

# Partial Breast Irradiation: An alternative to protracted Radiation in Breast Conservation Surgery.

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**Abstract :** Traditionally patients undergoing BCT have been given a protracted course of radiation to the whole breast, with or without nodal irradiation, lasting from 3 to 5 weeks. This protracted therapy has been a major deterrent to Breast Conservation Therapy and decreased patient compliance. Alternative methods of delivering radiation have been advocated to increase patient compliance and acceptability to radiation. These include Accelerated whole breast irradiation and Accelerated partial breast irradiation which includes modalities like interstitial brachytherapy, intracavitary brachytherapy, intraoperative radiation and external beam radiotherapy.

**Keywords:** *Breast irradiation, partial breast irradiation.*

## Introduction

Breast-conserving therapy is an accepted treatment option for women with stage I or II invasive breast cancer. Randomized trials and retrospective studies have shown unacceptably high local failures after breast conserving surgery without radiotherapy<sup>1</sup>. Local failure is known to compromise the long-term survival.

To prevent local recurrence, patients undergoing BCT have traditionally been given radiation to whole breast, with or without nodal irradiation. A protracted course of radiation is given, lasting from 3 weeks to 5 weeks followed by boost to the tumour bed. This prolonged treatment course has been a major deterrent to the wider use of breast conservation therapy. It has been seen that most recurrences in patients treated either with excision alone or excision plus radiotherapy are at or near the tumour bed. The distribution of tumour cells in the breast is confined to a relatively limited area around the index lesion<sup>2</sup>.

NSABP B-06 demonstrated approximately 30% recurrence rates in women not undergoing irradiation after breast conservation over a ten year period<sup>3</sup>. Local failure may be salvaged with mastectomy. However, early Breast Cancer trialists Collaborative Group meta analysis of randomized trials showed that group not receiving radiation had a higher rate of mortality due to breast cancer. The recurrences that occur as a local failure are in the vicinity of the lumpectomy site and are termed as 'true recurrence' or 'marginal miss'. Recurrences after 5 years appear at more distant sites from the first incident cancer and may include new primary breast cancers.

In the last 10 years alternative methods of delivering radiation treatment have been advocated to increase the patient compliance and acceptability to radiation. They are (a) accelerated whole breast irradiation and (b) accelerated partial breast irradiation.

Accelerated whole breast irradiation (42.5 Gy in 16 fractions) was compared to conventional irradiation (50 Gy in 25 fractions) without a boost in 1234 patients in a randomized trial by Whelan et al<sup>4</sup>. The authors reported no difference between two arms in survival, local control, cosmesis and complications. Accelerated partial breast irradiation delivers radiation to a smaller volume of breast in and around the tumour site in a shorter interval than 5 weeks. Accelerated partial breast irradiation (APBI) is delivered in 1-5 days and covers only the area immediately surrounding the lumpectomy site. It irradiates the surrounding breast tissue which is a highest risk of recurrence. The currently available methods for **accelerated partial breast irradiation** are:

(i) Interstitial brachytherapy implant (high dose rate or low dose rate)

- (ii) Intracavitary brachytherapy (balloon catheter)
- (iii) Intraoperative radiation (orthovoltage or electron beam)
- (iv) External beam (three-dimensional conformal beam, intensity modulated radiotherapy or proton beam).

The selection criteria for partial breast irradiation are quite strict such that the patients should be in an older age group (>45 years), tumour size <3 cm, lymph node-negative disease, invasive ductal carcinoma, wide negative margins of resection, negative post biopsy mammogram and absence of extensive intraductal component.

**Interstitial brachytherapy** The earliest results of interstitial brachytherapy were reported by Kuske et al<sup>5</sup>. 50 women underwent a wide local excision, axillary dissection and either a low dose rate or high dose rate brachytherapy in alternating blocks of 10 patients. Median age of the patients was 67 years and the women were eligible if tumours were T<sub>is</sub>, T<sub>1</sub> or T<sub>2</sub> <4 cm in greatest dimension with negative inked microscopic surgical margins and zero to three metastatic axillary lymph nodes. The brachytherapy target volume include 2 cm of breast tissue surrounding the excision cavity and the prescription isodose envelopes this volume. Low dose rate prescription dose is 45 Gy over 4 days at the rate of 50-75 cGy/hour and high dose rate patients receive a dose of 32 Gy in 8 fractions over 4 days, 2 fractions per day, 6 hours apart. A CT scan based 3 dimensional dose volume analysis can be used to determine the quality of interstitial implant. In another study reported by Vicini et al brachytherapy alone was compared to external beam therapy (60 Gy over 6 weeks) and the patients were followed up for a median of 5.7 years. No local or regional failures were detected and only one patient failed distantly in the high dose rate group. No significant adverse sequelae were noted and cosmetic results were reported good to excellent in 98% patients. No statistically significant differences were noted in the 5 year actuarial rates of recurrence for ipsilateral breast (3% versus 0%, p=0.17 or locoregional failure (4% vs 0%, p=0.37) between patients treated with external radiation and those treated with brachytherapy alone. Also, the authors noted no differences in overall survival or cause-specific survival.

**Intracavitary brachytherapy (Balloon Catheter or MammoSite)** MammoSite ® RTS is a new minimally invasive method of delivering radiation to the lumpectomy cavity. It is a small balloon holding a central catheter to carry the radioactive substance to the centre of the cavity. The balloon is left in the lumpectomy cavity and filled with saline water and contrast to distend into the cavity space. The central catheter is connected to a remote after-loading high dose rate machine and treatment is

delivered over 10 fractionated sessions, 6 hours apart over 5 days. Patient can take treatment as an outpatient and the balloon is deflated and removed after the last session of treatment without anaesthesia.

**Intraoperative Radiotherapy** An intraoperative radiation therapy technique (IORT) was developed by Veronesi et al<sup>6</sup>. A mobile linear accelerator using a robotic arm delivers electron beam energies from 3-9 Mega electron volts. Radiation is delivered using a perspex applicator directly into the lumpectomy cavity. An aluminum lead disk is placed between the breast and the pectorals muscle to protect the thoracic wall. A single fraction of 21 Gee has been estimated to be equivalent to 60 Gee over 30 fractions. Although the treatment was well accepted by patients, a large number of patients with a longer follow up mean follow up of 8 months) is yet to be reported to determine the efficacy and/or possible late side effects of such a large dose of radiation. The Target Trial is an international randomized controlled clinical trial comparing Single-Day Targeted Intraoperative Radiotherapy to Conventional Post operative Radiotherapy. This international study is designed to enroll 2,400 women, age 40 years or older with invasive breast cancer less than 3 cm in size.

**External Beam Conformal radiation** - Multiple CT-scan sections are obtained in the treatment position and a 3 dimensional plan is generated using advanced computer algorithms. The technique is best suited if the localization clips can be left in the lumpectomy cavity to determine the region of interest. It is possible to reduce the cardiac and lung dose while maintaining adequate tumour bed coverage with these techniques. Contralateral breast can also be spared the exit dose that is delivered by the lateral tangential field with conventional planning

Partial breast irradiation, accelerated partial breast irradiation may be an acceptable tool to augment breast preservation therapy in a resource limited country like India, however large randomized trial data in future will answer the question whether it should replace the conventional radiation.

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### Compiled by Dr. Chintamani

### Literature Review

**Role of p-glycoprotein expression in predicting response to neoadjuvant chemotherapy in breast cancer—a prospective clinical study.** Chintamani, Singh JP, Mittal MK, Saxena S, Bansal A, Bhatia A, Kulshreshtha P. *World J Surg Oncol*. 2005. 14; 3: 61.

The expression of p-glycoprotein at initial presentation has been found to be associated with refractoriness to chemotherapy and a poor outcome. Against this background a prospective study was conducted using C219 mouse monoclonal antibody specific for p-glycoprotein to ascertain whether pretreatment detection of p-glycoprotein expression could be utilized as a reliable predictor of response to neoadjuvant chemotherapy in patients with breast cancer.

Fifty (50) cases of locally advanced breast cancer were subjected to trucut biopsy and the tissue samples were evaluated immunohistochemically for p-glycoprotein expression and ER, PR status. The response to neoadjuvant chemotherapy was assessed clinically and by using ultrasound after three cycles of FAC regime (cyclophosphamide 600 mg/m<sup>2</sup>, Adriamycin 50 mg/m<sup>2</sup>, 5-fluorouracil 600 mg/m<sup>2</sup> at an interval of three weeks).

A significant relationship was found between the pretreatment p-glycoprotein expression and clinical response. The positive p-glycoprotein expression was associated with poor clinical response rates. When the clinical response was correlated with p-glycoprotein expression, a statistically significant negative correlation was observed between the clinical response and p-glycoprotein expression ( $p < 0.05$ ). There was another significant observation in terms of development of post NACT p-glycoprotein positivity. Before initiation of NACT, 26 patients (52%) were p-glycoprotein positive and after three cycles of NACT, the positivity increased to 73.5% patients. CONCLUSION: The study concluded that pretreatment p-glycoprotein expression predicts and indicates a poor clinical response to NACT. Patients with positive p-glycoprotein expression before initiation of NACT were found to be poor responders. Thus pretreatment detection of p-glycoprotein expression may be utilized, as a reliable predictor of response to NACT in patients

with breast cancer The chemotherapy induced p-glycoprotein positivity observed in the study could possibly explain the phenomenon of acquired chemoresistance and may also serve as an intermediate end point in evaluating drug response particularly if the adjuvant therapy is planned with the same regime.

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**Is drug-induced toxicity a good predictor of response to neo-adjuvant chemotherapy in patients with breast cancer?—a prospective clinical study.** Chintamani, Singhal V, Singh JP, Lyall A, Saxena S, Bansal A. *BMC Cancer*. 2004; 4: 48.

The change in expression of apoptotic markers (Bcl-2 and Bax proteins) brought about by various chemotherapeutic regimens is being used to identify drug resistance in the tumor cells. A prospective clinical study was conducted to assess whether chemotherapy induced toxic effects could serve as reliable predictors of apoptosis or response to neo-adjuvant chemotherapy in patients with locally advanced breast cancer.

50 cases of locally advanced breast cancer after complete routine and metastatic work up were subjected to trucut biopsy and the tissue evaluated immunohistochemically for apoptotic markers (bcl-2/bax ratio). Three cycles of Neoadjuvant Chemotherapy using FAC regime (5-fluorouracil, adriamycin, cyclophosphamide) were given at three weekly intervals and patients assessed for clinical response as well as toxicity after each cycle. Modified radical mastectomy was performed in all patients three weeks after the last cycle and the specimen were re-evaluated for any change in the bcl-2/bax ratio.

There was a statistically significant correlation observed between clinical, immunohistochemical response (bcl-2/bax ratio) and the drug-induced toxicity. Responders also had significant toxicity while non-responders did not show significant toxicity following neoadjuvant chemotherapy. The chemotherapy-induced toxicity was observed to be a cost effective and reliable predictor of response to neo-adjuvant chemotherapy.

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