Hypofractionated Radiotherapy for Breast Cancers - Preliminary Results from a Tertiary Care Centre in Eastern India

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Abstract

Background: The standard radiotherapy (RT) fractionation in breast cancers practised in India and worldwide is 50Gy in 25 fractions over 5 weeks to the chest wall or whole breast followed by tumour bed boost in case of breast conservation (BCS). A body of validated data exists regarding hypofractionation in breast cancer. We here report initial results for 135 patients treated at our centre with the START-B type of fractionation.

Materials and Methods: From May 2011 till July 2012, women with all stages of breast cancer (excluding metastatic), who had undergone BCS or mastectomy were planned for 40Gy in 15 fractions over 3 weeks to chest wall/whole breast and supraclavicular fossa (where indicated) followed by tumour bed boost in BCS patients. Planning was done using Casebow’s technique. The primary end point was to assess the acute toxicity and the cosmetic outcomes. Using cosmetic scales; patients were assessed during radiotherapy and at subsequent follow up visits with the radiation oncologist.

Results: Of the 135 patients, 62 had undergone BCS and 73 mastectomy. Mean age of the population was 52 years. 80% were T1&T2 tumours in BCS group whereas most patients in mastectomy group had T3&T4 tumours (60%). 45% were node negative in BCS group whilst it was 23% in the mastectomy group. Average NPI scores were 3.9 and 4.9, respectively. Most frequently reported histopathology was infiltrating ductal carcinoma (87%), grade III being most common (58%), 69% were ER positive tumours, and 30% were Her 2 Neu positive. Triple negative tumours accounted for 13% and their mean age was younger than the general population (43 yrs.) The maximum acute skin toxicity at the end of treatment was Grade 1 in 94% of the mastectomy group of patients and 71% in BCS patients. Grade 2 toxicity was 6% in mastectomy group and 23% in BCS group. Grade 3 was 6% in BCS group, no grade 3 toxicity in mastectomy patients and there was no grade 4 skin toxicity in any case. Post RT at 1 month; 39% of BCS patients had persisting Grade I skin reaction which was only 7% in mastectomy patients. At 3 months post RT, 18% patients had persisting hyperpigmentation. At 6 months 8% patients had persisting erythema in the BCS group only. 3% of BCS and 8% of mastectomy patients had lymph edema till the date of evaluation. Cosmetic outcome in BCS patients remained good to excellent 6 months post surgery and radiotherapy. 1 patient of BCS and 3 patients of mastectomy patients had developed metastatic disease at the time of evaluation.

Conclusions: Hypofractionated RT is well tolerated in Indian population with less acute skin toxicity and good cosmetic outcome. Regimens such as these should be encouraged in other centre to increase machine output time. The study is on-going to assess long term results.

Keywords: Hypofractionation - breast cancer - acute toxicity - skin toxicity - cosmetic outcome - India

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Introduction

Breast cancer (ICD 10: C50) is the second most common cancer among both sexes worldwide (Globocon, 2012). It is the most common cancer among women in both more developed as well as less developed countries. The age standardized incidence rate of breast cancer in India is 22.9% per 100,000 women (Globocon, 2008). As per the Indian Cancer registry, breast cancer is the leading cancer across all its Population Based Cancer Registries (PBCRs); 27.3% in Bangalore, 26.8% in Chennai and Delhi, 29.7% in Mumbai and 26.3% in Kolkata (PBCR 2009-2011), and in Hospital based registries (HBCRs) of Mumbai(30.3%), Thiruvananthapuram(28.5%) and Dibrugarh(14.8%). The Indian Cancer registry derives its data mainly from the metropolitan cities of the country which register a more urbane population. Selective reports from rural pockets of India (Mehrotra et al., 2008; Swaminathan et al., 2009; Manoharan et al., 2010; Nandi et al., 2013) have all reported cervix to be the leading cancer site in the country followed closely by the breast. The scenario will soon change as all the registries show an increasing trend in

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the percentage of breast cancer cases to the total number of cancer cases registered over the years. Bangalore and Chennai show more than 3% change over the years while Delhi, Bhopal and Mumbai show changes between 1-2% whilst on the other hand for cervical cancer, all the registries show a decreasing trend (Takiar et al., 2008). By 2020, breast cancer is set to overtake cervical cancer as the most common type of cancer among all women in India (Shetty, 2012).

Radiotherapy remains one of the most effective modalities of treatment for breast cancer. It is indicated in almost all cases of breast cancers that have undergone breast conservation surgery (EBCTCG 2011) and in selected cases where mastectomy has been performed (Gebski et al., 2006; Pierce, 2005). Increasing number of breast malignancies has rendered a huge burden on the radiotherapy departments trying to keep pace with the increasing number of treatments.

The standard fractionation schedule for adjuvant breast cancer radiotherapy adhered to in India and worldwide is a total dose of 50 Gy in 25 fractions over a period of 5 weeks. For the BCS patients a further boost dose of 10-15 Gy is required to improve local control extending the total treatment time to an average of 6-7 weeks (Bartelink et al., 2007). Therefore a fractionation schedule which will decrease the total treatment time to 3 weeks while providing the same cosmetic results and local control will provide logistic benefits not only for the patients but for the radiotherapy departments of the country as well.

Several trials have been done in the West considering hypofractionation in breast cancer. In 2002, Whelan et al., reported the 5-year results of their trial in which they compared whole breast radiotherapy dose of 50 Gy given in 25 fractions over 35 days versus a hypofractionated schedule of 42.5 Gy given in 16 fractions over a period of 22 days, after breast-conserving surgery in women with axillary lymph node negative breast cancer. Local recurrence rates and cosmetic outcomes were similar in both groups (Whelan et al., 2002). They subsequently updated their long term results in 2010 (Whelan et al., 2010) which re-affirmed their conclusions.

Hypofractionation in breast cancer has been practised extensively in the UK. START Trial A (START Trialists’ Group, 2008) randomized 2236 women with early breast cancer post surgery into three radiotherapy fractionation schedules of 50 Gy in 25 fractions, 41.6 Gy or 39 Gy in 13 fractions of 3-2 Gy or 3 Gy over 5 weeks. Loco-regional tumour relapse was the primary endpoint. After a median follow up of 5-1 years the rate of local-regional tumour relapse at 5 years was 3-6% after 50 Gy, 3-5% after 41.6 Gy, and 5-2% after 39 Gy. From a planned meta-analysis; estimates of α/β value obtained for tumour control was 4-6 Gy and for late change in breast appearance (photographic) it was 3-4 Gy. It was inferred that breast cancer and the dose-limiting normal tissues responded similarly to change in radiotherapy fraction size. START Trial B (START Trialists’ Group, 2008) compared 2215 women with early breast cancer (pT1-3a pN0-1 M0) with two fractionation schedules of 50 Gy in 25 fractions of 2 Gy over 5 weeks and 40 Gy in 15 fractions of 2.67 Gy over 3 weeks. After a median follow up of 6 years; the rate of loco-regional tumour recurrence at 5 years was 2-2% in the 40 Gy group and 3-3% in the 50 Gy group. This trial established that a hypofractionated schedule of 40 Gy in 15 fractions was equivalent to the standard schedule of 50 Gy in 25 fractions in terms of rates of tumour relapse and late adverse effects. Recently a 10 year update of both the START trials was reported. It stated that the 10-year rates of loco-regional relapse did not differ significantly between the 41.6 Gy and 50 Gy or the 39 Gy regimen groups in START A or between the 40 Gy group and the 50 Gy group in START B. It further revealed that normal tissue effects were actually less in the 39 Gy group and did not differ significantly between 41.6 Gy and 50 Gy groups in START A. Also in START-B, breast shrinkage, telangiectasia, and breast oedema were significantly less common in the 40 Gy group than in the 50 Gy group. (Haviland et al., 2013)

Sadly the data for hypofractionation in breast cancer from India is lacking. There has been no randomized controlled trial till date. We report the preliminary results of first 135 patients treated at our centre with START-B type of fractionation.

Materials and Methods

Breast cancer patients of all stages (excluding metastatic) who had undergone surgery; either breast Conserving Surgery (BCS) or mastectomy registered in the Department of Radiotherapy from May 2011 to June 2012 were included in the present study. A detailed history was taken, clinical examination was performed and all staging investigations were completed if they had not been performed earlier. Review of the histopathology report was done in the Department of Pathology for those patients who had been operated outside. Staging was done according to UICC-TNM classification (7th edition).

A proforma was made to assess baseline post surgery cosmesis of the operated breast with respect to the contralateral normal breast in case of BCS patients. It included breast distortion, breast shrinkage, breast oedema, induration, telangiectasia graded with a 4 point scale. Brachial plexopathy was evaluated with respect to pain, numbness, paraesthesia and motor weakness which too was graded with a 5 point scale. Grading was done on the basis of the perceived difference by a single radiation oncologist mostly, 0 for no change, 1 for slight change (usually less than 25%), 2 for moderate (25-50% change), 3 for severe (50-75% change). In case of brachial plexopathy too, grading was done as 0 for nil, 1 for slight (usually less than 25%), 2 for moderate (25-50% change), 3 for severe (50-75% change) and 4 for very severe (>75%).

CT simulation was done for all patients. Patients were planned supine, on All-in-one(AIO) solution breast board, arms above head supported on a low arm rest holding a central pole with knuckles recorded(whether up/down). The position was marked after set up for planning CT scan and for daily reproducibility during radiotherapy treatment. 5mm thickness non- contrast enhanced CT images were acquired from the level of mastoid to the umbilicus (given the SCF coverage required for the patients) on our
The present study reports 135 cases of breast carcinoma of all stages (excluding metastatic) registered in our department from the month of May 2011 till June 2012. Of this; 73 patients had undergone mastectomy and BCS had been done for the rest 62 patients. Mean age of the population was 52 years (48 years and 56 years in BCS and mastectomy group respectively). Right sided tumours were 76 in number and 59 were left sided cancers.

The tumours in the BCS group were mostly early staged tumours with pT1 being 22.5% (n=14) and pT2 being 59% (n=37). There were 9 cases of clinically and radiologically staged T3 and T4 tumours (T3=5, T4=4) accounting for 15% of total number of cases. The stage was not known in one patient and in 2 (3.22%) cases there was complete resolution of tumour following neo adjuvant chemotherapy. The nodal status was negative in 45% of cases (n=28). Among the node positive patients; 22 women (35%) had 1-3 nodes in the axilla (pN1), 4-9 lymph nodes (pN2) were detected in 5 women (8%) and pN3(>10 axillary lymph nodes) was reported in 3 (4.8%) women. The nodal status was unknown in 3 patients (4.8%) and there were 2 cases (3.2%) of DCIS. The mean tumour size (T) in the BCS group was 2.7 cm; mean number of nodes was 1 and a mean Nottingham Prognostic Index (NPI) calculated was 3.9. For the group of women who underwent mastectomy, higher staged tumours were reported more frequently. About 60% of tumours were staged T3 or higher [T3=33(45%), T4-11(15%)]. 46% of women had a tumour size of 2-5 cm (pT2=34) and only 4 cases (5%) had a tumour size of less than 2 cm. In 2 women the primary tumour size was not known. The nodal status was positive in 83% of cases with pN1=37%, pN2=16% and pN3=14%. The nodal status remained unknown in 2 cases. The mean T size in mastectomy group was 4.5cm, average number of nodes was 5 and an average NPI score was 4.9.

The most common reported histopathology was infiltrating ductal carcinoma; 91% in BCS cases (n=57) and 84% (n=62) in the mastectomy group. Invasive lobular carcinoma was reported in 2 cases of mastectomy group. Grade III tumours were most common in both BCS and mastectomy patients accounting for 53% (n=33) and 63% (n=46) respectively. About 22-23% women had a histopathology reporting grade II tumours across both BCS and mastectomy group of patients. Grading was not available for 8% of mastectomy and 11% of BCS patients.

Most of the patients were ER positive in both BCS (n=41, 66%) and mastectomy group (n=45, 72%). PR positivity was around 41-43% in BCS and mastectomy group, whereas Her 2 neu positivity was 37% in BCS group (n=23) and 30% in mastectomy group (n=45). The percentage of triple negative patients was 13-14% in both groups and their mean age was younger being 43years in BCS group and 44years in mastectomy group.

70% (n=44) patients received chemotherapy in BCS group of which 45% (n=28) had been prescribed a taxane based regimen. 10 patients (16%) had not been prescribed any chemotherapy and 2 patients (3.6%) did not opt for the same. 10 patients had received chemotherapy in the neoadjuvant setting (16%) whereas for the rest it was in the adjuvant setting. In the mastectomy group; 83% (n=61) patients received chemotherapy of which taxane based regimen was prescribed for 68%(n=50). 27%(n=20) received chemotherapy in the neoadjuvant setting whereas for the majority it was an adjuvant treatment (n=41, 56%). About 6%patients did not opt for any chemotherapy.
Skin toxicity grading was done according to RTOG criteria. During and by the end of radiation 45/62 (72%) patients had grade 1 skin reaction, 15/62 grade 2 (24%) and only 3/62 (4.8%) had grade 3 reaction in the BCS group with no grade 4 toxicity noted in any of the patients. In the mastectomy group; 94% patients had grade 1 skin reaction, 6% grade 2 with no patients reporting grade 3/4 toxicity.

At first follow up which was done 4-6 weeks after completion of RT about 24 (39%) patients had persisting grade 1 skin reaction in the BCS group which was noted in 7% (n=5) of mastectomy patients. At 3 months follow up post RT, 16% patients in the BCS group and about 2% patients in the mastectomy group were noted to have a persisting hyperpigmentation. At the completion of 6 months post radiotherapy 5 patients (8%) in the BCS group only had a persisting erythema.

At the time of analysis, lymphoedema was noted in 3 patients (4.8%) of BCS group and in 6 patients (8%) who had undergone mastectomy.

Baseline cosmesis
We assessed baseline cosmesis for patients who had undergone mastectomy surgery whilst the rest had been treated with a mastectomy. The mean age of the population was 52 years (48 years in BCS and 56 years in mastectomy patients) which is quite close to the mean age of the population of START Trials have proved the effectiveness of the same in their population. Till date no randomized controlled trial has been conducted in India. Clinicians in India remain skeptical to adopt a hypofractionated schedule for their patient population; who they feel belong to a different race than their western counterparts. The mean age of presentation is also younger in this population and patients mostly present with advanced stage of disease.

This study reports the preliminary results of 135 patients of breast cancer treated with the START Trial B hypofractionated schedule of 40Gy in 15 fractions over 3 weeks for chest wall and breast conserved patients (which were followed by a boost) between May 2011 and July 2012.

Of 135 patients, 45% patients had a breast conserving surgery whilst the rest had been treated with a mastectomy. Mean age of the population was 52 years (48 years in BCS patients and 56 years in mastectomy patients) which is quite close to the mean age of the population of START Trial B of 57 years. The patient population of Whelan et al. (2002) also reveals majority of the population to be of race than their western counterparts. The mean age of their population. Till date no randomized controlled trial has been conducted in India. Clinicians in India remain skeptical to adopt a hypofractionated schedule for their patient population; who they feel belong to a different race than their western counterparts. The mean age of presentation is also younger in this population and patients mostly present with advanced stage of disease.

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Most of the tumours were right sided malignancies (56%). Invasive ductal carcinoma was the most frequently reported histopathology accounting for 87% of all cases (91% in BCS and 84% in mastectomy group) followed

Discussion
Adjuvant hypofractionated radiotherapy for breast cancers has been practised in the UK for a long time. The START Trials have proved the effectiveness of the same in their population. Till date no randomized controlled trial has been conducted in India. Clinicians in India remain skeptical to adopt a hypofractionated schedule for their patient population; who they feel belong to a different race than their western counterparts. The mean age of presentation is also younger in this population and patients mostly present with advanced stage of disease.

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Most of the tumours were right sided malignancies (56%). Invasive ductal carcinoma was the most frequently reported histopathology accounting for 87% of all cases (91% in BCS and 84% in mastectomy group) followed
by invasive lobular accounting for 2% of cases in mastectomy group. There was 1 case of mixed ductal and lobular carcinoma in the mastectomy group. About 75% of cases reported in START Trial B were invasive ductal malignancies followed by invasive lobular malignancies accounting for 11% of cases. Mixed ductal/lobular accounted for about 2% of all cases. Grade III tumours were most common in our population in contrast to START Trial B population where majority of the cases were Grade II tumours (47%). Ontario trial too had lower grade tumours (Grade I=31%, Grade II-39%).

Most of the tumours in the BCS group were early staged tumours; p T1 and p T2 accounting for almost 80% of the cases. 45% of BCS cases were node negative; whereas in the mastectomy group tumours were of a higher stage with node positivity of about 70%. A look into the START trial population reveals 70% of tumours were upto 2 cm in maximum diameter. Node positivity was 20%. Thus the population was of early stage breast cancer cases. Again 90% of cases in START Trial had undergone BCS. In the Ontario trial too most of the tumours were 1-2 cm (50%), and about 20% of cases had a tumour size greater than 2 cm.

Majority of the tumours were ER positive (66% in BCS, 72% in mast); PR positivity ranged from 41-43% and Her 2 Neu positivity was about 22-23% across the population. About 13% cases were Her 2 Neu negative. If we look into the statistics of prevalence of hormone positivity in the subcontinent, it will reflect a similar picture. Faheem et al., reported a study detailing receptor positivity and its association with tumour characteristics in a breast cancer cohort from northern Pakistan; they showed ER, PR, and Her 2 Neu positivity to be 62%, 60%, and 38% in their patient population. Sofi et al., conducted a study in Srinagar with the objective of assessing hormone receptor positivity and its correlation with patient and tumour characteristics; he reported ER and PR positivity to be 66.3% and 63.4% respectively. Prevalence of receptor status in breast carcinoma patients in Eastern India revealed 75% ER positivity, 66.66% PR positivity and 25% Her-2/neu positivity (Chakrabarti et al., 2012). About 9-10% of cases were triple negative among the population and their mean age was younger (43-44 years).Clinico-pathologic features and survival on the basis of receptor status, a study done by Onitilo et al., revealed percentage of triple negative cases to be around 13% in his patient population of Marshfield Clinic/ St. Joseph’s Hospital Cancer Registry. (Sen et al., 2012) reported about 27% of triple negativity in his population of cases from Eastern India.

About 70% cases received chemotherapy; of which 45% were treated with taxane based regimen. The institutional protocol is FEC-D regimen (Roche et al., 2006) for node positive patients (3 cycles of 5 fluorouracil, epirubicin and cyclophosphamide 3 weekly followed by 3 cycles of tri weekly docetaxel) and FEC-75/FEC-100 for a total of 6 cycles in case of node negative patients. About 16% patients received chemotherapy in the neo-adjuvant setting in the BCS cases; this was done to downsize the tumours so that breast could be conserved, neo-adjuvant chemotherapy was received by 27% of cases in mastectomy group; these were locally advanced. Considering data of the START Trial B, only about 7% of patients received chemotherapy; of which 37% were treated with CMF regimen.

Most of the patients (83%) considering both in the BCS and mastectomy group had grade 1 reaction during and just after completion of radiation. Only about 5% patients had grade 3 reaction in the BCS group with no grade 4 toxicity noted in any of the patients. At the completion of 6 months post radiotherapy only 8% in the BCS group had a persisting erythema. Thus radiotherapy was very well tolerated by the Indian population with very less acute skin toxicity. De Antonio et al., assessed acute and late toxicity of using a hypofractionated schedule of 2.25 Gy to a total dose of 45 Gy to the whole breast and reported an incidence of 85% early reactions, consisting of skin erythema, in the hypofractionated group. Hijal et al., (2010) in his study of hypofractionated radiotherapy and adjuvant chemotherapy in breast cancer patients; reported an incidence of about 50% grade 1 skin reaction in patients who received radiotherapy and chemotherapy, 8% of grade 2 skin toxicity in the same group and 4% grade 3 reaction in the group of patients who did not receive any chemotherapy. There were no reported grade 4 toxicities. Pinnaro et al., (2010) in his study of 39 consecutive breast patients who underwent conservative surgery; refused adjuvant conventional radiotherapy regimen and were thus treated with an adjuvant accelerated hypofractionated radiotherapy schedule of 34 Gy in 10 daily fractions over 2 weeks to the whole breast, followed by an electron boost dose of 8 Gy in a single fraction to the tumour bed after 1 week; revealed that 49% had no acute skin toxicity at all. 41% patients had Grade 1, consisting in all cases of faint erythema, and 10% patients Grade 2 toxicity consisting of moderate erythema. The peak incidence of Grade 2 acute skin toxicity occurred at 1 week after the treatment ending with two patients having reactions confined to the boost area. No patient suffered Grade 3 or more acute skin toxicity.

About 40% patients had some distortion or shrinkage of the breast or induration around the scar post surgery. At the time of analysis these figures remained almost the same though there was a decrease in the induration around the scar. 25% patients had no detectable change in breast appearance post surgery, 8% patients had baseline oedema post surgery. At 6 months follow up 16% patients had an increase in breast size (Grade 1) post radiotherapy and in 16% patients there was no change post radiotherapy. In START trial B; change in breast appearance (photographic) of the patients was assessed on a 3-point graded scale (none, mild, marked). Changes in breast appearance and breast hardness (patients with breast-conserving surgery) were the most common changes recorded. They reported mild change for 30% patients and marked change for only 3% patients by 5 years. They also said change in breast appearance (photographic) was less likely after 40 Gy than after 50 Gy. Also there was a significantly lower rate of change in skin appearance after radiotherapy for 40 Gy than after 50 Gy.

No local recurrence was documented at the time of analysis. A total of 4 patients developed metastatic disease...
at the time of analysis (2.96%); though it is too early to comment upon loco-regional control rates and disease free survival.

We also looked into the logistic benefits of a hypofractionated schedule. 10 fractions of radiotherapy saved per patient resulted in 1.350 fractions saved per year. This meant that additional patients could be treated leading to reduced waiting list. Additional patients also meant more turnovers for the department over the year. A basic analysis of the machine maintenance cost was done which revealed a 40% reduction in the cost.

In conclusion, hypofractionation is very well tolerated in the Indian population; more than 80% of patients had grade 1 toxicity with the treated schedule. Grade 3 toxicity was less than 5% with conservation patients and there was no grade 3/4 toxicity with the mastectomy patients. Early cosmetic outcomes were good to excellent and at par with large western data sets. Early oncologic outcomes are encouraging as well. It offers considerable logistic benefits for both the patients and the treating departments. Long term data needs to be reported.

References


