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Comparative Analysis of Hypofractionation versus Conventional Fractionation During Chest Wall Irradiation in Carcinoma Breast Patients: A Dosimetric and Clinical Study

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Abstract

Introduction: Various dose fractionation schemes including conventional fractionation and hypofractionation, are in use for chest wall irradiation in carcinoma breast. Hypofractionation includes a higher dose per fraction with a smaller number of fractions with a biologically equivalent dose.

Aims: To study, analyse and compare the dosimetric and clinical outcomes using conventional fractionation versus hypofractionation. Methods and materials: This observational study includes 20 post-mastectomy patients and is randomized into two arms, with 10 patients in each arm. One arm received radiation as per conventional fractionation, and the other arm received it as per hypofractionation. 3 DCRT plans were generated, and doses to organs at risk were analysed and compared between the two groups. Patients were assessed for acute and late toxicities on follow-up, anda comparison was done between both groups.

Results: Mean dose (D mean) in ipsilateral spine, lung, esophagus, trachea, and, thyroid showed statistically significant difference. The V25 and D mean in the heart, Liver showed no statistically significant difference. Acute toxicities were higher in conventional groups, with higher grades, while late toxicities were equivalent.

Conclusion: Hypofractionation significantly reduces mean doses to organs at risk and toxicities, with comparable locoregional control; hence it is comparable to and can be used in place of conventional fractionation in post-mastectomy breast cancer patients for chest wall irradiation.

Keywords: Radiation; Breast cancer; Hypofractionation; Conventional.

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INTRODUCTION

Breast cancer is a major public health problem for women throughout the world. The incidence and mortality in the world in 2020 were 2.26 million (11.7%) and 684,996 (6.9%), respectively.[1] Management includes surgery, chemotherapy, radiation therapy, hormonal and targeted therapy. Surgeryis usually followed by radiation therapy. Radiation therapy uses various dose fractionation

schemes. Conventional fractionation includesa standard dose of 45-50.4 Gray (Gy) in 1.8-2.0 Gy fractions.[2] Hypofractionation includes a higher dose per fraction witha smaller number of fractions to reduce the overall treatment time. Our aim was to study, analyse and compare the dosimetric and clinical outcomes using conventional fractionation versus hypofractionation.

MATERIALS AND METHODS

After taking informed consent, 20 post-mastectomy breast cancer patients who attended the outpatient department between January 2020 to March 2021 were randomized in two arms with 10 patients in each and were included in this observational study.

Histologically proven breast cancer patients who underwent mastectomy and received Neo adjuvant or adjuvant chemotherapy and had a Karn of sky performance status (KPS) score of more than 70, with no distant metastasis andco-morbidities, were included in this study. The patients who defaul ted during treatment were excluded from the study. Patients' characteristics are given in table 1.

After inclusion, an or if it immobilization cast was prepared on the Breast board, and CT Simulation was done. 3 mm slices were then registered and transferred to the Eclipse treatment planning system. Clinical target volume (CTV), planning target volume (PTV), and organs at risk (OARs) like heart, spine, Right and left lung, esophagus, trachea, liver, thyroid gland, and opposite breast were delineated on the CT images using Radiation Therapy Oncology Group (RTOG) guidelines. CTV included chest wall muscle, pectoralis muscle, rib-pleural interface, and the draining lymphatic areas. To limit the inter observer variations, the target delineation in all plans was performed by the same treating physician.

In Group A, a dose of 50 Gy in 25 fractions, with 2 Gyper fraction, five days a week for five weeks,was prescribed to all the patients. A scar boost of 10 Gy in 5 fractions, with either photon or electron, was also given to some patients depending on the pathological features of the tumor. In Group B, a dose of 39.9 Gy in 15 fractions, with 2.66 Gy per fraction, five days a week for 3 weeks was prescribed to all the patients. Dose constraints for each organ at risk were used according to standard protocols, and three dimensional conformal radiation therapy (3DCRT) planning was generated for all patients. The dose constraints used are shown in table 2.[3]

In both the groups, 3DCRT with the field in the field (FIF),i.e., forward planningplans, were generated by using an Analytical anisotropic algorithm (AAA) with a 0.25 cc grid size.

During plan evaluation, the dosimetric parameters of all the plans generated by the 3 DCRT technique were compared objectively using the dose volume histograms (DVH), as shown in fig. 2. PTV coverage was compared on the basis of D95 (dose to 95% PTV), Dmean (mean dose), and Dmax (maximum dose). Dose to OARs such as ipsilateral lung, values of V20 (volume receiving 20 Gy) and Dmean; contralateral lung, values of V5 (volume receiving 5 Gy) and Dmean; heart, the value of V25 and Dmean; the esophagus, values of V45 (volume receiving 45 Gy) and Dmean; trachea, Dmean; thyroid, the value of V26 (volume receiving 26 Gy) and Dmean; liver, Dmean; and spine, Dmax were also seen and compared for patients in both the arms. The statistically significant difference between each set of dosimetric parameters was known by calculating the p-value using the Mann-Whitney U test. A value of <0.05 was considered significant.

The treatment was delivered with Medical Linear Accelerator Clinac DMX (Varian Medical Systems Pvt. Ltd., Palo Alto, CA, USA). Orthogonal Portal Images (OPI) or Cone Beam CT (CBCT) images were taken using on board imaging system (OBI) associated with (Clinac) to verify the patient's position. After verifying and applying the required shift, plans were delivered.

All the patients in both the arms were regularly monitored for acute toxicities during the course of radiotherapy and post-radiotherapy for late toxicities up to a period of 6 months. The acute and late toxicities were noted and recorded according to the grades as per CTCAE (Common terminology criteria for adverse events) version[5,4] and RTOG.[5] Required statistical tests (mean, standard deviation, etc.) were applied wherever required in analysing dosimetric parameters and toxicities.

Table 1: Characteristics of Study Population

Number of patients	20
Age (years)	Range: 27-80; Mean: 54;
Gender	Female
Tumor site	Breast
Side of breast	Right: 60%; Left: 40%
Histology	Infiltrating ductal carcinoma: 85%; Others: 15%
Stage	Stage I-IIA (TNM staging)

Table 2: Dose constraints for organs at risk (OARs)

Organs at risk	Dose constraints
Ipsilateral lung	V20 <10%
Contralateral lung	V5 <60%
Heart	V25 <20%
Spine	Dmax 1% <45Gy
Esophagus	V45 <33%
Liver	Mean dose <32Gy
Trachea	Mean dose <44GY
Thyroid	V26 <20%

V20 = volume receiving 20Gy, V5 = volume receiving 5Gy, V25 =volume receiving 25Gy,

V45 = volume receiving 45Gy, V26 = volume receiving 26Gy. Dmax = Maximum dose received by 1%.

RESULTS

The dosimetric comparison of all the OARs was done using an appropriate statistical test. The mean dose received by theipsilateral lung is 13 +_2Gy and 17.8+_ 2.7Gy. The V20 volume is 300+_ 66 and 371+_ 100cc in the hypofractionation and conventional fractionation group, respectively, i.e., in conventional fractionation the ipsilateral lung received higher doses which is statistically significant (p-value of 0.165 for V20 and 0.0007 for mean dose). The mean V5 (volume receiving 5 Gy) and the D Mean for contralateral lung in both groups were statistically not significant with a p-value of 0.217 and 0.089 respectively. The V25 (volume receiving 25 Gy) is 25.87 and 24.66 and the D meanis 406 and 409, respectively for hypofractionation and conventional fractionation group and was statistically not significant with a p value of 1.02 and 0.853 respectively. Hence, we can say that both fractionation schedules produce similar effects and are feasible for treatment. (Table 3)

The V45 (volume receiving 45 Gy) (0.0007 and 0.353mm^3) and the D mean(282 and 499) in esophagusinthe hypo fractionation and conventional fractionation groups was statistically significant with a p-value of 0.004 and 0.028 respectively. The D mean in trachea in both the groups was statistically significant with a p-value of 0.043.The V26 (volume receiving 26 Gy) in thyroid in both groups was statistically not significant with a p-value of 0.315, while the D mean in thyroid was statistically significant with a p-value of 0.001. The D mean in liver in both the groups was statistically not significant with a p-value of 0.739. The difference between Dmax (the highest dose received by at least 1% volume of spine) in the spine is 21.7, and 40.01 in both the groups was statistically significant with a p-value of 0.0003. (Table 4). Hence hypofractionation is a better option than conventional fractionation and reduces the overall treatment time.

The acute and late toxicities in the conventional fractionation and hypofractionation groups were compared. Grade III Skin reactions were seen in the Conventional group and none of the patients had Grade III reactions in Hypo fractionated group which was statistically significant with a p-value of 0.002. None of the patients in both the groups showed any Contralateral breast oedemaor Radiation induced pneumonitis and showed no statistically significant difference in both groups (Table 4). Two and three patients showed mild arm e dema in Hypo fractionation and conventional fractionation groups respectivelywhich was not statistically significant with a p value of 0.5. Fisher's Exact test was applied. None of the patients showed any Post-radiation fibrosis ortelangiectasis in contralateral breast. Also none of the patients showed radiation induced fibrosis in lungs in both the groups and wasstatistically not significant.

Table 3: Comparison of mean doses to organs at risk

Organs at risk	Dosimetric Parameters	Conventional fractionation (Mean ± SD)	Hypofractionation (Mean ± SD)	P value
Lung ipsilateral	V20 (mm3)	371.46 ± 101.8	300 ± 66.8	0.165
	Dmean (cGy)	1782.63 ± 279.82	1305.58 ± 220.33	0.0007
Lung contralateral	V5 (mm3)	3.70 ± 8.94	0.639 ± 1.81	0.217
	Dmean (cGy)	48.68 ± 16.21	48.11 ± 52.92	0.089
Heart	V25 (mm3)	24.66 ± 31.30	25.87 ± 35.09	1.0295
	Dmean (cGy)	409.95 ± 361.18	406.78 ± 324.01	0.853
Esophagus	V45 (mm3)	0.353 ± 0.593	0.00079 ± 0.00086	0.004
	Dmean (cGy)	499.7 ± 272.48	282.24 ± 263.26	0.028
Trachea	Dmean (cGy)	730.56 ± 302.16	435.48 ± 311.54	0.043

Thyroid	V26 (mm3)	4.25 ± 1.169	4.58 ± 5.57	0.315
	Dmean (cGy)	2270.98 ± 491.04	1242.43 ± 745.27	0.001
Liver	Dmean (cGy)	143.8 ± 168.03	158.26 ± 158.11	0.739
Spine	Dmax (cGy)	4001.04 ± 731.10	2173.22 ± 1434.16	0.0003

SD = Standard deviation. V20 = volume receiving 20Gy, V5 = volume receiving 5Gy, V25 = volume receiving 25Gy, V45 = volume receiving 45Gy, V26 = volume receiving 26Gy. D max = Maximum dose received by 1%. D mean = mean dose. mm3 = cubic millimeter. C Gy =Centigray.

Table 4: Comparison of acute toxicities between conventional and hypofractionation groups

Acute Toxicity	Hypofractionation Group (Number of patients)				Conventional Group (Number of patients)				P Value
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	
Skin reactions	7	3	0	0	0	6	4	0	0.002
Contralateral breast edema	10	0	0	0	10	0	0	0	Not significant
Radiation induced pneumonitis	10	0	0	0	10	0	0	0	Not significant

Chi square test applied.

Table 5: Comparison of late toxicities between conventional and hypofractionation groups

Late Toxicity	Hypofractionation Group (Number of patients)				Conventional Group (Number of patients)				P Value
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	
Arm edema	8	2	0	-	7	3	0	-	0.5
Post-radiation fibrosis	10	0	0	-	10	0	0	-	Not significant
Telangiectasis in contralateral breast	10	0	0	-	10	0	0	-	Not significant
Radiation induced fibrosis	10	0	0	0	10	0	0	0	Not significant

Productive cough also showed no statistically significant difference in both groups. (Table 5).

DISCUSSION

Females with breast cancer are usually prescribed radiotherapy after tumour excision or mastectomy and the effective dose of radiation is adjusted to balance the risk of local recurrence against the risk of harmful effects on the healthy tissues. Treatment with Radiotherapy reduces the risk of local relapses by about 70% and reduces breast cancer mortality.[6] The most frequently used schedule is 50 Gy in 25 fractions over 5 weeks. This schedule is based on an assumption that a high dose delivered in small fractions of 2•0 Gy to keep the amount of normal tissue damage to a minimum as well as gaining the maximum level of tumour control. This perception was strengthened because the early studies of hypofractionation did not use adequate reductions in the total dose and reported unacceptably high rates of normal tissue injury.[7]

Normal and malignant tissues varies in response to dose per fraction and is termed as fractionation sensitivity. The lower the ratio α / β, the greater is the effect of dose per fraction on normal and malignant tissues. Healthy tissues of the breast and ribcage with α/β value of 5 Gy and are sensitive to dose per fraction,[8] so small change in fraction size can produce a large change in the effect of radiotherapy on these tissues. This sensitivity is typical of late reacting normal tissues which takes months or years to develop atrophy or fibrosis after radiotherapy.

Some trials have tested the hypothesis that

breast cancer cells are as sensitive to the fraction size as the normal tissues of the breast and underlying rib cage.[9,10] If confirmed, these findings could indicate that small fraction sizes of 2•0 Gy or less offer no therapeutic advantage, and that a more effective strategy would be to deliver fewer but larger fractions to a lower total dose. Between 1986 and 1998, the Royal Marsden Hospital (RMH) and Gloucestershire Oncology Centre (GOC) in the UK, 1410 patients were taken up for whole breast radiotherapy after breast conservation surgery were randomised to 50 Gy in 25 fractions in 5 weeks or 39 Gy in 3•0 Gy per fractions and 42•9 Gy in 3•3 Gy per fractions in 3 weeks.[9,10] The primary endpoint was late normal tissue effects and local tumour control as a secondary endpoint. The results were consistent with breast cancer having a similar sensitivity to fraction size as the late reacting healthy tissues without affecting the local control and cosmesis.[11]

Another Canadian trial,[12] which compared whole breast irradiation of 42.5 Gy in 16 fractions over 22 days with 50Gy in 25 fractions over 35 days in post -lumpectomy breast cancer patients, showed that there was no difference in disease free and overall survival rates with equivalent global cosmetic outcomes in both the groups. It was concluded that 22-day schedule was an acceptable alternative to the conventional 35-day schedule without affecting the results and toxicity.

The results of START A trial are consistent with the hypothesis that breast cancer is as sensitive to dose per fraction as the normal tissues. In START A trial, 41•6 Gy in 13 fractions was similar to the control regimen of 50 Gy in 25 fractions in terms of normal tissue effects and also in terms of local tumour control. In the START A trial[2] also it was observed that skin reactions were more in the 50 Gy group as compared to 41.6 Gy group and 39 Gy group, which is similar to our study. This result is also consistent with START B Trial, in which 40 Gy in 15 fractions over 3 weeks were found to be at least as safe and effective as 50 Gy in 25 fractions. The combined trials present increasing evidence that hypofractionation is a safe and effective approach to the breast cancer radiotherapy and the similar results are seen in our study also.

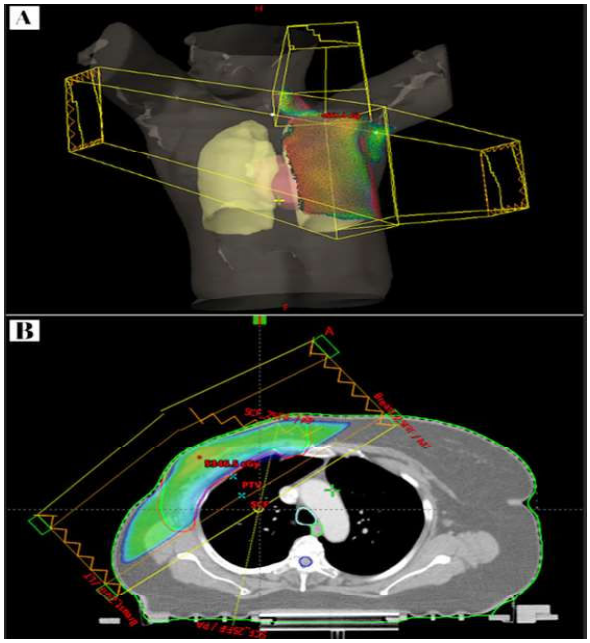

Fig. 1: 3D-CRT field arrangement in a post-mastectomy breast cancer patient *A*. Cross-sectional view. *B*. Three dimensional view.

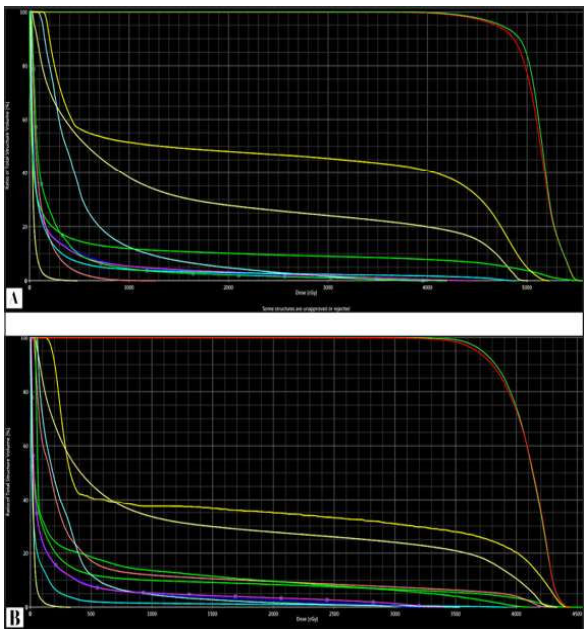

Fig. 2: Dose volume histogram (DVH) comparing target volume coverage and doses to organs at risk in postmastectomy breast cancer patient undergoing radiation therapy using *A*. Conventional fractionation and *B*. Hypofractionation.

Other acute side effects, like contralateral breast edema and radiation induced pneumonitis, were similar in both the groups with no significant difference. Hence, it can be concluded that acute toxicities are less common and less severe in hypofractionation group as compared to the conventional group.

The most commonly observed late normal tissue

effect was arm edema on the ipsilateral side. The arm edema was found to be equivalent in frequency and severity in both the groups. In START A trial[2] it was observed that rates of moderate or marked normal tissue effects were lower after 39 Gy group as compared to 50 Gy group, with a significantly lower rate of change in skin appearance in 39 Gy group. These results are based on long term follow up of the patients of up to five years in START A trial, hence cannot be compared with the results in our study which is only based on follow-up of six months to one year. Further follow-up of patients in our study groups is required to make more precise conclusions.

Other late side effects like post-radiation fibrosis in contralateral breast, telangiectasis in contralateral breast, radiation induced lung fibrosis, and productive cough were found to be similar in both the groups with no significant difference. In the START A trial, it was observed that moderate or marked breast induration, telangiectasia, and breast edema were significantly less common in the 39 Gy group than in the 50 Gy group.[13]

In the START B trial,[13] there was no difference between the two treatment arms for the primary end point of locoregional failure. It was observed that for the late normal tissue, breast shrinkage, telangiectasia, and breast edema were significantly less common in the hypofractionation group than in the conventional fractionation group. And these results are comparable to the results drawn from our study.

In this study, we have analysed the dosimetry of OARs and the acute and late toxicities of hypofractionation and conventional fractionation groups and compared the two groups in all of these parameters. We have shown that irradiation of chest wall with hypofractionation is equivalent to that with conventional fractionation in terms of these parameters and can be considered an alternative to conventional fractionation with a better toxicity profile, lesser treatment time, and better patient compliance. No locoregional recurrences were observed during the follow up period.

One of the limitations of our present study is smaller sample size and equivalent number of patients with right and left sided disease, which is significant regarding doses to OARs which can be affected by the laterality of the disease.

CONCLUSION

We conclude that in patients with early stage carcinoma breast who underwent mastectomy, hypofractionation shows comparable results to conventional fractionation for post-operative radiation therapy in terms of locoregional control. Hypofractionation shows significant advantages over conventional fractionation in terms of duration of treatment, lesser side effects, and better patient compliance.

Hence, hypofractionation schedule can be employed in place of conventional fractionation when the patient is an eligible candidate, prefers shorter course of treatment, wants to avoid distressing side effects of radiation and when the patient load on the treatment facility is high and patient care cannot be compromised.

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