiotherapy