DOI: 10.21276/aimdr.2020.6.2.RT2

Original Article ISSN (O):2395-2822; ISSN (P):2395-2814

A Prospective Study to Assess Clinical Results and Dosimetric Differences of Conventional vs Hypofractionated Postmastectomy Radiotherapy

Bidisha Naskar Ghosh[1], Bikramjit Chakrabarti[2], Harris Mahammad Sepai[3], Rajarshi Goswami[4]

[1]Associate Professor, Department of Radiotherapy, IPGME&R and SSKM Hospital, Kolkata.
[2]Assistant Professor, Department of Radiotherapy, IPGME&R and SSKM Hospital, Kolkata.
[3]RMO cum clinical tutor, Department of Radiotherapy, IPGME&R and SSKM Hospital, Kolkata.
[4]Post-graduate student, Department of Radiotherapy, IPGME&R and SSKM Hospital, Kolkata.

Received: February 2020
Accepted: February 2020

ABSTRACT

Background: Breast cancer is a major public health problem for women throughout the world. Heart and lung are at risk of radiation toxicities when post-mastectomy radiation therapy is considered for left sided breast cancers. Hypofractionated radiotherapy, if used, is likely to deliver higher dose per fraction to organs at risks. Our study aims at comparing clinical outcome and equivalent dose of 2 Gray ($EQD2_{(3)}$) to organs at risk after both fractionations. **Methods**: Patients of breast cancers treated by modified radical mastectomy were randomized to receive either radiation with a total dose of 50 Gy in conventional fractionation or hypo-fractionated external beam radiation (42.6 Gy in 16 fractions, single fraction daily for 5 days a week). For patients treated with hypofractionated radiotherapy, dose prescription was done twice for same set of beams. Once in conventional fractionation, and again after hypofractionation with calculation of EQD_2 to organs at risk, namely heart and lung. Clinical outcomes and dosimetry of both fractionations were compared. **Results**: Both arms demonstrated equivalent disease outcome. Hypofractionated dose prescription revealed highly significant dose reduction. Since dose received in hypofractionated arm was significantly lower with comparable disease control, there is a strong reasoning to believe that late toxicities will be much lower in hypofractionated arm. **Conclusion**: Hypofractionated radiotherapy is safe for left sided postmastectomy radiotherapy even when cardiotoxic systemic therapy is used. It delivers significantly much lower dose equivalent to heart and lungs. This may reduce their toxicities in long term follow up.

Keywords: Hypofractionated, Outcome, Post-mastectomy, Radiotherapy.

INTRODUCTION

Breast cancer is a major public health problem for women throughout the world. Across the world, it is the most commonly detected cancer and the foremost cause of death among female cancers.[1] Although it is somewhat more common in the left than in the right, it may appear in both breasts simultaneously (1% to 2%).[2] Heart, in addition to lung is at risk of radiation toxicities when post-mastectomy radiation therapy is considered for left sided breast cancers. This risk is increased with use of adjuvant cardiotoxic systemic therapies. Hypo fractionated radiotherapy, if used, is likely to deliver higher dose per fraction to organs at risks, namely heart and lung. However, there is no comparative study between effects of conventional and hypofractionated postmastectomy radiation therapy with or without cardiotoxic systemic therapy. Our study aims at comparing this with evaluation of clinical and equivalent dose of 2 Gray ($EQD2_{(3)}$) to organs at risk.

Name & Address of Corresponding Author
Dr. Bikramjit Chakrabarti,
Assistant Professor,
Department of Radiotherapy,
IPGME&R and SSKM Hospital, Kolkata.

MATERIAL AND METHODS

Postmastectomy patients of histologically proven, ductal adenocarcinoma of breast with good performance status and normal routine investigations and renal, liver function tests, fit from cardiologic point and registered during February to September 2016 were included in our study. Patients not meeting above inclusion criteria were excluded from our study. Sixty one patients were included in our study.

Patients were randomized by blind envelope method to receive either chemoradiation with a total radiation dose of 50 Gy in conventional fractionation or hypo-fractionated external beam radiation (42.6 Gy in 16 fractions, single fraction daily for 5 days a week) using computerized three-dimensional treatment planning and started within 3 weeks of

completion of chemotherapy. During external beam irradiation, all patients were treated based on imaging data with clinical correlation. Clinical assessment, blood, otorrhinolaryngeal examination along with imaging and endoscopy, when required, were done periodically during follow up. Disease free survival at the end of three years and toxicities of treatment by Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 were recorded for all cases.

For patients treated with hypofractionated radiotherapy, dose prescription was done twice for same set of beams. Once in conventional fractionation, and again after hypofractionation with calculation of EQD_2 to organs at risk, namely heart and lung.

IBM SPSS Statistics® software version 20 was used for statistical analysis. $P < 0.05$ was considered statistically significant. Clinical outcomes were compared by Fisher's exact test. Friedman's non-parametric test was used for dosimetric comparison.

RESULTS

A total of 61 postoperative patients suffering from left sided breast cancer were included in our study. Of them, 30 received hypofractionated radiotherapy, whereas, 31 received radiotherapy using conventional fractionation. Dosimetric comparison of all 30 patients treated by hypofractionation were done after using two dose fractionation methods in same computerised plan.

Table 1: Comparison of patient profile

	Conventional fractionation	Hypofractionation	P value
Total number of patients	31	30	
Median age	50 years	48 years	
History of smoking	1	Nil	1.00
History of diabetes	4	3	1.00
History of hypertension	8	6	0.76
Hypothyroidism	Nil	3	0.11
Received anthracycline chemotherapy	28	25	0.24
Received trastuzumab	15	10	0.30
Left sided disease	21	18	0.60
Premenopausal	10	9	1.00
Margin positive	6	8	0.55
Inadequate nodal dissection	10	11	0.79
ER negative	8	11	0.41
PR negative	13	17	0.31
Her2 positive	12	10	0.79

Table 2: Crosstab comparison of outcome against recorded disease status (both fractionations).

Parameter 1	Parameter 2	P value
Side of disease	Mean heart dose	0.047
Side of disease	Mean lung dose	0.078
T stage	Positive margin postoperatively	<0.001
N stage	Inadequate nodal dissection	0.008

Table 3: Comparison of dose volume parameters between two dose prescription methods

		Median dose or volume		P value
		Conventional	Hypofractionated	
Mean lung dose	Absolute	11.78 Gy	9.78 Gy	< 0.001
	EQD2 ($\alpha/\beta = 3$)	11.78 Gy	7.44 Gy	< 0.001
Ipsilateral lung (V20%)		41.35 %	39.04 %	< 0.001
Total lung (V20%)		23.51 %	22.16 %	< 0.001
Mean heart dose	Absolute	11.43 Gy	9.74 Gy	< 0.001
	EQD2 ($\alpha/\beta = 3$)	11.43 Gy	7.35 Gy	< 0.001
Heart (V30%)		13.75 %	10.16 %	< 0.001

Table 4: Difference in clinical outcome between two arms

	Conventional	Hypofractionation	P value
Disease free survival at 2 years	30	28	0.61
Echocardiographic changes	9	11	0.59
Lung function changes	5	3	0.37

Patient profile were comparable in both arms [Table 1]. Crosstab comparison of outcome against recorded disease status revealed significant relationship between T stage and postoperative margin positivity, N stage and inadequate nodal dissection and side of disease with mean heart dose [Table 2]. When compared with conventional fractionation, hypofractionated dose prescription revealed highly significant ($p < 0.001$) dose reduction [Table 3] namely, mean lung dose, mean heart dose, and dose to 20% volume of ipsilateral and total lung and 30% volume of heart. Both

conventional fractionation and hypofractionated arm demonstrated equivalent (p> 0.05) disease outcome [Table 4]. Since dose received in hypofractionated arm was significantly lower with comparable disease control, there is a strong reasoning to believe that late toxicities will be much lower in hypofractionated arm.

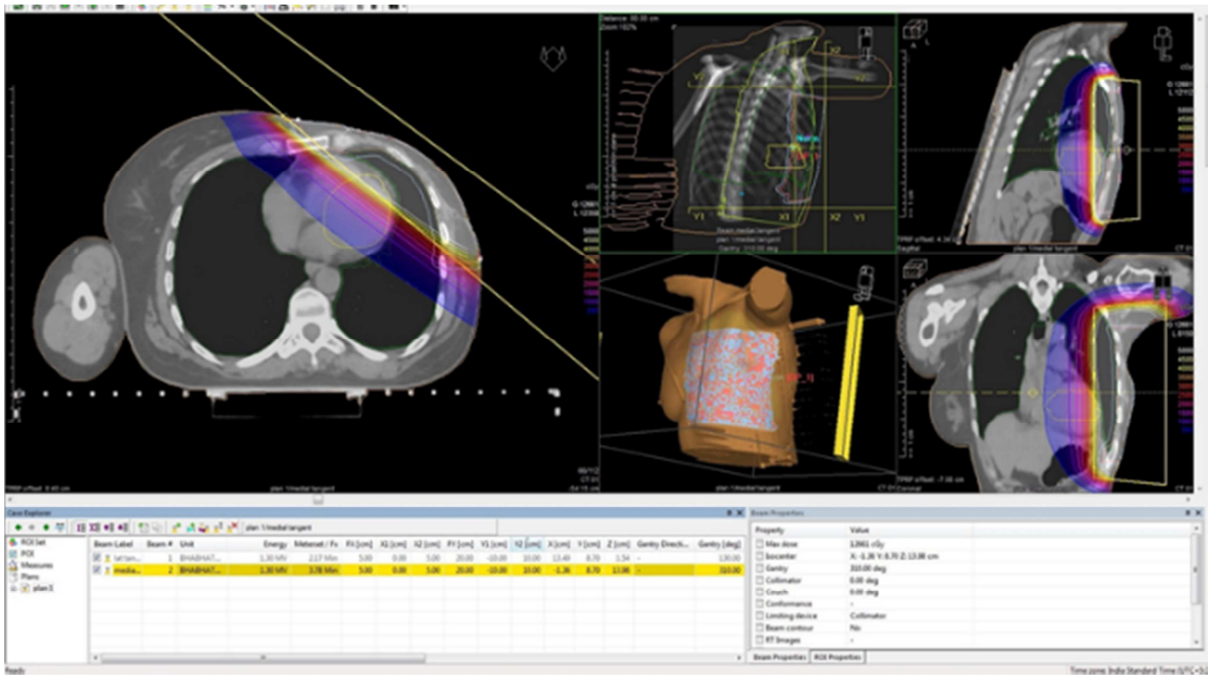

Figure 1: Screenshot of radiotherapy treatment plan for treating left sided breast cancers after mastectomy showing portion of heart and lungs included in tangential portals.

DISCUSSION

Evidence has long been accumulating that radiation therapy involving the heart can result in premature ischemic heart disease. A population-based case-control study in Scandinavia found that rates of major coronary event increased linearly with the mean dose to the heart by 7.4% per Gy with no apparent threshold.[3] This increase started within the first 5 years after RT and continued into the third decade after RT. A large study by Paszat et al.[4] reviewing effects of post-lumpectomy radiation therapy revealed that women with left-sided radiation therapy had a significantly higher fatal myocardial infarction compared with right-sided radiation therapy (2% vs 1%, p = .02). Adjusting for age at diagnosis, the relative risk for fatal myocardial infarction with left-sided post-lumpectomy radiation therapy was 2.10. Patients with left-sided treatment also experienced a persistent reduction in ejection fraction compared with those receiving right sided treatment.[5]

SEER-Medicare database analysis by Patt et al.[6] concluded that there is an increased risk and direct link between radiation and the location of the grade 4-5 coronary stenosis although there were no significant differences for hospitalization for ischemic heart disease in patients with left- versus right-sided cancers. Collectively, these data suggest that although there may be excess cardiac morbidity using tangential fields to treat left-sided breast cancers.

Pre-existing cardiac risk factors increase major coronary events after irradiation of left chest wall. Smoking and use of cardiotoxic therapies like adriamycin, epirubicin, and trastuzumab increases this risk.[7-9] Radiation oncologists should be careful during planning in cases of immediate postmastectomy reconstruction and internal mammary lymph node irradiation because these have a greater potential of irradiation of the heart (in left-sided cancers) and lung.[10]

Earlier studies had suggested excess ischemic heart disease and ten year mortality in the left-sided cancer group.[11] There is no totally safe radiation dose to the heart. So the heart dose should be kept as low as possible. Thus, when treating patients with left-sided breast cancer, exclusion of heart from the beam's eye view should be undertaken.[5] Studies from centres of excellence suggested that it is possible to achieve excellent target coverage and spare normal tissues appropriately through careful treatment planning.[12] Zagar and Marks,[13] pointed out that improved radiation techniques, including custom blocking of the heart are likely to minimize risks and improve the therapeutic ratio. Other techniques to spare heart are heart block, prone breast board, deep inspiratory breath hold (DIBH). These techniques are particularly important in cases of irradiating the internal mammary region.[5] It is particularly notable

that benefits in decreasing cardiac dose with DIBH appear to be of greater magnitude in patients receiving postmastectomy radiotherapy compared to whole-breast irradiation following breast conservation surgery, because of the need to treat larger surgical bed including scars.[14] Internal mammary irradiation should be considered when indicated.[15] Use of standard tangential beams revealed lowest mean dose to both left lung and heart while partially wide tangent technique was the most appropriate balance of target coverage and normal tissue sparing.[16,17] Although it is clearly prudent to minimize exposure of the heart during radiation therapy, using modern techniques, the available evidence does not suggest a higher incidence of cardiac mortality in left-sided radiation therapy.[5] The issue of cardiac irradiation, however, has more importance in patients with ductal carcinoma in situ or low-risk invasive cancers, where there is no likely survival impact of radiation therapy.

Although both conventional and hypofractionated radiotherapy is used for post-mastectomy radiotherapy, no studies have compared these two methods either by clinical outcome or dose volume parameters. Our study aimed at this.

CONCLUSION

Hypofractionated radiotherapy is safe for left sided postmastectomy radiotherapy even when cardiotoxic systemic therapy is used. It delivers significantly much lower dose equivalent to heart and lungs. This may reduce their toxicities in long term follow up. Hypofractionation may be a better option over conventional fractionation for post-mastectomy chest wall irradiation for left sided breast cancers. Trials with larger number of patients and longer follow up should be conducted.

REFERENCES

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65(2):87-108.
2. Haagenson C. Diseases of the breast. Philadelphia, PA: WB Saunders, 1986.
3. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013;368(11):987–998.
4. Paszat LF, Mackillop WJ, Groome PA, et al. Mortality from myocardial infarction following postlumpectomy radiotherapy for breast cancer: a population-based study in Ontario, Canada. Int J Radiat Oncol Biol Phys 1999;43(4):755–762.
5. Halperin, Edward C., et al. Perez and Bradys Principles and Practice of Radiation Oncology. 7th ed., Wolters Kluwer, 2019.
6. Patt DA, Goodwin JS, Kuo YF, et al. Cardiac morbidity of adjuvant radiotherapy for breast cancer. J Clin Oncol 2005;23(30):7475–7482.
7. Taylor C, Correa C, Duane FK, et al. Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. J Clin Oncol 2017;35(15):1641–1649.
8. Shapiro CL, Hardenbergh PH, Gelman R, et al. Cardiac effects of adjuvant doxorubicin and radiation therapy in breast cancer patients. J Clin Oncol 1998;16(11):3493–3501.
9. Shapiro CL, Recht A. Side effects of adjuvant treatment of breast cancer. N Engl J Med 2001;344(26):1997–2008.
10. Motwani SB, Strom EA, Schechter NR, et al. The impact of immediate breast reconstruction on the technical delivery of postmastectomy radiotherapy. Int J Radiat Oncol Biol Phys 2006;66(1):76–82.
11. Darby SC, McGale P, Taylor CW, et al. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. Lancet Oncol 2005;6(8):557–565.
12. Jethwa KR, Kahila MM, Whitaker TJ, et al. Immediate tissue expander or implant-based breast reconstruction does not compromise the oncologic delivery of post-mastectomy radiotherapy (PMRT). Breast Cancer Res Treat 2017;164(1):237–244.
13. Zagar TM, Marks LB. Breast cancer radiotherapy and coronary artery stenosis: location, location, location. J Clin Oncol 2012;30(4):350–352.
14. Moran MS, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. J Clin Oncol 2014;32(14):1507–1515.
15. Thorsen LB, Offersen BV, Dano H, et al. DBCG-IMN: a population-based cohort study on the effect of internal mammary node irradiation in early node-positive breast cancer. J Clin Oncol 2016;34(4):314–320.
16. Severin D, Connors S, Thompson H, et al. Breast radiotherapy with inclusion of internal mammary nodes: a comparison of techniques with three-dimensional planning. Int J Radiat Oncol Biol Phys 2003;55(3):633–644.
17. Pierce LJ, Butler JB, Martel MK, et al. Postmastectomy radiotherapy of the chest wall: dosimetric comparison of common techniques. Int J Radiat Oncol Biol Phys 2002;52(5):1220–1230.

How to cite this article: Ghosh BN, Chakrabarti B, Sepai HM, Goswami R. A Prospective Study to Assess Clinical Results and Dosimetric Differences of Conventional vs Hypofractionated Postmastectomy Radiotherapy. Ann. Int. Med. Den. Res. 2020; 6(2):RT05-RT08.

Source of Support: Nil, **Conflict of Interest:** None declared