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Research Article

Result and outcome of shorter fractionation schedule for post-operative cancer breast patients

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ABSTRACT

Background: The purpose of this prospective study is to determine the effectiveness and cosmetic outcome of shorter fractionated radiotherapy in post-operative invasive breast cancer patients.
Methods: Between July 2009 and June 2011, 216 post-operative cancer breast patients were treated with this regimen on cobalt60. The chest wall and supraclavicular area were treated using a tangential parallel pair, & direct supraclavicular portal with wedges as necessary, to a dose of 40 Gy / 15 fractions (study group) (133 cGy for tangential and 266 cGy for supraclavicular field each). (Control Group received 50 Gy / 25#) No additional boost was given. The median duration of follow-up surviving patients are 3 years.
Results: From July 2009 to July 2011 (2 years), 216 histopathologically proven cases of Invasive ductal carcinoma of Breast were included in this study. All patients with early and locally advanced stage breast cancer were treated with hypofractionated and conventional schedule of radiotherapy. At baseline 80.19% in the study and 75.45% of patients in the control group were being rated as excellent or good. At 2 years, the percentages of patients with an excellent or good cosmetic outcome were 75.80% in the study and 73% in the control group. Grade II skin reactions were more in control (60%) as compared to study group (49%). A radiation schedule delivering 40 Gy / 15 # seems to offer control rates of locoregional tumour relapse & late adverse effects at least as favourable as the standard schedule of 50 Gy / 25#.
Conclusion: Shorter fractionation schedule is very much effective in preventing recurrent breast cancer and it provides a high level of patient satisfaction as well as reduce money and overall treatment time. Its shorter duration offers the added advantage of a more efficient use of resources and greater patient convenience.

Keywords: Hypofractionation, Ca breast, Toxicity, Cosmesis

INTRODUCTION

Breast Cancer is the most prevalent cancer of women worldwide. Worldwide breast cancer incidence accounts for approximately 25% of all cancers diagnosed in women and almost 15% of all cancer deaths. It is one of the most common malignancies in the Western world and has the highest incidence in North America.

The estimated incidence of cancer in India is 1.2 million cases and prevalence is about two million cases. About 25% increases is expected by the year 2015.[1] There is an increasing trend in rates of breast cancer in the urban population of the country (Yeole & Kurkute. 2003);[2] (Satyanarayana and Asthana, 2008).[3]

The breast cancer risk varies with age groups; for example, the risk from birth to 39 years is 1:229 (0.44%),

from age 40-59 years 1:24 (4.14%), from age 60-70 years 1:13 (7.53%), and from birth to death the probability of developing breast cancer is one in seven (13.4%) (Jemal et al. 2007).[4]

Treatment of breast cancer includes surgery, chemotherapy; radiotherapy & hormonal therapy. Most of the patients are post-operative i.e. with post mastectomy status. As yet no 'low risk' group has been identified where surgery alone gives adequate local control. Adjuvant radiotherapy given following surgery for primary carcinoma of the breast has been shown to reduce the incidence of locoregional recurrence from 3o% to 10.5% at 20 years and breast cancer deaths by 5.4% at 20 years.[6] The purpose of radiation treatment following surgery is to minimize the risk of recurrent cancer in the treated chest wall, with as little toxicity as possible so that good cosmesis and functions are maintained.

The first result of Canadian randomized trial testing 42.5 Gy in 16 fractions against 50 Gy in 25 fractions are consistent, suggesting equivalence in terms of local control and breast cosmesis for the 16 fraction regimen. The standardization of breast Radiotherapy (START) trials were initiated by the then UK coordinating committee for cancer research (now national cancer research institute) to test the effects of radiotherapy schedules using fraction size larger than 2.0 Gy. START trial A[7] tested two dose levels of 13-fractions regimens over 5 weeks in order to measure the sensitivity of normal and malignant tissues to fraction size. START Trial B[8] compares 40 Gy in 15 fractions of 2.67 Gy in 3 weeks with a control group of 50 Gy in 25 fractions over 5 weeks. Loco-regional tumor relapse rates were comparable with slighty superior cosmetic outcome in hypofractionated arm. Any fraction size of 3.2 Gy or less as seen in both START A and B trials led to similar results in terms of both local control and cosmesis.

The result of these trials has tremendous implications for both the patients of breast cancer and health care system. It is a known fact that prolonged daily treatments make a substantial impact on reduction of quality of life experienced by women with breast cancer, treated with radiotherapy as shown by randomized trial. Apart from quality of life benefits because of convenience and less time in the hospital, it has a tremendous logistic advantage. Presently radiotherapy for breast cancer accounts for 25-30% of radiation therapy burden. The shorter schedule also will permit more efficient use of resources, in that up to 50% more women can be treated with existing equipments and personnel.

METHODS

This prospective and comparative study was undertaken in the department of radiotherapy & oncology, Pravara rural hospital, Loni. As breast conservation surgery was not feasible at our rural centre due to unavailability of specialized surgeons, all the patients had post-mastectomy status.

Histopathological proven post-operative cases of breast cancer patients were randomly assigned during the period from July 2009 to July 2011. Total 216 patients included were divided into two groups, control group (Conventional radiotherapy) and study group (Hypofractionated radiotherapy).

Patients assessment was done clinically as well as hematological and radiological investigations were done. Staging was done.

Treatment schedule

Both Study and control group received six courses of CMF/CAF on three weekly basis for six cycles in each patient before radiotherapy. Hormonal therapy (Tab tamoxifen 20mg 1 HS) was given for 5 years depending upon the positivity of hormonal status. Patients in study group received hypofractionated radiotherapy (40 Gy in 15# for 3 weeks).

Conventional radiotherapy was given in control group in a dose of 50 Gy in 25# for 5 weeks. Cobalt 60 beam was used for the radiation treatment. Chest wall was treated with a medial and lateral tangents using megavoltage radiation with the following technique. Generally patients were positioned on inclined breast board with arm above head. Thus reducing the slope of the anterior chest wall, making the sternum almost parallel to the couch and therefore minimizing the collimation required in the tangential beams. Patients in whom the supraclavicular portal is indicated the superior border of the tangential breast portal is placed at the angle of Louis. Medial border is placed at midline, lateral at the mid-axillary line or 2cm beyond the palpable breast and the inferior border 2cm below the palpable breast. An accurate contour using plaster of Paris strip or contouring wire was taken at the center of the field. The accuracy of the contour is a critical step in the planning as the isocentre is derived from this contour. Planning was done on the central contour and appropriate wedges were added to achieve a homogenous dose distribution.

After completion of treatment, patients were examined monthly, first up till 6 months and then 3 monthly for 2 years.

RESULTS

From July 2009 to July 2011 (2 years), 216 histopathologically proven cases of Invasive ductal carcinoma of breast were included in this study. This study was limited to the results of 216 patients with early and locally advanced stage breast cancer treated with hypofractionated and conventional schedule of radiotherapy.

Table 1: Patients characteristics.

		Study group (106)	Control group (110)
Age	Median age	48	51
Habitat	Urban	42	45
	Rural	64	65
Stage	I	5	4
	II	85	88
	III	16	18
Menopausal status	Premenopausal	42	38
	Perimenopausal	20	35
	Postmenopausal	44	37
Surgery	MRM	60	56
	SM+AX	15	21
	SM	31	33
Side	Left	62	54
	Right	44	56
Hormonal status	ER+	30	35
	ER-	27	30
	PR+	27	20
	PR-	20	22
	Unknown	02	03
Hormone therapy	Yes	59	68
	No	47	42
Skin reaction grade	I	36	37
	II	53	65
	III	17	8

106 patients were randomly assigned to receive hypofractionated radiotherapy (Study group) and 110 patients to receive conventional radiotherapy (Control group).

Hypofractionated radiotherapy was given to a dose of 40 GY in 15 fractions over a period of 3 weeks, and conventional radiotherapy was given to a dose of 50 Gy in 25 fractions over a period of 5 weeks.

Both groups received 6 courses of chemotherapy in which majority of patients (82%) took CAF regime and hormonal therapy (depending upon the hormonal status).

Patients characteristics

82% patients were in stage II and 18% in stage III.

As breast conservation surgery was not feasible at our rural centre due to unavailability of specialized surgeons, all the patients had post-mastectomy status. Overall 35% of patients had incomplete axillary clearance both in study and control group respectively. Patients recorded in this study were maximally from rural area (65%) and most of them were in low socioeconomic status(71%). None except surgery and of the patients previously received radiotherapy, chemotherapy.

Cosmetic outcome

At baseline 80.19% in the study and 75.45% of patients in the control group were being rated as excellent or good. At 2 years, the percentages of patients with an excellent or good cosmetic outcome were 75.8% in the study and 73.0% in the control group. Grade II skin reactions were more in control (60%) as compared to study group (49%).

Table 2: Cosmetic outcome.

Outcome	Study group			Control group		
	Baseline	1.5 Years	2 Years	Baseline	1.5 Years	2 Years
Poor	0	0	23	0	0	35
Fair	0	45	47	0	55	36
Good	49	61	36	51	55	39
Excellence	57	0	0	59	0	0

Late radiation toxicity

Chest wall stiffness, arm oedema & radiation pneumonitis were the common side effects seen. Most of the patients tolerated radiation well & took treatment without interruption. 4% in the study and 3% patients in control group had developed radiation pneumonitis as a late complication. The incidence of arm edema was greatest in those patients who had both radical axillary surgery and radiotherapy to the axilla.

DISCUSSION

A revolutionary breakthrough might be on the horizon in breast cancer treatment. This disease is the leading cancer in women, and radiation therapy is an integral part of the management for a large percentage of post-mastectomy patients. Throughout the world, radiation therapy centers are struggling to keep pace with the ever-growing need for radiation therapy in patients with breast cancer. The beneficial effect of radiotherapy after surgery has been unequivocally demonstrated in randomized trials. Radiotherapy after surgery not only improves local

recurrence but also improves survival. Conventional radiotherapy after surgery usually implies giving a dose of 50 Gy in 25 fractions, that is 2 Gy per fraction over 5 weeks.

In this regard, there has been recent interest in hypofractionation, which means giving higher dose per fraction to target area and thereby allowing a lesser overall treatment time. A typical course of radiation therapy lasts nearly for 5-6 weeks in post- mastectomy patients. Conventionally, a dose per fraction per day of 1.8 to 2 Gy has been used in treatment of breast cancer, stemming from concern that fraction sizes of larger than 2 Gy might increase the likelihood of the late effects on healthy tissue toxicity and impairing cosmesis in breast cancer patients. A number of reports of cosmetic assessment with schedules using 1.8 to 2.0 Gy per fraction have been published with 60% to 90% of patients reporting good to excellent cosmetic outcome, high recurrence free survival and overall survival.

Therefore, a technique which reduces the treatment time by half (3 weeks instead of the present 5-6 weeks) while maintaining cosmetic and control rates needs to be viewed with great interest. Recent studies examining 13 to 16 fractions of hypofractionated radiation therapy (using larger dose per fraction) compared with the present 25 fractions are providing crucial supportive evidence.[9-11.]

In this study, 216 early stage breast cancer patients were recruited within 2 years period. 17 patients experienced local breast cancer recurrence as a first event: 8 in the study and 9 in the control group. At 2 years, local recurrence free survival was 97.2% in the study and 96.8% in the control group. 6% & 8% of patients died due to metastatic disease in study & control group respectively. Almost 85% of patients were satisfied with their treatment in study group & 60% in control group. 3% & 4% of patients had developed radiation pneumonitis as a late complication in both study & control group respectively.

At baseline 80.19% in the study and 75.45% of patients in the control group were being rated as excellent or good. At 2 years, the percentages of patients with an excellent or good cosmetic outcome were 75.8% in the study and 73.0% in the control group. These results do suggest that the intended short 3 weeks schedule of radiotherapy has not only achieved a high level of local control but also been cosmetically acceptable and satisfactorily tolerable.

START A trial randomized 2236 patients (at 17 centres in UK) with early breast cancer after primary surgery to receive radiotherapy with 2 Gy (45 Gy / 25#) versus 3 Gy (39 Gy / 13#) versus 3.2 Gy (41.6 Gy / 13#) in same treatment time of 5 weeks. After a median follow-up of 5 years, the estimated absolute difference in 5 years locoregional relapse rates compared with 50 Gy were 0.2% (95% CI-1.3% to 2.6%) after 41.6 Gy and 0.9% (95% CI -0.8% to 3.7%) after 3.9 Gy.

Similarly START B trial randomized 2215 patients of early breast cancer (at 23 centres in UK) to receive 50 Gy / 25# at 2 Gy / # over 5 weeks versus 40 Gy / 16# at 2.67 Gy / # over 3 weeks. After a median follow-up of 6 years, locoregional tumor relapse rates were comparable with slighty superior cosmetic outcome in hypofractionated arm. Fraction size of 3.3 Gy / # was superior in terms of local control in START A, although it yielded inferior cosmetic outcomes. Any fraction size of 3.2 Gy or less as seen in both START A and B trials led to similar results in terms of both local control and cosmesis. Interestingly, the hypofractionated arm in the START B trial had lower rate of distant metastasis and overall mortality compared with the conventional fractionation arm.

The results of these trials have tremendous implications for both the patients of breast cancer and health care system. It is a known fact that prolonged daily treatments make a substantial impact on reduction of quality of life experienced by women with breast cancer, treated with radiotherapy as shown by randomized trial.[12] Apart from quality of life benefits because of convenience and less time in the hospital, it has a tremendous logistic advantage. Presently radiotherapy for breast cancer accounts for 25-30% of all radiation therapy burden[13]. The shorter schedule also will permit more efficient use of resources, in that up to 50% more patients can be treated with existing equipments and personnel.

CONCLUSION

- Hypofractionation is a technique which reduces the treatment time by half (3 weeks instead of the present 5-6 weeks) while maintaining cosmetic and control rates, needs to be viewed with great interest.
- In this study, 106 patients were randomly assigned to receive hypofractionated radiotherapy (Study group) and 110 patients to receive Conventional radiotherapy (Control group).
- Majority of the patients were in the age group of 45-60 years.
- Most common side was left side of breast in which upper medial quadrant involvement was commonly seen. Patients recorded in this study were maximally from rural area (65%) and most of them were in low socioeconomic status (71%).
- Cosmetic outcome at baseline were being rated as excellent or good in 80.19% in the study and 75.45% in the control group. At 2 years, the percentages of patients with an excellent or good cosmetic outcome were 75.8% in the study and 73.0% in the control group.

- Grade II skin reactions were more in control (60%) as compared to study group (49%). Late radiation Toxicity such as Chest wall stiffness, arm oedema & radiation pneumonitis were the common side effects seen.

- All the patients tolerated radiation well & took treatment without interruption. 4% in the study and 3% patients in control group had developed radiation pneumonitis as a late complication (after 6 months).

Hence the above mention data shows that, after surgery for early and locally advanced breast cancer, a Radiotherapy schedule delivering 40 Gy in 15 fractions over 3 weeks seems to offer locoregional tumour control, good cosmesis and rates of late normal tissue effects at least as good as the accepted international standard of 50 Gy in 25 fractions over 5 weeks.

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Ethical approval: The study was approved by the institutional ethics committee

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