wjpmr, 2017,3(11), 187-192

SJIF Impact Factor: 4.103

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Research Article

ISSN 2455-3301

WJPMR

HYPO FRACTIONATION VERSUS CONVENTIONAL FRACTIONATION IN POST MASTECTOMY ADJUVANT RADIATION IN BREAST CANCER

Dr. Aravindh Sivanandan Anand M. D.*[1] and Dr. Rose Maria John M. D.[1]

Department of Radiotherapy and Oncology, Government Medical College, Thiruvananthapuram, Kerala, India.

***Corresponding Author: Dr. Aravindh Sivanandan Anand M. D.**

Department of Radiotherapy and Oncology, Government Medical College, Thiruvananthapuram, Kerala, India.

Article Received on 19/10/2017 **Article Revised on 10/11/2017** **Article Accepted on 01/12/2017**

ABSTRACT

Background: Low alpha by beta value of breast cancer provides a radiobiological rationale for radiation treatment in breast cancer. Randomized control trials and meta-analyses has proved beyond doubt comparable efficacy and toxicity for hypo fractionation after breast conservation surgery. But the evidence is limited after post mastectomy. **Objective:** The objective of this retrospective study is to assess the control rate of disease and toxicity after hypofractionated radiation and compare with the conventional fractionation. **Methods:** It was a retrospective study of all consecutive patients who received either conventional 50 Gy/25 fraction (Arm A) or 42.5Gy/16fraction (Arm B) as adjuvant post mastectomy radiation to chest wall +/- drainage areas. The departmental patient database were used for the study purpose and prepared proforma used for entering the relevant patient and treatment details. **Results:** A total of 109 patients were enrolled for the study, with 23 patients in Arm A and 86 patients in Arm B. The median follow up period was 56 months. The local recurrence rate was 8.7% in arm A while it was 11.6% in Arm B (p= 1.000). Overall recurrence was 26.1% & 31.4. % respectively (P=0.623). The mean overall survival 59.3% and 53.9% (p =.098) respectively. 4 year O.S was 91.3% & 74.4% respectively (p=0.0838). 4 year DFS was 77.7% & 67.6% respectively (p=0.3512). Toxicities in both arms were comparable **Conclusion:** In breast cancer post mastectomy hypofractionated radiation treatment is a viable & scientifically proved option with reduced patient burden and comparable toxicity to conventional fractionation.

KEYWORDS: Breast cancer, mastectomy, hypofractionation.

INTRODUCTION

The role of post mastectomy radiation (PMRT) is well established in women at high risk of local recurrence like T3-T4 disease, ≥4 positive lymph nodes and positive margin. Radiation may also be considered for <4 positive lymph nodes or inadequately dissected axilla where the tumour size is >3cm or high risk pathological features or close margin (<1mm) where the treating oncologist feels that there is high chance for local recurrence. In view of the findings from the EBCTCG metanalysis it is reasonable to recommend post mastectomy radiotherapy to women with 1-3 positive lymph nodes at it reduced both local recurrences and breast cancer mortality.

A total of 50 Gy in 25 daily fractions delivered over 5 weeks is often considered the "standard" adjuvant radiotherapy prescription. Hypofractionated regimes such as 42.5 Gy in 16 daily fractions or 40 Gy in 15 daily fractions following breast-conserving surgery have proven to be equally effective and achieve similar or better cosmetic and normal tissue outcomes for both invasive and in situ diseases and when treating the regional nodes.[1]

Four randomized trials i.e; the Royal Marsden Hospital/Gloucestershire Oncology Center (RMH/GOC) trial.[2,3] the UK Standardization of Breast Radiotherapy (START) trial A and B[4,5] and the Canadian trial[6] have supported the establishment of hypofractionated whole breast irradiation with the publication of 10-year outcomes.

The radiobiological rationale for hypo fractionation is that studies have estimated the α/β for breast cancer to be 4.0 Gy, which is similar to that of late-reacting normal tissues. The meta-analysis of RMH/GOC and START A trial after the 10-year outcome of the START trial provided an adjusted α/β value of 3.5 Gy for local regional relapse[5] and 3.1 Gy for adverse effects.

Hypofractionated irradiation, based on precedent studies over the past two decades, offers an opportunity for improved patient convenience, lower healthcare costs, and greater access to care without sacrificing treatment outcomes.[7]

The British Columbia randomized trial of post mastectomy radiation used 37.5 Gy in 16 daily fractions

to chest wall and 35 Gy in 16 daily fractions to mid axilla. This trial randomly allocated 318 premenopausal women with node-positive breast cancer treated with modified radical mastectomy, to full loco-regional radiation including the chest wall, axilla, supraclavicular fossa and a direct field over the internal mammary nodes, or no adjuvant radiation. PMRT used in this British Columbia trial achieved similar reductions in the risk of loco-regional recurrence, distant metastases, and death compared to the concurrently reported Danish trials that used a more conventional dose, 50 Gy in 25 daily fractions. These data demonstrate that a hypofractionated RT schedule is enough to achieve cancer control end points. Short fractionation does not compromise loco regional control.[8,9]

In the Phase II prospective study from Memorial Sloan Kettering Cancer Center study[10] PMRT at a dose of 36.63 Gy in 11 fractions of 3.33 Gy over 11 days to the chest wall and the draining regional lymph nodes, followed by an optional mastectomy scar boost of four fractions of 3.33 Gy was delivered. It is one of the shortest courses of PMRT delivered i.e; in 11 fractions to the chest wall and nodes and 15 fractions inclusive of a boost. The study demonstrated low toxicity and high local control with this schedule. 69 women with stage II to IIIa breast cancer were enrolled in the study, of whom 67 were eligible for analysis. After a median follow-up of 32 months, there were no grade 3 toxicities. There were 29 reported grade 2 toxicities, with grade 2 skin toxicities being the most frequent (16 of 67; 24%). There were two patients with isolated ipsilateral chest wall tumor recurrences (2 of 67; crude rate, 3%). Three-year estimated local recurrence-free survival was 89.2% (95% CI, 0.748 to 0.956). The 3-year estimated distant recurrence-free survival was 90.3% (95% CI, 0.797 to 0.956).

Data supporting hypofractionated PMRT is limited especially in Indian scenario. So we retrospectively evaluated a short course hypofractionated PMRT (42.5Gy/16fr) with conventional (50Gy/fr) fractionation.

OBJECTIVES OF STUDY

Primary objective of the study was to study the efficacy of hypofractionated post mastectomy radiation and compare with conventional fractionation. Secondary objective was to study the common toxicity in both group of patients.

METHODS

This is a retrospective study of 109 patients treated in our institution with adjuvant radiation with either 50Gy/25fr or 42.5Gy/16fr. Patients were divided into two arms. Arm A- 50 Gy/25fr & Arm B- 42.5Gy/16fr. The database of all patients satisfying the inclusion and exclusion criteria were studied in detail and all the relevant details were recorded in an already prepared proforma. The data included patient & tumour characteristics, treatment & follow up details. For each patient, a file detailed the following items: Breast cancer developed age, family history, age at menopause, hormone replacement therapy, comorbidities, type of surgery, RT modalities (volumes/dose), chemotherapy and/or hormonal therapy. Histopathological features assessed were tumour size, axillary nodal involvement, histological subtype (ductal, lobular, mixed), SBR (Scarff, Bloom and Richardson) grading, excision quality, presence of vascular or lymphatic emboli, Her-2 oncoprotein over-expression and hormone receptor status (HR). Treatment outcomes assessed included local recurrence-free survival, overall survival and acute toxicities. The study was in accordance to the declaration of Helsinki in its latest version.

RT was delivered 4–8 weeks after surgery or 4–6 weeks after chemotherapy. Chest wall radiation of either 50Gy/25fr or 42.5Gy/16fr was delivered by two opposed tangential fields. SCF and axilla were treated by same dose by photon direct field.

Patient received systemic chemotherapy, adjuvant trastuzumab and hormonal therapy as per the indications and institutional protocol.

During the treatment, a weekly consultation was performed by a radiation oncologist. The acute skin toxicity was assessed by the CTCAE scale (Common Terminology Criteria for Adverse Events). After treatment, the patients were assessed once in every 4 months in order to evaluate the oncological outcome and possible toxicities. An annual mammogram was performed as well as other clinical examinations and in case of any significant clinical symptoms relevant imageology were done.

Statistics

The continuous variables were described by the median and/or the mean ± standard deviation. The qualitative variables were described by the distribution of their modalities. Local recurrence-free survival was defined as the period between the date of initial surgery and the date of local recurrence. It was calculated using the Kaplan-Meier method. The groups in question were compared using Student's test (or the Mann-Whitney non-parametric test if necessary) for continuous variables and by Pearson's Chi2 test (or Fisher's exact test if necessary) for qualitative variables. The local recurrence-free survival curves were compared using the log rank test for the variables in classes and using the univariate Cox model for continuous variables. P-value of significance was set at 5%.

RESULTS

Patient characteristics

The median age of patents in Arm A was 46 yrs and Arm B was 50 yrs. 52.2% and 69.4% of the enrolled patients were postmenopausal in Arm A&B respectively.

Majority of the patients in both arms did not have any comorbid conditions.

Tumour characteristics

Most common tumour size status was T2 for Arm A while it was T3 status in Arm B. More than 78% in the conventional arm and about 71% in hypofractionated arm were early breast cancer. In both the arms the most common histopathology was invasive ductal carcinoma. In Hypofractionated arm one patient was lobular and one was papillary type whereas in conventional arm all patients were invasive ductal carcinoma. 100% of the tumour in both the arms were high grade (either Gr 2 or Gr 3) in both the arms. More than 56% in the arm A and more than 80% in Arm B were hormone positive (either ER or PR positive) tumour. The incidence of HER2neu positivity in the study arms range between 21-24%.

Table1: Patient and treatment characteristics.

Variable	Arm A n= 23 (21.1%)	Arm B n=86 (78.9%)
Median age	46	50
Post-Menopausal	12(52.2)	59 (69.4)
Comorbidities		
No comorbidity	16(69.6)	54(62.8)
Hypertension	2 (8.7)	15(17.4)
Diabetes Mellitus	4 (17.4)	13(15.1)
Hypertension & Diabetes	1(4.3)	4(4.7)
T status		
T_X	1(4.3)	4(4.7)
T1	1(4.3)	5(5.8)
T2	12(52.2)	27(31.4)
T3	7(30.4)	36(41.9)
T4	2(8.7)	14(16.3)
N status		
Nx	7(30.4)	11(12.8)
N0	6(26.1)	19(22.1)
N1	2(8.7)	24(27.9)
N2	5(21.7)	25(29.1)
N3	3(13)	7(8.1)
Early breast cancer	18(78.3)	61(70.9)
Locally advanced breast cancer	5(21.7)	25(29.1)
HPR		
IDC	23(100)	84(97.7)
Lobular	0	1(1.2)
Papillary	0	1(1.2)
Grade		
1	0	0
2	20(87)	88.2
3	3(13)	11.8
ER		
positive	8(34.8)	32(37.2)
negative	15(65.2)	54(62.8)
PR		
positive	5(21.7)	37(43)
Negative	18(78.3)	49(57)
ER/PR positive (HR positive)	13 (56.5)	69 (80.2)
HER 2 neu		
Positive	5(21.7)	21(24.4)
Negative	16 (69.5)	57(66.2)
Not done	2(8.6)	8(9.3)
Side of cancer Left	n=14(60.8)	n=20(23.25)
right	n=9(39.2)	n=66(76.74)

Treatment characteristics

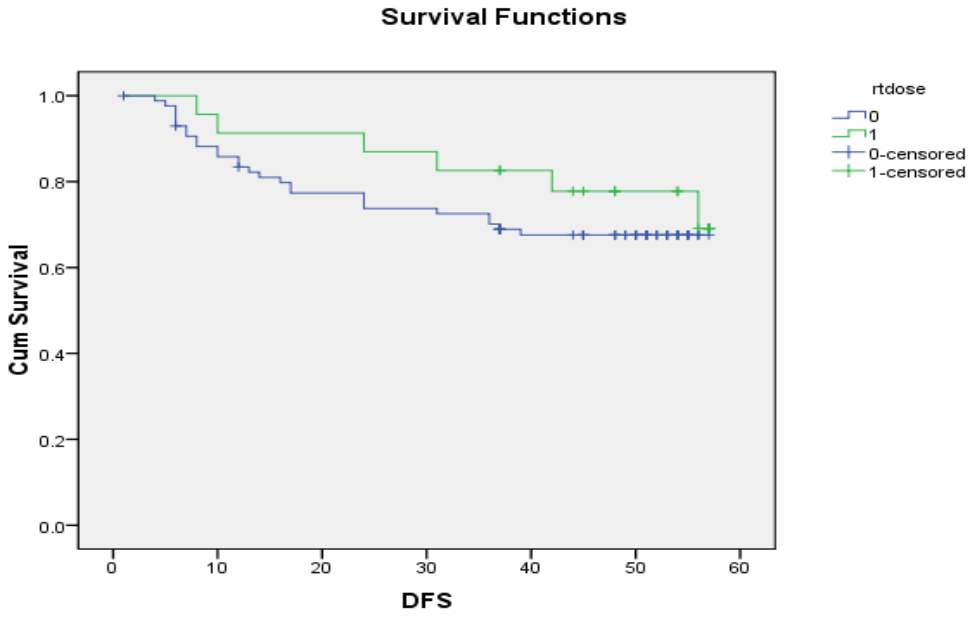
The most commonly used chemotherapy cycle in both the arms were FEC for 6 cycles with 82.5 % in arm A and 74.4% in arm B. 4.3% in Arm A and 22.1% in Arm B received ACX4 followed by Paclitaxel x4. Remaining set of patients received TACX 6 cycles.

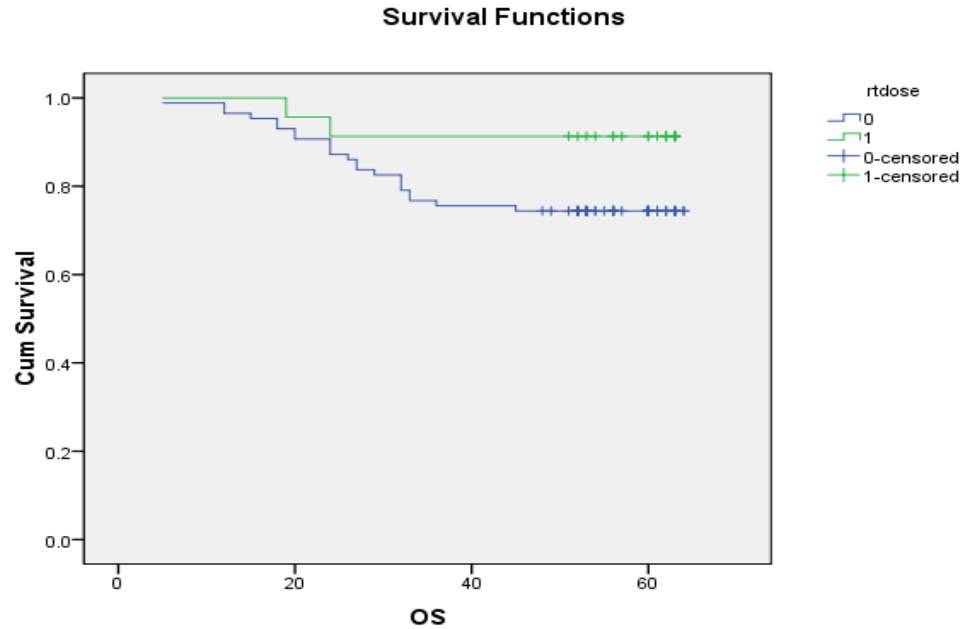
Of the total 108 patients enrolled for the study n= 23(21.1%) received conventional fractionation and formed Arm A while remaining 78.9 %(n=109) received hypofractionated radiation and formed Arm B. Most commonly used hormonal therapy in our study in postmenopausal female was aromatase inhibitors with letrozole being the most commonly used. All the premenopausal female who were receptor positive received tamoxifen.

The median follow up period was 56 months. During this follow up period 6(26.1%) patients in the conventional arm and 27 patients in the hypofractionated arm (31.4%) developed recurrence. Of the recurrences 2(8.7%) in arm A and 10 (11.6%) in Arm B had loco-regional recurrence while 4(17.4) and 17(19.8%) had systemic relapse respectively. Most common site of loco-regional recurrence was chest wall in Arm A, n=1(50%) while it was only n=2(20%) in arm B. In arm B most common site of loco regional recurrence was drainage areas. The most common site of systemic metastases was lung in arm A, n=2(50%) while it was liver n=9(47.4%) in arm B. In arm A bone and brain was the next common site (25% each) of metastases. In Arm B lung, brain and bone were the next common sites with n=7 (36.8%), n=2(10.5%), n=1(5.3%) respectively.

The Mean disease free survival was 49.4% and 43.8% in arm A&B respectively (p value-0.368). The Mean overall survival in conventional arm was 59.3% and in hypofractionated arm it was 53.9 % (p value-0.098).

4 year O.S in Arm A & B was 91.3% & 74.4% respectively (p=0.0838). 4 year DFS was 77.7% & 67.6% in Arm A &B respectively (p=0.3512).





The assessed acute toxicities was cutaneous toxicity and it was mostly grade 1. Skin toxicity was grade 1 81 % and 83% in arm A&B respectively. The incidence of grade 2 skin toxicity was 11.7%, and 9.8% in arm A & B respectively and no patients experienced grade 3skin toxicity. No long-term toxicity, particularly cardiac and lung toxicity, was documented but majority of Arm B patients right side.

DISCUSSION

Breast cancer forms a health care burden for Kerala which has the highest literacy rate and the best health care indices in India. In this single institutional retrospective study postmenopausal female between 45 and 55 years formed the major share. Tallying with the international data the most common histopathological subtype was invasive ductal carcinoma but we see that almost 100% of the patients were high grade (grade2/3). It is already reported in several Indian studies and also in another study by the same author, that the disease has high burden and less hormone positivity due to the advanced nature of the disease at presentation. HER-2/neu gene amplification and protein over-expression has been reported in 20-25% of cases and was traditionally associated with poor prognosis due to an aggressive tumour phenotype, increased metastasis and poor survival.[12] The Her2neu positivity is 26.6% in our study, which is a little on the higher side when compared to other studies.

In this study all consecutive patients satisfying the inclusion and exclusion criteria were analyzed retrospectively. The major share i.e.; belonged to the hypofractionated arm may be due to the physicians being more inclined to give hypofractionated regimen to reduce the fraction numbers and thereby curtailing the long waiting for radiation in the institution and also to reduce the burden for the patients traveling from distant places. It is also observed that majority of the patients in the hypofractionated arm are right sided tumour (76.74%) and this again is a bias as the physician were tempted to avoid heart from the radiation fields as in post mastectomy scenario the evidence for hypo-fractionation was only evolving during the treatment period of these patients. Some of the trials in which post mastectomy hypofractionated radiation was given are given in table2.

Table 2: Trials which included post mastectomy hypofractionated radiation patients as well.

Trial	cohort	fractionation	Mastectomy patients	Local recurrence rate (5yr)
Start A[4]	1487	41.6 Gy/13 fr vs 39 Gy/13 fr	15 %	3.2 % vs 4.6 %
Start B[6]	1110	40 Gy/15 fr	8 %	2 %
Ortholan[13]	150	32.5 Gy/5 fr	28.5 %	-
Ko DH et al[14]	133	40 Gy /16fr	100%	2.4%

In our study the failure rate during the median follow up period of 56 months was 26.1% and 31.4% favoring the conventional arm. But this difference in any- failure rate was statistically insignificant. But the local recurrence rate was almost similar i.e.; 8.7% & 11.6% respectively. The difference noted was thus in the systemic recurrence. But our study being a retrospective study and since there was no matching between the two arms the difference observed in systemic recurrence, though not significant may be due to bias. But as noted in the trials mentioned in the table 2, the local recurrence rate in both conventional and hypofractionated arms are comparable.

The acute to skin toxicity was comparable. There was no documented long term cardiac or lung toxicity. But being a retrospective study the assessment of toxicity has limitations. Our results may be partly explained by a short hindsight, since cardiac toxicity is known to appear after a longer period of follow up.

CONCLUSION

Hypofractionated radiation treatment after mastectomy has a comparable local control rate as that for conventional fractionation with acceptable toxicity and shorter treatment time. Henceforth it is a viable option especially for developing countries like India where the disease burden is high due to the high population. Our study has limitations of being a retrospective study with unmatched arms. Hence RCT addressing this subject in Indian patients will definitely benefit the society as a whole.

ACKNOWLEDGEMENTS

We full heartedly acknowledge Dr Suma Susan Meloot M.D for the help delivered for statistical analysis.

FUNDING

No Funding Sources.

CONFLICT OF INTEREST

None Declared.

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee.

REFERENCES

1. Theodora A Koulis, Tien Phan, and Ivo A Olivotto.
2. Yarnold J, Ashton A, Bliss J, et al. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast

cancer: long-term results of a randomised trial. Radiother Oncol, 2005; 75: 9–17. [PubMed]
3. Owen JR, Ashton A, Bliss JM, et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. Lancet Oncol. 2006; 7: 467–71. [PubMed]
4. START Trialists' Group. Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol, 2008; 9: 331–41. [PMC free article] [PubMed]
5. Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol, 2013; 14: 1086–94. [PubMed]
6. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med, 2010; 362: 513–20. [PubMed]
7. Kyung Su Kim et al, Hypofractionated whole breast irradiation: new standard in early breast cancer after breast-conserving surgery, Radiat Oncol J., 2016; 34(2): 81–87.
8. Ragaz J, Olivotto IA, Spinelli JJ, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst., 2005; 97: 116–126. [PubMed]
9. Badiyan SN, Shah C, Arthur D, et al. Hypofractionated regional nodal irradiation for breast cancer: examining the data and potential for future studies. Radiother Oncol, 2014; 110: 39–44. [PubMed]
10. Atif J. Khan et al. Hypofractionated Postmastectomy Radiation Therapy Is Safe and Effective: First Results From a Prospective Phase II Trial DOI: 10.1200/JCO.2016.70.7158 Journal of Clinical Oncology, 2017; 35(18): 2037-2043.
11. Anand AS. Study on the role of primary systemic chemotherapy with anthracycline combination schedule in locally advanced breast cancer: long term follow up data. Int J Res Med Sci, 2015; 3: 3474-81.
12. Emde A, Köstler WJ, Yarden Y. Therapeutic strategies and mechanisms of tumourigenesis of HER2-overexpressing breast cancer. Crit Rev Oncol, 2012; 84: e57. [PMC free article] [PubMed]
13. Ortholan C, Hannoun-Lévi J-M, Ferrero J-M, Largillier R, Courdi A. Long-term results of adjuvant hypofractionated radiotherapy for breast cancer in elderly patients. Int J Radiat Oncol Biol Phys, 2005; 61: 154–62.
14. Ko DH et al. Hypofractionated radiation treatment following mastectomy in early breast cancer: the Christchurch experience. J Med Imaging Radiat Oncol, 2015; 59(2): 243-7. doi: 10.1111/1754-9485.12242.