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A Prospective Study on Toxicity, Quality of Life and Local Control of Post Mastectomy External Shorter Course of Irradiation

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Abstract

Background: In India majority of cancer breast are diagnosed in locally advanced stage. Surgery, chemotherapy and radiotherapy is mainstay of treatment The standard radiotherapy schedule for breast cancer deliver 50 Gy in 25 fractions in 2Gy over 5 weeks, but non-standard regimes delivering a lower total dose using fewer larger fractions (hypo fractionation). Long-term follow up confirms that appropriately dosed hypo fractionated radiotherapy is safe and effective for patients with early breast cancer. The present study was planned to compare the efficacy of two radiation scheduled.

Materials and Methods: This was a single centre, non-stratified, single blind, non placebo- controlled, parallel group intervention study with imbalanced randomization done at our institute. Adult Patients of 30 to 65 years of age, Histologically post operative modified radical mastectomy (MRM) carcinoma of breast with registered and assessed. Arm A 40 Gy in 15 fractions over 3weeks. Arm B 50 Gy in 25 fractions over 5weeks.

Result: 108 patients were included in the study, 58 in arm A and 50 patients were in arm B. None of patients of arm A had skin toxicity greater than grade II. In arm II 29 patients had skin toxicity grade III and 4 patients had skin toxicity grade IV. 10 patients had grade II skin toxicity. There was no statically difference in quality of life and local control in both arms. But difference in term of acute toxicity and treatment break due to grade IV reaction.

Conclusion: Hypo fraction radiotherapy lesser acute skin toxicity with lesser treatment time with comparable local control and similar cosmetic with standard dose and fractions However, larger study with longer follow up required for assessment of late toxicity and overall survival.

Introduction

Breast cancer is the second most common cancer among both sexes worldwide Globocon [1]. It is the most common cancer among women in developed Countries. The age standardized incidence rate of breast cancer in India is 22.9% per 100,000 women Globocon [2]. 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%), Thiruvanantapuram (28.5%) and Dibrugarh (14.8%) [3]. In our institute JK Cancer it is 3rd most common cancer.

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. [4], Manoharan et al. [5], Nandi et al. [6] 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 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% Takiar et al. [7]. By 2020, breast cancer is set to overtake cervical cancer as the most common type of cancer among all women in India.

Multiple factors are associated with an increased risk of developing breast cancer including having family history, particularly in mother or siblings, a past medical history of uterine cancer or colon cancer; early menarche and/or late menopause; no pregnancy or first pregnancy after age 30; radiation exposure; post menopausal oestrogen therapy; use of oral contraceptive. Genetic analysis led to discovery of dominant genetic mutation in two tumour suppressor gives BRCA-1 and BRCA-2 localised to chromosome 17 and 13 respectively.

The standard management of operable LABC is by initial modified radical mastectomy. Systemic therapy is also an integral part of treatment because of high risk of metastasis. Post mastectomy radiation is indicated to decrease the high risk (20-40%) of loco-regional failure even after adjuvant systemic therapy. Loco-regional control rates range 85-95% for 10year survival of 40-45% operable stage III breast cancer treated with modified radical mastectomy, adjuvant systemic therapy and post mastectomy radiation. A statically significant improvement in reoccurrence free survival was occurred in patent treated with pre-operative or post-operative radiotherapy with that of modified radical mastectomy alone (Stockholm studies) [8]. In 1997, Overguard et al. [9] concluded that in a randomized trial that addition of post-operative radiation to mastectomy and adjuvant chemotherapy reduces loco regional recurrance and prolongs survival in high risk pre menopausal woman with breast cancer [10].

In 1997, Regas et al. [10] concluded that in a randomized trial that the radiotherapy combined with chemotherapy after modified radical mastectomy decreases risk of systemic and loco-regional relapse and reduces mortality. The international standard radiotherapy regimen after breast conservation surgery or mastectomy for early breast cancer delivers 25 daily doses (fractions) of 2.0 Gy to a total dose of 50 Gy over 5 weeks. This schedule has evolved pragmatically, and is based on an assumption that a high total dose delivered in small fractions of 2.0 Gy keeps the amount of normal tissue damage to a minimum while gaining the maximum level of tumour control. This perception was strengthened when early studies of hypo fractionation, which did not use adequate reductions in total dose, reported unacceptably high rates of normal tissue injury [11]. Normal and malignant tissues vary in their responses to radiotherapy fraction size, termed fractionation sensitivity. Responses are described by a model in which the sensitivity (measured by the degree of tissue damage for normal tissues, and tumour recurrence rates for malignant tumours) to fraction size is represented by the ratio of two constants α and β [12]. The lower the ratio of α to β (expressed in Gy), the greater the effect on normal and malignant tissues of changes in fraction size. Healthy tissues of the breast and ribcage are sensitive to fraction size, with α/β values 5 Gy or less [13], so small changes in fraction size can produce relatively large changes in the effects of radiotherapy on these tissues.

An alpha/beta value of around 2.8 Gy for late normal tissue changes in the breast is derived from the estimated equivalence of 41.6 Gy in 13 fractions and 50 Gy in 25 fractions over 5 weeks, in line with trial predictions. Yarnold j et al. [14] Breast cancer tissue is probably just as sensitive to fraction size as dose-limiting healthy tissues. If this finding is confirmed, radiotherapy schedules can be greatly simplified by the delivery of fewer, larger fractions without compromising effectiveness or safety, and possibly Owen jr et al. [15].

Alternative schedules based on a lower total dose delivered in fewer, larger fractions (hypo fractionation) were introduced in the UK and Canada several decades ago on an empirical basis. The first results of a Canadian randomized trial testing 42.5 Gy in 16 fractions against 50 Gy in 25 fractions are consistent with these findings, suggesting equivalence in terms of local control and breast cosmesis for the 16-fraction regimen. (Start trial A) [16] Results of retrospective studies of hypo fractionated radiotherapy in early breast cancer suggest satisfactory outcomes in terms of tumour control and late adverse effects if modest increases in fraction size are combined with appropriate downward adjustments to total dose.

A radiation schedule delivering 40 Gy in 15 fractions seems to offer rates of local-regional tumour relapse and late adverse effects at least as favourable as the standard schedule of 50 Gy in 25 fractions. (Start trial B) [17]. Long-term follow up confirms that appropriately dosed hypo fractionated radiotherapy is safe and effective for patients with early breast cancer. (10year follow up results of two start trials) [18] Study suggests that breast irradiation with 40 Gy given over 3 weeks after breast conserving surgery for screen detected breast cancer gives a high level of local control out to 5 years Magee B et al. [19].

Hypo fractionated RT is well tolerated in Indian population with reduced acute skin toxicity and good cosmetic outcome. Regimens such as these should be encouraged in other centres to increase machine output time. The study is on-going to assess long term results Nandi et al. [20]. These long repair halftimes for late effects in human normal tissues have to be considered in order to gain the full benefit from fractionation schedules employing multiple fractions per day. Benzten Sm, Saunders mi et al. [21]. Cosmetic assessment shows that patients are more satisfied with the result than their treating consultants, and that 81% have scored themselves as having an excellent or very good result more than 5 years after treatment. Benson et al. [22] Short fractionation produces acceptable cosmetic results for the majority of women if there are no contraindications to RT and in the absence of significant post-operative breast induration Olivotto IA et al. [23].

Materials and Methods

The case material for the study will be selected from the cross section of patients registered at the J. K. Cancer Institute

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Histologically proven post MRM carcinoma of breast with biopsy was registered and assessed

a. Arm A

40 GY in 15 fractions over 3weeks.

b. Arm B

50 GY in 25 fractions over 5 weeks.

Patients included are histologically proven cases of locally advanced carcinoma breast, Post mastectomy with clear tumour margins, hemogram with Hb>10gm/dL; TLC>4000/cmm, Platelet count >100,000/cmm, Renal function tests with Blood urea < 40mg/dL and Serum creatinine< 1.5mg/dL. Liver function tests with SGOT < 35 IU/L and SGPT < 40 IU/L. The patients having any of the following conditions will be excluded from the study, Prior radiation for the same disease, Cases with distant metastasis, Pregnant or lactating patient. All the patients included in the study were being carefully and regularly assessed weekly during treatment. Detailed clinical evaluation for the tolerance of each patient to the delivered treatment is done by thorough local examination of the patient for local disease status along with observation of acute reaction every weekly.

Radiation reactions will be assessed by Radiation Therapy Oncology Group (RTOG) criteria and WHO toxicity criteria Radiation Therapy Oncology Group (RTOG) acute morbidity scoring criteria are relevant from day 1, the commencement of radiation, through day 90 and thereafter, the RTOG criteria for late effects are to be utilized. Assessment at the completion of treatment All the patients wear assessed after four weeks after the completion of treatment, to detect acute complications like skin reaction. All the patients wear followed up regularly on OPD every month for a period of 6months after completion of treatment and 3 monthly till closer of study. At every visit, each patient will be clinically evaluated for treatment related complications. The results of the study regarding safety, tolerability, toxicity and response in all the groups was documented. For Statistical analysis data was arranged using SPSS software version 19. Descriptive studies wear done for all parameter, kaplain-meair analysis was used for survival analysis p value <0.05 was considered as statically significant.

Results

Total 108 patients were enrolled in study that were post MRM and received 6 to 8 cycles of chemotherapy .than patients randomised in two groups. Both arms were well balanced in terms of age, stage, hormone receptor status. At the end radiotherapy patients were assessed for acute toxicity with RTOG criteria. In arm A 20 patients had grade I, 38 patients were grade II and none of patients have grade III/ IV reaction. In arm B 2 patients had grade I, 15 patients had grade II, 29 patients grade III, and 4 patients had grade IV. Nearly all the patients of grade IV reaction had treatment break after 20 to 21 fractions All patients of grade IV reaction require treatment break for one week. Median follow up was 18 month. At time of analysis 4 patients were dead due to metastasis, two in each arm. Two patients in arm A failed locally and two patients failed distantly one in lung and other brain. In arm B two patients failed locally one in axilla and other in chest wall, two patients failed distantly one in liver and other in lung.

Discussion

Our study aimed to provide a robust evidence base for clinical practice in breast radiotherapy by comparing a commonly used 15-fraction schedule with the international standard based on 25 fractions of 2•0 Gy. The analysis of acute skin reactions suggests that 40 Gy in 15 fractions over 3 weeks causes statistically significant less reaction to skin and sub cutaneous tissue than a standard regimen of 50 Gy in 25 fractions over 5 weeks. This observation is consistent with the START Trial B, which suggest that 40 Gy in 15 fractions over 3 weeks is equivalent in terms of late normal tissue effects in the breast to a total dose of 50Gy delivered in 2•0 Gy fractions [17]. Quality of life in 40 Gy arm was observed to be better than in 50 Gy arm. Treatment time is 2 week less in 40 gy arm appears to be more convenient and economical for patients. The patient quality of life self-assessments of normal tissue effects in START Trial B are also consistent with this relation, suggesting 5-year estimates in favour of the 40 Gy group in most of the assessed normal tissue effects.

A median follow-up of 10.2 month is too short to allow assessment of all the potential late normal tissue effects such as cardiac damage. Follow-up of all women within the trial is continuing in order to assess the long-term effects of the fractionation schedules. However, the RMH/GOC pilot data with a median of 10 years' follow-up showed that although estimates of absolute rates of normal tissue effects change with time, the relative effects of different fractionation schedules remain unchanged. The short-term priority is to protect the heart from exposure to radiotherapy; something that is possible with advanced radiotherapy technologies. Since the local-regional as well as distant relapse rate was seems higher in 40Gy arm than 50Gyarm but it was statistically not significant. On comparison with other prognostic factors such as sample size, age, stage of disease, chemotherapy used, hormone receptor status in relapsed patients both the group has similar features. However 64% patients of study belongs to less than 50yr age group and 56% were pathologically stage III, can be the reason of more chances of relapse but there were no statistically significant difference in both the arm.

This raises a question about the efficacy of hypo fractionated radiotherapy especially in advanced stage breast cancer. A long term follow-up required to estimate the exact figure of loco regional and distant relapse.

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Since both the arms are equally balanced in terms of hormone receptor status and all receptor positive patients received either tamoxifen or letrozole, it is less likely a cause of difference in loco regional relapse rate. There are many factors which affect relapse, including others which were unknown in the trial. The purpose of randomization is to ensure a balance in the unknown as well as the known prognostic factors. We cannot ascribe the survival difference to any biological or treatment-related factor, and can only conclude that this difference might be due to chance and could diminish with further follow-up. Long-term follow-up of these women is continuing, to verify whether the relative effects of the schedules remain stable over time, in terms of late normal tissue effects as well as relapse and survival.

The only other large trial with which our study can be compared is START B which has given 40Gy in 15 fraction in 3 week, Canadian trial that tested 42•5 Gy in 16 fractions of 2•6 Gy fractions over 22 days against 50 Gy in 25 fractions over 35 days in 1234 women after tumour excision for early breast cancer. The 5-year local relapse rates were 2•8% after the shorter schedule and 3•2% after the standard 5-week regimen (absolute difference 0•4%, 95% CI - 1•5 to 2•4%).The similarity of normal tissue effects is consistent with the results of START Trial B. On the same assumptions applied above, 42•5 Gy in 16 fractions is equivalent to 50 Gy in 25 fractions in terms of late-onset normal tissue effects in the breast and chest wall16. Reliable comparison of tumour control is limited by the small number of relapses in both the Canadian study (44 events) and in START Trial B (65 events). But all the previous trials were included early stage breast cancer patients only.

Conclusion

After surgery for breast cancer, a radiotherapy schedule delivering 40 Gy in 15 fractions over 3 weeks seems to offer significantly less acute toxicity as well as cosmetic appearance which is statistically significant. But in terms of loco regional recurrence as well as distant recurrence 40 Gy shedule appears to equal effective. A long term follow up on the patients of this study will analyze the exact figure of loco regional relapse as well as distant relapse.

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