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Prospective single arm study to assess the feasibility and tolerability of hypo-fractionated post mastectomy radiotherapy in patients with carcinoma breast

Balu George
Assistant Professor, Department of Radiation Oncology, Believers Church Medical College, Thiruvalla, Kerala, India

Abstract
Aim: To conduct single arm prospective trial to assess the feasibility and tolerability of hypo-fractionated post mastectomy radiotherapy.
Objectives: To study the tolerability of hypo-fractionated post- mastectomy radiotherapy in terms of acute toxicities, especially dermatitis. Feasibility in terms of target coverage and dose limits to organs at risk were studied.
Methods: A single arm prospective study was done on patients diagnosed to have carcinoma breast with indications for post mastectomy radiotherapy and are willing for 3D Conformal Radiotherapy. The dose delivered was 40Gy in 15 fractions to chest wall alone or chest wall and supraclavicular regions. Weekly clinical examinations were done to assess toxicities. DVH data were collected to study the influence of regions treated on CTV coverage, dose to organs at risk. Data entry was done in Micrsoft Excel and analysed using SPSS 16.0. Frequencies and percentages were calculated for discrete variables. The association between the outcome variables was tested using Chi square test.
Results: 8.3% of patients developed Grade III dermatitis. None of the patients developed Grade IV toxicities. It was noted that the median V10Gy (26.1 % vs 16.9 %, p value 0.003) and V12Gy (25.2 % vs 16.23 %, p value 0.003) for ipsilateral lung was significantly high when there was addition of supraclavicular field.
Conclusion: Hypofractionated radiotherapy is a tolerable treatment regimen. Obese, left-sided breast cancer patients who require supraclavicular irradiation may benefit from IMRT.

Keywords: feasibility, Tolerability, radiotherapy, carcinoma

Introduction

Breast cancer is one disease, the management of which keeps evolving and continues to baffle the clinician from ages. Breast cancer is a disease with potential for systemic spread with high risk of local recurrence. Essentially, the treatment of invasive breast cancer has surgery and radiation therapy as the modes for local control of the disease and chemotherapy for addressing the systemic micrometastasis.

Modified radical mastectomy is followed up with radiation therapy to the chest wall, supraclavicular or the axillary region according to specific indications.

Treatment of breast cancer spans across six to eight months and radiation therapy contributes to about five weeks.

To reduce the workload on machines, many centres started using shorter radiotherapy schedules with larger doses per fraction.

Evolving radiobiological concepts that opened gates to research aimed at reducing the treatment duration from five weeks to three weeks, have proved that it is feasible in terms of tumour control and safety. The concept of hypofractionated radiotherapy was initially applied to breast cancer as early as 1986([1]) in the United Kingdom.

The concept of hypofractionated radiotherapy has not become the standard of care in India.

The shorter treatment schedule is supposed to reduce the burden on treatment units and indirectly reduce the cost of treatment. Indian breast cancer scenario will definitely benefit from this well-established treatment regimen.

Materials and Methods

The study was conducted in the Department of Radiotherapy over a period of 11 months.The proposal of the study was approved by the Institutional Review Board (IRB) and the Ethics Committee (EC). All post mastectomy patients who were seen in the Department of Radiotherapy were screened for the study according to the preset inclusion and exclusion criteria.

Inclusion Criteria

1. Age above 18 years and less than 70 years
2. Any patient requiring post mastectomy radiotherapy.
3. Enrollment possible within 42 days of surgery or last cycle of Chemotherapy

Exclusion Criteria

1. Patients who had Breast Conservation surgery
2. Collagen Vascular disease
3. Poor performance status (ECOG >3)
4. Pregnancy and breastfeeding.
5. Patients who had immediate reconstruction after mastectomy.
6. Close or positive surgical margin 1 mm or less

7. Axillary nodal involvement with extranodal extension
8. Metastatic breast cancer
9. Prior history of radiation therapy to the chest.
10. Transmural myocardial infarction within last 6 months
11. Medical, psychiatric or other condition that may prevent the patient from receiving the protocol therapy or informed consent.
12. Unstable angina or congestive heart failure requiring hospitalization within the last six months.
13. History of interstitial lung disease or active lung infection

Sample Size

Since this was a pilot study to assess the feasibility of hypofractionated radiotherapy in patients with carcinoma breast, it was decided to study 20 patients for assessing the tolerability.

Method

Eligible patients were explained about the study, its purpose, benefits and side effects in detail. An information sheet was given to the patient which provided details of the study. Consent forms were submitted by the willing patients.

Radiotherapy was scheduled as soon as the surgical wound has healed or after three weeks of prior chemotherapy. Routine blood tests were done to rule out neutropenia. Patient immobilization was done in the simulator using a breast board.

CT centres were marked and tattooed. The clinical boundaries of chest wall were marked on the body.

The details of the patient setup were documented. On the day of the scan, the CT centres and clinical boundaries of the chest wall, scar and the drain sites were marked with radiopaque markers.

Contrast enhanced CT scan from C4 to the level of adrenals was obtained in the treatment position with a slice thickness of 5 mm.The CT images were imported to the planning system (Eclipse External Beam Planning V10.0.42; Varian Medical Systems, Palo, Alto, CA).

The RTOG contouring guidelines were followed in delineating the Clinical Target Volume and the Organs at Risk.

Regions treated

Chest wall

Supraclavicular Region

Supraclavicular field was added if there were four or more positive axillary nodes.

RTOG guidelines

The RTOG contouring guidelines were used to contour the chest wall, supraclavicular regions and the organs at risk.

Chest wall- Clinical Target Volume (CTV)

The chest wall craniocaudally extends between the caudal border of head of clavicle and the level where there is loss of CT apparent contralateral breast.

Antero-posteriorly the contour extends between the skin and the rib-pleural interface (includes Pectoralis muscle, chest wall muscles and ribs).

The chest wall contour extends between the rib-sternal junction to the mid axillary line (excludes Latissmus dorsi muscle)

Supraclavicular region- Clinical Target Volume (CTV)

The supraclavicular region was contoured craniocaudally between the caudal edge of Cricoid cartilage to the caudal edge of the Clavicular head and antero-posteriorly between the Sternocleidomastoid muscle and the anterior Scalene muscle.

Medially the volume excludes the trachea and thyroid gland and the lateral edge of the Sternocleidomastoid muscle forms the lateral boundary cranially and the junction of first rib and clavicle caudally.

Organs at Risk (OAR)

Lungs

Bilateral lungs were contoured separately and combined lung volume is also generated.

Heart

The superior aspect (or base) begins at the level of the inferior aspect of the pulmonary artery passing the midline and extend inferiorly to the apex of the heart.

Dose Prescription

Table 1

Total dose (Gy)	Dose per fraction (Gy)	No of Fractions	Fractions per week	Treatment time (weeks)
40.05	2.67	15	5	3

Steps Involved In 3d-Crt

1. Patient immobilization was done on breast board and the clinical references and the centers were marked and tattooed. A planning CT scan of thorax was obtained with 5mm slice thickness.
2. Delineating the Clinical Target Volume (CTV) and the Organs at Risk (OAR) on the planning CT images at the contouring station was done.
3. Beam selection and planning was done to see dose distribution using Plato treatment planning system. Both 6MV and 15 MV beams were used. Bolus was applied Whenever applicable.
4. Plan evaluation was done using Dose Volume Histogram (DVH) and isodose distribution after which the final plan was selected.
5. Digitally Reconstructed Radiographs (DRR) were developed for comparison with the electronic portal image.
6. Treatment execution

The following guidelines were considered for finalizing the plan:

Lower dose limit
More than 95% of the Clinical Target Volume should receive more than 90 % of the prescribed dose.

Upper dose limit
Less than 2 % of the volume should receive more than or equal to 107 % of the prescribed dose.
Less than 7 % volume should receive more than or equal to 105 %
Global max should be less than 110 % of the prescribed dose.

Ipsilateral lung
The volume of ipsilateral lung receiving 12Gy ($V_{30\%}$) or V_{12Gy}) should be less than 17 %.

Heart
The volume of heart receiving 2Gy should be less than 30%.
The volume of heart receiving 10Gy should be less than 5%.

Contralateral breast
Maximum dose to the contralateral breast is less than or equal to 330cGy.

Data on Dose Volume Parameters
The details regarding the dose-volume parameters were obtained from DVH and entered in a data sheet. For those patients with chest wall and supraclavicular region as clinical target, the DVH combining both the regions was used for obtaining the relevant dose-volume parameters.

Weekly Assessment
Clinical examination was done particularly looking for dermatitis over the chest wall. Dermatitis was graded according to the RTOG Acute Radiation Morbidity Scoring Criteria. Weekly follow up details were entered in an assessment form.
Patient demographic data was entered in a data sheet. Treatment was interrupted in case of Grade 3 dermatitis. Radiation therapy was not resumed until the reactions subsided to Grade I.

Post Treatment Follow Up
Patients were followed up for six weeks post radiation therapy to assess for radiation dermatitis. Pulmonary Function Test is advised three months after the completion of the treatment.

Statistical Analysis
Data entry was done in Micrsoft Excel and was analysed using SPSS 16.0 (Statistical Package for Social Sciences). Frequencies and percentages were calculated for discrete variables like grades of radiation dermatitis. Mean, median and standard deviation were calculated for continuous variables such as age, BMI etc. The association between the outcome variables was tested using Chi square test. The data was represented graphically using bar diagrams and histograms. Correlation between variables was studied.

Results
The target sample size for this feasibility study was 20. Twelve patients were recruited by the end of the study period.

Overview of Patients
58% of patients belonged to the age group 46-55 years and the mean age was 50 years (Figure 4.1).

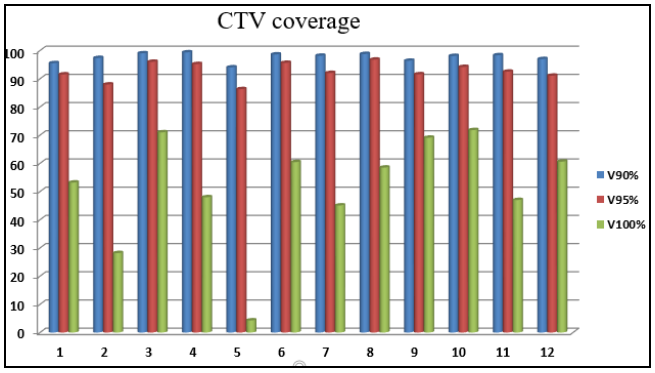

Fig 1

The study group consisted of 42% healthy individuals, 42% overweight, 8% with Grade I and another 8% with Grade II obesity. Diabetes mellitus and hypertension was the most common co-morbidities noted. There were seven patients with left sided breast cancer and five with right sided disease. Two women had mastectomy elsewhere. There were six patients with Stage IIIA, four with IIA, one with IIIB and another patient who underwent surgery at a different centre was staged as TxNxM0. Four of the patients had upfront surgery, seven received neoadjuvant chemotherapy and one patient received neoadjuvant hormonal therapy. Five patients received treatment to the chest wall and supraclavicular region where as seven of them received only chest wall irradiation. The patient characteristics are given in Table 1.

Table 1: Demographic and clinical characteristics

Age	
<35	1
36 - 45	2
46 – 55	7
56 – 65	2
>65	0
BMI	
Healthy	5
Over weight	5
Grade I obesity	1
Grade II obesity	1

Premenopausal	7
Postmenopausal	5
Patients with no co-morbidities	5
Patients with co-morbidities	7
	Diabetes mellitus - 1
	Hypertension- 2
	Diabetes mellitus, Hypertension- 1
	Dyslipidemia- 1
	Diabetes mellitus, Hypertension, Coronary artery disease- 1
	Hypetension, Bronchial Asthma- 1
Laterality	
Left	7
Right	5
Stage	
II A	4
IIIA	6
IIIB	1
TxNxM0	1
Estrogen receptor	
Positive	8
Negative	4
Progesterone receptor	
Positive	6
Negative	6
Her 2 neu	
Positive	2
Negative	10
Triple negative	4
Had neoadjuvant chemotherapy	7
	Anthracycline - 4
	Anthracycline and Taxane - 3
Did not have neoadjuvant chemotherapy	5
Had adjuvant chemotherapy	11
	Anthracycline- 4
	Taxane – 4
	Anthracycline and Taxane – 3
Did not have adjuvant chemotherapy	1
Regions treated	
Chest wall	7
Chest wall and supraclavicular region	5

All the patients completed the prescribed treatment without any major complications.

The patients were followed up for a period of six weeks to assess acute toxicity.

One of the patients subsequently developed distant metastasis (pulmonary). Others are disease free at the time of last follow up

Dvh Parameters

Clinical Target Volume

The lower dose limit applied for the CTV was that more than 90% of the CTV should receive 95% or more of the prescribed dose ($V_{95\%}$ > 95%). The upper dose limit constraints were, $V_{107\%}$ <2%, $V_{105\%}$ <7% and Global maximum <110%.

CTV coverage was analyzed by dividing the cases into two groups according to the regions treated (Table 2).

Table 2: CTV coverage with respect to regions treated

CTV	Chest wall			Chest wall and supraclavicular regions			p value
	1st quartile	Median	3rd quartile	1st quartile	Median	3rd quartile	
$V_{90\%}$	95.54	98.34	99.04	96.70	97.38	98.45	0.530
$V_{95\%}$	91.55	92.52	95.66	89.54	91.60	95.50	0.755
$V_{100\%}$	45.07	47.99	60.44	43.34	60.60	70.45	0.343

Chest wall and Chest wall along with supraclavicular region

The median CTV $V_{95\%}$ was 92.52% when chest wall was treated alone and 91.60% when chest wall and supraclavicular regions were treated. Both CTV $V_{90\%}$ and $V_{95\%}$ were better when chest wall alone was treated, but this difference was not statistically significant. The median $V_{90\%}$ was 98.34% in patients who received chest wall radiation alone compared to 97.38% in patients who received supraclavicular radiation in addition to the chest wall radiation. This variation in $V_{90\%}$ was not statistically significant (p value 0.530). The range of

V90% values was broader when only chest wall was treated (Table 3) The median $V_{95\%}$ values were 92.52% and 91.60% for chest wall irradiation alone and combined chest wall-supraclavicular irradiation respectively (Table 3). The range of $V_{95\%}$ was similar among the two groups and ranged between 86.33–96.02% and 87.98–96.80. The first and third quartiles were 91.55% and 95.66% in the chest wall group (Table 3) The median V100% was 60.6% in the chest wall-supraclavicular group and 47.99% in the chest wall alone group (Table 3).

Table 3: CTV Coverage

Patient	V90%	V95%	V100%
1	95.54	91.55	53.2
2	97.38	87.98	28.18
3	99.04	96.02	71
4	99.37	95.23	47.99
5	94.05	86.33	4.3
6	98.63	95.66	60.44
7	98.17	92.06	45.07
8	98.8	96.8	58.5
9	96.4	91.6	69.1
10	98.1	94.2	71.8
11	98.34	92.52	47
12	97	91.1	60.6

Upper Dose Limits

The hot spots, V105% and V107% were well within the tolerance limits (<7% and <2% respectively). The hot spots were analyzed by dividing the patients into two groups according to the regions treated: Chest wall and Chest wall & supraclavicular region

The CTV Global maximum doses ranged between 104-108% in the group of patients who received chest wall radiation and 104-107% in the group of patients who received the supraclavicular irradiation in addition. The median Global maximum dose was same (106%) in both the groups (Table 4).

Table 4: Upper dose limits with respect to regions treated

CTV	Chest wall			Chest wall – supraclavicular			p value
	1st quartile	Median	3rd quartile	1st quartile	Median	3rd quartile	
G max	106	106	107	104	106	106.50	0.343
$V_{105\%}$	1.96	3.43	5.50	0.45	3.10	7.05	0.876
$V_{107\%}$	0	0.14	0.49	0	0	0.35	0.639

The median V 105% was 3.43% and 3.10% respectively for chest wall alone and combination of supraclavicular and chest wall regions (Table 4). The values ranged between 0 and 9 % in both the groups. The range of V107% was 0 – 0.78% in the chest wall group and 0-0.50% in the chest wall-supraclavicular group. The median value was 0 in the two-regions group, where as median V107% was 0.14% in the single region group.

Ctv Coverage and Bmi

There was a positive correlation between BMI and CTV 95%, which implied that higher the BMI, higher is the CTV V95%. But this was not statistically significant in view of the small sample size.

Organs at Risk

The organs at risks studied were ipsilateral lung, heart, contralateral lung, combined lung and contralateral breast. V_{10Gy}, V_{12Gy} and V_{20Gy} for the ipsilateral lung and V_{2Gy} and V_{10Gy} for the heart were documented. The dose constraint attempted to achieve was the volume of the ipsilateral lung receiving 12Gy to be less than 17%. The ipsilateral lung volume receiving ≥12Gy ranged from 7.43% to 35%. The contralateral lung V_{10Gy} and V_{20Gy} were found to be 0, which means that no part of the contralateral lung received 20Gy or 10Gy. The dose constraint for ipsilateral lung could be met for only four patients (V12Gy <17%). The remaining 8 patients had >17% of their ipsilateral lung receiving 12Gy or more. Among these 8 patients, 3 of them had V12Gy ≤ 20% (Table 5).

Table 5: Ipsilateral Lung volumes receiving 10Gy, 12Gy and 20Gy

Patients	V10Gy	V12Gy	V20Gy
1	20.99	20.2	18.12
2	21.61	20.85	18.36
3	20.06	19.42	17.43
4	14.99	14.19	11.75
5	19.06	18.18	15.51
6	15.62	14.93	12.91
7	7.94	7.43	5.83
8	22.4	21.1	17.3

9	37.6	35	32.1
10	30.8	29.5	25.7
11	16.96	16.23	13.97
12	26.1	25.2	21.5
Mean	21.17	20.18	17.54
SD	7.72	7.25	6.77

The $V_{10Gy,}$ V_{12Gy} and V_{20Gy} which are the volumes of lung receiving 10Gy, 12Gy and 20Gy respectively was higher for those patients who had supraclavicular field in addition to the chest wall Field. The Mann-Whitney test was applied and it was found that the V_{10Gy} and V_{12Gy} were significantly (p value 0.003) higher when both the regions were included as the target (Table 6).

Table 6: Ipsilateral lung dose volume data based on regions treated

Lung volume	Chest wall			Chest wall and supraclavicular			p value
	1st quartile	Median	3rd quartile	1st quartile	Median	3rd quartile	
V10Gy	14.99	16.9	20.06	22.34	26.10	34.20	0.003
V12Gy	14.19	16.23	19.42	20.98	25.2	33	0.003
V20Gy	11.75	13.97	17.3	17.83	21.5	29.25	0.010

V10Gy ranged between 7.94 % and 20.99 % in the group of patients who received chest wall irradiation alone. The range of V10Gy was 21.61% to 37.6% in chest wall-supraclavicular group.

The median V_{12Gy} in the group of patients who had supraclavicular region in addition to the chest wall was 25.2% compared to the group of patients who received only chest wall irradiation 16.23% (p value 0.003). The first and the third quartiles values of V12Gy for chest wall irradiation was 14.19 % and 19.42%, which implies that 50 % of patients in this group had their V12Gy values in this range.

The median values were 13.97 % and 29.25 % respectively for patients who received radiation to chest wall alone and supraclavicular-chest wall irradiation. Median V_{20Gy} was significantly higher in the patients who received supraclavicular treatment in addition to chest wall (p value 0.010).

Combined lung

Combined lung volume receiving 10Gy ($V10_{Gy}$) was less than 17% in eleven of the twelve patients. One patient had a V_{10Gy} of 19%.

Heart

The dose constraints we attempted to achieve was V10Gy ≤ 5% and V2Gy ≤ 30%. V2Gy ≤30 % could be achieved in 7 out of 12 patients and V10Gy ≤ 5 % was achieved in 6 out of 12 patients.

Volume of heart irradiated according to laterality of the disease

The volume of heart receiving 2Gy and 10Gy were significantly (p value 0.003) higher in patients with left sided breast cancer (Table 7).

Table 7: Heart dose-volume parameters according to laterality of the disease

Heart volume	Left chest wall			Right chest wall			P value
V2Gy	1st quartile	Median	3rd quartile	1st quartile	Median	3rd quartile	0.003
	27.66	35.7	44.07	2.35	2.80	9.21	
V10Gy	8.31	12.70	14.26	0	0	0.5	0.003

The median V2Gy in patients with left sided disease was 35.7% and 2.8% in patients with right sided disease (Table 7). The difference in the volume of heart receiving 2Gy is depicted in Figure 4.20. The first and third quartiles for V2Gy in left side irradiation were 27.66 % and 44.07 %(Table 7).

Median V10Gy in the patients who received left chest wall irradiation was 12.7% where as the median value in right chest wall irradiation was 0%. Figure 4.21 depicts the range of V10Gy values among the two groups.

Contralateral breast

The dose constraint that we tried to achieve was to keep the mean dose to the contralateral breast ≤ 330cGy. The mean contralateral breast dose ranged between 38cGy and 126.5cGy. The mean of all the patients' contralateral breast mean dose was 65.24cGy. All the patients had contralateral breast dose well within the tolerance limit.

Acute Toxicities

Patients tolerated the treatment well without any Grade IV toxicities. The acute toxicities that were noted in the study group were fatigue, dermatitis and mucositis (throat irritation). Dermatitis and fatigue were the most common side effects noted (Table 8).

Table 8: Acute side effects

	week 1	week 2	week 3	week 4	week 5	week 6	week 7	week 8	week 9
Fatigue	1	5	3	1	0	0	0	0	0
Dermatitis	2	8	12	4	3	1	0	0	0
Cough	0	4	3	0	0	0	0	0	0
Throat irritation	0	2	1	0	0	0	0	0	0

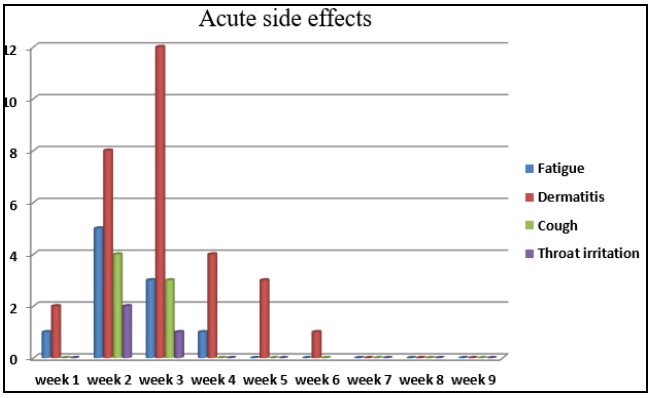

Fig 2: Acute side effects during and after treatment

Dermatitis

None of the patients developed Grade IV dermatitis. One patient developed Grade III dermatitis by week 4 (the week after completion of radiotherapy). She completed treatment on 24.4.2013, Grade III reaction was documented on 1.5.2013, and by 8.5.2013 the reaction subsided (Figures 3, 4, 5). Majority (10 out of 12) of the patients had only Grade I dermatitis and only one patient developed Grade II dermatitis (Table 9).

Table 9: Week wise incidence of dermatitis

Dermatitis	Week 1	Week 2	Week 3	Week 4	Week 5
Grade I	2	8	11	2	2
Grade II	0	0	1	1	0
Grade III	0	0	0	1	0
Grade IV	0	0	0	0	0

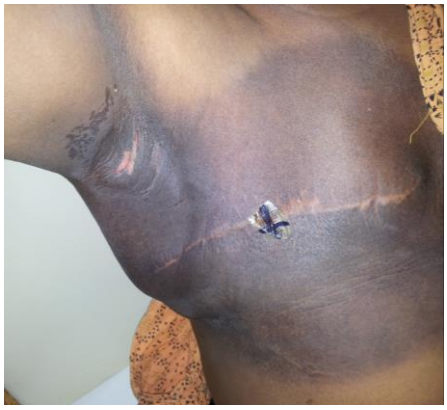

Fig 3: Grade 3 dermatitis

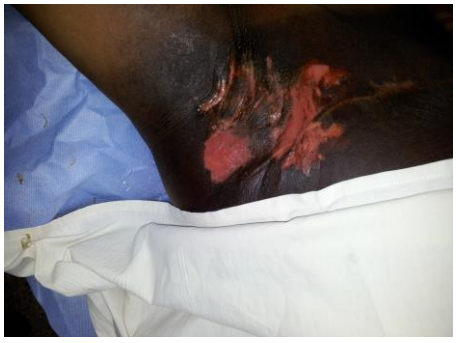

Fig 4: Grade 3 dermatitis

Fatigue

Only 5 of the patients developed mild fatigue during the three week of treatment. They were able to continue the activities without any limitations.

Overall Treatment Time

The overall treatment time varied between 18 to 24 days. The mean overall treatment time was 20.83 days.

Treatment Breaks

There were no breaks in treatment due to patient related reasons. Three patients had 1 day each of break in treatment due to machine related issues.

Follow Up

Patients have been followed up regularly and the longest follow up is 9 months. None of the patients had local recurrence within this short follow up period. Six out of the twelve patients had completed more than three months of follow up at the time of this analysis. Out of these six patients only three had pre and post radiotherapy Pulmonary Function Tests done. Pre and post radiation therapy Forced Vital Capacity (FVC) was compared, the results of which are given in Table 10.

Table 10: Pre and post radiotherapy FVC

	FVC in litres		FVC in % (Post bronchodilator/predicted)	
	Pre RT	Post RT	Pre RT	Post RT
1	2.92	2.52	95.4	83.6
2	1.61	1.69	62.5	71
3	1.79	1.76	66.9	64.8

FVC above 80 % is normal. There was no significant change in FVC values pre and post irradiation. One of the patients had low FVC at baseline and this was attributed to Bronchial asthma.

Discussion

Hypofractionated radiotherapy for carcinoma breast is a safe and effective form of treatment in terms of toxicities, locoregional tumor control and survival. Our study focused on testing this hypothesis in our patients who are heterogeneous among themselves, but at the same time quite different from the population that were recruited in the landmark trials on hypofractionation for breast carcinoma. The UK Standardization of Breast Radiotherapy (START) trials are the landmark trials which forms the broad base for evidence for hypofractionated radiotherapy for patients with breast cancer. START B trial was a randomized controlled trial which compared the conventional standard schedule with the hypofractionated regimen (40Gy in 15 fractions, 3 weeks). The patients in the trial had breast conservation surgery predominantly and only about 8% had undergone mastectomy. We conducted a single arm, prospective study to assess the feasibility and tolerance of hypofractionated radiotherapy in patients who have undergone mastectomy.

The CTV coverage in patients who received supraclavicular regional irradiation in addition to the chest wall irradiation

was as good as in patients whose chest wall only was treated (Table 3). In our study, it was noted that as the BMI of the patient increased, the CTV coverage (V95%) also increased. But, Koh *et al* has reported that in obese patients, the coverage for supraclavicular volume tends to be poor as the supraclavicular fossa will be deep. They recommend IMRT for better coverage of supraclavicular region, especially for obese patients [2]. Out of the twelve patients in our study, only five patients received supraclavicular radiation and hence it was not feasible to analyze correlation between BMI and CTV coverage in this subgroup as the numbers are small.

The dose constraints for ipsilateral lung dose could not be met for all patients especially in those who received supraclavicular irradiation (Table 6). Addition of supraclavicular irradiation has contributed significantly to the lung dose. This was consistent with the data from Yang *et al*, which also reports higher lung dose with supraclavicular irradiation [3]. The constraint was extrapolated from the protocol of the Fast Forward trial which is set for hypofractionated whole breast irradiation, whereas our patients received post mastectomy radiotherapy [4]. This could be the explanation for not being able to meet the dose constraint for lung in most of the patients in our study.

The volume of heart receiving 2Gy should be less than or equal to 30% - again a constraint followed in the Fast Forward trial. The median V2Gy in our study population was 35.7% in patients who received left chest wall irradiation (Table 7). The cardiac toxicities can take up to 15 years to develop and hence these patients need to be followed up on long term basis.

In our study, it was difficult to attain optimum balance between target coverage and dose constraints to organs at risk using 3DCRT in a subset of patients. These were patients with left sided tumour and those who required supraclavicular irradiation. These patients may benefit from IMRT in terms of target coverage and dose to organs at risk.

There were 12 patients in the study and there were no incidence of any form of Grade IV acute toxicity in them, during the three weeks of treatment and six weeks of follow up (Table 9). This was in concordance with the results of a study by Hijal *et al*, which assessed dermatitis in patients undergoing hypofractionated radiotherapy following breast conservation. They reported that most of the patients developed Grade I dermatitis only [5]. Among the 156 evaluable patients, five patients developed Grade III dermatitis and no patient developed Grade IV toxicity. Indication for axillary radiation was an exclusion criterion in our study. Axilla has abundant sweat glands and the presence of skin creases makes it the commonest region which develops moist desquamation [6].

The low incidence of serious dermatitis in our study might be due to the fact that patients who required axillary radiation were excluded from our study, which might be true for the study done by Hijal *et al* also. This means that, safety of hypofractionated radiotherapy needs validation in patients who requires axillary irradiation. One of the patients developed Grade III dermatitis, in the week following completion of treatment. The dermatitis subsided to Grade I, within a week with conservative measures. But Somaya *et al* has reported that dermatitis lasts longer (about 5 weeks) in patients who receive hypofractionated radiotherapy [7]. The DVH of this particular patient was reviewed to find out if any hot spot was on the skin. There were no high dose regions on the skin. The possible reasons for the occurrence of Grade III dermatitis could be that her BMI was high (29.8 kg/m^2 overweight) and the skin creases in the lateral aspect of chest wall, towards the axilla. Though she was a Diabetic, the skin reactions healed within a week without getting secondary infection. Long term cosmetic outcome was better in the hypofractionated arm of the START B trial. As our study included only post mastectomy cases, cosmesis was not an outcome variable.

Limitations

The number of patients included in the study was small. Due to the small sample, some of our results were not statistically significant. Patients who required axillary irradiation were not included in the study, thereby limiting our experience with hypofractionated radiotherapy in treating the axilla. The Left Anterior Descending (LAD) coronary artery is the structure that receives maximum dose when left chest wall is irradiated [8]. In our study, dose to LAD was not studied. LAD coronary artery is the structure that is commonly affected by myocardial infarction.

The benefits of hypofractionated radiotherapy, in terms of financial benefits and Quality of Life of patients were not studied. Late effects on normal tissues require long term follow up. Locoregional control also requires minimum of five years of follow up. This was not feasible during the term of this study.

Conclusion

Hypofractionated post mastectomy irradiation was well tolerated by our patients in terms of acute toxicities. There were no significant toxicity upto six weeks post treatment. The rate and severity of acute side effects were comparable with conventional radiotherapy. Patients were very satisfied about the convenience of this shorter radiotherapy schedule. As far as feasibility was concerned, we conclude that Three Dimensional Radiotherapy based hypofractionation might not be feasible in all patients. There is a subset of patients who may benefit from IMRT. Obese patients, with left sided disease and who also require supraclavicular irradiation might benefit from IMRT.

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