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HYPOFRACTIONATION RADIATION TREATMENT IN CARCINOMA BREAST: AN AADHAR HOSPITAL EXPERIENCE

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ABSTRACT

BACKGROUND: Post-operative radiation treatment to chest wall and draining lymph nodes after surgery in carcinoma breast is an established treatment. Start A and Start B trials had suggested that shorter course of radiation can be delivered without compromising efficacy and minimal side effect.

MATERIAL, METHODS & RESULT: At AADHAR HOSPITAL a retrospective study of carcinoma breast patients presenting to department of radiation from Jan 2017 to Dec 2019. Total of 157 patients were eligible for evaluation and divided in two groups: Group I- standard fractionation (50 Gy/28 F/5.3 wks in MRM patients and a boost of 10Gy/5 F/1 wk for BCS patients, n=90) and Group II hyprofractionation (41 Gy/15F/ 3 Wks to MRM and 7 Gy/ 3F/ 3 days to BCS patients, n=57). All the patients were assessed after radiation, two weeks after radiation, 6 weeks after radiation and at last FU. Radiation toxicity, any local recurrence and any cardiac or respiratory events were noted during this period. There was no difference in the two groups.

CONCLUSIONS: Hypofractionation should be the new standard of care and should be offered to most women as it is more convenient and cost-effective. This approach can be both safe and effective and shows even lesser acute radiation toxicity.

KEYWORDS : Carcinoma Breast, Hypofractionation, radiation in carcinoma breast

INTRODUCTION

Carcinoma of Breast ranked number one cancer among Indian females, with age adjusted rate as high as 25.8 per 100,000 women and mortality 12.7 per 100,000 women. Breast cancer projection for India during time periods 2020 suggests the number to go as high as 17979001. Radiation therapy is an essential and critical part in the management of carcinoma of breast. The adjuvant radiotherapy after radical surgery resulted in an improvement rate of local recurrence by 2⁄3 to 3⁄4 (70%) as compared to surgery alone. Radiation contributes improvement of overall survival when combined with systemic therapy[2,3].

Numerous trials had established the efficacy of post - operative radiation treatment to chest wall and draining lymph nodes when compared with surgery alone. The standard chest wall radiation is daily fraction sizes of 1.8 Gy or 2 Gy are commonly used4-10.

A meta-analysis by Early Breast Cancer Trialists' Collaborative Group (EBCTCG) for radiation treatment and surgery for early stage breast cancer have shown that breast-conserving surgery (BCS) followed by whole breast RT is equivalent to mastectomy and is superior to BCS alone in terms of local control and overall survival.[11,12]

It has been proved in randomized trials, that the relative risk reductions from Radiation Treatment after BCS did not depend on the dose/fractionation used. However, standard post-BCS fractionation requires daily treatment of 1.8–2 Gy/d for 5–6 weeks, with or without a boost.[13–17]

Evidence has been accumulating over the past two decades, from the prospective randomized trials, which compares shorter RT courses to 50 Gy in 25 daily fractions. These trials have confirmed that shorter courses of RT are equally effective compared to longer Radiation schedules for women with invasive18–23 or in situ breast cancer,24–27 if the total dose of Radiation is appropriately reduced. Shorter Radiation courses also result in improved quality of life, convenience and lower treatment delivery resources28. It has been suggested that shorter fractionation schedule should be the new standard of care after BCS for early stage breast cancer 29.

The linear quadratic model of fractionation effects has been used to describe the relationship between fraction size/total dose and tissue response.30 The biological effects of various Radiation Treatment schedules can be estimated by using a linear quadratic formula based on the dose delivered every day, the total number of treatments, the time duration over which the treatment was delivered, and a tissue end point-specific constant called the α/β ratio. The α/β ratios are lower for slowly responding tissues, including late fibrosis effects in normal tissues, whereas α/β ratios are higher for more rapidly proliferating tissues, including many tumors. Two approaches to estimate the equivalence of different RT schedules have been proposed, the relative biological effective dose (BED) model and the equivalent dose at 2 Gy per fraction (EQD2) model.31 Whole breast Radiation Therapy schedules using 15–16 daily treatments following BCS have become widely accepted in few parts of world.

Breast cancer cells seem to possess fraction sensitivities similar to normal tissues; thus, the primary rationale for prolonged fractionation is not applicable. The reported α/β ratio (the linear quadratic parameter describing how sensitive cells are to high fractional doses) for breast cancer is approximately 4 Gy, which is quite low and similar to normal tissues.32 For this reason, shorter and more convenient schedules have been studied. These hypofractionated (HF) schedules are now considered an acceptable, and even preferred, standard of care in the adjuvant, intact-breast population. The largest randomized trials to study HF were the UK START A and B trials.

The START A trial randomly assigned women with pT1-3a, pN0-1 breast cancer after either lumpectomy or mastectomy (15%) to one of three radiation treatment arms, with treatment time remaining constant, spanning 5 weeks.32 The control arm was standard fractionation (50 Gy in 25 fractions) versus 39 Gy in 13 fractions versus 41.6 Gy in 13 fractions. Simultaneously, the START B trial randomly assigned women who had undergone a lumpectomy or mastectomy (8%) with pT1-3a, pN0-1 breast cancer to standard fractionation in 5 to 6 weeks versus 40 Gy in 15 fractions over 3 weeks.33 There was no difference in loco regional recurrence in either the START A or B trials,34 and late breast changes seemed to be better with HF. Still, data for the Post Mastectomy Radiation Therapy setting are lacking, and hypofractionation is not routinely considered because of potential toxicity, particularly when irradiating regional lymph nodes and patients who have undergone breast reconstruction[34].

It has been observed that adjuvant breast RT is associated with a small but statistically significant increased risk of cerebrovascular and cardiac complications leading to hospitalizations or deaths,35–38 and second malignacies,39 but it was also observed that these risks were not higher among patients treated with hypofractionation (2.7 Gy/d) as compared to 2 Gy/d RT schedules. One report suggested that severe hypofractionation (43 Gy in 10 daily fractions) may increase the risk of cardiac injury.38 However, in the START A and B trials, the rate of confirmed ischemic heart disease in patients with left-sided breast cancer was not different between short and longer fractionation, although at a follow-up of 10 years, somewhat early for this end point.40 Also to avoid cardiac injury, to achieve more uniform dose distribution, to decrease heart dose, to decrease lung dose, to achieve less scatter dose to contralateral breast, absence of physical wedge, better dose distribution for bilateral disease every effort should be made to exclude the heart from the therapeutic beam, no matter what fractionation is used[40].

Providing whole breast RT in 15–16 treatment sessions is more convenient and preferred by patients compared to RT extending over 5–7 weeks and has been associated with more prompt recovery and improved quality of life compared to longer RT courses28. Shorter RT schedules significantly reduces resource utilization and are beneficial to the capacity and sustainability of the health care system.31 Development of radiation-induced brachial plexopathy (RIBP) is of concern in hypofractionated treatment to the supraclavicular lymph nodes.

Two decades of observations from randomized trials and institutional series have demonstrated that following BCS, whole breast doses of 40 Gy/15 fr or 42.5 Gy/16 fr are as safe and effective as 50 Gy/25 fr. Evidence has been obtained from randomized trials and institutional series that hypofractionation is also effective and safe for adjuvant treatment of the regional lymph nodes. However, short fractionation is not appropriate for all patients. Patients with postoperative complications, those with large breasts for whom a maximum dose of 107% is not achievable, or patients with implants for augmentation or reconstruction have an increased risk for late fibrosis or cosmetic deterioration following RT. They should receive a whole breast or chest wall dose that is biologically less intense,[41].

Astro has laid down guideline for hypofractionation schedule of radiation treatment as shown in Table [115].

MATERIAL & METHODS

We at AADHAR HEALTH INSTITUTE, HISAR conducted a retrospective analysis of our patients of carcinoma breast who presented at the department of radiation oncology for post-op adjuvant radiation treatment. We changed our practices after January 2019 from standard treatment, and adopted treating patients with hypofractionation schedule as per the START TRIAL B. From 2016 to 2018, all patients of carcinoma breast who presented to our department, were treated with standard fractionation i.e. 50 Gy/ 28 F/ 5.3 wks. in mastectomy patients and in breast conservation surgery patients were given boost of 10Gy/ 5 F/ 2 wks. to tumor bed. From January 2019 we started treating patients with 41.6 Gy/15 F /3 wks. to mastectomy patients and a boost of 6.4Gy/3 F / 3 d to tumor bed in breast conservation patients.

Table I: Astro Guideline for hypofractionation radiation treatment in Ca Breast[15]

Hypofractionated Whole Breast RT ASTRO Consensus Statement	Indications Beyond ASTRO Guidelines
• 50 years or older, • T1-2, N0, • Breast Conservation Surgery • No chemotherapy, • Dosimetric criteria: – Dose minimum >93% – Dose maximum <107%	• < 50 years of age • High-grade tumours, Ductal carcinoma in situ (DCIS), • Regional nodal irradiation; • Patients with large breasts.

All patients presenting to department of radiation for adjuvant radiation treatment were biopsied and had undergone radical surgery in the form of modified radical mastectomy (MRM) or lumpectomy (wide local excision of lump) with axillary clearance (breast conservation surgery BCS). All patients were females of more than 20 years of age and were married. All patients had undergone chemotherapy with Epirubicin and Taxol based regimens after surgery. Almost all patients were investigated for ER/PR and HER-2- neu receptors. In patients where HER-2-neu receptors were 3+, were offered treatment with inj. Transtuzumab (FINHER protocol or for one year or as per the affordability of the patients). Hormone manipulation was done in patients with ER/PR receptor positive after radiation treatment.

We analyzed the data on the basis of: feasibility at a peripheral center, toxicity profile during radiation treatment and after the radiation on follow up and short-term recurrences if any in both the groups.

A total of 195 patients of carcinoma breast presented to Department of radiation oncology from 1st Jan 2017 to 31 Dec 2019. Out of these 195 patients only 147 patients were included for evaluation. Forty - eight patients (with metastasis to brain, extensive metastases or where palliative radiation treatment were delivered), were excluded from the retrospective analysis. One patient had double malignancy (breast with esophagus) and four patients had bilateral breast, these were also excluded from the analysis.

Patients were divided in two groups: Group I - radiation treatment given was standard fractionation to a dose of 50Gy /28 F/ 5.3 wks. to chest wall and drainage area. In Group II - radiation treatment was delivered with hypofractionation schedule to a dose of 41.6 Gy/15 F/ 3 wks. to chest wall and drainage area. A boost of 10Gy/ 5 F/ 1 wks. or 6.4 Gy/ 3F/ 3 d were given in breast conservation patients in respective groups. In Group I 90 patients were eligible for retrospective analysis whereas 57 patients were eligible in Group II. The detailed demographic profile is given in table II. The two groups were fairly matched. Two patients in group II had metastatic disease and were considered for analysis as they had metastasis in bone at one site and had good response to chemotherapy.

In all patients, 4 clamp chest orifit was made for immobilization. Planning CT Scan neck, chest and upper abdomen was done for simulation and was mandatory. Radiation treatment were started after three to four weeks of chemotherapy. No hormonal treatment was given along with radiation treatment. Patients were planned with eclipse planning system version 13.7.

Table II: Demographic Profile Of The Two Groups Group I(n=90) Group II(n=57)

Characteristics	Number of patients	Number of patients
Age – years		
<30	8	2
31-40	18	10
41-50	24	23
51-60	23	17
61-70	13	5
>70	4	Nil
Staging		
Tx	0	1
T0	0	1
T1	6	5
T2	43	36
T3	30	10
T4	9	4
N0	17	19
N1	30	12
N2	23	18
N3	15	8
M1	1	2
ER +ve	41	26
PR +ve	35	25
Her-2neu +ve	32	21
Triple -ve	14	4
Type of Surgery		
MRM	70	41
BCS	20	16
Radiation Therapy		
3-DCRT	35	16
IMRT	24	13
IGRT	31	28
Laterality		
Right	43	26
Left	47	31

Plan were executed with cone beam CT scan on day 1 in all patients and then according to protocol of IMRT/IGRT. We delivered a dose of 5040 cGy/ 28F/5.3 wks. to chest wall in Group I (standard protocol) and 4160cGy/15 F/ 3 wks. in Group II with a α/β ratio of 3.02 using linear quadratic equation and one fraction per day/ five fraction per week were delivered. Tangential fields were used for planning and limiting dose to deeper structure as per standard of care. The heart was excluded from primary beam using MLC and restricted breathing by chest compression by orifit. No part of heart received more than 2 Gy per fraction and total mean dose was kept less than 5 Gy in left laterality (on right side tumor, less than 2 Gy) was achieved. Dose homogeneity with in the target volume was required to be within 95% to 115% of the prescribed dose was achieved. Draining lymph nodes were treated with a supraclavicular and anterior axillary fields were used. Brachial plexus was not contoured but to restrain the dose, a maximum dose exceeding 107% was not allowed in supraclavicular and axillary volumes.

RESULTS

All the patients were reviewed weekly during the radiation treatment, on the last day of radiation, after two weeks of completion of radiation and after 4 weeks of first follow up. Details of the radiation induced side effect is given in table III. Acute radiation dermatitis maximum of Grade II reaction was seen in 90% of patients of group I in fifth week and in nearly 60% of patients in group II on first follow up that is after 15 days of radiation. No Grade III/IV toxicity was seen. No untoward incident was observed that may result in stopping of radiation in both the groups. No other significant side effect was observed in both the group. No cardiac event occurred in any patients in both the groups. On follow up, we don't find any cardiac toxicity or any significant brachial plexopathy. Few patients had incidences of lymphedema (maximum grade II) to the operated arm after two months (six months of surgery) of radiation treatment. None had severe Lymphedema even at the last follow up. Group I patients had maximum follow up of approximately of three years (patients where first radiation treatment delivered in January, 2017) and in Group II was one and a half year (patients where radiation treatment ended in January 2019)

Table III: Radiation induced toxicities (maximum grade II) during and after radiation treatment

	GROUP I (n = 90)				Group II (n = 57)			
	At the end of RT	After 2wksof radiation	After 4 wksof 1st FU	At last FU	At the end of RT	After 2 wks. of radiation	After 4 wksof 1st FU	At last FU
Cutaneous	83	34	Nil	Nil	3	21	Nil	Nil
Odynophagia	19	7	Nil	Nil	13	4	Nil	Nil
Lymphedema	13	27	34	49	4	11	13	22
Respiratory events	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
Cardiac events	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
Brachial plexopathy	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil

After one and half months of completion of radiation treatment, the patients were reviewed after every three months and routine investigation USG abdomen, X ray Chest were done to rule out any metastasis. Two patients from group I developed local recurrences after two years and none from Group II had local recurrence.

Our retrospective analysis has lesser follow up of group II patients (around one and half years) and also the number of patients were less. More patients are being recruited in group II that is, in the hypofractionation arm.

CONCLUSION

We conclude that a shorter Radiation Treatment course (41 Gy in 15 F over three weeks in post mastectomy and 47 Gy in 18 F over three and half weeks) is feasible at peripheral centers with lesser toxicity. Hypofractionation should be the new standard of care and should be offered to most women as it is more convenient and cost-effective. This approach can be both safe and effective and shows even lesser acute radiation toxicity.

FUTURE DIRECTION

A multi centric, prospective, randomized, larger study involving a greater number of patients and longer follow up should be conducted.

AUTHORS' CONTRIBUTIONS

The presented work was performed in collaboration with all authors. Dr. Arun Kumar Aggarwal, Dr Tejpal Sharma, Dr. Bharat Bhushan, and Anuradha Rani contributed equally to this work. Dr. Lovenish Goyal, and Dr Harish and are members of Tumor board. All authors have read and approved the final version of the manuscript.

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