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Original Research Paper

Oncology

A PROSPECTIVE RANDOMISED STUDY OF HYPOFRACTIONATED RADIOTHERAPY VERSUS CONVENTIONAL RADIOTHERAPY IN POSTOPERATIVE EARLY STAGE CARCINOMA OF BREAST

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ABSTRACT This prospective single institution study compared the effects of conventional and hypofractionated radiotherapy on local control and toxicities in post-operative early breast cancer. 63 patients were randomised to control arm [50 Gray in 25 fractions over 5 weeks] and study arm [Hypofractionation arm of 40 Gy in 15 fractions over 3 weeks]. After median follow up of 12 months, 61 patients (31 in the control arm and 30 in the study arm) were evaluable. The two groups were comparable in terms of age distribution, age of menarche, parity, performance status, stage, primary site, histological grade and molecular profile. There was no statistically significant difference in Local control and side effects in both the arms. The Hypofractionated schedule had the advantage of decreased workload, increased compliance and reduced cost of treatment. It is an acceptable alternative in post-operative breast cancer patients.

KEYWORDS : Early Breast cancer, Hypofractionation, Local control

INTRODUCTION

Breast cancer is the most common cancer in women, accounting for 24.2% of all cancers. Breast cancer incidence in developed countries is higher, while relative mortality is greatest in less developed countries[1]. In Indian women too breast cancer has overtaken cervical cancer as the commonest cancer and is the leading cause of cancer death[2].

Breast cancer patients require multidisciplinary team approach incorporating diagnostic imaging, surgery, chemotherapy and histopathological assessment including molecular-based studies, radiation and if indicated, biologic and hormonal therapies. Radiotherapy (RT) reduces the risk of local relapse and increases overall survival and is offered to nearly all patients after conservative surgery and to selected patients after mastectomy[3].

The standard RT regimen after breast conservative surgery for early breast cancer delivers 25 daily fractions of 2 Gray to a total dose of 50 Gray followed by 10 to 16 Gray in 5 to 8 fractions as a boost to the tumour bed[4]. Hypofractionated radiotherapy delivers larger dose radiation fraction over a shorter period of time. It provides local tumour control and overall survival in a more feasible and cost-effective treatment schedule[5].

MATERIALS AND METHODS

The prospective randomized study was conducted on post-operative biopsy proven early breast cancer patients attending the Radiotherapy Department of Burdwan Medical College from January 2017 to July 2018. All postoperative (Breast Conservative Surgery or Mastectomy) histologically proven Stage I & II carcinoma breast cases having Karnofsky performance status ≥ 70 were included. Patients with previous history of radiotherapy to chest wall and positive resection margin were excluded. After Institutional Ethics Committee approval, proper explanation and written informed consent the patients were randomised to Arm A or Arm B. External beam adjuvant radiotherapy was delivered by Telecobalt Machine [THERATRON 780 C] to chest wall by tangential fields and by anterior field to supraclavicular, infraclavicular and axillary area in node positive disease after simulation and 2D plan. Control Arm A received 50 Gy in 25 fractions over 5 weeks. Study Arm B (Hypofractionated arm) received 40 Gy in 15 fractions over 3 weeks.

All patients were assessed for acute toxicities by clinical examination and questionnaire using radiation therapy oncology group (RTOG), common toxicity criteria (CTC) and European organization for research and treatment of cancer (EORTC) questionnaire for quality of life (QOL). Patients were followed up weekly during radiation to assess acute toxicities and were examined one month after the completion of the treatment for assessing the recovery from acute toxicity. Thereafter they were evaluated every two months up to one year and every three months thereafter.

The present study aimed to look for the role of Hypofractionated regimen as an alternative to Conventional radiotherapy in the post-operative radiation setting for treatment of Early stage breast carcinoma. Primary endpoint of the study was Loco-regional control in both arms. Secondary endpoint of the study was - Acute and Late Toxicities and Quality of Life (QoL).

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS version 20. For categorical variables, Chi Square and Fisher Exact tests were used, while for continuous variables, the mean and Standard Deviation (SD) were compared using Independent samples t'test with 95% Confidence Interval (CI). All tests were 2-tailed and p value less than 0.05 was taken as significant.

RESULTS AND ANALYSIS

Out of 65 patients assessed for eligibility 63 patients were allotted into Control (Arm A) and Study (Arm B) arms after fulfilling the eligibility criteria. 1 patient of control arm was lost to follow-up and 1 patient of study arm discontinued treatment. At the end of study, 61 patients including 30 in the study arm were evaluable. Baseline profiles of both groups were comparable in terms of age distribution, age of menarche, parity, performance status, extent of lymph-node dissection, stage, anatomical side, anatomical quadrant, histological grade and molecular profile.

Table No 1: Baseline profiles of groups

Age Group	Control arm (n=31)	Study arm (n=30)
Below 40 years	6(19.35%)	4 (13.33%)
40-59yrs	19(61.29%)	21 (70%)
60-74yrs	6(19.35%)	5(16.67%)
Age of menarche in years		
10	1(3.23%)	2(6.67%)
11	10(32.26%)	8(26.67%)
12	8(25.81%)	9(30%)

13	11(35.48%)	9(30%)
14	1(3.23%)	2(6.67%)
Parity		
No child	6(19.35%)	4(13.33%)
1 child	10(32.26%)	8(26.67%)
2 children	8(25.81%)	10(33.33%)
3 children	4(12.90%)	5(16.67%)
4/more children	3(9.68%)	3(10%)
Karnofsky Performance Status		
70	2 (6.45%)	3(10%)
80	14(45.16%)	16(53.33%)
>90	15(48.39%)	11(36.67%)
Lymph-node dissection		
Adequate	23(74.20%)	22(73.33%)
Inadequate	8(25.80%)	8(26.67%)
Anatomical side		
Right breast	14(45.16%)	16(53.33%)
Left breast	17(54.84%)	14(46.67%)
AJCC Staging		
IB	2(6.45%)	3(10%)
IIA	19(61.29%)	17(56.67%)
IIB	10(32.25%)	10(33.33%)
Quadrant of breast involved		
Upper outer quadrant	15(48.39%)	13(43.33%)
Upper inner quadrant	3(9.68%)	5(16.67%)
Central	6(19.35%)	6(19.35%)
lower outer quadrant	3(9.68%)	3(10%)
lower inner quadrant	4(12.90%)	4(13.33%)
Grading		
Grade I	5(16.13%)	4(13.33%)
Grade II	21(67.74%)	22(73.33%)
Grade III	5(16.13%)	4(13.33%)
ER receptor status		
ER positive	8(25.81%)	6(20%)
ER negative	2(6.45%)	4(13.33%)
Unknown	21(67.74%)	20(66.67%)
PR receptor status		
PR positive	7(22.58%)	7(23.33%)
PR negative	3(9.68%)	3(10%)
Unknown	21(67.74%)	20(66.67%)
HER 2 status		
HER 2 positive	2(6.45%)	2(6.67%)
HER 2 negative	8(25.81%)	6(20%)
Unknown	21(67.74%)	22 (73.33%)

Response evaluation

Follow up period ranged from 6 months to 18 months with a median follow up of 12 months. At last follow up, 3.23% patients of control arm and 3.33% patients of study arm had local recurrence and this was confirmed by histopathology. The loco-regional control rate of control and study groups were 96.77% and 96.67% respectively at the end of study. The loco-regional control was comparable in both arm of the study the difference was not statistically significant (chi square value 0.0006 and p value 0.9812)

Comparison of toxicity profile

Skin toxicity, oesophageal reactions and radiation pneumonitis were the commonest toxicities. Grade I, grade II and grade III skin toxicity were 15 (48.39%), 9 (29.03%) and 2 (6.45%) in control arm while those in the study arm were 16 (53.33%), 10(33.33%) and 2 (6.67%) respectively. The difference was not statistically significant (p value 0.9946). Oesophageal reaction in control arm were less in comparison to study arm (p value 0.6866) but was not statistically significant. Grade I pneumonitis was 1 (3.23%) in control arm while it was 2 (6.67%) in study arm (p value=0.5344).

Incidence of pneumonitis was comparable in both arms. Lymphedema was recorded and graded according the changes of arm circumference during follow up compared to pre-radiotherapy measurement. Lymphoedema was 3 (9.68%) in control arm and 4 (13.33%) in study arm. Difference was not statistically significant (p value 0.6542)

Table 2: Response evaluation & Toxicity

Disease status at last follow up	Control arm (n=31)	Study arm (n=30)
Local recurrences	1 (3.23%)	1 (3.33%)
No evidences of disease	30 (96.77%)	29 (96.67%)
Skin toxicity CTCAEv3		
Grade 1	15(48.39%)	16 (53.33%)
Grade 2	9(29.03%)	10(33.33%)
Grade 3	2 (6.45%)	2(6.67%)
Oesophageal reactions CTCAE		
Grade 1	6(19.35%)	7(23.33%)
Grade 2	1(3.22%)	2(6.67%)
Pneumonitis		
No pneumonitis	30(96.77%)	28(93.33%)
Grade I	1(3.23%)	2(6.67%)
Lymphoedema		
No lymphedema	28(90.32%)	26(86.67%)
Any grade lymphedema	3(9.68%)	4(13.33%)

Quality of life in both arms was assessed using the EORTC QLQ-C30 (version 3.0) and the QLQ-BR23 instruments[6,7]. Higher scores in functioning and global health status/ QoL scales indicate a higher level of functioning and a better QoL, respectively, whereas higher scores in symptom scales represent a higher level of symptom. The score obtained are depicted below. QoL in this study was measured at the time of response evaluation.

Table 3: Quality of Life assessment

QOL scales	Study Arm	Control arm
FUNCTIONAL SCALE scores		
Physical function PF2	89 (73- 93)	90 (80 – 100)
GLOBAL HEALTH/ QOL		
SYMPTOM SCALE SCORES		
PAIN PA	29(0-67)	30 (0-67)
FATIGUE FA	37(11-56)	36(22-44)
NAUSEA VOMITING NV	61(33-83)	58(33-83)
APPETITE LOSS AP	61(33-100)	57(33-100)
SYMPTOM SCALE OF BR23		
Systemic therapy side effects	55(33-76)	53(33-76)
Arm symptoms	46(22-89)	45(22-89)
Breast symptoms	41(25-75)	42(25-75)
Upset by hair loss	48(0-100)	49(0-100)
FUNCTIONAL SCALE OF BR23		
Body image	67(33-92)	70(42-92)
Sexual functioning	47(33-67)	49(33-67)
Sexual satisfaction	49(0-100)	55(33-100)
Future perspective	32(0-67)	39(0-67)

DISCUSSION

Carcinoma of breast is primarily treated by surgery followed by adjuvant chemotherapy, radiotherapy, directed therapy and hormonal therapy depending on histopathological and immunohistochemistry report.

The present study evaluated differences between two arms of treatment for early-stage breast cancer- conventional radiotherapy of 50 Gy in 25 fractions and hypofractionated radiotherapy of 40 Gy in 15 fractions.

In an overburdened radiotherapy department Hypofractionated radiation therapy offers the advantage of a more efficient and productive use of resources; machine time, staffing of treatment units, lower expenses in addition to far better patient convenience[8]. Hypofractionation, with larger radiation dose per fraction increases the possibility of late normal tissue damage[9,10]. However, the linear quadratic model predicts that the normal tissue toxicity is not increased when the fraction dose is modestly increased and the total dose is reduced[11]. Various hypofractionated radiotherapy trials confirm it as effective as the conventional radiation[12,13] regardless of disease stage or type of breast surgery[14].

Herbert et al studied 1335 breast cancer patients with grade 3 diseases (T1–T2, N0, M0). 252 patients underwent conventional fractionation of 45–50 Gy in 25 fractions and 1083 patients received a hypofractionated schedule of 42.5–44 Gy in 16 fractions. The 10-year cumulative incidence of local relapse was 6.9% in the hypofractionated group and 6.2% in the conventionally fractionated group (p = 0.99). These results show that there were no significant differences between the hypofractionated schedule and conventional fractionation in terms of local recurrence[15].

The START Trialists 'Group compared long-term local relapse rates between hypofractionated radiotherapy and conventionally fractionated schedules. These studies showed that hypofractionated radiotherapy and conventional treatment method produced comparable results. (START A and START B. Haviland et al., 2013)[16].

El Sayed et al stated that hypofractionated radiation was safe and showed acceptable toxicity rate. Incidence of skin toxicity and radiation induced pneumonitis were comparable between hypofractionated and conventional radiation arms[17-19].

Eldeeb H et al compared three fractionation schedules in post mastectomy patients enrolled into three groups. Although acute skin reactions were higher in the hypofractionated arms, there was no significant difference in the local recurrence rates or late radiation effects[20].

Ko DH et al retrospectively analysed 133 post-mastectomy patients treated with hypofractionated radiotherapy to determine whether hypofractionated radiotherapy yields acceptable efficacy and toxicity. Patients were treated with 40 Gy in 16 daily fractions. The median follow-up period was 5.03 years. Three patients had local recurrence as a first event, resulting in 5-year local recurrence-free survival of 97.6%. Five-year overall survival and 5-year breast cancer survival were 74.7% and 77.7% respectively[21].

These results are in concurrence with our study results, as both the arms had acceptable toxicity and efficacy.

Prolonged follow-up and detailed survival analysis were beyond the scope of this study.

SUMMARY AND CONCLUSION

In our study similar results were seen in both conventional and hypofractionated arms in terms of local control and toxicities. Acute and late reactions in the hypofractionation group were slightly higher but were not statistically significant.

As hypofractionated schedules have shown similar response in terms of tumour control and normal tissue effects with the advantage of decreased workload, increased compliance and reduced cost of treatment, it can be considered as an alternative in radiation treatment for post mastectomy breast cancer patients.

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