

EFFICACY OF HYPOFRACTIONATED RADIOTHERAPY IN LOCO-REGIONAL TUMOR CONTROL IN BREAST

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ABSTRACT

Objective: To evaluate the efficacy of hypofractionated radiotherapy (HFRT) in locoregional control (LRC) in breast cancer.

Study Design: Descriptive case series.

Place and Duration of Study: Oncology Department of CMH Rawalpindi, from Jan 2014 to Oct 2014.

Material and Methods: Fifty three female patients with histopathologically confirmed breast cancer and Eastern Cooperative Oncology Group performance status (ECOG-PS) ≤ 2 were enrolled in the study. These patients required post-operative radio-therapy to intact breast/ chest wall / residual breast tissue were treated using linear accelerator. Lateral/medial tangential and ipsilateral supraclavicular fields were employed to a dose of 39 Gy in 13 fractions with 6 MV photon beam. The ipsilateral axilla was also radiated if required to same dose with postero-anterior field. Scar boost was administered using 6 MeV electron beam to a dose of 7.5 Gy in 3 fractions in patients with high risk features for local recurrence like high grade, positive axillary nodes, lymphovascular invasion and close or positive surgical resection margins. Patients were followed up weekly during radio-therapy (RT) and three monthly after completion of RT for a period of 6 months. Any suspicious lesion was subjected to biopsy. Data analysis was done with the help of the Statistical Package for the Social Sciences (SPSS) version 19 software, which included descriptive analysis. Loco-regional control (LRC) and loco-regional recurrence (LRR) rates were calculated. LRC was no recurrence of tumor/tumor control in chest wall, axilla, residual breast tissue, and/or infraclavicular/supraclavicular lymph nodes. LRR was appearance of nodules / lesion at local site which was biopsied and confirmed histopathologically.

Results: Fifty three female patients with histopathologically confirmed breast cancer and ECOG-PS ≤ 2 requiring post-operative radio-therapy to intact breast/chest wall/ residual breast tissue were treated. The mean age was 47 years (age range, 20-70 years). Modified radical mastectomy (MRM) was performed in 47 (88.7%) patients and breast conserving surgery (BCS) in 6 (11.3%) patients. The commonest histological subtype was Invasive Ductal Carcinoma (IDCA) observed in 47 (88.7%) patients. Three (5.7%) patients had stage I disease, 16 (30.2%) patients had stage II and stage III included 34 (64.2%) patients. Four (7.5%) patients had T1 disease, 19 (35.8%) had T2, 18 (33.9%) had T3 and 12 (22.6%) patients had T4 disease. Node positive disease was present in 45 (85%) patients. LRC and LRR rates were 98.1% and 1.9% respectively.

Conclusion: It is concluded that HFRT is a simple and effective protocol for LRC in breast cancer in our set up. Large scale randomized trials and longer follow up is needed to confirm the results.

Keywords: Breast radiotherapy, Hypo-fractionation.

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INTRODUCTION

Post operative RT has been proven to be effective and standard of care in LRC in breast cancer^{1,2}. The standard conventional RT delivers a

dose fraction of 1.8-2 Gy per day, for a period of 5 to 7 weeks. In comparison, HFRT delivers larger dose radiation fraction over a shorter period of time. HFRT has been shown to provide local tumor control, as a logistically more feasible and cost effective treatment schedule³.

Optimum radiation dose and schedule finding clinical trials with acceptable toxicity have been conducted for best outcome.

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Comparable results in terms of local tumor control and toxicity have been achieved with HFRT protocols to conventional schedules in randomized trials⁴. This has led to development of shorter courses of irradiation that has decreased the overall treatment time and costs.

The standard conventional RT schedule delivers 50 Gy in 25 fractions over 5 weeks to intact breast/chest wall/residual breast tissue with scar boost dose of 10 to 16 Gy in 5 to 8 daily fractions. Many HFRT regimens have evolved internationally on the basis of advancement in radiobiology that led to precise equivalent dose calculations⁵. HFRT protocol include 42.5 to 47.8 Gy in 16 to 20 fractions over 21 to 22 days to whole breast/residual breast /chest wall with scar boost dose of 7 to 8.1 Gy in 3 fractions in 3 days³.

Linear quadratic calculations done for HFRT using Biologic Equivalent Dose (BED) have been found to be equivalent to those performed with the standard regimen using 2 Gy per day fractions³. These inferences are made after analysis of data from clinical trials of altered fractionation schemes based on radiobiological principles. With this background, we have adopted an HFRT protocol in our center for LRC that comprises of 39 Gy in 13 fractions to whole breast/residual breast/chest wall followed by boost of 7.5 Gy in 3 fractions to the scar¹⁰.

Conventional radiation takes six weeks to complete. This causes great logistic inconvenience and is a major cause of poor compliance to treatment. In this regard, HFRT protocol is a logistically and cost-effective alternative option. The problem of workload on our busy centers will also be alleviated. The rationale of this study was to evaluate the efficacy of HFRT with dose of 39 Gy in 13 fractions to whole breast/residual breast /chest wall followed by scar boost of 7.5 Gy in 3 fractions in LRC in breast cancer in our population.

PATIENTS AND METHODS

This study was conducted between January 2014 to October 2014 at department of Oncology,

CMH Rawalpindi, Pakistan. This was a descriptive case series. The following criteria was used to enroll patients.

Female gender, patients with age ≥ 20 and ≤ 70 years, patients with histopathologically confirmed carcinoma of breast, patients after surgery (BCS/MRM) with any one of the following features: with tumor size ≥ 5 cm, four or more involved axillary lymph nodes, extra-capsular extension (ECE) of nodal disease, close or positive post operative surgical resection margins was included in the study.

Patients with more than one malignancy and who have received previous radiation therapy to chest wall, patients with ECOG-PS ≥ 3 were excluded for the study.

Fifty three female patients from Oncology out patient department (OPD) and indoor patient department at CMH, Rawalpindi were enrolled by non-probability consecutive sampling. Patients were treated with linear accelerator employing lateral and medial tangential fields to a dose of 39 Gy in 13 fractions with 6 MV photon beam. Ipsilateral axilla was included in supraclavicular field and was radiated to same dose with antero-posterior field using 6MV photon beam in patients with node positive extra-capsular disease (ECE) in axilla. Scar boost was administered using 6 MeV electron beam to a dose of 7.5 Gy in 3 fractions in patients with high risk features for local recurrence like high grade, positive axillary nodes, lymphovascular invasion and close or positive surgical resection margins. Patients were examined clinically every week during RT and three monthly for 6 months after completion of RT. Any suspicious lesion was subjected to biopsy. On completion of 6 months of follow up, patients were subjected to mammography/ sonomammo-graphy /CT scan chest /MRI chest wall (in selected cases) to evaluate any local recurrence.

Data analysis were done with the help of SPSS version 19 software, which included descriptive analysis. Mean was calculated for quantitative variable like age. Locoregional

control (LRC) and loco-regional recurrence (LRR) rates were calculated. LRC was no recurrence of tumor/tumor control in chest wall, axilla, residual breast tissue, and/or infraclavicular/supraclavicular lymph nodes. LRR was

RESULTS

Fifty three female patients with histopathologically confirmed breast cancer and ECOG-PS ≤ 2 requiring post-operative radiotherapy to intact breast/chest wall/residual

Table-I: Number of patient and tumor characteristics.

Age (years) mean (range)	47 (20-70)
<u>Menopausal status</u>	
Pre	26
Post	27
<u>Histopathologic type</u>	
Invasive ductal	47
Invasive lobular	3
Invasive micropapillary	1
Medullary	1
Phylloides	1
<u>Grade</u>	
1	6
2	31
3	16
<u>Tumor size</u>	
pT1	4
pT2	19
pT3	18
pT4a	4
pT4b	8
<u>Nodal stage</u>	
pN0	8
pN1	13
pN2	17
pN3	15
<u>Estrogen receptor status</u>	
Positive	27
Negative	20
Unknown	6
<u>Her2neu status</u>	
Positive	23
Negative	23
Unknown	7
<u>Progesterone receptor status</u>	
Positive	25
Negative	22
Unknown	6
<u>Chemotherapy</u>	
Yes	52
No	1
<u>Hormone therapy</u>	
No	28
Yes	25

appearance of nodules / lesion at local site which was biopsied and confirmed histopathologically.

breast tissue were treated. The mean age was 47 years (age range 20-70 years). Forty seven (88.7%)

patients underwent Modified Radical Mastectomy and 6 (11.3%) patients were treated with BCS. Postoperative surgical resection margins were positive in 5 (9.4%) patients and it was negative in 43 (81.1%) patients. Six (11.3%) patients had grade 1 disease, 31 (58.5%) had grade 2 and 16 (30.2%) patients had grade 3 disease (table-I).

Histopathological subtypes included forty seven (88.7%) patients of Invasive Ductal Carcinoma (IDCA). Three (5.7%) patients of Invasive Lobular Carcinoma (ILCA) and 1 (1.9%) case of each subtype of Invasive Micropapillary, Phylloides and Medullary carcinoma were seen. Estrogen receptor (ER)/ progesterone receptor (PR) positive patients were 27 (50.9%) and ER/PR negative were 20 (37.7%). Human epidermal receptor (HER 2 neu) positive patients were 23 (43.4%) and negative were 23 (43.4%).

Three (5.7%) patients had stage I disease, 16 (30.2%) patients had stage II and stage III included 34 (64.2%) patients. Four (7.5%) patients had T1 disease, 19 (35.8%) had T2, 18 (33.9%) had

DISCUSSION

Radiotherapy is an integral part of treatment in breast cancer after surgery and chemotherapy. It has been proven that adjuvant radiotherapy markedly improves LRC in high risk cases i.e. patients with high grade, positive axillary nodes, lymphovascular invasion and close or positive surgical resection margins⁴. After surgery and chemotherapy patients requiring radiotherapy can either be treated with radiation protocol using conventional or altered fractionation schedule. The main determinants of fractionation schedule is the availability of number of machines in an institution and logistic facilities.

Conventional fractionation delivers radiation over a period of 6-7 weeks. This schedule increases departmental workload and results in poor compliance on part of patient. So the need of the hour was to adopt a schedule of delivering RT in shorter time period with equal efficacy and acceptable toxicity. The main reluctance was toxicity by delivering larger dose per fractionation. However, clinical research and advances in radiobiological principles over

Table-II: Locoregional control and locoregional recurrence rates in various studies employing hypofractionated radiotherapy protocols.

S No.	Study	LRC	LRR
1	Start A	-	5.3%
2	Start B	-	2.2%
3	Fujii et al	90%	-
4	Whelan et al	96.8%	-
5	Our study	98.1%	1.9%

T3 and 12 (22.6%) patients had T4 disease. Out of 53 patients, thirteen (24.5%) patients had N1 disease, 17 (32.1%) had N2 and 15 (28.3%) patients had N3 disease. Extranodal extension (ENE) was seen in 43 (81.8%) patients (table-I).

Skin erythema was found in 38 (71.1%) patients and radiation pneumonitis was observed in 3 (5.7%) patients. Locoregional control was seen in 52 (98.1%) patients whereas 1 (1.9%) patient developed chest wall recurrence which was confirmed by histopathology.

period of time has yielded a number of shorter RT protocols i.e. HFRT. Equivalent efficacy and acceptable toxicity profile has been achieved with HFRT in comparison with conventional RT schedules. Therefore, we employed HFRT protocol of 39 Gy in 13 fractions followed by 7.5 Gy boost in 3 fractions, in our center and observed the efficacy in terms of loco-regional tumor control¹⁰. No such study has been carried out in our center before.

In our study, we treated 53 female breast cancer patients having ECOG-PS ≤ 2 , with our

HFRT protocol post operatively. Majority of patients were in age group from 40 to 70 years. The number of pre and post menopausal patients were equal in our study. The commonest histology in our patient population was IDCA and these findings are in consistent with those published by Tahereh Ghasemi et al⁶. ER/PR positive patients were 50.6% whereas these were 60.2% patients in a study by Fahim et al⁷.

The equivalence of conventional and HFRT protocols in terms of LRC has been demonstrated in number of studies (table-II). Recently, five year data was reported from two landmark trials. The United Kindom (UK) Standardisation of Breast Radiotherapy (START) Trial A randomized patients with early breast cancer (pT1-3a) N0-1 M0, receiving either 50 Gy/25 fractions in 2 Gy per day versus 41.6 or 39 Gy/13 fractions in 3 Gy per day. LRR was 3.6% in 50 Gy, 3.5% in 41.6 Gy and 5.2% in 39 Gy group respectively⁸. UK START B Trial randomized early breast cancer patients (pT1-3a N0-1M0) after surgery to 50 Gy/25 fractions or 40 Gy in 15 fractions, LRR was 2.2% in 40 Gy group and 3.3% in 50 Gy group. The results are consistent with those of our study⁹.

Another short RT schedule, 40 Gy in 15 fractions, has been used at Christie Hospital in Manchester, UK. They reported results of 2159 treated patients that are comparable to those reported from other centres i.e. LRR upto 11%¹⁰. This protocol is now becoming the "standard" in the UK, especially after the encouraging results of the START trials. Other non-randomized studies have reported similar results. Fujii et al reported equivalent results in terms of LRC upto 90% with a short fractionation schedule of 42.5-47.8 Gy/16-20 fractions³. Whelan et al yielded LRC upto 96.8% with HFRT protocol^{11,12}. LRC in our study was seen in 52 (98.1%) patients and LRR was observed in 1 (1.9%) patient. These results are comparable with standard conventional treatment protocols as well as with HFRT protocols.

In our study, radiation pneumonitis was seen in only 3 (5.7%) patients which was treated with steroids and patients recovered clinically. The common toxicity which was observed in our study was skin erythema seen in 38 (71.1%) patients in contrast to a study by letizia et al in which acute skin erythema was seen in 85% patients in HFRT group¹³.

The potential limitations of our study are there was only one arm of the patients. Number of patients with MRM were more than patients who had BCS. Period of follow up in our study was shorter which is six months, efficacy and adverse effects may take longer time to be evaluated. With longer follow up LRC, LRR and toxicities may be interpreted more effectively.

CONCLUSION

It is concluded from our study that HFRT is a simple, effective and safe treatment protocol for LRC in breast cancer. After the availability of data from international studies, short protocol RT should be adopted as standard as it is resource saving and logistically convenient as well.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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