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A COMPARATIVE STUDY OF HYPOFRACTIONATED RADIOTHERAPY VERSUS CONVENTIONALLY FRACTIONATED RADIOTHERAPY IN POST MASTECTOMY BREAST CANCER PATIENTS

Radiotherapy

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ABSTRACT

This is a prospective randomized study to compare efficacy and tolerability of hypofractionated radiotherapy (HRT) with conventionally fractionated radiotherapy (CRT) in post mastectomy breast cancer patients in terms of Acute and late toxicities and Locoregional recurrences. 73 patients were analyzed (36 in HRT arm and 37 in CRT arm) . The median follow up was 8 months (3-19 months). Grade 1acute dermatitis was observed in 63.8% patients in HRT group and 67.5% in CRT group (p=0.74). Grade 2 dermatitis in 25% of HRT and 24.3% of CRT (p=0.97) . Grade 1 acute oesophagitis was seen in 63.8% in HRT and 62.1% in CRT (p=0.88). Grade 2 acute oesophagitis was seen in 11.1% in HRT and 16.2% in CRT (p=0.52). 11.1% in HRT group and 13.5% in CRT group experienced grade 1 pneumonitis (p value= 0.75). 16.6% in HRT group and 21.6% in CRT group had grade 1 lymphedema (p value=0.59). 2.7% of CRT group had grade 2 lymphedema that is statistically insignificant (p=0.32). 27.7% in HRT group and 29.7% in CRT group had grade 1 (p = 0.85). 2.7% in HRT and 2.7% in CRT group experienced grade 2 chronic dermatitis (p=1.21) . 16.6% In HRT group and 18.9% in CRT group had grade 1 chronic oesophagitis (p =0.80). No grade 3 or grade 4 toxicities were seen in any group. One patient in CRT group had recurrence at ipsilateral supraclavicular fossa. None of the patients in HRT group had any loco regional recurrences.

KEYWORDS

Postmastectomy breast cancer, hypofractionated radiotherapy, conventionally fractionated radiotherapy, acute and late toxicities.

INTRODUCTION

Breast cancer is the leading type of cancer worldwide among females, with highest incidence of 2.3 million new cases according to GLOBOCAN 2020 and also it is the leading cause of cancer death in women (15.0% worldwide). Indian data also showed that breast cancer is the leading type of cancer (26.3%) and leading cause of cancer death in females with 10.6 to 12.1% mortality rate [1]. According to ICMR 2018, 10.7 per cent increase in breast cancer was seen in India in the last five years from 1.45 lakh cases in 2012 to 1.62 lakh cases in 2018 to 1.78 lakh cases in 2020.

Breast cancer is usually treated with multimodality approach which includes surgery, chemotherapy, radiation therapy, hormonal therapy and targeted therapy [2].

Various meta-analysis done on the breast cancer showed a significant decrease in the loco regional recurrence rates and mortality rates with the use of adjuvant radiotherapy in post mastectomy breast cancer patients [3,4].

The adjuvant radiotherapy is usually delivered as conventionally fractionated regimen which includes a total dose of 50 Gy delivered in 25 fractions, at the rate of 2Gy per fraction, 1 fraction per day, 5 fractions per week. This conventional regimen is based on a historical assumption that breast cancer is less sensitive to changes in the dose per fraction [5].

Radiobiologically, the linear-quadratic model predicts that the normal tissue toxicity is not increased when the dose per fraction is modestly increased and the total dose is reduced in breast tissue [6]. Thus, the potential advantage of hypo fractionation includes an improvement in cell killing by increasing dose per fraction and by reducing the duration of treatment. This is supported by few retrospective analyses which suggested that breast cancer might be much more sensitive to increase in radiation dose per fraction [6, 7]. Also, many prospective randomized trials have confirmed the no inferiority results of hypo fractionated radiotherapy (HRT) to conventionally fractionated radiotherapy (CRT) in post-BCS patients [6,8,9,10], only few studies were conducted in post mastectomy patients in establishing similar outcome.

Hence, there is growing interest in delivering post mastectomy radiotherapy with hypo fractionated schedules, because shorter and more convenient hypo fractionated dose schedules might help to treat more patients at reduced cost with equivalent survival and toxicity when compared to conventional RT. At our centre, majority of the patients present with locally advanced breast cancer who had undergone mastectomy and completed systemic chemotherapy and/or targeted therapy. With this background, we have conducted this prospective randomized study to compare hypo fractionated radiotherapy (HRT) with conventionally fractionated radiotherapy (CRT) regimen in post mastectomy breast cancer patients.

MATERIAL AND METHODS

This is a prospective randomized observational study conducted from March 2018 to July 2019 in histopathologically proven non metastatic carcinoma breast patients who underwent mastectomy and received neoadjuvant or adjuvant systemic chemotherapy. Patients were evaluated before radiotherapy with complete history and physical examination, ultrasound abdomen and pelvis, chest x ray, complete hemogram, renal function tests and liver function tests.

CT simulation and planning was done as per standard protocol. All patients were randomly allocated into 2 groups by computer generated random number tables. Hypo fractionated radiotherapy (**HRT)** group received 40 Gy in 15 fractions, at the rate of 2.667 Gy per fraction, 1 fraction per day, 5 fractions per week for 3 weeks and conventional radiotherapy (**CRT)** group received 50 Gy in 25 fractions, at the rate of 2 Gy per fraction, 1 fraction per day, 5 fractions per week, for 5–6 weeks, both delivered by 3DCRT technique.

All patients were reviewed weekly during radiation treatment and monthly after the completion of Radiation treatment for a period of 6 months. During each clinical visit, patients were assessed for acute and late toxicities including dermatitis, pneumonitis, oesophagitis, and lymphedema.

Symptoms occurring during the course of treatment and within 90 days after completion of treatment were classified as acute toxicities. Symptoms occurring any time after 3 months of completion of

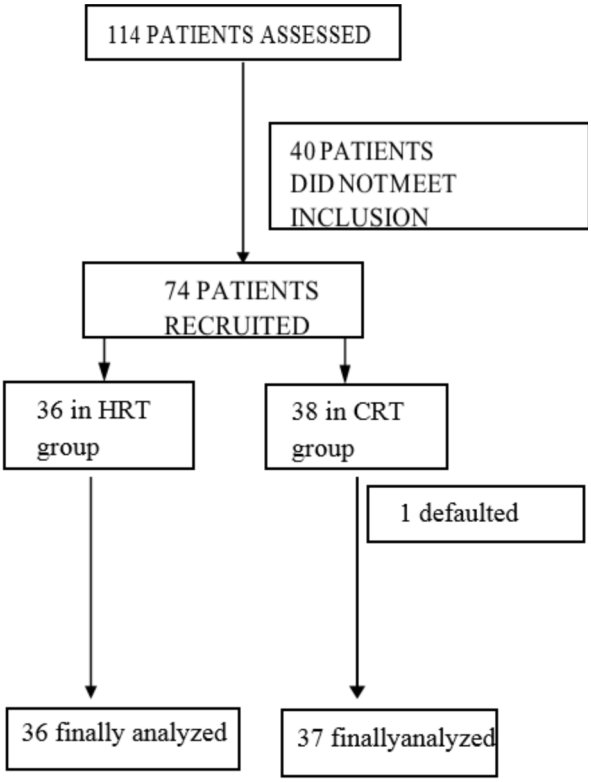
treatment were defined as late toxicities. All toxicities were graded according to RTOG Acute and Late Radiation Morbidity Scoring Criteria.

Statistical Analysis

Study parameters were entered in Microsoft office excel sheet (Microsoft Redmond Washington). All parameters between two groups were compared by Pearsons Chi-square test. Statistical tests were performed using IBM SPSS Software version 21 and p value < 0.05 is taken to denote statistically significant relationship.

RESULTS

Totally, 114 breast cancer patients were assessed during the study period. Among them, 40 patients who did not meet inclusion criteria were excluded from the study. A total of 74 patients were randomized but one patient in CRT group defaulted during RT. 73 patients were analyzed finally (36 in HRT arm and 37 in CRT arm). The median follow up was 8 months (3-19 months). Patient distribution in both the arms is shown in the flowchart 1.



Baseline patient characteristics, tumor characteristics and treatment characteristics are shown in table 1.

Table 1: Baseline Patient Characteristics, Tumor Characteristics And Treatment Characteristics

	HRT GROUP N = 36	CRT GROUP N = 37
AGE (YEARS)		
<40	4	2
41-50	15	16
51-60	8	11
>60	9	8
STAGE		
IIA	5	2
IIB	9	11
IIIA	14	17
IIIB	3	2
IIIC	5	5
Treatment protocol		
Number of patients	36	37
Radiation dose (Gy)	50	40
Number of fractions	25	15
Dose per fraction (Gy)	2	2.66
I/L SCF irradiation	29	31
NACT	10	15
Adjuvant CT	26	22
Hormonal therapy	26	27

NACT: Neoadjuvant chemotherapy, CT: Chemotherapy, I/L SCF: ipsilateral supraclavicular fossa

ACUTE TOXICITIES:

SKIN TOXICITIES:

Grade 1 dermatitis was observed in 63.8% patients in HRT group and 67.5% patients in CRT group (p=0.74). Grade 2 dermatitis seen in 25% patients of HRT and 24.3% patients with no statistical significance in between two arms (p=0.97). Grade 3 and grade 4 reactions were not seen in both arms.

OESOPHAGITIS:

63.8% patients in HRT group and 62.1% patients in CRT group had grade 1 acute oesophagitis (p=0.88). 11.1% patients in HRT group and 16.2% patients in CRT group had Grade 2 acute oesophagitis (p=0.52). There were no grade 3 or grade 4 oesophagitis in both the arms. There was no statistical significance in terms of dysphagia between two arms.

PNEUMONITIS:

4 patients (11.1%) in HRT group and 5 (13.5%) patients in CRT group experienced grade 1 pneumonitis (p value= 0.75). None of the patients in either arm experienced grade 2 or more pneumonitis.

LYMPHEDEMA:

Lymphedema is an established complication of both ALN dissection (ALND) and axillary RT. This data is in comparison with baseline post operative lymphedema. 6 patients (16.6%) in HRT group and 8 patients (21.6%) patients in CRT group had grade 1 lymphedema (p value=0.59). 1 (2.7%) of CRT group had grade 2 lymphedema that is statistically insignificant (p=0.32). None of the patients in both the arms experienced grade 3 or grade 4 lymphedema.

LATE TOXICITIES:

Skin toxicity was the most common late toxicity being experienced by patients in both groups followed by oesophagitis. None of the patients had late pneumonitis or lymphedema. No grade 3 or grade 4 toxicities were seen in any group.

SKIN TOXICITIES:

10 (27.7%) patients in HRT group and 11 (29.7%) in CRT group had grade 1 chronic dermatitis (p value= 0.85). 1 (2.7%) in HRT and 1 (2.7%) in CRT group experienced grade 2 toxicities. There is no statistically significant difference between the two groups (p=1.21). None of the patients in both the arms experienced grade 3 or grade 4 late skin toxicities.

OESOPHAGITIS:

6 (16.6%) In HRT group and 7 (18.9%) in CRT group had grade 1 chronic oesophagitis with no significant difference between the two groups (p value=0.80)

LOCOREGIONAL RECURRENCES:

One patient in CRT group had recurrence at ipsilateral supraclavicular fossa.

None of the patients in HRT group had any loco regional recurrences

DISTANT METASTASIS:

3 patients in HRT arm had distant metastasis among which 2 had brain metastasis and 1 patient had liver metastasis. 3 patients in CRT arm had distant metastasis to bone, brain and liver respectively.

Disease status during last follow up in terms of locoregional recurrence and distant metastasis is shown in Table 3.

Table 3: Showing Disease Status During Last Follow Up In HRT And CRT Arms

	HRT Group (36)	CRT Group (37)	P Value
No Evidence Of Locoregional Disease	36 (100%)	36 (97.29%)	
Locoregional Recurrence	0	1 (2.7%)	0.32 Not Significant
Distant Metastasis	3	3	

DISCUSSION

Breast cancer is the most commonly diagnosed cancer (25.8%, i.e. about one in 4 of all new cancer cases diagnosed in women worldwide are breast cancer) and leading cause of cancer death in women.[1] Multimodality approach i.e surgery, chemotherapy, endocrine therapy and radiation therapy remains the primary therapeutic modalities in the management of breast cancer. Adjuvant radiation therapy eradicates any tumor deposits remaining following surgery, which reduces locoregional recurrence (LRR) and improves breast cancer-specific and overall survivals.

Conventional adjuvant radiotherapy to chest wall after modified radical mastectomy is delivered as 50 Gy in 25 fractions within 5 weeks. Hypofractionated radiotherapy uses a smaller number of fractions and larger doses per fraction more than 2 Gy. Many randomised trials, few prospective and few retrospective have proven the noninferiority of hypofractionated radiotherapy compared with conventional radiotherapy. In almost all the studies, majority of study subjects were post BCS, with fewer number of study subjects with post mastectomy status as in START trials 85% of study subjects belong to post BCS status with 15 % of patients being post mastectomy. [5] The 10-year results of landmark The UK Standardisation of Breast Radiotherapy (START) trials confirmed that 40 Gy in 15 fractions over 3 weeks is at least as safe and effective as 50 Gy in 25 fractions over 5 weeks. [5]

The current study is a prospective randomised study conducted to compare the efficacy and tolerability of HRT versus CRT in post mastectomy breast cancer patients. The two groups in this study had almost similar distribution in terms of clinical, tumor and treatment characteristics. By current study, we found that both HRT and CRT were equally efficacious in terms of toxicities and patient tolerability.

The present study results were comparable with Wang et al study, [11] which is a recently published randomised study conducted in 820 subjects conducted from 2008 to 2016 with the primary end point of 5 year loco regional recurrence and acute and late radiation toxicities, overall survival and disease free survival as secondary end points.

SKIN TOXICITY:

In our study, majority of subjects had Grade 1 toxicities, with 63.8% patients in HRT arm and 67.5% patients in CRT arm followed by Grade 2 skin toxicities 25% in HRT and 24.3% in CRT group both grades being statistically insignificant between two groups. This is comparable with Wang et al study [11] which also showed 89% patients and 87% patients with grade 1 and 2 acute skin toxicities in hypofractionated and conventional arm respectively with no statistically significant difference. Grade 3 skin toxicities were not found in present study subjects which is in contrary with Wang et al study [11] which showed grade 3 skin toxicities in 3% and 8% patients in hypofractionation and conventional arm respectively with statistically significant difference showing that hypofractionated radiotherapy was associated with less frequent grade 3 acute skin toxicities.

OESOPHAGITIS:

Dysphagia began to appear from the second week onwards. In terms of acute dysphagia, 63.8% patients in HRT group and 62.1% patients in CRT group had grade 1 acute oesophagitis. 11.1% in HRT group and 16.2% in CRT group had grade 2 oesophagitis. These results were statistically insignificant. The dysphagia was managed appropriately with standard treatment including dietary modifications, topical anesthetics such as viscous lidocaine, proton pump inhibitors. Similar results were seen in Kartick Rastogi et al study [12] in which 92% patients in hypofractionation arm and 90% patients in conventional arm had none or less than grade 2 dysphagia with no statistically significant difference.

PNEUMONITIS:

As per Wang et al study [11], 18% of patients in hypofractionation arm and 17% of patients in conventional arm had grade1 and grade 2 pneumonitis. Symptomatic (ie, grade 2) radiation pneumonitis occurred in less than 5% of patients in both hypofractionated and conventional fractionation groups with no significant difference. Deshmukh et al[14] prospective study among 56 post mastectomy breast cancer patients by giving hypofractionated radiotherapy. None of the patients developed any symptomatic evidence of radiation pneumonitis at three months after completion of treatment In our study, 11.1% patients in HRT group and 13.5% patients in CRT group had grade 1 pneumonitis and the difference is statistically insignificant. Grade 2 or higher pneumonitis were not seen in our study. It might be due to smaller sample size.

LYMPHEDEMA:

Lymphedema is an established complication of both ALN dissection (ALND) and axillary RT. In comparision with the baseline postoperative lymphedema, 6 (16.6%) patients in HRT arm and 8 (21.6%) of patients in CRT arm grade 1 lymphoedema (p value= 0.59). 1 (2.7%) patient in CRT arm had grade 2 lymphedema (p=0.32), with no statistically significant difference between both groups. Many risk factors are associated with development of lymphedema in breast cancer patients. Kocak et al[13] reported that there seems to be a higher risk for developing lymphedema in patients with advanced disease at diagnosis, older age, greater BMI (obesity), and longer follow-up. The current study results were similar with KartickRastogi et al study[12] in which 44 (92%) patients in hypofractionation arm and 45 (90%) patients in conventional arm had less than grade 2 lymphedema with no statistically significant difference(p=0.95). These were also comparable with Wang et al[11], in which 97% of patients in hypofractionation arm and 98% in conventional arm had none or grade 1-2 lymphedema that is statistically insignificant (p=0.96). Mortimer et al[15]noted that there was a significant increase in prevalence with increasing time since treatment in patients who had received radiotherapy, but not in patients treated with surgery alone. Moreover, they suggested that at least 3 years' follow-up was required for this tendency to manifest itself, particularly following radiotherapy. Hence, number of other factors need to be considered and a longer follow up is required to comment up on lymphedema in breast cancer patients.

LOCOREGIONAL RECURRENCES:

One patient in CRT group who has been irradiated to right chest wall and supraclavicular fossa had recurrence at ipsilateral supraclavicular fossa. None of the patients in HRT arm had local or regional recurrences. 36 patients (100%) in HRT group and 36 patients in CRT group had no evidence of any locoregional disease during follow up. This current study results are comparable with other studies conducted by Wang et al[11], Pramod K S et al[16], Pinitpatcharalert et al [17], which also showed no significant difference in terms of local control rates and locoregional recurrences. After a median follow-up of 58·5 months, Wang et al [11] reported that 60 (7%) patients had developed locoregional recurrence, 31 patients in the hypofractionated radiotherapy group and 29 in the conventional fractionated radiotherapy group and the 5-year cumulative incidence of locoregional recurrence was 8·3% in the hypo- fractionated radiotherapy group compared with 8·1% in the conventional fractionated radiotherapy group. In another study, after a median follow up of 39 months, Pinitpatcharalert et al [17] reported that Five-year Locoregional control was 86.6% in conventional arm and 85.8% in hypofractionation arm (p = 0.852) with no significant difference. In a study conducted by Pramod K S et al [16], among 58 patients with 10.2 months median follow up, in hypofractionation arm, 2 patients had locoregional recurrence in the form of chest wall recurrences and among 50 patients in conventional arm, 2 patients developed locoregional recurrences, one in chest wall and the other in axilla with no significance difference between the two arms and they concluded that hypofractionation is similar to conventional fractionation in terms of toxicities and locoregional recurrences.

DISTANT METASTASIS:

3 patients in each group had distant failure. In HRT group, two patients developed brain metastasis post RT for which whole brain radiotherapy (WBRT) was given and is on palliative chemotherapy. One patient developed liver metastasis and is on palliative chemo. In CRT group, one patient developed bone metastasis for which palliative symptomatic RT was given and is on palliative chemo, one patient developed brain metastasis treated with WBRT and is on chemotherapy, one patient developed liver metastasis and is on palliative chemotherapy.

CONCLUSION

By this study, we concluded that hypofractionated radiotherapy is comparable to conventional radiotherapy in terms of toxicities and locoregional tumor control and locoregional recurrences. Hence, it can be offered as a safe and effective alternative to conventional RT for postmastectomy breast cancer patients in adjuvant settings with short duration of treatment, it has an added advantage of increased

compliance of patients which helps to treat more number of patients in high volume centers and at reduced cost. However, the results need to be evaluated with multicenteric trials with larger sample size and longer follow up.

Limitations

1. Smaller sample size
2. Shorter follow up period

List Of Abbreviations:

HRT - Hypofractionated Radiotherapy
CRT - Conventionally Fractionated Radiotherapy
MRM- Modified Radical Mastectomy
BCS - Breast Conserving Surgery
PMRT- Post Mastectomy Radiotherapy
RT – Radio Therapy
3DCRT- 3 Dimensional Conformal Radiotherapy
NACT - Neoadjuvant chemotherapy

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