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Original Article

Oncology Section

Retrospective Analysis of Efficacy and Toxicity of Hypo-fractionated Radiotherapy in Breast Carcinoma

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ABSTRACT

Introduction: The conventional dose fractionation of adjuvant radiotherapy (RT) to whole breast is 45–50 Gy in 25 fractions as 1.8–2.0-Gy per fraction. Lumpectomy cavity with a 1.5–2-cm margin receieves additional 10- 16 Gy doseas boost. Alternative dose fraction schedules used in various randomised trials have established the role of hypofractionated radiotherapy (HRT) in early breast cancer. HRT allows time and cost saving thus better patient compliance. However the efficacy and toxicity of HRT in locally advanced breast cancer is still under evaluation.

Aim: To study the toxicity and efficacy of Hypofractionated Radiotherapy (HRT) as compared to Conventional Radiotherapy (CRT) in breast cancer at our centre.

Materials and Methods: A retrospective analysis of breast cancer patients treated between October 2012- September 2014 with adjuvant radiation therapy as CRT or HRT. The data of these patients was retrieved and analysed regarding demographic profile, stage at presentation, pathological type, extent of surgery, chemotherapy, efficacy and toxicity of HRT. The toxicity assessment was done as per RTOG toxicity criteria. The data were analysed using SPSS software version 20.0.

Results: A total of 100 patients with carcinoma breast who received radiotherapy over two years were analysed. Age ranged from 18-90 years, mean 49.15 ± 12.7 years. Fifty-five patients were post-menopausal, predominant clinical feature was painless lump in the breast (98%). Early stage (Stage I and II) constituted 41%, locally advanced disease in 59%. Modified radical mastectomy was done in 75%, breast conserving surgery in 25%. A 56 patients received HRT and 44 were treated with CRT. The most common acute toxicity was skin grade I. An 18% patients in HRT arm and 30% patients in conventional arm developed grade II skin toxicity (p=0.23). Dysphagia grade I was seen in 10% cases in CRT arm and 12% in HRT arm. The median follow-up period was 11.3 months with 2 loco-regional failures in each arm.

Conclusion: HRT seems to be equally efficacious and no more toxic than CRT in carcinoma breast even in unselected sub-group of patients.

Keywords: Altered fraction, Nodal irradiation

INTRODUCTION

Breast cancer is the most common cancer among women. The number of estimated new cases of breast cancer in 2016 is approximately 246,660 and estimated death is 40,450 [1]. In the post mastectomy or post lumpectomy setting, Radiotherapy (RT) improves loco-regional control and overall survival [2-6]. The international “gold standard” radiotherapy fractionation remains 50Gy in 1.8-2 Gy per fraction, however, various randomized studies have suggested that hypo fractionated regimes provides a viable alternative to this standard approach in early breast cancer [7-13]. The advantages of Hypo-Fractionated RT (HRT) include better patient compliance due to short course and increased utilization of existing RT resources. This is of special importance in our scenario where the availability of RT resources is a major limiting factor. The purpose of this study was to retrospectively analyse the efficacy and toxicity of hypo-fractionated radiotherapy in breast cancer at our center.

MATERIALS AND METHODS

The present study comprised a retrospective analysis of breast cancer patients who were treated from October 2012 to September 2014, in the Department of Radiation Oncology at Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, U.P., India. Patients included in the present study had histologically proven invasive carcinoma, and received adjuvant radiation therapy with either CRT or HRT. The dose and fractionation used was based upon the treating physician’s discretion and conviction for the chosen fractionation schedule. Clinical staging was done according to TNM (AJCC-7th edition) [14]. Patients were assessed regarding demographic profile, stage at presentation, pathological type, extent of surgery and chemotherapy. The treatment policy was based upon the stage at presentation. The planning Computed Tomography (CT) scan (5 mm slice thickness) was obtained in the supine position using “wing-board” with both arms raised above the head. Clinical Target Volume (CTV) and Organs At Risk (OAR) were contoured using Radiation Therapy Oncology Group, (RTOG) contouring guidelines. The CTV was expanded by 5mm to create the planning target volume (PTV). A three dimensional conformal radiotherapy planning was done with XIO version 5.0, Elekta and treated on Elekta Infinity/Synergy linear accelerator using tangential wedged fields to treat breast or chest wall matched with supraclavicular field ± axilla wherever indicated, 6 MV/10 MV photons used and dose prescription for anterior field done at 3cm depth. For each patient, Dose Volume Histograms (DVHs) for the target and OARs were obtained. PTV± supraclavicular and axillary field treated to a total dose of 50Gy in 25 fractions in CRT arm whereas 42.4Gy in 16 daily fractions in HRT arm. An additional dose of 10-16Gy in 5-8 fractions was delivered in patients with BCS with electrons, prescription done to cover the lumpectomy cavity with 90% isodose line.

As per the institutional protocol patients were regularly followed up weekly during RT and monthly thereafter till 6 months and at 4-6 months subsequently. The data was already present in the patient information file and for the study, this information was collected and analysed. History and clinical examination was done to see loco regional control and distant control. Assessment of the acute and late toxicities was done using RTOG toxicity criteria. Mammogram was advised annually and if symptoms were

suggestive of distant metastasis relevant investigation was done. The data were analysed using SPSS software version 20.0. The categorical variables were mentioned as number and percentage.

RESULTS

A total of 100 patients of carcinoma breast who received radiotherapy over two years at our centre were included in the study with no exclusions [Table/Fig-1]. Demographic data and disease characteristics are present in [Table/Fig-1]. As there was one male patient, menopausal status of 99 patients is given in [Table/Fig-1]. The data regarding hormonal status was available in 70 cases; 28 (40%) cases had Estrogen Receptor (ER) positive, 24 (35%) had Progesterone Receptor (PR) positive disease. Triple negative disease was seen in 17 (22.8%) cases. Adequate axillary dissection was done in 80% as in four patients axilla was not addressed and in the rest pathology reports showed, less than 10 lymph nodes removed. Chemotherapy (CT) was completed in 95% cases; the most common chemotherapeutic regimen used was 5-Flouro-uracil, Epirubicin, and Cyclophosphamide (FEC). Taxane based CT was used in 38 cases, Herceptin was given in 4 cases, Lapatinib given in 2 cases that eventually had distant failure in brain.

A total of 100 patients underwent RT, 56 patients received HRT and remaining 44 were treated with CRT [Table/Fig-2]. Nodal irradiation was done in 97% of patients. In terms of dose volume histogram parameters to OAR, volume of ipsilateral lung receiving 20Gy dose ranged from 18% to 30% and mean heart dose ranged from 0.8 Gy to 9 Gy. Overall the most common acute toxicity was skin grade I [Table/Fig-3,4]. An 18% patients in HRT arm and 30% patients in CRT arm developed grade II skin toxicity which was statistically not significant (p=0.23); 1 patient in each arm developed grade IV toxicity, both these patients underwent Breast Conserving Surgery (BCS) and developed toxicity in axilla. One patient in each arm developed lymphoedema; both of these underwent level III axillary dissection. Dysphagia grade I was seen in 11.36% cases in CRT arm and 12% in HRT arm. None of the patients in either arm reported of dry cough; pain, numbness and tingling in arm or shoulder. When assessed separately, toxicity profile in post MRM patients was similar [Table/Fig-4]. The median follow-up period was 11.3 months. Treatment outcomes are shown in [Table/Fig-3]. The most common site for distant metastasis was bone followed by lung.

Characteristics	Total patients N (%)
Number	**100 (100%)**
Age Group (years)	
<31	8 (8%)
31-50	46 (46%)
51 and above	46 (46%)
Gender	
Female	99 (99%)
Clinical Features	
Lump	98 (98%)
Axillary lymphadenopathy	25 (25%)
Menopausal Status	
Post-menopausal	55 (55%)
Pre-menopausal	39 (39%)
Peri-menopausal	5 (5%)
Quadrant	
Upper outer	44 (44%)
Upper inner	16 (16%)
Lower outer	10 (10%)
Lower inner	5 (5%)
Central	25 (25%)
Histopathological Type	
Invasive ductal carcinoma	94 (94%)
Invasive lobular carcinoma	5 (5%)
Medullary carcinoma	1 (1%)
Stage at Presentation	
IB	5 (5%)
IIA	12 (12%)
IIB	24 (24%)
IIIA	33 (33%)
IIIB	22 (22%)
IIIC	4 (4%)

[Table/Fig-1]: Patient and tumour characteristics.

Total N=100)	Conventional Radiotherapy	Hypo fractionated Radiotherapy
Modified Radical Mastectomy (MRM) (N=75)	34 (45%)	41 (55%)
Breast Conserving Surgery (BCS) (N=25)	10 (40%)	15 (60%)

[Table/Fig-2]: Distribution of patients in two radiotherapy fractionation schedules.

	Conventional Radiotherapy N (%)	Hypo fractionated Radiotherapy N (%)
Total	44 (100)	56 (100)
Local failure	2 (4.5)	2 (3.5)
Distant failure	4 (9)	5 (8.9)
Toxicity	-	-
Skin Grade I	30 (68)	45 (80)
Grade II	13 (30)	10 (18)
Grade III	-	-
Grade IV	1 (2)	1 (2)
Dysphagia Grade I	5 (11.36)	7 (12)
Pulmonary	-	-
Lymphoedema	1 (2)	1 (2)

[Table/Fig-3]: Efficacy and toxicity profile for all patients.

	Conventional Radiotherapy N (%)	Hypo fractionated Radiotherapy N(%)
Total	34 (100%)	41 (100%)
Local failure	2 (5.8)	2 (4.8)
Distant failure	3 (8.8)	4 (9.7)
Toxicity		
Skin Grade I	24 (70.588)	34 (82.926)
Grade II	10 (29.4)	7 (20.588)
Grade III	-	-
Grade IV	-	-
Dysphagia Grade I	3 (8.8)	5 (12.19)
Pulmonary	-	-
Lymphoedema	1 (3)	1 (2.439)

[Table/Fig-4]: Efficacy and toxicity profile for post MRM patients.

DISCUSSION

The role of RT for breast cancer in reducing the local and regional relapse has been established in many randomized trials and meta-analyses [2-4]. The earliest prospective study that addressed the role of HRT came from the Royal Marsden Hospital, where around 1400 women were randomized to one of three arms following BCS: 50Gy in 25 fractions, 39Gy in 13 fractions, or 42.9Gy in 13 fractions with all schedules delivered over 5 weeks. At 10-years, local recurrence rates were 12.1%, 14.8% and 9.6% for women receiving standard fractionation, 39Gy in 13 fractions, and 42.9Gy in 13 fractions respectively, with a significant increase in local recurrence for the 39Gy cohort compared with the 42.9Gy cohort. However, all of the patients had undergone BCS and irradiation to the supra- clavicular fossa and axilla was delivered to 20.6% of patients in this study [7,8].

In the Canadian trial, 1234 women with early breast cancer were randomized after BCS to accelerated HRT (42.5Gy/16 fractions) or standard course (50Gy/25 fractions). The results were comparable between two groups of patients in terms of local control and

adverse events with a median follow-up of 12 years [9,10]. The UK START Trial A included 2236 patients randomized to CRT versus two different schedules of HRT (41.6 or 39Gy in 13 fractions) over 5 weeks. In the START B trial, 2215 patients with breast cancer were randomized to standard whole breast CRT (50Gy/25fx) or HRT (40Gy/15fx) in 3 weeks. Both trials showed similar outcomes with respect to local recurrence at median follow-up of 9.3 and 9.9 years respectively and improved toxicity and appearance outcomes noted in the HRT arm [11-13].

Despite the similarity of the results, these studies differed in multiple parameters i.e., patient profile, use of systemic therapy, type of surgery done, nodal irradiation and radiation boost among the three trials. In the Canadian study, boost irradiation was not given and only 10.9% received adjuvant systemic therapy; women with large breast size were also excluded. Whereas, in the START A and B, 35% and 22% of patients respectively received adjuvant systemic therapy; exclusion was not done based on breast size. More importantly the late toxicity and adverse cosmetic outcome were measured and reported differently in these landmark trials [9,10].

There is a paucity of data with regard to HRT in the Post-Mastectomy Radiotherapy (PMRT) with or without regional nodal irradiation setting. START A (15% PMRT, 14% regional RT) and B (8% PMRT, 7% RT) trials included these patients, but as the proportion of these patients was small, a conclusive analysis could not be done. A recent update of these trials addressed the PMRT subset; these patients receiving HRT did not develop significantly more normal tissue effects with regard to, chest pain or swelling, chest wall appearance, shoulder/arm function, and lymphoedema as compared to the standard fractionation PMRT [13]. However, the HRT arm of the START A trial received radiotherapy over 5 weeks rather than 3 weeks. In one study, where 32% underwent nodal irradiation, no cardiac or pulmonary toxicities were observed [14]. Precise data on lymphoedema occurrence is lacking, but the few available literature data do not report increased incidence of lymphoedema among the patients treated by HRT [13,15-17].

The impact of the modern anthracycline and taxane-based regimens in patients treated with HRT is unknown. In one study patients treated with adjuvant CT (mainly anthracycline-based) showed a significant increase of late subcutaneous toxicity and a poor objective cosmetic outcome. But the rate of high grade scores remained low [18].

RECOMMENDATION

Hypo-fractionated radiotherapy seems to be equally efficacious and no more toxic than conventional fractionation in carcinoma breast. As is evident it is an audit of services provided at a center to a mixed bag of patients and the follow-up period is short thus, not much can be inferred conclusively. Only 80% patients had adequate axillary dissection as in four patients axilla was not addressed and in the rest pathology reports showed less than 10 lymph nodes removed. However, prospective randomized studies with larger patient number with longer follow up are required to assess the long term toxicity profile such as subcutaneous fibrosis, lymphoedema, telangiectasia, pulmonary fibrosis, precocious cardiovascular disease etc., and survival.

CONCLUSION

Hypo-fractionated regime potentially offer treatment with similar clinical outcome but with lesser hospital visits and thus, clear cost and resource saving which leads to lesser cost and is economically viable.

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