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Original Research Paper

Oncology

EVALUATION OF WHOLE BREAST IRRADIATION IN COMPARISION WITH ACCELERATED PARTIAL BREAST IRRADIATION USING CONFORMAL RADIOTHERAPY IN POST LUMPECTOMY CARCINOMA BREAST

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ABSTRACT

Introduction: Breast-conserving surgery followed by radiation therapy to the intact breast is now accepted as the standard of care for majority of women with early stage invasive breast cancer. Breast-conserving therapy offers an obvious cosmetic advantage that may enhance quality of life and lead to less psychological and emotional treatment-related distress. With the advent of time, hypofractionation came in to the effect based on three major trials [1,2] . Based on the benefit and biological effectiveness observed with hypofractionation, concept of Accelerated Partial Breast Irradiation (APBI) was derived to irradiate the tumor bed only with a margin, as majority of the recurrences are observed within 2cm of the tumor bed [3]. **Aim and objectives:** To perform a comparative evaluation of conventional whole breast irradiation and 3-dimensional conformal accelerated partial breast irradiation given in post-lumpectomy patients of early stage breast cancer for - (a) Acute radiation toxicity (b) Cosmetic assessment (c) Local control of disease. **Materials and methods:** Forty patients of histologically proven, post lumpectomy cases of stage I and stage II carcinoma breast suitable for APBI were enrolled in this study. Patients were evaluated at the Department of Radiotherapy PGIMER, Chandigarh.Patients were treated by either conventional WBI or APBI after randomisation into two arms, twenty in each. Patients of control arm were treated by conventional WBI and study arm by APBI using 3DCRT technique. Computerised tomography based planning was done for different field arrangements of APBI. **Inclusion criteria:** Unicentric primary cancer with any histology type,Age at presentation 45 yrs,Tumor size < 3cm, unifocal or unicentric,Nodal positivity < 3,No metastasis,Lumpectomy or quadrantectomy with clear margin of > 2mm,Full informed consent obtained from patient, Follow up at our centre. **Exclusion criteria:** Extensive intraductal component,History of prior primary malignancy,History of prior irradiation to chest,Patients who received neoadjuvant chemotherapy,Pregnant or lactating women,Collagen vascular disorders.The selection criteria of this study was same as that of RTOG-0413/NSABP-39 PROTOCOL[28,30] except for the age which was ≥ 45years. **Results:** Acute skin toxicity analysis showed slightly higher toxicity in APBI arm than whole breast irradiation arm at end of 1 month and 6 months.Breast edema was observed in 15% of WBI arm and 30% of APBI arm, showing higher incidence in APBI arm. Pigmentary changes were almost comparable between WBI arm and APBI arm (15% vs 20% respectively). At 6 months, subcutaneous fibrosis grade II-III were seen in 20% of WBI arm and in 50% of APBI arm. Clearly depicting higher percentage of toxicity in APBI arm.Good and excellent cosmetic scores were seen in 85% and 95% of WBI arm and APBI arm respectively, at the median follow up of 1 year and hence favouring APBI arm. **Conclusion:** Accelerated partial breast irradiation using 3DCRT is technically feasible and should be preffered over whole breast irradiation in carefully selected early stage breast cancer patients

KEYWORDS : Accelerated Partial Breast Irradiation(abpi), Post Lumpectomy Radiation.

Introduction

Breast cancer being the most frequently diagnosed cancer in women, surgery is the primary modality of treatment. Upto mid 20th century radical mastectomy remained the mainstay of surgical therapy. Breast-conserving surgery followed by radiation therapy to the intact breast is now accepted as the standard of care for majority of women with early stage invasive breast cancer. Breast-conserving therapy offers an obvious cosmetic advantage that may enhance quality of life and lead to less psychological and emotional treatment-related distress. With the advent of time, hypofractionation came in to the effect based on three major trials [1,2] . Based on the benefit and biological effectiveness observed with hypofractionation, concept of Accelerated Partial Breast Irradiation (APBI) was derived to irradiate the tumor bed only with a margin, as majority of the recurrences are observed within 2cm of the tumor bed [3].

Aim and objectives

To perform a comparative evaluation of conventional whole breast irradiation and 3-dimensional conformal accelerated partial breast irradiation given in post-lumpectomy patients of early stage breast cancer for - (a) Acute radiation toxicity (b) Cosmetic assessment (c) Local control of disease.

Materials and methods

Forty patients of histologically proven, post lumpectomy cases of stage I and stage II carcinoma breast suitable for APBI were enrolled in this study. Patients were evaluated at the Department of Radiotherapy PGIMER, Chandigarh.

Patients were treated by either conventional WBI or APBI after randomisation into two arms, twenty in each. Patients of control arm were treated by conventional WBI and study arm by APBI using 3DCRT technique. Computerised tomography based planning was done for different field arrangements of APBI.

Inclusion criteria

1. Unicentric primary cancer with any histology type
2. Age at presentation 45 yrs
3. Tumor size < 3cm, unifocal or unicentric
4. Nodal positivity < 3
5. No metastasis
6. Lumpectomy or quadrantectomy with clear margin of > 2mm

Full informed consent obtained from patient.

Exclusion criteria

1. Extensive intraductal component
2. History of prior primary malignancy.
3. History of prior irradiation to chest
4. Patients who received neoadjuvant chemotherapy
5. Pregnant or lactating women

6. Collagen vascular disorders

The selection criteria of this study was same as that of RTOG-0413/NSABP-39 PROTOCOL except for the age which was ≥ 45years.

Procedure and methodology

Patients were recruited as soon as they present in radiotherapy out- patient department from surgery department after lumpectomy, preferably after a post operative period of 3-4 weeks.A planning CT scan was done for each patient. The patients were positioned on a breast board with sternum parallel to the table, and the ipsilateral arm abducted above the head. Before the CT scan skin marks were placed to enable the patient repositioning during treatment.

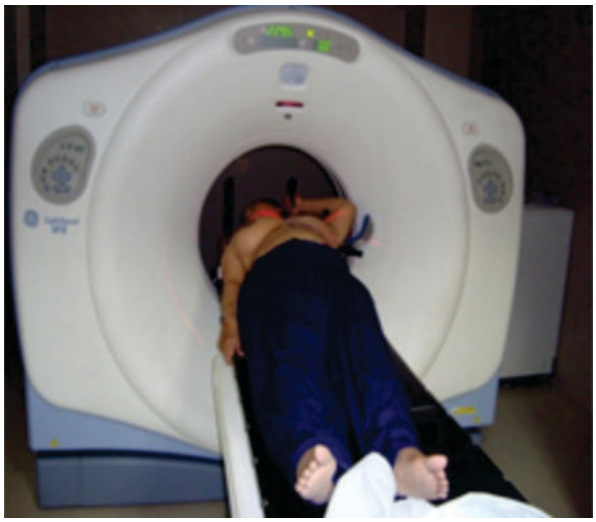


Figure: 1 CT-simulation

Figure-1 shows position of the patient during the simulation. Patients were scanned from level of larynx to the level of upper abdomen, including both lungs with a scan thickness and index of 2.5mm. The CT scan included the complete left and right lung, both breasts and the heart.

Then CT images were transferred to the treatment planning system. The lumpectomy cavity was identified on the planning CT with the help of surgical clips or by using ultrasound localisation. The gross tumor volume (GTV) was defined by lumpectomy cavity contoured on each CT slice.The clinical target volume (CTV) consisted of GTV uniformly expanded in three dimensions by 1 cm.

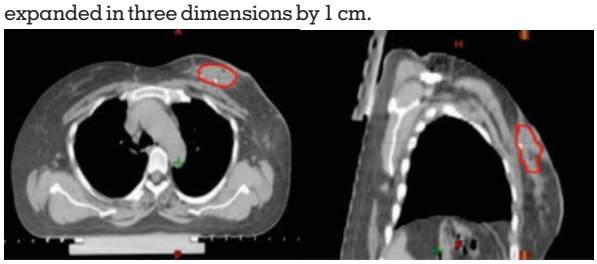


Figure: 2.lumpectomy Cavity (gtv)

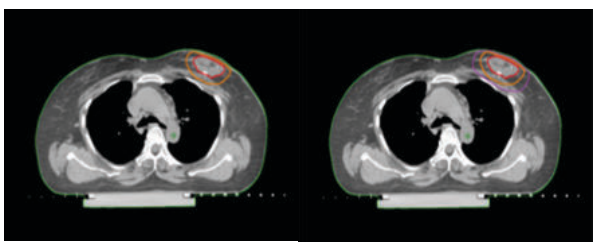


Figure: 3 clinical Target Volume.

Figure: 4 Planning Target Volume

The PTV consisted of CTV uniformly expanded in three dimensions by 1 cm margin. The PTV excluded skin, variably defined as between 2 and 5 mm from the external surface and also excluded chest wall defined as being 5mm from the lung-chest wall interface. It was to account for treatment set-up uncertainties and breathing motion, planning target volume (PTV) was calculated from the CTV using uniform three dimensional expansion of 1 cm. The ipsilateral whole breast was defined to lie within the radioopaque markers and as deep as the anterior chest wall muscles. The cranial extent of heart included the infundibulum of right ventricle, the right atrium and right auricle but excluded the pulmonary trunk, ascending aorta and superior vena cava. The lowest external contour of heart was the caudal border of mediastinum. The pericardium was also excluded from the heart volume.

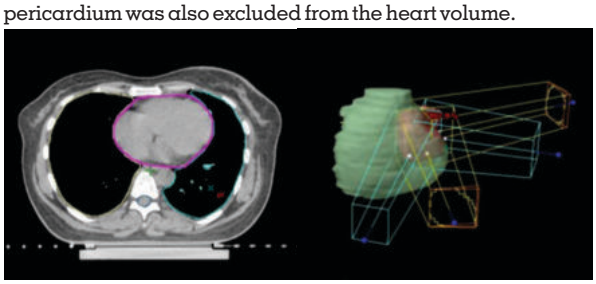


Figure: 5 Organs at risk **Figure: 6 Beam arrangement**

Both the lungs were contoured seperately. The contralateral breast was contoured as the breast parenchyma is visible on CT images. After contouring target volumes and organs at risk (OAR), standard conventional whole breast tangential field plans were generated for the WBI arm patients and 3DCRT plans were generated for the APBI arm patients. 3DCRT plans generated for APBI arm involved 2-4 coplanar beams.

The diagram (fig-6)shows 2 coplanar beam arrangement with setup fields :-

Dose prescribed was 40 Gy in 16 fractions for 3weeks for whole breast rectangular plans ie., for twenty patients in WBI arm. Twenty patients in APBI arm were treated to 34 Gy in 10 fractions. These patients were treated twice daily over 5 consecutive days. The minimum time interval between two fractions was 6 hours.

Assessment of toxicity :

Assessment of toxicity was done as per RTOG scores and LENT SOMA scale

Cosmetic assessment

Assessment of cosmesis was done Harvard/RTOG/NSABP/ Breast cosmesis grading scale.

Results

Table 1 : patient characteristics

	Whole breast arm	apbi arm
No.of patients	20	20
Age (mean)	49	52
Tumor size (mean)	1.8	2.1
Side (r:l)	9:11	8:12
Involved quadrant	UOQ – 8 UIQ – 1 LOQ – NIL LIQ – 4 CENTRAL Q - 7	UOQ – 10 UIQ – 3 LOQ – 2 LIQ – NIL CENTRAL Q – 5
Menopausal status Premenopause Postmenopause	 7 6	 13 14

Skin and subcutaneous toxicities:

All these 40 patients were assessed separately for radiation

induced skin and subcutaneous toxicities as per RTOG scores, immediately after the completion of treatment, at 1 month follow up, after 6 months and at the end of 1 year follow up, The results of these grading are observed as follows :

Acute radiation toxicities

Early skin toxicity: During assessment at 1 month post radiation, grade 1 reactions were seen in 15 patients of APBI arm (75%) and in 12 of whole breast arm (60%). And grade II reactions were observed in 6 (30%) of APBI arm and in 5 patients (25%) of whole breast arm. Grade III – IV skin reactions were observed in 2 patients (10%) of APBI arm and was not observed in any patients of whole breast arm, indicating slightly higher percentage of acute toxicity in APBI arm but not significant. However no treatment interruption was observed in either of the arm due to acute toxicity.

Early-late radiation toxicities:

Skin toxicity: At the end of 6 months post-radiation, grade I skin reaction were observed in 1 patients (5%) of whole breast arm and in 2 (10%) patients of APBI arm. Similarly, grade II reactions were seen in 2 patients (10%) of APBI arm and thus indicating slightly more late skin toxicity in those patients treated in APBI arm .

Cosmetic assessment:

At the end of 1 month cosmetic assessment was done, excellent cosmesis were observed in 4 (20%) patients of whole breast arm and in 5(25%) of APBI arm , good cosmesis were observed in 13 (65%) of whole breast arm and in 11 (55%) of APBI arm. Cosmesis were fair to poor in 3 (15%) of patients of whole breast arm and in 4 (20%) of APBI arm. Thus cosmetic score was almost equal in both the arms at the end of 1 month.

Subcutaneous toxicity: During assessment at 6 months post-radiation, grade I subcutaneous toxicity was observed in 9 patients (45%) of whole breast arm and in 10 patients (50%) of APBI arm. Grade II subcutaneous toxicity was observed in 3 patients (15%) of whole breast arm and in 8 patients (40%) of APBI arm. Grade III subcutaneous toxicity was observed in only 1 whole breast patient (5%) and in 2 (10%) patients of APBI and no grade IV toxicity.

Cosmetic score: At 6 months follow up, excellent cosmetic score was observed in 5 (25%) of the WBI patients and in 7 (35%) of APBI arm and good cosmesis was observed in 12 patients (60%) of WBI arm and in 11 patients (55%) of APBI arm. And fair cosmetic score was seen in 2 (10%) and 2 (10%) patients respectively and bad cosmesis in 1 (5%) patient of WBI arm.

Pigmentary change:

At the end of 6 months, 3 (15%) patients in WBI arm and 4 (20%) patients in APBI arm had grade I pigmentary change. None had grade II pigmentary change.

Breast edema:

At the end of 6 months, 3 patients of WBI arm and 5 patients of APBI arm had breast edema. Only one patient of APBI arm was symptomatic and to note, that patient also received docetaxol based chemotherapy

Late radiation toxicities

Late subcutaneous toxicity :

At the end of 1 year, grade I subcutaneous toxicity was observed in 4 (20%) patients of WBI arm and in 10 (50%) patients of APBI arm. Grade II toxicity was observed in 2 (10%) patients of WBI arm and in 2 (10%) patients of APBI arm. No grade III toxicity was observed at the end of 1 year.

Cosmesis:

At the end of one year, excellent cosmesis was observed in 6 (30%) patients of WBI arm and in 7 (35%) patients of APBI arm. Good cosmesis were observed in 11 (55%) patients of WBI arm and in 12 (60%) patients of APBI arm. Fair cosmesis in 2 (10%) patients of WBI arm and 1 (5%) patient of APBI arm. Bad cosmesis in only one patient (5%) of WBI arm.

Discussion

The concept of partial breast irradiation originated from the observation that the vast majority of ipsilateral breast tumour recurrences arose in the vicinity of the original index lesion. Ipsilateral breast tumour recurrence (IBTR) in the tumour bed and at margins has been found to be as high as 50-60% of all local recurrences in various studies. In the NSABP-06 trial, at a follow-up of 25 years the cumulative incidence of IBTR was 39.3% in lumpectomy alone arm and 14.2% in patients who received postoperative radiotherapy. Ninety five percent of these patients were found to develop IBTR at or close to the same quadrant as the index tumour.[27]

The role of APBI is well defined in the conservative treatment of early stage breast cancer patients. Several randomised controlled trials have shown the benefit in terms of cosmesis, cost effectiveness and control rates equivalent to that of conventional whole breast irradiation. APBI has also shown significant normal tissue sparing with minimal acute and late toxicities.[8-15]

Extensively studied technique of APBI, having a long follow up are with multicatheter interstitial brachytherapy.[5,26] Although the method of delivery of APBI is well established with interstitial brachytherapy, there is no standard method. The external beam RT technique is gaining importance in the recent past because of its convenience, easy availability, noninvasive, real time image guidance to overcome the motion artifacts and due to the lack of expertise in brachytherapy. This technique is attractive to the patients because it eliminates the need for procedural trauma to the breast. Compared with brachytherapy, 3D-CRT APBI also permits much greater dose homogeneity. However 3D-CRT APBI can result in greater nontarget breast tissue doses than brachytherapy-based techniques.[8] In our study 51.2% of whole breast reference volume received 17Gy (50% of prescribed dose). Taghian et al. in their study reported 40% of the nontarget breast tissue received 16 Gy (50% of prescribed dose).[8]

Delivering APBI by intensity modulated radiotherapy (IMRT) technique is being explored. However for delivering APBI, IMRT may not hold a great deal of advantage over 3DCRT technique, having similar dose distribution at the cost of time [25] and the prime concern in delivering IMRT is the inter and intra fraction organ motion which needs real time image guidance. So 3D-CRT still remains better option to deliver APBI by external beam.

The lumpectomy cavity defined based on the clinical details and the surgical scar is erroneous at many times. Hence, the dimensions as well as depth for tumour bed should be determined either by fluoroscopy or CT combined with surgical clips, or an ultrasound. There by interobserver variation in delineating the lumpectomy cavity can be minimised.[31-33]

Recent concern is application of large fraction size to relatively large volume in EBRT as opposed to MIB can potentially increase the early and late toxicities resulting in adverse cosmesis. In this study we have compared conventional whole breast irradiation with APBI using 3DCRT. Normal tissue dosimetric constraints used in this study were similar to RTOG 0413/NSABP B-39 protocol.[30]

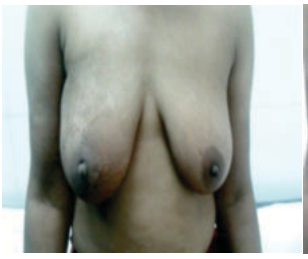
Skin toxicity

Bourgier et al. showed in their study showed that 8% (2/25) of

patients had moist desquamation reaction at 1 month[9]. In our study grade III-IV reactions were seen in 10% of APBI arm patients only, but not in the WBI arm, comparable to the other studies. Also this clearly shows increased percentage of acute skin toxicity in APBI arm.

Pigmentary change

Chen et al. in a similar study observed hyperpigmentation in 41% of APBI arm patients treated by 3DCRT, after treatment during follow up[34]. Bourgier et al. studied APBI using 40GY at 4Gy fraction showed 44% patients had colour change at 6 months[9]. In our study at 6 months, 15% of WBI arm and 20% of APBI arm patients had grade I pigmentary change, thus comparable between the arms. To note that pigmentary changes are relatively less in our study corroborating the less total dose used. Our observation showed that pigmentary changes also reversed on follow up.



PICTURE 7: (APBI) pigmentary changes

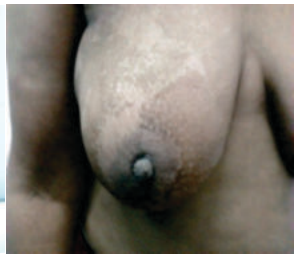


fig -8 A closure view

Breast edema:

Breast edema was observed in 15% of WBI arm and 30% of APBI arm, showing higher incidence in APBI arm, also comparable to other similar studies. One patient in APBI arm was symptomatic with persistent edema for 10 months. As this patient received docetaxol based chemotherapy, edema can be attributed to it. Chen et al. in their study observed 30% of patients had breast edema in APBI arm treated using 3DCRT.[34] Bourgier et al. observed breast edema in 12% of patients at 6 months after treatment.[9]

Also Vicini et al. evaluated erythema, hyperpigmentation, breast edema and fibrosis at 6, 24, and 36 months after treatment. All factors stabilized by 3 years post treatment with grade I or II rates 0%, 0% , 0% and 18% respectively. Only 2 patients (3%) developed grade III toxicity which resolved with time.

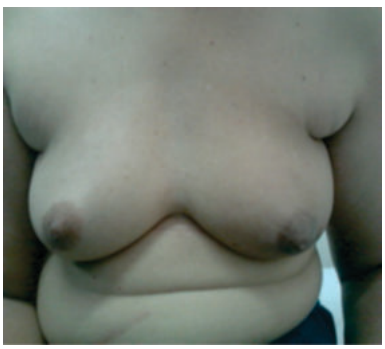


Fig-9 Showed Good Cosmesis.(ABPI).

Thus indicating the fact that these early-late radiation reactions improves with time and better appreciated in these long-term follow up studies. [35]

Conclusion

1. Acute skin toxicity analysis showed slightly higher toxicity in APBI arm than whole breast irradiation arm at end of 1 month and 6 months.
2. Breast edema was observed in 15% of WBI arm and 30% of APBI arm, showing higher incidence in APBI arm.
3. Pigmentary changes were almost comparable between WBI arm and APBI arm (15% vs 20% respectively).
4. At 6 months, subcutaneous fibrosis grade II-III were seen in 20% of WBI arm and in 50% of APBI arm. Clearly depicting higher percentage of toxicity in APBI arm.
5. Good and excellent cosmetic scores were seen in 85% and 95% of WBI arm and APBI arm respectively, at the median follow up of 1 year and hence favouring APBI arm.
6. Although slightly increased, toxicities were well tolerated in APBI arm with significant dose reduction to OAR.Till date neither local nor systemic failure were observed in both the arms. Long term follow up is needed to see the failure pattern and late complications.

So to conclude, Accelerated partial breast irradiation using 3DCRT is technically feasible and should be preffered over whole breast irradiation in carefully selected early stage breast cancer patients

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