Original Article

Patterns of Failure and Arm Disability Following Postmastectomy Hypofractionated Chest Wall Radiotherapy in Resource-Constrained Tertiary Care Practice Setting: A Mono-Institutional Experience

Anis Bandyopadhyay, Arnab Kumar Ghosh[1], Bappaditya Chhatui[1], Dhiman Das[1]

Department of Radiotherapy, NRS Medical College, [1]Department of Radiotherapy, Medical College, Kolkata, West Bengal, India

Abstract

Introduction: Radiotherapy for breast cancer has evolved over the years in terms of technique and dose fractionation. Hypofractionation for whole-breast radiotherapy has equivalent local control and toxicity profile compared to standard fractionation; however, evidence of the same for post modified radical mastectomy chest wall irradiation is scarce in terms of local control and complications. We undertook this study to determine whether hypofractionated (HF) chest wall irradiation gives comparable outcomes to standard fractionation in terms of locoregional control and late effects like arm and shoulder disability in resource-constrained setup. **Materials and Methods:** Breast cancer patients presenting at the outpatient department (OPD) from March to December 2015 who underwent postmastectomy chest wall irradiation were taken for the study. Radiotherapy was delivered by clinical planning using THERATRON 780c with cobalt 60, with tangential fields for chest wall and single anterior field for axilla and supraclavicular region. Patients were treated with either conventional fractionation of 50 Gy in 25# or HF to 42.5 Gy in 16 fractionation to both chest wall and regional nodes. Data were analyzed for patient profile, toxicity, and local and distant failure. Late complications in terms of upper limb morbidity was calculated using QuickDASH(short version of disabilities of arm, shoulder and hand questionnaire) score for patients presenting at OPD from June to November 2019 for follow-up. **Results:** The sample size in the HF and standard arm was 40 and 34, respectively. The hypo# arm had a significantly more number of patients with >3 lymph nodes positive (P = 0.044). The median follow-up of 41 months, the standard and hypo# arm had 6 and 7 failures respectively. The 3-year disease-free survival was 82.4% and 82.5% in the respective arms (P = 0.925). No Grade II or Grade III acute toxicity was noted in both the arms. No Grade II skin or subcutaneous toxicity was noted. The mean QuickDASH score was 5.84 in the standard arm and 6.54 in the HF arm (P = 0.727, Mann–Whitney U test, Nonsignificant). However, the QuickDASH score was found to be significantly more in patients who had a large interfiled distance or who had received axillary radiation. **Conclusion:** Postmastectomy HF chest wall radiotherapy may be a good alternative to conventional fractionation radiotherapy in terms of locoregional control with no difference in acute toxicity and late complications.

Keywords: *Hypofractionated radiotherapy, postmastectomy chest wall radiation, postmastectomy radiotherapy, shoulder and arm disability*

Introduction

Breast cancer is the most commonly diagnosed cancer among Indian females accounting for an incidence of 27.7% and the most common cause of death.[1] The population-based cancer registry data collected from five major cities also reflect a major rising trend in breast cancer cases.[2] However, due to lack of awareness and paucity of screening measures, most patients present at a locally advanced stage, warranting the inclusion of radiotherapy in the multi-modality treatment plan.

Breast cancer radiotherapy has evolved over the years in terms of techniques and dose fractionation. The past decades have seen major interest in the use of hypofractionated (HF) treatment protocols in whole-breast radiotherapy after breast-conserving surgery (BCS). The rationale behind this is the alpha/beta ratio of breast tissue which behaves like a late reacting tissue, thus would benefit from hypofractionation.[3] Evidence from large randomized controlled trials from the UK and Canada showed that moderate hypofractionation is noninferior to conventional fractionated (CF) radiotherapy

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Address for correspondence:
Dr. Anis Bandyopadhyay, Department of Radiotherapy, NRS Medical College, 138 AJC Bose Road, Kolkata - 700 014, West Bengal, India.
E-mail: anish_b123@yahoo.com

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in terms of disease control, survival, and late toxicity, and there may be a tendency toward improvement in locoregional control rate.[4-8] The UK START studies have reported 10-year locoregional recurrence (LRR) of 6.3%, 8.8%, and 4.3% in the HF arms (41.6 Gy, 39 Gy, and 40 Gy arms, respectively), while the Canadian trial reported a 10-year LRR of 6.7%.[4-6]

An important concern about hypofractination was the possible increased incidence of late toxicities. One arm of START A and the HF arm of START B trials have reported less incidence of moderate/marked breast induration, telangiectasia, and breast edema.[4,5] Shoulder stiffness and arm edema were not significantly higher with hypofractionation.[4-6] The long-term results from START trials suggest that appropriately dosed HF lymphatic radiotherapy is safe, according to patient- and physician-assessed arm and shoulder symptoms. Meta-analyses and systemic reviews also revealed no increased cardiac events, brachial plexopathy, or rib fractures occurred with HF regimen

Although many of the above trials included postmastectomy radiation, they constituted only a small proportion. In the UK START B and START A trials, only 8% and 15% of patients had not undergone BCS. Postmastectomy radiation predominates the practice scenario in most state-run hospitals in India and the use of hypofractionation for postmastectomy radiotherapy (PMRT) is widely practiced in many institutions. Although the radiobiological rationale behind the use of hypofractionation in PMRT lacks clarity, reducing the overall treatment time helps in increasing treatment volume, thereby reducing waiting time.[9] However, there is a concern of late complications, especially where locoregional nodal irradiation is employed.

We conducted an audit to explore the hypothesis that moderately HF PMRT provides similar locoregional control as compared to CF radiotherapy, without increasing late toxicity. The most common hypofractionation schedule followed in our institution is that of Canadian OCOG 93-010,[6] delivering a dose of 42.56 Gy, 2.66 Gy/fraction. The majority of the patients are treated in a cobalt 60 machine by clinical planning. We conducted this study to determine whether HF PMRT with 42.5 Gy in 16 fractions delivered 5 days a week gives a comparable outcome to the CF schedule of 50 Gy in 25 fractions in terms of locoregional control and late complications, especially arm and shoulder disability.

Materials and Methods

We selected 74 patients who attended the Radiotherapy Outpatient Department (OPD) of Medical College Kolkata during the period of 2015–16. The selection criteria included patients of invasive breast carcinoma who had undergone modified radical mastectomy (MRM) with a minimum of 10 axillary lymph nodes sampled. Patients having ECOG performance status score >2,[10] post-MRM flap reconstruction/arm morbidity, preexisting mobility restriction of an arm, and metastatic breast cancer were excluded from the study. Patients were nonrandomly assigned to receive either hypofractionation or standard fractionation schedule based on the clinician's discretion.

Radiotherapy technique

All patients were treated by manual two-dimensional (2D) or clinical planning. Patients were positioned on a flat couch, arm abducted at 90°, and forearm flexed above the head. The neck was rotated toward the contralateral side if supraclavicular lymph nodes were to be treated. A vertical line was drawn from the sternoclavicular joint of the treatment side down up to 2 cm below the contralateral breast crease. A perpendicular bisector from this vertical line is drawn across the operated chest wall up to the midaxillary line. A plaster of Paris bandage was placed along the bisector to reproduce the chest wall contour on paper and measure the tangential beam dimensions, interfield distance (IFD), and couch shift positions. Postoperative computed tomography (CT) scan of the thorax was used to assess the lung volume inside the tangential fields at the contour reference and to determine whether half-beam blocking was required or not. Planning was done by either the skin-to-axis distance or skin-to-surface distance method.

For the supraclavicular field (SCF), the inferior margin was at the upper border of chest wall fields, superior margin at the cricothyroid notch, medial margin 1 cm lateral to the medial chest wall margin, and lateral margin at the junction of medial two-third and lateral one-third of the clavicle. The specific indication for axillary irradiation was the presence of extranodal extension. For the axillary field, the lateral border of the SCF was extended up to the insertion of the deltoid.

The total prescription dose was 42.56 Gy, 2.66 Gy/fraction in the HF arm, and 50 Gy, 2 Gy/fraction, in the CF arm, delivered 5 days per week. Tangential portals were used for the chest wall and a single anterior portal for the SCF and axilla.

Patients in both the arms received postoperative adjuvant chemotherapy with four cycles of doxorubicin and cyclophosphamide followed by four cycles of paclitaxel. The doses of doxorubicin, cyclophosphamide, and paclitaxel were 60 mg/m^2, 600 mg/m^2, and 175 mg/m^2 respectively. Chemotherapy was delivered in three-weekly cycles. Trastuzumab was added to paclitaxel if indicated.

Follow-up and data collection

During the treatment, patients were reviewed weekly for toxicity. The first follow-up was done at 6 weeks. Further follow-up schedule was every 2 months for the first 6 months, every 3 months for the next 18 months, every 6 months for the following 3 years, and annually thereafter.

Acute toxicity was categorized as those developed within the first 6 months of follow-up. Follow-up was done only by clinical examination and yearly mammography.

When disease failure was suspected, it was evaluated by radiological investigations (contrast-enhanced CT scan, magnetic resonance imaging, bone scan, and positron-emission tomography CT whichever was applicable based on availability) and confirmed by biopsy. Acute and late toxicity was assessed based on Radiation Therapy Oncology Group toxicity criteria,[11] upper limb morbidity was scored using an 11 point questionnaire. The primary endpoint for survival analysis was disease-free survival (DFS) and LRR-free survival (LRRFS).

Disability of arm, shoulder, and hand

Complications of radiotherapy may lead to upper limb disability. Disabilities of arm, shoulder and hand (DASH) is a 30-item function scale that assesses patient symptoms relating to upper limb movement. However, for a quicker assessment in the OPD setting, we used a smaller version of the scale called QuickDASH.[12] The QuickDASH is an 11-item scale, each item scored on a Likert scale. The cumulative score can be between 0 and 100. QuickDASH was calculated in clinically controlled patients during their follow-up visits between June and November 2019.

Data analysis

Patient characteristics, tumor, and treatment parameters were evaluated using descriptive statistics, and distribution of the same in the two arms was compared using the Chi-square test. Chi-square test was used for comparison of disease failure and acute and late toxicities between the two arms. DFS and LRRFS were represented by the Kaplan–Meier plot and the log-rank test was used as a test of significance. For shoulder morbidity, Mann–Whitney *U*-test was used to compare QuickDASH scores, and the Chi-square test was used to test the association of QuickDASH with IFD and axillary radiation.

Results

Basic patient and treatment characteristics are tabulated in Table 1. There were 40 patients in the HF arm and 34 patients in the CF arm. The number of premenopausal patients was 18 and 15 in HF and CF arms, respectively (P = 1, Chi-square). About 65% and 64.7% of patients belonged to pathological Stage III disease in the HF and CF arms, respectively (P = 0.585, Chi-square test). Twenty six patients in the HF arm were Grade 2 and 14 patients were Grade 3. In the CF arm, 19 patients were Grade 2 and the rest were Grade 3. About 65% and 62% of patients in the HF and CF arms, respectively, were hormone receptor positive. Ten patients in HF and eight patients in the CF group were triple negative.

The HF arm has a significantly higher number of patients with greater than three nodes positive (62.5% vs. 35.3%). The radiation target volume included chest wall only in 23 patients, chest wall and supraclavicular lymph nodes in 31 patients, and chest wall and axillary and supraclavicular lymph nodes in 20 patients.

The median follow-up was 41 months in both the arms. There were 6 (17.6%) failures in the HF arm and 7 (17.5%) in the CF arm (P = 0.612, nonsignificant, Chi-square test) [Table 2]. In the HF arm, there was one chest wall and nodal recurrence each, and five distant metastases. There was no chest wall recurrence, 2 nodal recurrences, and 4

Table 1: Patient characteristics, pathological stage, and radiation technique

	Study (HF) (%)	Control (CF) (%)
Median age (years)	48	46
Menstrualhistory		
Pre	18 (45)	15 (44.11)
Post	22 (55)	19 (55.88)
Pathologicalstage		
II	14 (35)	12 (35.3)
III	26 (65)	22 (64.7)
Grade		
2	26 (65)	19 (55.9)
3	14 (35)	15 (44.1)
LN positivity		
Negative	7 (17.5)	7 (20.6)
1-3 positive	8 (20)	15 (44.1)
>3 positive	25 (62.5)	12 (35.3)
Planning technique		
SAD	27 (67.5)	28 (82.4)
SSD	13 (32.5)	6 (17.6)
Radiation target		
CW	9 (22.5)	14 (41.2)
CW + SCF	18 (45)	13 (38.2)
CW + Ax + SCF	13 (32.5)	7 (20.6)

SAD: Skin to axis distance, SSD: Skin to surface distance, SCF: Supraclavicular field, CW: Chest wall, Ax: Axillary, LN: Lymph node

Table 2: Distribution of disease failure

	Study (HF) (%)	Control (CF) (%)	*P*
Locoregional or distant failure	6 (17.6)	7 (17.5)	0.612 (χ^2)
Clinically controlled disease	28 (82.4)	33 (82.5)	

HF: Hypofractionated, CF: Conventional fractionated

Table 3: Pattern of disease failure in the two arms

	Study (HF)	Control (CF)
CW recurrence	0	1
Nodal recurrence	2	1
Distant metastasis	4	5
Controlled	28	33

HF: Hypofractionated, CF: Conventional fractionated, CW: Chest wall

distant metastases in the CF arm [Table 3]. The median DFS was not reached. The 3-year DFS was 82.4% and 82.5% in the HF and CF arms, respectively. The Kaplan–Meier for DFS and LRRFS were nonsignificant (log-rank $P = 0.925$ and 0.837, respectively). The 3-year LRRFS was 93.9% in the HF arm and 94.9% in the CF arm [Figure 1].

The toxicity profile is tabulated in Table 4. No Grade I or II acute toxicity was noted in either arm. Grade I acute dysphagia was higher in patients of HF arm who received supraclavicular radiation; however, it was not significant statistically. Grade I late skin toxicity was more in the HF arm, although not significant. No Grade II late skin or subcutaneous toxicity was observed in either arm. Three incidences of lymphedema were noted, 2 in HF and 1 in CF arm. Brachial plexopathy was not reported in any patient during the study period. No bone fracture was reported during follow-up in patients with locoregionally controlled disease. The mean QuickDASH score was 6.54 in the HF and 5.84 in the CF arm and ($P = 0.727$, Mann–Whitney U test, Nonsignificant). However, the QuickDASH score was found to be significantly more in patients who had a large IFD or who had received axillary radiation [Table 5].

Discussion

HF external beam radiotherapy has been a major interest in the treatment of breast cancer over the past two decades. However, it is used mostly for whole breast radiotherapy (WBRT) following BCS for early breast cancer. In India, about 30%–60% of patients present with locally advanced breast cancer,[13] owing to lack of health education and would require mastectomy with axillary nodal dissection. Even if a patient is diagnosed clinically with early breast cancer, BCS is not favored in resource-constrained centers due to the lack of modern imaging facilities.[14] In the radiotherapy practice setting, the majority of patients are referred after mastectomy and require chest wall irradiation.

Four major randomized trials of hypofractionation have mainly addressed the issue of WBRT following BCS.[3-6] Some patients in the Start B and Canadian trial had undergone PMRT; however, there is not enough evidence to justify routine use of HF chest wall irradiation, especially when using primitive techniques. Various trials have addressed this issue.[9,15-19] None of these trials have shown the inferiority of HF chest wall radiotherapy in terms of disease control and late toxicity.

The median age in our study is 47 years. Our cohort is younger than the study sample of the major randomized trials. The median age was 57 years in the UK START trials,[4,5] and it was 49–57 years in the HF PMRT trials.[15-17] Almost 81% of patients in our study had lymph node-positive disease, whereas it was only 29% and 23% in START A and B trials, respectively. All patients in our study received adjuvant chemotherapy, whereas it was not consistent in the reported HF PMRT and WBRT trials.[6,16] This reflects that our study cohort was at a higher recurrence risk than the historical samples. Chitapanarux *et al*. and Sun *et al*. have employed boosting of the chest wall following PMRT, we did not include PMRT boost in our study protocol.[16,17]

Our study has reported DFS and LLRFS of 82.4% versus 82.5% and 93.9% versus 94.9% in the HF and CF arms, respectively. Five-year rate of any events in the HF arms of START trials was 11.7%, 24.3%, and 10.4%.[4,5] For HF PMRT, Chitapanarux *et al*. have reported a 5-year DFS and LLRFS of 70% and 96% in the HF arm.[16] Sun *et al*. have reported a 5-year DFS of 75.1% versus 74.6% in the HF and CF arm, respectively.[17] Khan *et al*. reported 3-year LRRFS of 89.2%.[15] Early Indian data on the benefit of hypofractionation were available from a study by Yadav BS *et al*.[18] who showed that 5-year local control and overall survival were 94.4% and 81%, respectively. With a median follow-up of 58.5 months, Wang *et al*. reported that a 5-year incidence of LRR was 8.3% versus 8.1% in HFRT and CFRT arms, respectively.[9] DFS and LLRFS in our HF arm correlate well with the PMRT trials but not with the WBRT trials.

The 39 Gy HF arm of START A and 40 Gy HF arm of START B have shown less moderate/marked breast induration, telangiectasia, and breast edema than the CF arm. The Canadian trial has shown no significant difference for skin toxicity and subcutaneous toxicity between the HF

Table 4: Acute and late toxicity

	Study (HF)	Control (CF)	*P*
Skin toxicity, acute (%) – Grade I	7 (20.58)	11 (27.5)	0.339
Dysphagia – Grade I	14/20	28/31	0.07
Skin toxicity, late (%) – Grade I	9 (26.5)	13 (32.5)	0.379
Subcutaneous toxicity, late (%) – Grade I	5 (14.7)	5 (12.5)	0.523
Lymphedema (%)	2 (5.9)	1 (2.5)	0.438

HF: Hypofractionated, CF: Conventional fractionated

Table 5: Quick disability of arm, shoulder, and hand score in terms of inter field distance and axillary radiation

	QuickDASH <5 (%)	QuickDASH >5 (%)	*P* (χ^2)
Interfield distance (cm)			
IFD <=16	19 (90.5)	2 (9.5)	<0.001
IFD >16	12 (30)	28 (70)	
Axillary radiation			
No axillary radiation	27 (62.8)	16 (37.2)	0.004
Axillary radiation	4 (22.2)	14 (77.8)	

DASH: Disability of arm, shoulder, and hand, IFD: Interfield distance

and CF arms.[6] In the PMRT studies, Chitapanarux *et al*. have reported a significantly higher Grade 2 late skin and subcutaneous toxicity in the HF arm. Sun *et al*. reported similar Grade 2 toxicities between the two arms and less Grade 3 skin toxicity in the HF arm.[17] Khan has reported Grade 2 skin and subcutaneous toxicity of 2.4% and 1.4%, respectively.[15] Our study sample did not present with any Grade 2 toxicity during the follow-up period. Incidence of Grade 1 skin, subcutaneous toxicity, and dysphagia was nonsignificant between the two arms.

No significant difference in lymphedema was noted between the HF and CF arm of our study (5.9% vs. 2.5%). PMRT studies in the literature have also reported lymphedema of 2%–4.5% in the HF arm,[15,16] with no significant difference between HF and CF arms. UK START trials have reported arm edema of 11.9%, 6.4%, and 2.8% in the 41.6 Gy, 39 Gy, and 40 Gy HF arms, respectively.[20] The higher incidence of lymphedema in the 41.6 Gy arm of START A could be due to large sample size, large fraction size, and longer follow-up.

Shoulder stiffness was reported in the UK START studies.[20] After 10 years of follow-up, shoulder stiffness was reported to be 8.8%, 7.1%, and 7.5% (50 Gy, 41.6 Gy, and 39 Gy arms respectively) in START A and 2.9% and 3.1% (50 Gy and 40 Gy) in START B.[20] Among PMRT trials, shoulder disorder was comparable in the two arms of Sun *et al*.[17] We have incorporated a subjective evaluation of upper limb morbidity by QuickDASH scoring, which was unique, not employed in the previous studies. We have reported a comparable mean score between the two arms. The score was related to the IFD and axillary radiation. Patients receiving axillary radiotherapy and having IFD more than 16 cm had significantly higher scores than those with IFD <16 cm and/or not receiving axillary radiation. Thus from the distribution of QuickDASH score, we may conclude that patients with larger IFD or receiving axillary RT may benefit from 3D conformal RT.

Our study has various limitations such as inadequate sampling, short follow-up for reporting failure, and late complications. With a median follow-up of 41 months, 3-year DFS was 82.4% and 82.5% in the HFRT and CFRT arm, respectively. This is comparable with results from historical cohorts. In our study, we have not noted any Grade II or III toxicity during the follow-up period. The exclusion of build-up bolus and boost from the treatment planning may be attributed to less severe acute skin toxicity. Less severe acute reactions may lead to less severe late skin and subcutaneous toxicities. However, local control was satisfactory at per with historical cohorts.

Another drawback of our study was that we had not included cardiac morbidity assessment in the follow-up plan for the patients, thus was not reported. Our study is unique in the sense that we have only employed clinical and manual contoured plans to deliver HF radiation to the chest wall and regional nodes for the whole cohort. The humeral block was not used and dose limitations of the organ at risk could not be assessed. However, we have reported good DFS and favorable toxicity profile justifying the use of HF radiotherapy in a resource-constrained setup.

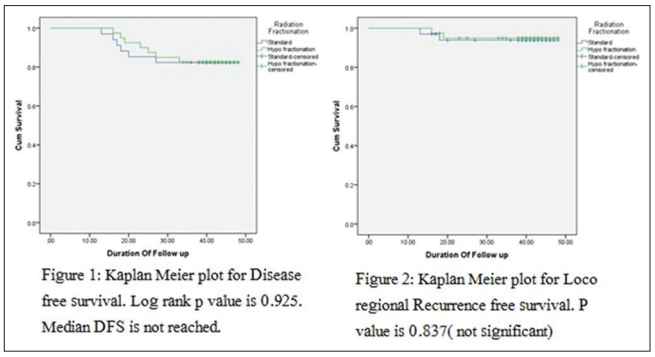

Figure 1: Kaplan Meier plot for Disease free survival. Log rank p value is 0.925. Median DFS is not reached.

Figure 2: Kaplan Meier plot for Loco regional Recurrence free survival. P value is 0.837(not significant)

Figure 1: Kaplan–Meier plot of disease-free survival and locoregional recurrence-free survival

Conclusion

Postmastectomy hypofractionated chest wall radiotherapy may be as good as standard fractionation radiotherapy in terms of locoregional control with no difference in acute and late complications. This holds for even patients treated with 2D techniques, clinical marking using cobalt 60.

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Conflicts of interest

There are no conflicts of interest.

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