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A Comparative study between two different Radiotherapy fractionation regimens in patients of Carcinoma Breast

Sanjay Singh Chandel[1], Ashutosh Mishra[2], A.K. Nigam[3], Durgesh Shukla[4]*

ABSTRACT

Introduction

Breast cancer is one of the most common types of cancer in females throughout the world. Early diagnosis and prompt treatment is very important in patients of breast cancer. Various treatment modalities are being employed to treat breast cancer which includes surgery, chemotherapy, radiotherapy, hormonal therapy and immunotherapy. This study emphasizes the radiotherapy part by comparing two different radiotherapy schedules.

Aim

To compare two different radiotherapies fractionation regimens in terms of better compatibility with respect to patients and institute.

Material and methods

In this study we have divided 80 patients in two groups which are Conventional Fractionation Radiotherapy (CFRT) arm and Hypofractionation Radiotherapy (HFRT) arm. External beam radiotherapy with 50 Gy in 25 fractions of 2.0 Gy/fraction over 5 weeks was given in the former arm, while 40 Gy in 15 fractions of 2.67 Gy/fraction over 3 weeks to the later arm. External beam radiotherapy (EBRT) was given by Bhabhatron II with radioactive cobalt - 60 isotope as the source of radiation having 1.25MeV energy. After completing radiotherapy, patients were followed up every three monthly and reviewed. Patients were assessed in terms of toxicities associated with both the regimens and compliance of patients towards treatment. Institutional feasibility was also observed in terms of patient's load management.

Results

Inference drawn from this study is that, either of the two schedules can be employed when toxicities as a criterion is considered, because both schedules are responsible for more or less late toxicities. In terms of compliance, patients were more compliant in the HFRT arm than CFRT and the result was not statistically significant.

Conclusion

A radiation schedule delivering 40 Gy in 15 fractions seems to offer lower rates of late adverse effects at least as favorable as the standard schedule of 50 Gy and 25 fractions, though statistically it is not significant when we compare it with the CFRT arm. HFRT aids in treating large numbers of patients in a shorter time. HFRT favors choice of schedule in terms of patient's and institutional benefit. Thus, HFRT can be considered as a radiotherapy schedule of choice in highly patient loaded government institutes.

Keywords: Breast Cancer, Hypofractionation, Radiotherapy, Toxicities

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2*Corresponding author: Ashutosh Mishra, Senior Resident, Radiation Oncology, GRMC Gwalior; 1.Sanjay Singh Chandel, Professor and HOD, Radiation Oncology, GRMC Gwalior; 3. A.K. Nigam, Professor& Dean, Radiation Oncology, GRMC Gwalior; 4.Durgesh Shukla, Demonstrator cum Statistician, Department of Community medicine, GRMC Gwalior

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INTRODUCTION

Breast cancer is a malignant disease and is a most common cancer in women. All women, especially as they age, are at risk of developing breast malignancy. When diagnosed at early stages, breast cancer has a very good prognosis and is treatable by various modalities. Local treatments are employed to remove, kill or destroy cancer cells in the local area. It includes surgery and radiation therapy. Systemic treatments are employed to destroy or control cancer cells all over the body. It includes chemotherapy and hormonal therapy.

Radiation therapy uses high energy X-rays beams to kill cancer cells. Radiation therapy is usually planned after surgical management of breast cancer. Since Radiotherapy is an important modality without which treatment of breast cancer is considered incomplete, various Radiotherapy regimens based on time dose fractionation are being employed. It is well accepted that post mastectomy radiotherapy (PMRT) improves long-term outcomes by reducing local recurrence and cancer mortality in breast cancer after mastectomy [1, 2]. The current conventional fractionated radiotherapy (CFRT) is 50 Gy fractionation divided into 25 fractions of 2 Gy over 5 weeks, once a day [3]. However, this daily treatment takes five or more weeks, causing inconvenience to patients in terms of life, work, time as a result could be affected socioeconomically and emotionally [4]. The aim of hypo fractionated radiotherapy (HFRT) is to shorten the overall treatment time for patients by increasing the single dose of radiation, thereby providing greater convenience while bringing greater cost effectiveness and less resource waste to the entire healthcare system [5]. The commonly used hypo fractionated scheme is 43.5 Gy in 15 fractions over 15 days or 42.56 Gy in 16 fractions over 16 days [6].

Methodology

The objective was to directly compare the safety and effectiveness through Randomized Control Trials, between HFRT and CFRT among breast cancer patients. Eighty patients who had breast cancer (stage I and II) were selected for study. They were enrolled in the department of Radiation Oncology, GR Medical College Gwalior from January 2012 to December 2014. Patient's details are charted in Table 1. Retrospective and prospective evaluation of 80 women was conducted. The selection of the patients for this study had stringent selection criteria. Eligibility criteria were age between 25 to 65 years, females, no prior chest irradiation and were available for follow-up. Histopathologically, all selected patients were deemed malignant with infiltrating ductal carcinoma as subtype in the HPE report. All patients were operated (Mastectomy) and have received 6 cycles of chemotherapy CAF (Endoxon, Adriamycin, 5FU) or CEF (Endoxon, Epirubicin, 5FU). There were two arms in which patients were divided randomly. External beam radiotherapy with 50 Gy in 25 fractions of 2.0 Gy/fraction over 5 weeks was given in one arm, while 40 Gy in 15 fractions of 2.67 Gy/fraction over 3 weeks to another arm. External beam radiotherapy (EBRT) was given by Bhabhatron II with radioactive cobalt -60 isotope as the source of radiation having 1.25MeV energy. Patients were treated with a megavoltage beam in tangential portals. Dose was prescribed to a calculation point in the breast, within 2 cm of the chest wall–lung interface. Patient positioned in supine position, ipsilateral arm abducted and externally rotated and neck tilted to opposite side. Inclusion of the undissected low axilla (levels I and II) in radiation fields was permitted if clinically indicated. A working committee that consisted of physicians, senior residents, nurses, medical physicists, and radiotherapy technicians was given the task of reviewing available data for the support of each directive, specifying patient selection criteria, and providing prescription, dosimetry, and simulation instructions. Written and informed consent of all the selected patients were obtained. All patients were evaluated before commencing radiation therapy. They were also evaluated weekly during and after completion of Radiotherapy by Radiation Oncologist for normal tissue reaction and tumor response.

Dosage of hormonal therapy in patients with hormone receptors positive (ER/PR/ Her2 neu) was unaltered. Routine investigations were conducted and supportive treatment was given if required. Toxicities were assessed and graded as per Radiation Therapy Oncology Group (RTOG) criteria. Patients were assessed and examined after completion of Radiotherapy and then at 6 weeks followed by 3 monthly bases up to 2 years then 6 monthly. Hemogram, ultrasonography and chest X-ray were carried out if it seemed indicated.

Patients' characteristics

Table 1: Characteristics of patients in both the arms.

Characteristics	Conventional RT group (Arm A)	Hypofractionated RT group (Arm B)	p-value	Test (Chi Square test/ t-test)
Mean Age	45.6 ± 8.3	48.2 ± 8.1	0.16	1.41
Menstrual status **1. Premenopausal** **2. Postmenopausal**	 21 19	 24 16	0.50	0.45
Pathological Staging **1. Stage I** **2. Stage II** **3. Stage III** **4. Stage IV**	 0 T2N0= 2 T2N1= 4 T3N0= 6 T2N2= 8 T1N2= 17 T3N1=2 T4N2= 1 0	 0 T2N0= 4 T2N1= 2 T3N0= 8 T2N2= 6 T1N2= 15 T3N1=5 T4N2= 0 0	0.48	1.47
Grade **1. Grade 1** **2. Grade 2** **3. Grade 3**	 0 31 9	 2 28 10	2.20	0.33
Chemotherapy **1. Neoadjuvant Chemotherapy** **2. Adjuvant Chemotherapy**	 30 10	 28 12	0.62	0.25
Surgery- Radiation Gap	55.2 days ± 12.6	51.1 days ±10.2	0.11	1.60
Tumor site **1. Upper Outer Quadrant** **2. Lower Outer Quadrant** **3. Upper Inner Quadrant** **4. Lower Inner Quadrant**	 27 2 11 0	 25 5 10 0	0.49	1.41

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Results

40 women were treated with 50 Gy group and 40 women to the 40 Gy group. After a median follow-up of 22 months the rate of local-regional tumor relapse was almost similar in both groups. Acute radiation reaction was slightly higher in the 40 Gy group. Photographic and patient self-assessment indicated lower rates of late adverse effects in 40 Gy arm compared to 50 Gy arm.

Table 2: Treatment adherence of patients with two different radiotherapy schedules

Adherence to Treatment	Conventional RT Arm	Hypofractionated RT Arm	p- value	Chi-square test
Compliant	32	36	0.21	1.57
Non-Compliant	8	4		

Table 2 shows compliance of patients to radiotherapy. Compliance rate was observed better in the hypofractionation arm where the mean gap between regular treatments was 1 day, while in the conventional arm, a mean gap of 3 days was observed in between regular treatments.

Table 3: Treatment associated toxicities in two different radiotherapy schedules

Treatment Toxicities	Conventional RT Arm	Hypo fractionated RT Arm	p-value	Chi-square test
Dysphagia				
Grade 0	33	32	0.73	0.61
Grade 1	4	6		
Grade 2	3	1		
Grade 3	0	1		
Grade 4	0	0		
Acute Dermatitis				
Grade 0	5	4	0.20	4.59
Grade 1	15	16		
Grade 2	16	20		
Grade 3	4	0		
Grade 4	0	0		
Chronic Dermatitis				
Grade 0	34	35	0.65	0.85
Grade 1	5	3		
Grade 2	1	2		
Grade 3	0	0		
Grade 4	0	0		

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Radiation Pneumonitis **Grade 0** **Grade 1** **Grade 2** **Grade 3** **Grade 4**	36 2 2 0 0	33 4 3 0 0	0.61	0.99
Lymphedema **Grade 0** **Grade 1** **Grade 2** **Grade 3** **Grade 4**	35 4 1 0 0	36 4 0 0 0	0.60	1.01

Table 3 shows toxicities parameters due to Radiotherapy in both the arms. This table elucidates that high grade Dysphagia, Chronic Dermatitis and Radiation Pneumonitis were observed more in hypofractionated RT arm, on the other hand, high grade Acute Dermatitis, and Lymphedema were observed more in Conventional RT arm. Though, there were differences observed in terms of toxicities in both the arms, the results were statistically insignificant.

DISCUSSION

The conventional radiation treatment schedule after breast conservative surgery is 50 Gy in 25 daily fractions of 2 Gy over 5 weeks. However, a shorter treatment scheme (like 40.5 Gy in 15 fractions managed within approximately 3 weeks) is both safe and equally effective in such cases. The most recent National Comprehensive Cancer Network (NCCN) guidelines recommend the conventional fractionated radiotherapy (CFRT) schedule for PMRT, which consists of a total dose (TD) of 45.0 Gy to 50.4 Gy given in 25 to 28 fractions over 5 weeks or more and delivered to the chest wall and regional lymph nodes. HFRT in breast cancer is being proposed as an improved approach against traditional conventional radiotherapy based on the dynamics of breast cancer proliferation. The main purpose of HFRT is to protect normal tissues from unnecessary radiations and specifically kill tumor cells with maximum lethality. Therefore, in this study, we used data to verify the authenticity of the theory.

Due to the increase of dose per fraction and the decrease of the total dose, an important concern for HFRT has been whether to increase the toxicity and reduce the tumor control rate or not [7]. As per previous reports, breast cancer has a low ratio of α/β over the range of 2.0~4.0 Gy, and this low α/β ratio suggests that the efficacy of hypo fractionated radiotherapy regimens is equivalent to conventional fraction [8]. In Lancet Oncology, 2019, Wang et al. [9] report 5-year outcomes of a randomized, non-inferiority, open-label, phase 3 trial in China that compared postmastectomy HFRT with CFRT directed to the chest wall and the supraclavicular and level III axillary nodal regions in 820 patients with locally advanced breast cancer (at least four positive axillary lymph nodes). There were no significant differences in the 5-year cumulative incidence of loco regional recurrence, 5-year overall survival or 5-year disease-free survival between groups. Furthermore, acute and late toxicities were similar in both groups. This finding suggests that hypo fractionated postmastectomy radiotherapy (HF PMRT) is safe and effective for patients of breast cancer, having low toxicities and high local control rates. In addition, 15% (336/2236) and 8% (177/2215) of patients with postmastectomy HFRT were included in the START A and START B trials, respectively, and there was no significant difference in local recurrence or late toxicities between the two groups over a long-term follow-up of 10 years [10].

However, as per study conducted by Yarnold et al., the α/β value of breast cancer was calculated and was found to be low, approximately 4 Gy, which falls in the range 0.75–5.01 Gy. Also, the α/β value of normal breast tissue is about 3 Gy, suggesting that the sensitivity of breast cancer tissue to dose segmentation was similar to that of normal tissue [11]. In other words, HFRT could theoretically be similarly effective without a significant increase in adverse effects, making it more beneficial to breast cancer patients [12].

The Ontario [13], due to its long-term follow-up, provided especially strong evidence of non-inferiority of this method in comparison with conventionally fractionated radiotherapy. According to Hall et al. [14], "laboratory data demonstrated that, although early reactions match an appropriate adjustment of the total dose, large and fewer dose fractions are associated with more intense late reactions. Hall also inferred that "the treatment protocol with several large fractions lead to more pronounced late reactions, if the total dose is titrated to create equal early influences and a fractionated scheme. Hypo fractionated radiotherapy could aid in cancer care by mitigating financial toxicity and can be performed in most cancer centers, even at small-scale hospitals. Studies have reported that the cost of using hypo fractionated whole breast irradiation (WBI) in the United States is 31.7% lower than that of conventional fractionated WBI [15], and one study in Asia also indicated that the total cost of treatment for hypo fractionated WBI compared to conventional fractionated WBI was reduced by about one-third [16].

It should be noted that although hypo fractionated PMRT is not the same as Conventional fractionated radiotherapy in terms of dose distributions, the treatment technique and radiotherapy fraction are similar, and it can still shorten the treatment cycle, reduce the time of patient trips to the hospital, and save medical resources, which is more cost-effective. This issue is even more important in low/ middle-income countries. After analyzing the adverse reactions, we have categorized all of them according to grades. Our analysis revealed that, compared to CFRT, HFRT has significantly lower all grade and moderate/marked acute skin toxicity. Zhou et al. [17] and Andrade et al. [18] came to the same conclusion that HFRT was associated with less grade 2/3 acute skin toxicity. Furthermore, we also observed a significant improvement in terms of less pain suffered by patients in the HFRT group. The improvement in acute skin toxicity and pain relief may be due to the fact that acute toxicity is more dependent on the total dose than the fraction size [19]. Thus, HFRT may minimize the acute toxicity by decreasing the total radiation dose.

CONCLUSION

A radiation schedule delivering 40 Gy in 15 fractions seems to offer lower rates of late adverse effects at least as favorable as the standard schedule of 50 Gy and 25 fractions, though statistically it is not significant when we compare it with the CFRT arm. HFRT aids in treating large numbers of patients in a shorter time. It also helps in psychological satisfaction in patients, as most of the patients want to get treatment done as early as possible to get rid-off economic strain, mental stress etc. they are going through. As a result of our study, we suggest that 40 Gy in 15 fractions are safer and better radiotherapy regimen for highly patient loaded government set up with similar adverse effects.

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