Original Article

Indian Journal of Cancer Education and Research
Volume 5 Number 2, July - December 2017
DOI: http://dx.doi.org/10.21088/ijcer.2321.9815.5217.4

A Comparative Analysis of Acute Toxicities in Hypofractionated Radiotherapy Vs Standard Fractionation in Early Breast Cancer Post Breast Conservation Therapy

Madisetty Adilakshmi[a], Rayarakula Madukar Rajaiah[b], C. Sanjeeva Kumari[c]

Author's Affiliation: [a]Assistant Professor [b]Senior Resident, [c]Professor, Department of Radiotherapy, MNJIO and RCC, Osmania Medical College, Hyderabad – 500095, Telangana, India.

Corresponding Author: Rayarakula Madukar Rajaiah, Senior Resident, Department of Radiotherapy, MNJIO and RCC, Osmania Medical College, Hyderabad – 500095, Telangana, India.
E-mail: mnjad1962@yahoo.com

Received on 10.07.2017, **Accepted on** 31.07.2017

Abstract

Aim: The aim of the present study is to compare the acute toxicities between the accelerated course of hypo fractionated whole breast irradiation and conventional standard fractionation of Radiotherapy. *Objectives*: To determine the acute toxicities of skin. To determine the influence of breast volumes on acute skin toxicities. *Materials and Methods*: This is a single institutional prospective trial done in females who are known cases of early breast cancer treated by breast conservation therapy and referred to the department of radiotherapy for radiation. These patients meet the inclusion and exclusion criteria. This was conducted in Department of Radiation Oncology, MNJ institute of oncology and regional cancer centre, red hills, Hyderabad. A total of 40 cases were included in the study. 20 cases in the study arm and 20 cases in the control arm. The study is conducted during the period of august 2014 to November 2016. *Inclusion Criteria* was that age was 20-80 years, ECOG performance score of 1-2, pathologically proven breast cancer, treated with breast conservation surgery, margins negative, AJCC stage 1 and 2 i.e. T_1-T_2, N_0-N_1. *Exclusion Criteria* was age <20 years and >80 years, bilateral breast cancer, prior H/O radiation to chest, metastatic disease at presentation, patients who do not give an informed consent. *Results*: Out of 40 patients, 20 patients were in the conventional arm and 20 patients were in the hypo fractionated arm. Compared to patients in the CF arm, patients in the hypofractionated arm had lesser number of grade 2 or more acute skin reactions. There was no statistical significance between the volume of breast and severity of reactions in the study. As there was homogenous dose distribution in the PTV (100 ± 7), there was no correlation between Dmax and the skin toxicities. As the follow up period was less, no comments could be made regarding local control rates and distant metastases. Hypofractionated radiotherapy had logistical advantages like less hospital stay, lesser financial expenditure and lesser burden on the radiotherapy equipment and personnel. Hence, hypofractionated radiotherapy can be safely practiced as an alternative to conventional fractionation. *Conclusion*: A comparative analysis of acute toxicities in hypofractionated radiotherapy vs standard fractionation in early breast cancer post breast conservation therapy was performed. No conclusion can be drawn from our study about locoregional recurrence because of the very short follow up period.

Keywords: Hypofractionated Radiotherapy; Breast Conservation Therapy.

Introduction

Globally, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in women. In the United States, breast cancer is the most commonly diagnosed cancer and the second most common cause of cancer death in women. The annual incidence of breast cancer as reported by GLOBOCAN 2012 is 43.1 (Age-Standardised Rate (ASR)) WORLDWIDE with annual mortality of 12.9(ASR). In INDIA there were 1,44,937 newly diagnosed cases in the year 2012 at the rate of 25.8(ASR) with annual mortality of 12.7(ASR) [1]. Radiation Therapy (RT) has an established role in the adjuvant treatment of breast cancer, either as whole breast irradiation for patients after a breast conserving surgery (BCS) or as chest wall irradiation for high risk patients after Modified Radical

Mastectomy (MRM). The use of adjuvant radiotherapy has reduced the incidence of locoregional recurrence rates, and has improved the long-term survival in patients with breast cancer. Breast conserving surgery followed by radiation therapy to the intact breast is now clearly established as the most acceptable standard of care for the majority of women with early stage breast cancer. It provides survival equivalent to that of total mastectomy and axillary clearance. Hence it is the appropriate method of primary treatment for most cases with stage 1 or 2. Recommended techniques for breast conservation therapy are wide local excision of the primary tumor, preferably with clear margins, axillary lymph node dissection, and breast irradiation.

The radiation doses used traditionally were 45 to 50 Gy, usually with a boost of 10 to 20 Gy. Conventionally, a dose per fraction of 2 Gy per fraction has been used in the treatment of breast cancer patients. A typical course of radiation therapy lasts for about 5 weeks. One of the most significant trial in addressing the issue of local relapse following lumpectomy alone was from the NSABP-06. In this study the cumulative risk of recurrence in the ipsilateral breast 20 years after surgery was 14.3% for women who underwent irradiation following lumpectomy and 39.2% among those who underwent lumpectomy alone without irradiation. A recent EBCTCG meta-analysis of breast conservation trials was published in lancet oncology 2011. The meta-analysis consisted individual patient data from 10,801 patients from 17 randomised trials of radiotherapy versus no radiotherapy after breast conservation surgery.

This meta-analysis showed that radiotherapy reduced the 10-year risk of first recurrence from 35% to 19.3% and reduced the 15 year risk of breast cancer death from 25.2% to 21.4% [2]. The past decade has seen advances in techniques for delivery of postoperative radiation that aim to preserve the high rates of local control but either optimize the treatment for each individual's anatomy, reduce acute or long-term toxicity, or improve cost and convenience of care. Hypofractionation represents one of the most prominent areas of radiation research for breast cancer of the past decade. Hypofractionation refers to the use of fewer, larger-dose radiation treatments of greater than 2Gy per day (42.5 /16# /22days or 40Gy/15#/3weeks) as compared to conventional radiation fraction sizes of 2 Gy per day(50GY/ 25#/ 5 weeks). Consequently, it offers the patients a convenience of shorter total treatment duration, and a potential to reduce expenses [3-5]. Hypo fractionated EBRT has been studied extensively in the West, and has been shown to be non-inferior to conventional fractionation in terms of survival and morbidity. As a result, the hypo fractionated radiotherapy regimen has become the preferred option in countries like the UK and Canada. WBRT is associated with acute toxicities that involve the area treated [skin]. This study was conducted to compare acute toxicities of hypo fractionated external beam radiotherapy vs standard fractionated radiotherapy in patients with early breast malignancy after breast conservation study.

Materials and Methods

This is a single institutional prospective trial done in females who are known cases of early breast cancer treated by breast conservation therapy and referred to the department of radiotherapy for radiation. These patients meet the inclusion and exclusion criteria. This was conducted in Department of Radiation Oncology , MNJ institute of oncology and regional cancer centre, red hills, Hyderabad. A total of 40 cases were included in the study. 20 cases in the study arm and 20 cases in the control arm. The study is conducted during the period of august 2014 to November 2016.

Inclusion Criteria was that age was 20-80 years, ECOG performance score of 1-2, pathologically proven breast cancer, treated with breast conservation surgery, margins negative, AJCC stage 1 and 2 i.e. T_1-T_2, N_0-N_1.

Exclusion Criteria was age <20 years and >80 years, bilateral breast cancer, prior H/O radiation to chest, metastatic disease at presentation, patients who do not give an informed consent.

Methodology: Approval for the study was taken from the Institutional Ethics committee of Osmania Medical College. All patients who have undergone BCS were taken after meeting the inclusion and exclusion criteria. They were informed about the study and consent was taken. After the consent was taken, the patients were enrolled in the study. For all the cases a detailed history was taken and complete physical examination was done. Baseline investigations like hemogram, biochemistry panel, X-ray chest PA view, USG abdomen and pelvis, 2-D EHCO for left sided breast cancers are done. The details of the patient's stage, chemotherapy, surgery, and post-operative histopathological details are studied and documented. After the data is documented, the patient is planned for adjuvant radiotherapy to the whole breast alone or along with the regional lymph nodes depending upon the clinical/pathological staging.

Observations and Results

The present study was a prospective analytical study conducted in department of Radiotherapy, MNJIO & RCC, Hyderabad from august 2014 to november 2016. The patients were selected according to the inclusion and exclusion criteria as mentioned earlier. A total of 40 patients of early stage breast cancer were enrolled in this study and analyzed. All patients underwent baseline evaluation as per protocol. The treatment arms consisted of 50 Gy in 25 fractions at 200 cGy per fraction over 5 weeks followed by 10 Gy boost in 5 fractions (CF) and 40 Gy in 15 fractions at 2.67 Gy per fraction over 3 weeks followed by 10 Gy boost in 4 fractions (HF). The patients were evaluated for skin toxicities weekly during RT and at 1 and 3 months.

A total of 40 patients were enrolled in the study after undergoing breast conservation surgery (BCS) from august 2014 to November 2016 with 20 patients receiving conventional fractionation (Arm-A) [CF] and 20 patients receiving Hypo fractionation [HF] treatment (Arm-B). The mean age of the patients in CF arm is 42 and mean age in the HF arm is 40.65.

Most of the patients in the CF and HF arms were premenopausal. In CF arm 17 patients were premenopausal and 3 patients were postmenopausal whereas in HF arm 15 patients were premenopausal and 5 patients were postmenopausal. The histology of all patients in both CF and HF arms is IDCC. The nuclear grade of the tumor in both arms was 2 or 3 in all cases. In CF arm the nuclear grade is 2 in 13 pts. and 3 in 7 pts. In CF arm the nuclear grade was 2 in 11 patients and 3 in 9 patients. The proportion of right sided breast cancers in the CF group is 55% [11/20] and in HF arm is 50% [10/20]. The proportion cancers that are left sided breast in CF arm are 45% [9/20] and in HF arm are 50% [10/20]. All the patients belong to early stage breast cancer. Most cases belonged to the Tumor stage 2 [T2]. 3 pts. in the CF group were node positive and 6 cases in the HF group were node positive. SCF region is treated in cases of node positive. 3 cases in CF arm and 6 cases in HF arm were given treatment for SCF region. Hormonal receptor status was evaluated in both arms. In CF group, 9 pts were ER positive, 6 pts were PR positive and 7 pts were HER2 neu positive. In HF group, 7 pts were ER positive, 7 pts were PR positive and 8 pts were HER2 neu positive.

Patients were followed up to 3 months. In the CF group, 13 patients (65%) had grade-2 and 3 patients (15%) had grade 3 reactions, while in HF group, only 6 patients (30%) had grade-2 reactions and none of them showed grade-3 reactions. Most of the patients in the HF group had grade-1 skin reactions 14/20 (70 %), while in CF arm, only 4 patients (20%) had grade 1 skin reaction. None of the patients in both the arms showed grade-4 skin reaction. There is a statistically significant difference between the two groups.

Table 1: Shows cancer characteristics

Patient Characteristics	CF	HF
Mean age	42	40.65
Menstrual status	Pre M.:17	Pre M.:15
	Post M.:3	Post M.:5
Side	RT:11	RT:10
	LT:9	LT:10
Histology	IDCC:20	IDCC:20
Nuclear grade	Grade 2: 13	Grade 2: 11
	Grade 3: 7	Grade 3: 9
T Stage	T2: 15	T2: 17
	T3: 5	T3: 3
N Stage	N0: 17	N0: 14
	N1: 3	N1: 6
SCF Field treated	3/20	6/20
ER positive	7	9
PR positive	7	6
HER2 neu positive	8	7

Table 2: Shows analysis of skin toxicity

Grade of skin toxicity	HF arm	CF arm	p value
G0	0	0	
G1	14 (70%)	4 (20%)	
G2 & G3	06 (30%)	16 (80%)	0.001

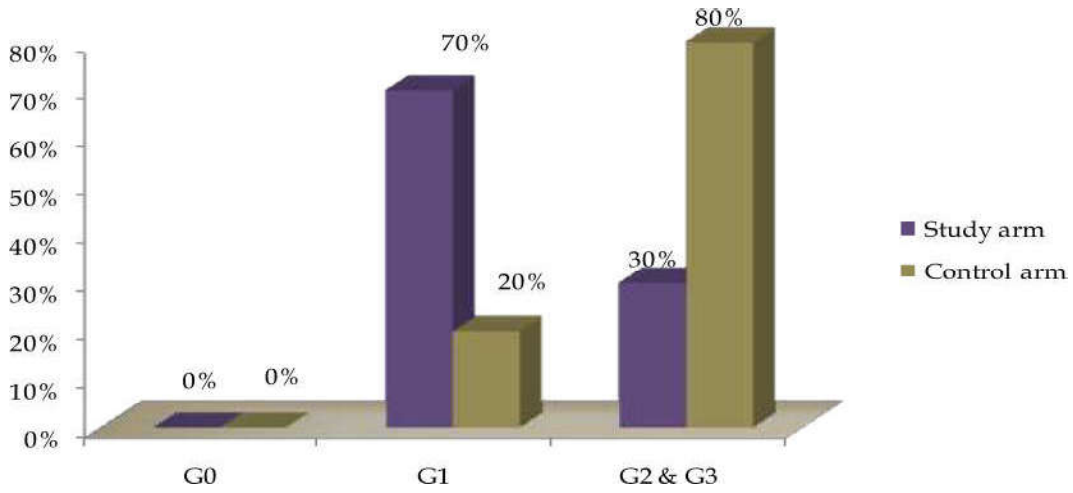

Fig. 1: Shows analysis of toxicity

Mean Heart Doses

In the CF arm, the mean heart doses in right sided cancers is 0.74 whereas that in left sided breast cancer is 5. In the HF arm, the mean heart doses in right sided cancers is 0.71 whereas that in left sided breast cancer is 4.7.

Lung Doses: The mean lung doses in the ipsilateral side in CF arm is 10 Gy and in HF arm is 9.06 Gy. The mean V20 in CF arm is 12.36% and in HF arm is 12.63%. In cases of node positive, where the SCF is also treated the mean V20 of the CF arm is 15.3% and in HF arm is 15.9%.

Breast Volume and Skin Toxicity: Breast volumes are contoured manually as per RTOG guidelines.

In the CF arm, 4 patients who had maximum of grade 1 reactions only had a mean breast volume of 1080.63±329.49 cc. 13 patients who had maximum of grade 2 skin reactions had a mean breast volume of 1102.90±299.30 cc. 4 patients who had maximum of grade 3 skin reactions had a mean breast volume of 1181±0.0 cc.

There is no statistical significance between the volume of breast tissue irradiated and grade of skin reactions in CF group.

Table 3: Shows breast volume and skin reaction in CF group, breast volume and skin reaction in HF group

Grade of skin Reaction	Breast volume(cc) Mean ± SD	P-Value
1	1080.63±329.49 cc	
2	1102.90±299.30 cc	0.5
3	1181±0.0 cc	
Grade of skin Reaction	**Breast volume (cc)**	**P-Value**
1	916.68±202.0	
2	902.85±187.0	0.7

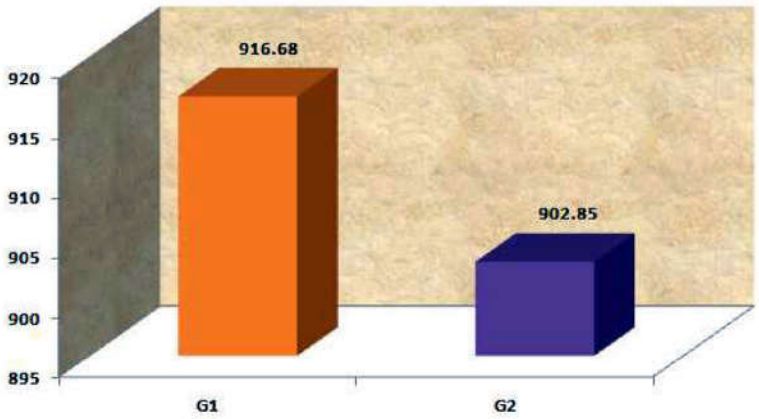

Fig. 2: Shows breast volume and skin reaction in HF group

In the HF group, 14 patients had maximum of grade 1 skin reactions and their mean breast volume is 916.68±202.0 cc. 6 patients had maximum of grade 2 skin reactions and their mean breast volume is 902.85±187.0. There is no statistical significance between the volume of breast tissue irradiated and grade of skin reactions in HF group.

Discussion

The present study is a single institutional prospective analytical study of patients with histo-pathologically proven early breast cancers, undertaken at Department of Radiation Oncology, Mehdi Nawaz Jung Institute of Oncology & Regional Cancer Centre (MNJIO & RCC), Hyderabad. Forty patients were enrolled and randomized into 2 arms. These patients had undergone initial surgery i.e. BCS (lumpectomy + axillary dissection) at our Surgical oncology department. Following surgery, all the patients were referred to the radiotherapy department for further management. As all the patients had T stage of 2 or more, they had received adjuvant chemotherapy. The adjuvant chemotherapy regimen given was 4 cycles of Adriamycin and cyclophosphamide followed by 4 cycles of paclitaxel in all patients of CF arm and 17/20 patients in the HF arm. 3/20 patients in the HF arm had received 6 cycles of FAC chemotherapy. The adjuvant radiotherapy was planned after 4 weeks of last cycle of chemotherapy. The dose fractionation in the HF arm was 40 Gy in 15 fractions over 3 weeks at 2.67 Gy per week followed by an electron boost of 10 Gy at 2.50 Gy per fraction in 4 fractions whereas the dose fractionation in the CF arm was 50 Gy in 25 fractions over 5 weeks at 2 Gy per fraction followed by electron boost of 10 Gy in 5 fractions at 2 Gy per fraction. The local control and overall survival benefits of adjuvant radiotherapy for women with breast cancer have been established by many studies. These studies include:

NSABP B-06: This trial included 1853 patients of early breast cancer (stage 1 and 2). Patients were randomized into 3 arms; total mastectomy, lumpectomy alone or lumpectomy + radiation (50 Gy). On 20 years of follow up, no significant difference in DFS and OS was observed, but addition of RT to lumpectomy reduced the local recurrence rates from 39% to 14%.

MILAN TRIAL: This trial included 570 patients who were randomized to surgery (quadrantectomy + axillary dissection) alone or surgery + radiation (60 Gy). On follow up of 10 years, addition of RT had reduced the local recurrence rate from 23.5% to 5.8%.

Swedish Trial: This trial included a total of 1187 patients who were randomized to lumpectomy alone or lumpectomy + RT (50Gy). On follow up of 5 years, the LF rate was reduced from 14%-4% on addition of RT. A recent meta-analysis of EBCTCG was published in LANCET oncology in 2011. This meta-analysis included individual patient data from 10,801 women in 17 randomised trials to study the effect of radiotherapy after breast conservation therapy.[2] The findings of this meta-analysis showed that: Radiotherapy reduced the 10-year risk of any recurrence (locoregional or distant) from 35% to 19.3% and the 15-year risk of breast cancer mortality from 25.5% to 17.2%. In pN_0 disease, Radiotherapy reduced the 10-year risk of any recurrence (locoregional or distant) from 31% to 15.6% and the 15-year risk of breast cancer mortality from 20.5% to 17.2%. In cases of node positive, Radiotherapy reduced the 10-year risk of any recurrence (locoregional or distant) from 63.7% to 42.5% and the 15 year risk of breast cancer mortality from 51.3% to 42.8%. These studies have established the role of adjuvant radiotherapy in early breast cancer post BCS. The dose fractionation used in most of these trials was 50 Gy in 25 # at 200 cGy per fraction. This standard regimen is based on the assumption that breast cancer cell is less sensitive to changes in the dose per fraction than the dose limiting healthy normal tissue. If this is true, then small (2 Gy) fractions to a high total dose of 50 Gy or more spares the healthy normal tissues relative to the cancer. However retrospective analysis of clinical data suggested that the breast cancer may be much more sensitive to changes in radiation dose per fraction than most other cancers. This led to multiple studies in breast cancer with high dose per fraction (hypofractionation). A hypo fractionated schedule is one that delivers a dose larger than 2 Gy per fraction (with a lower overall dose). Hypo fractionated schedules are potentially attractive in the treatment of breast cancer. The α/β ratios of these tumors are thought to be the same or less than the surrounding late reacting normal tissues. Breast tumors have an α/β ratio of about 4 Gy. These low α/β ratios are thought to reflect the characteristically slower proliferation rates of breast cancer cells compared with other tumor types. As a consequence of this slower proliferation, these tumors respond in a similar manner to late -responding normal tissue rather than early responding normal tissue [6]. Evidence supporting the hypofractionation therapy are:

RMH (Royal Marsden Hospital): A total of 1410 patients pT1-3 N0-1, were randomized to 50 Gy in 25#, 39 Gy in 13 #, 42.9 Gy in 13#. 10 years In Breast Tumor Recurrences were 12.1%, 14.8%, 9.6% respectively [7].

Ontario Clinical Oncology Group

1234 pathologically node negative patients treated with BCS were randomized to 50 Gy in 25# vs 42.5 Gy in 16#. There was no difference in 10 year LR (6.2 vs 6.7), DFS and OS [8].

START A: 2236 patients of early breast cancer subjected to BCS or mastectomy, were randomized to 41.6 Gy in 13#, 39 Gy in 13# and 41.6 Gy in 13#. 5-year local recurrence rate in the group receiving 50Gy, 41.6 Gy and 39 Gy were 3.2%, 3.2% and 4.6% respectively. Changes in breast appearance at 5 years that were self-evaluated as moderate or large were comparable in the groups receiving 50 Gy and 41.6 Gy, and significantly better with regard to skin appearance after 39 Gy than after 50 Gy ($p = 0.004$) [9].

START B: 2215 early stage breast cancer patients treated with BCS or mastectomy were randomized to 50 Gy in 25# over 5 weeks and 40 Gy in 15# over 3 weeks. The 5-year local recurrence rates in the groups receiving 40 Gy and 50 Gy were 2.0% and 3.3%, respectively ($p = 0.21$). No significant differences were found in patient self- evaluated cosmetic effect, except for better skin appearance after the dose of 40 Gy ($p = 0.02$) [10]. The present study was aimed at comparing acute toxicities in standard fractionation vs hypofractionation.

Age: Age of the patients included in the both arm A and arm B were matched to avoid the bias caused by difference in the age. In CF arm: Age distribution was 20-30yrs. - 0 (0%), 30-40 yrs. - 11 (55%), 40-50 yrs. - 8 (40%), and 50-60 yrs. - 1(5%). In HF Arm: Age distribution was 20-30yrs -1 (5%), 30-40 yrs-10(50%), 40-50yr - 5 (25%) and 50-60 yrs. - 4 (20%). Mean age of presentation in arm A was 40 yrs. and mean age at presentation in arm B was 40.65 yrs.

Menstrual Status: Menstrual status of patients in both the arms were matched to avoid bias. Most of the cases were pre-menopausal in both arms. In CF arm: 17 patients (85%) were premenopausal and 3 cases (15%) were postmenopausal. In HF arm: 15 patients (75%) were premenopausal and 5 patients (25%) were postmenopausal.

Side: In CF arm: 11 (55%) patients were side sided and 9 (45%) patients were left sided. In HF arm: 10 patients (50%) were right sided and 10 patients (50%). The side of the breast cancer was also matched to avoid any bias.

Histology: The histology was IDCC in all patients of both arms. Hence, the bias related to histology was avoided.

Nuclear Grade: In CF arm: the nuclear grade was 2 in 13 (65%) of the patients and 7 (35%) patients had nuclear grade 3. In HF arm: the nuclear grade was 2 in 11 (55%) of the patients and 9 (45%) patients had nuclear grade 3. The nuclear grade in both the arms was matched to avoid any bias.

Tumour (T) and Nodal (N) Distribution: Tumour (T) stage: In CF arm, 75% (15/20) of T2, 25% (5/20) of T3 patients were included. In HF arm, 85% (17/20) of T2, 15% (3/20) of T3 patients were included. Majority of patients included were T2 (75%) in CF arm and (85%) in HF arm and others were T3 (25% in CF arm and 15% in HF arm) lesions. With respect to T, CF arm HF arm were comparable.

Nodal (N) Stage: In CF arm, 17/20 (85%) of patients were node negative and in HF arm 14/20 (70%) were node negative. In CF arm, 3/20 (15%) patients presented with N1 stage. In HF arm, 6/20 (30%) patients were presented in N1 stage. Most of the patients presented with N0 (85% of CF arm and 70% of HF arm). With respect to nodal (N) stage at presentation, arm A and arm B were comparable.

SCF Field Irradiation: Node positive patients were treated with SCF field. In CF arm, 3/20 patients were irradiated with SCF field and in HF arm, 6/20 patients were treated with SCF field. The 2 arms were comparable with regards to SCF field irradiation.

Chemotherapy: As the Primary Tumor stage of all the cancers in both the arms was more than T2, all the patients had received chemotherapy. In the CF arm, 20/20 patients had received adjuvant chemotherapy (4 cycles of AC followed by 4 cycles of Taxol). In the HF arm, 18/20 patients had received adjuvant chemotherapy (4 cycles of AC followed by 4 cycles of Taxol) and 2/20 patients had received 6 cycles of FAC. Both the arms were comparable with respect to chemotherapy.

Hormonal Therapy: Estrogen Therapy: In CF arm, 7/20 patients were ER positive and in HF arm, 9/20 patients were ER positive.

Progesterone Therapy: In CF arm, 7/20 patients were PR positive and in HF arm, 6/20 patients were PR positive. In CF arm, 5/20 patients were positive for both ER and PR receptors and in HF arm, 6/20 patients were positive for both ER and PR receptors. All the patients positive for ER/PR receptor were advised hormonal therapy with tamoxifen/letrozole depending upon their menstrual status. 8/20 patients in the CF arm and 9/20 patients in the HF arm were kept on hormonal therapy. Both the arms are comparable with respect ER/PR positive to hormonal therapy.

HER2-neu: 8/20 patients in the CF arm and 7/20 patients in the HF arm were positive for HER 2 neu.

These patients were explained about transtuzumab therapy but as they could not afford the anti HER2 therapy, Herceptin was not given.

Acute Toxicity: Acute toxicity was graded using RTOG acute toxicity criteria. In the CF arm 13 patients (65%) had grade-2 and 3 patients (15%) had grade 3 reactions. In HF group, only 6 patients (30%) had grade-2 reactions and none of them showed grade-3 reactions. Most of the patients in the HF group had grade-1 skin reactions 14/20 (70 %), while in CF arm, only 4 patients (20%) had grade 1 skin reaction. This is consistent with the combined results from the START A and START B trials, where a change in skin appearance occurred significantly less often in the hypo fractionated radiation arm (39 Gy and 40 Gy arms) when compared with the 50 Gy arm (39 Gy HR 0.63 95% CI 0.47, 0.84, p = 0.0019 and 40 Gy HR 0.76 95% CI 0.60, 0.97, p = 0.0262).

Breast Volume and Skin Toxicity: In the CF arm, 4 patients who had maximum of grade 1 reactions only had a mean breast volume of 1080.63±329.49 cc. 13 patients who had maximum of grade 2 skin reactions had a mean breast volume of 1102.90±299.30 cc. 4 patients who had maximum of grade 3 skin reactions had a mean breast volume of 1181±0.0 cc. There is no statistical significance between the volume of breast tissue irradiated and grade of skin reactions in CF group.

In the HF group, 14 patients had maximum of grade 1 skin reactions and their mean breast volume is 916.68±202.0 cc. 6 patients had maximum of grade 2 skin reactions and their mean breast volume is 902.85±187.0. There is no statistical significance between the volume of breast tissue irradiated and grade of skin reactions in HF group. A study from Vicini and colleagues showed that patients with breast volumes > 1600 cc had more acute skin toxicity compared to those with breast volumes < 1000 cc. Another study showed 27% RTOG G 2 erythema and 0% G 3 erythema in patients with breast volumes < 975 cc, while patients with breast volumes > 1600 cc developed 59% RTOG G 2 and 3% G 3I erythema (p=0,002) [11].

D max and Skin Toxicity: As the maximum dose is <107% of the prescribed dose in all the patients in the study, we could not find any specific correlation between maximum dose and acute skin toxicity. Chen and coll. demonstrated that larger volume receiving >53.9 Gy was a significant predictor of radiation induced skin toxicity. Higher volume receiving 107% of prescribed dose within PTV and volume receiving 110% of prescribed dose within treated volume, and no prophylactic topical therapy for irradiated skin, were associated with higher incidence of acute radiation dermatitis [12].

Locoregional Failure and Distant Metastases: Patients were assessed weekly during the radiation therapy for acute skin reactions that develop during treatment, at the completion of RT, after 1 month and 3 months after Radiation therapy. All the patients were further followed every 2 months. The maximum period for which a patient was followed was 2 years and the minimum period was 2 months. None of the patients in the HF arm and CF arm had locoregional or distant metastases. Fisher and colleagues summarized their data concerning breast volume and skin toxicity as follows: patients with small breasts developed ≥ erythema G1 in 11–21%, patients with medium sized breasts in 36-39% and patients with large breasts in 43-50% [13]. A possible explanation for this correlation might be that EBRT treatment plans of larger breast volumes have much more dose inhomogeneities than that of smaller breasts. These dose inhomogeneities may lead to partial hot spots followed by increased skin toxicities.

Conclusion

A comparative analysis of acute toxicities in hypofractionated radiotherapy vs standard fractionation in early breast cancer post breast conservation therapy was performed. No conclusion can be drawn from our study about locoregional recurrence because of the very short follow up period.

References

1. http://globocan.iarc.fr/Pages/online.aspx.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011;378:1707.
3. Freedman GM. Hypofractionated radiation therapy in the treatment of early-stage breast cancer. Curr Oncol Rep. 2012 Feb;14(1):12-9.
4. Chatterjee S, Mallick I, Achari R. Hypofractionation in breast cancer: is it fair to generalise the data? Clin Oncol (R Coll Radiol). 2012 Apr;24(3):228.
5. Munshi A, Budrukkar A. Hypofractionated radiation therapy in breast cancer: a revolutionary breakthrough or a long way to go? J Clin Oncol. 2007 Feb1;25(4):458-9.
6. K.J. Ray, N.R.Sibson, and A.E.Kiltie. Treatment of Breast and Prostate cancer by Hypofractionated Radiotherapy: Potential Risks and Benefits. Clin Oncol. 2015 Jul;27(7):420-426.

7. Owen JR, Ashton A, Bliss JM, et al. Effect of radiotherapy fraction size on tumour control in patient with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. Lancet Oncol 2006;7:467–71.
8. Whelan TJ, Pignol JP, Levine MN, et al. Long-term result of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010;362:513–20.
9. The START Trialists' Group: 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.
10. The START Trialists' Group: the UK standardisation of breast radiotherapy (START) trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol 2008;371:1098–107.
11. Vicini F. Higher per daily treatment-dose radiation therapy or standard per daily treatment radiation therapy in treating patients with early-stage breast cancer that was removed by surgery.Available from: http://clinicaltrials.gov/show/NCT01349322.
12. Chen MF, Chen WC, Lai CH, Hung CH, Liu KC, Cheng YH: Predictive factors of radiation-induced skin toxicity in breast cancer patients. BMC Cancer 2010, 10:508.
13. Fisher J, Scott C, Stevens R, et al: Randomized phase III study comparing Best Supportive Care to Biafine as a prophylactic agent for radiation-induced skin toxicity for women undergoing breast irradiation: Radiation Therapy Oncology Group (RTOG) 97–13. Int J Radiat Oncol Biol Phys 2000;48:1307–1310.