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Accelerated Partial Breast Irradiation Versus Traditional Whole Breast Ir-radiation in Early Stage (I&II) Breast Carcinoma

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Abstract: ***Background:The goal of accelerated partial breast ir-radiation (APBI) is both to reduce the duration of radiation therapy treatment to less than a week and to improve local control by increasing the dose to tumor bed .Many randomized trials had repoted between 75% and 90% of local recurrence are in the quaderant of original tumor, and therefore, it is anticipated that important residual cancer will be in the APBI fields. The aim of this study was the assessment of treatment outcomes and toxicities, the primary end points were disease free survival (DFS)and overall survival(OAS) in both groups .Secondary end point was radiation toxicities. Patients &Methods:70 patients of early breast carcinoma randomized into two groups :group A (35 patients treated with 3D conformal RT using photons, radiation dose :38.5 Gy /3.85 Gy/Fx.delivered BID over 5-7 days with an interfraction interval of 6 hours or more(APBI)), and group B (35 patients with 3 D conformal RT in convevtional dose 40 Gy /2.5 Gy /Fx/ 5 Fx per week/15 days WBI). Results: Median age was 44 years ., the majority of patients with stage II disease (64.3%), and 77% of patients had hormonal receptor positive disease.After a median follow up of 30 months, DFS &OS rates for the whole group (70 patients) were 79% and 83%, respectively. DFS was 86% in group A versus 80% in group B and OS was 90% &88% in group A&B respectively without statistical significance difference (P >0.05) Regarding late radiation toxicities no difference between groups although late toxicity was higher in group B. Conclusion: In early stage invasive breast carcinoma (T1, T2 N0-N1 M0) after breast conserving therapy (BCT), using of APBI technique compared to conventional WBI, after a median follow up 30 months, showed comparable results regarding (DFS, OAS& cosmotic results).These results suggest that APBI technique could achieved the goal of adjuvant radiation therapy in BCT without inferiority in DFS &OAS with comparable cosmotic results.***

Keywords: breast cancer, accelerated partial breast irradiation, whole breast irradiation.

1. Introduction

Currently, irradiation to entire breast known as whole – breast irradiation is the standard of care following breast conserving therapy (BCT) .A multicentre randomized trial (NSABP-39) is ongoing to determines the effectiveness of partial-breast irradiation (PBI)techniques compared with whole-breast irradiation(WBI)[1, 2].Radiation treatment to axilla is rarely after complete axillary dissection in patients with more than 10 positive nodes.The combination of both axillary lymph node dissection (ALND) and radiation treatment to axilla can greatly increase the risk of lymphedema, with reported rates of more than 50%.Although RT to the whole breast is considered the standard treatment course, administering partial breast irradiation may be an effective treatment (Grade B)[3] .Accelerated partial breast irradiation (APBI) can significantly reduce the overall treatment time of adjuvant RT, and its efficacy has been shown in non-randomized trials[4, 5] .A phase II trial that included 199 patients with early stage breast cancer treated with partial breast brachytherapy, using either high dose rate (HDR) or low dose rate (LDR) brachytherapy. Matched-pair analysis with women treated with whole breast RT was performed.At a median follow up of 65 months, the local failure rate was 1% and the results observed were comparable to those achieved with whole breast RT [6].

The aim of the study was the assessment of treatment outcomes and toxicities, the primary end points were disease free survival (DFS)and overall survival(OAS) in both groups. Secondary end point was radiation toxicities.

2. Patients &Methods

This study was conducted in Clinical Oncology & Nuclear Medicine Department, Zagazig University Hospitals in the duration from April 2011 to June 2016, 70 patients with early stage(I &II) breast cancer were randomized after breast conserving surgery to A group that included 35 patients treated with accelerated partial breast irradiation (APBI) using 3 D conformal RT(3DCRT) using photon beam, in a dose 38.5 Gy /3.85 Gy/Fx.delivered BID over 5-7 days with an interfraction interval of 6 hours or more., and group B was included 35 patients treated with conventional whole breast irradiation (WBI) in a dose 40 Gy /2.5 Gy /Fx/15 days and breast boost 10 Gy in 5 fractions. **Radiotherapy techniques:** Patients were simulated using C.T. images included the entire thoracic region from level of third cervical vertebra to the diaphragm, **Immobilization :**The position of the patient must remain identical for localization on a CT scanner or simulator and during subsequent treatment.The patients were treated supine using an immobilization device which secures both arms above the head. A system of medial and lateral tattoos and orthogonal laser lights alignment of the patient and consistency of set-up were ensured. An inclined plane was used with fixed angle positions. **Target volume definition:** The clinical target volume (CTV) in **Partial breast irradiation** defined as lumpectomy cavity as localized by 3D ultrasound and planning CT, The planning target volume (PTV) was CTV

plus 1-2 cm all around.**InWhole Breast**:CTV defined as the whole breast and lumpectomy cavity. The planning target volume (PTV) included the entire breast defined by inspection and palpation with a 2 cm margin, extending from the anterior midline to the mid-axillary line. Superior and inferior margins to the PTV were at the sternal notch and 2 cm below the inframammary fold (or overlapping breast tissue), respectively.Breast boost of 10 Gy in 5 fractions in a week. The treatment delivered by photon beam using linear accelerator machine(Linac, Elekta 151204, precise plan, release 2.12, 477.08)**.** Early and late toxicities were scored according to the radiation therapy oncology group(RTOG) criteria in both groups of patients [7] .**Assessment of treatment outcomes and toxicities** :In the present study, the primary end points were disease free survival and overall survival in both groups .Secondary end point was radiation toxicities. Disease free survival was defined as the interval from enrollment of patients to date of the first event (relapse, progress, or death) or to date of last follow up .Overall survival was defined as the interval from enrollment to the date of death from any cause or to last follow up.

Statistical analysis:The study cut off point was June 2016 .DFS &OS rates were estimated using Graphed prism program, and comparison between both groups (A&B) by Log rank test .Data on radiation related toxicities and disease relapse in two studied groups were compared using the Chi-square test .The P-value reports are two tailed and an alpha level of 0.05was used to assess statistical significance.

3. Results

Table 1: Showed patients & disease characteristics in both groups, no statistical significant difference between patients in the study groups

Variable	Group A (35)		Group B (35)		P value
	NO	%	NO	%	
Age					
< 50 years	19	54.28	22	62.85	
≥ 50 years	16	45.71	13	37.14	
Stage					
Stage I	12	34.28	13	37.14	
Stage II	23	65.71	22	62.85	
Horrmonal receptor status					
+ve	27	77.14	27	77.14	
-ve	8	22.85	8	22.85	P
Tumor grade					>0.05
G1	8	24.2	6	17.14	
G2	19	54.28	20	57.14	
G3	8	24.2	9	24.3	
Ovarian ablation					
No	32	91.42	29	82.85	
Yes	3	8.57	6	17.14	
Adjuvant ChTh					
FAC	28	80	32	91.42	
CMF	7	20	3	8.57	

Table 2: Early & late effects of RT in both groups.

Variable	Group A 35		Group B 35		P value
	NO	%	NO	%	
Derrmatitis					
GI	14	40	16	45.7	>0.05
GII	3	8.57	6	17.14	
GIII					
Late toxicity					
Fibrosis	1	2.85	3	8.57	
Fat necrosis					
Telangectasia					
Nipple retraction	1	2.85	2	5.7	

Seventy patients included in this study showed an age incidence ranged from 28-65 years, with the median age of 44 years. The majority of patients were of < 50 years of age, with stage II disease (64.3 %), (77.14%) of patients had hormonal receptor positive disease, All underwent BCT and all received adjuvant chemotherapy (ChTh) (FAC, OR CMF) .There were no statistical significant difference between both groups regarding these variables (P > 0.05) age at diagnosis(P=0.17), HR (P=0.66), disease stage (P=0.06) and fractionated schedule(P=0.35). Table (1). After a median follow up of 30 months, DFS& OS rates for the whole group (70 patients) were 79% &83%, respectively (Fig 1&2) there were no statistical significant difference regarding any of the studied factors .In the present study, univariate analysis showed that patients in group A had nearly similar 3-year OS rate to those in group B (Fig 1) 90% versus 88%, with nearly similar DFS (P > 0.05) without significant statistical difference (Fig 2)86% versus 80%.

In the current study, the incidence of G1 dermatitis was 40% and 45.7% in group A &B respectively, and grade 2 dermatitis, were 8.57% and 17% in both groups A &B respectively(P>0.05) .The incidence of late skin toxicity 5.7% versus 14% respectively (P>0.05) grade 2 radiation induced pneumonitis (3% versus7%) in group A &B respectively (P>0.05).(Table 2). Regarding disease relapse, the incidence were comparable between both groups 14% versus 20%, respectively (P=0.34).(Fig 2)

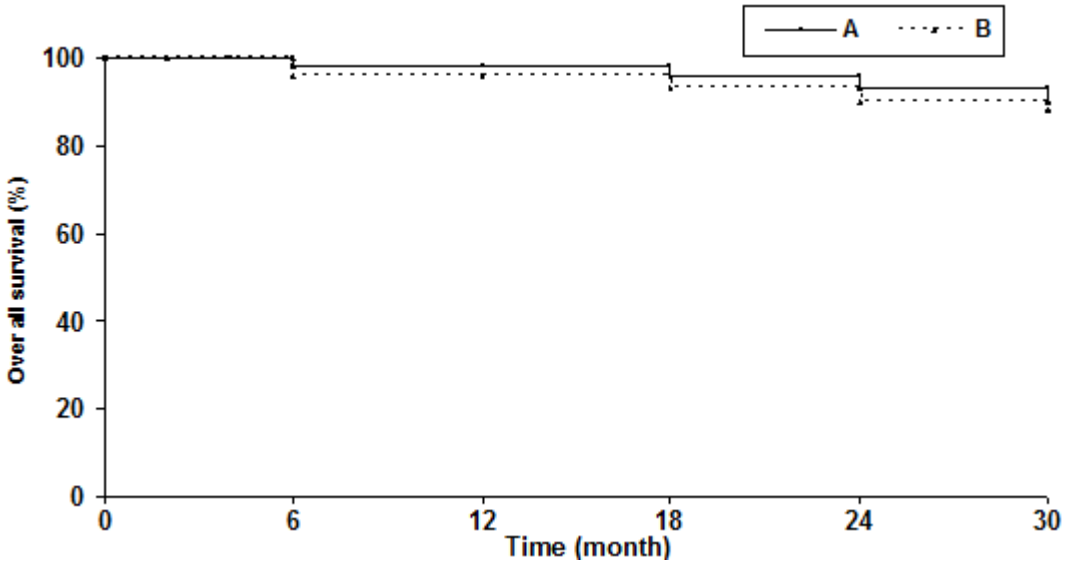

Figure 1: Over all survival (OS)

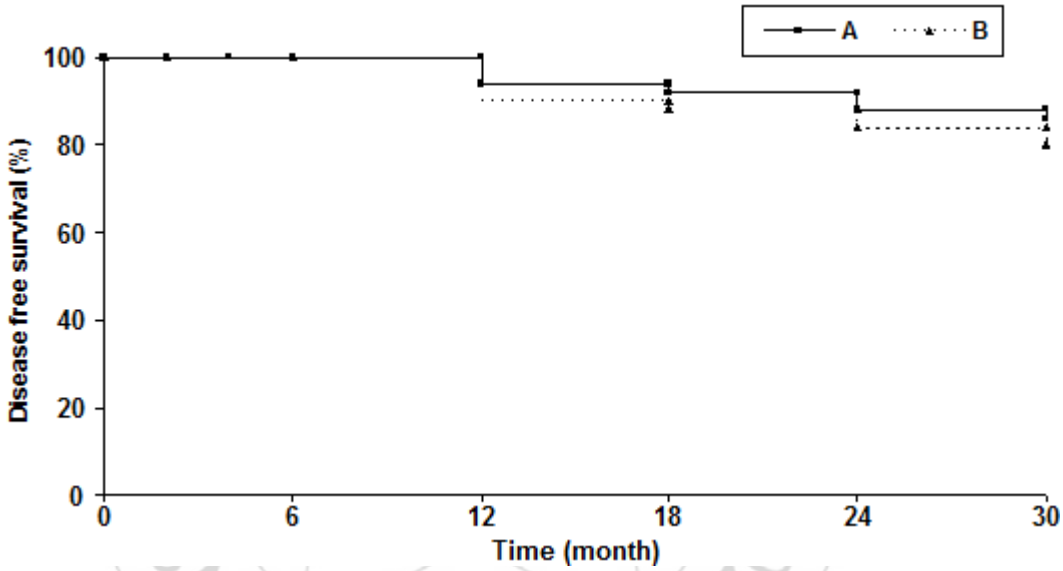

Figure 2: Disease free survival (DFS)

4. Discussion

Adjuvant whole breast irradiation following breast conserving therapy (BCT) is considered to be the standard and has been shown to have the risk of local recurrence among all subgroups of women[8].This metaanalysis of individual data for 10801 women in 17 trials of radiotherapy versus no radiotherapy after BCT showed that the 10-year risk of recurrence was reduced from 35% to 19%.Radiotherapy has also been shown to reduce the risk of breast cancer death at 15 years from 20.5% to 17.2% with one cancer death avoided for every four recurrence prevented. For women at low risk of local recurrence the absolute benefit of radiation therapy is small and a number of trials have examined whether radiation therapy can be safely omitted in older women (> 70 years) with low risk cancer and free margins[9]. One study randomized 636 women aged >70 years with clinical stage T1N0M0 ER-positive breast cancers treated with BCT to tamoxifen plus radiation therapy or to tamoxifen alone. At 12 years follow up, 98% of the women who received radiation therapy were recurrence free compared with 90% of those who did not receive radiation therapy ;there was no difference statistically in survival [10] .The PRIME 2 trial randomized 1326 women aged > 65years with T1-2 N0M0 ER-positive breast cancer (with clear margin), to adjuvant hormonal therapy alone or hormonal therapy plus radiation therapy .At 5 years follow up, the risk of ipsilateral tumor recurrence was 1.3% with radiation therapy and 4.1% without[11] . The optimal time of radiotherapy after BCT is not well defined .The effect of a delay (ranging from more than 77 days to 16 weeks) in starting radiation therapy has been examined in many retrospective series with the majority suggesting there is no reduction in locoregional control with delayed radiation therapy[12-15] Although, it is considered good practice to start radiation therapy as soon as possible after surgery (if no chemotherapy is given) .Forty Gy in 15 fractions over 3 weeks has been adopted as standard practice in UK following publication of START trial which showed no difference in locoregional recurrence rates and less late toxicity with 40 Gy compared with 50 Gy in 25 fractions[16].There is increasing interest in adjuvant breast radiation therapy with fewer, larger fractions.The FAST trial rabdomized 915 women (age > 50 years) with node negative breast cancer to either 50 Gy in 25 fractions in 5 weeks or 28.5 Gy or 30 Gy in 5 once-weekly fractions of 5.7

Gy or 6 Gy per fraction.At 3 year follow up, 28.5 Gy arm was comparable to 50 Gyin 25 fraction in terms of cosmosis but the 30 Gy in 5 fractions was founed to adversely affect cosmotic appearance[17].The FAST-forward trial has completed recruitement of 4000 women .This trial randomized women between 40 Gy in 15 fractions compared to two other schedules, 27 Gy in 5 fractions over one week or 26 Gy in 5 fractions over one week[18]. The goal of (APBI) is both to reduce the duration of radiation treatment to less than a week and to improve local control by increasing the dose to tumor bed .Some where between 75% and 90% of local recurrence are in the quadrent of the original tumor[2, 4-6], and therefore it is anticipated that important residual cancer will be in the APBI fields.At least 4 randomized trials, together enrolling >3.300 women have been undertaken.The results of these trials are very provocative, but the techniques in each of the four studies are quite different and reported follow up is generally short[3].In the largest of these studies women were randomized to WBI (40-56 Gy) using a conventional dode schedule or to TARGIT, which consist of a single dose of low energy X-ray therapy delivered into the tumor bed over 20-35 minutes immediatly following the surgical removal of tumor[6, 19, 20] .This delivers about 20 Gy to surface of tumor bed and 5-7 Gy at depth of 1cm .The median follow up is only 2.5 years .The ipsilateral breast recurrence is low in the both arms (3.3% for TARGIT, 1.3% for WBI, P=0.042).In the present study, after a median follow up of 30 months ; the disease free survival in APBI arm(Group A) was 86% compared to 80% in conventional WBI arm (Group B) .The difference is statistically non significant (P>0.05).The difference between our results and the results of Vaidya et al., 2010 &Vaidya et al., 2012 may be due to different techniques in APBI arm and due to patient characteristics in WBI arm.The lower results in the present study may be due to the use of 3-D conformal radiation therapy as a technique for APBI arm and more due to patient characteristics as the patients in Vaidya et al were selected as;(small, low grade tumors, ER-positive and few or no lymph node metastase).The RAPID trial compared the use of APBI to the tumor bed using 3-D conformal RT with standard WBI and found an increased risk of poor cosmosis with APBI)[21].In the present study, the incidence of grade I dermatitis were 40% and 45.7% in group A &B respectively, Grade 2 dermatitis were 8.57% and 17% in both groups respectively (P<0.05) .The incidence of late skin toxicity was 5.7% and 14% in both groups (P>0.05)and that difference was statistically insignificant at time of closure of the study (30 months) .ELIOT trial compared 21 Gy intraoprative RT with electron to standard WBI (50 Gy /25 fractions) :At five years the rate of ipsilateral tumor bed recurrence was higher with intraoprative RT arm[22].In the current study, univariate analysis showed that patients in both groups had more or less similar 30 months over all survival rates (Fig 2) with nearly similar DFS rates Fig (1). In conclusion : In early stage invasive breast carcinoma (T1, T2 N0-N1 M0) after BCT, using of APBI technique compared to conventional WBI, after a median follow up 30 months, showed comparable results regarding (DFS, OAS& cosmotic results). These results suggest that APBI technique could achieved the goal of adjuvant radiation therapy in BCT without inferiority in DFS &OAS with comparable cosmotic results.More cases with longer follow up periods are needed for APBI technique to replace conventional WBI.

References

[1] Julian T.B., Costantino J.P., Vicini F.A., et al.Early Toxicity results with 3-D Conformal External Beam Therapy (CEBT) from the NSABP B-39/RTOG 0413 Accelerated Partial breast irradiation (APBI) trial.Int J Radiat Oncol Biol Phys 63(5) :1531-1537 .

[2] Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N. Eng. Med. 2010;362:513-20.

[3] Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). Int J Radiat Oncol Biol Phys. 2009; 74:987-1001.

[4] Bartelink H, Horiot JC, Poortmans PM, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. J. Clin Oncol. 2007, 25:3259-65.

[5] Werkhoven E, Hart G, Tlnteren H, et al. Nomogram to predict ipsilateral breast relapse based on pathology review from the EORTC 22881-10882 boost versus no boost trial. Radiother Oncol 2011; 100: 101-7

[6] Vaidya JS, Joseph DJ, Tobias JS, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomized, non-inferiority phase 3 trial. Lancet. 2010;376:91-102.

[7] Cox J.D., Stetz J., Pajak T.F.:Toxicity Criteria of the Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) .Int J Radiat Oncol Biol Phys.1995, 31:1341-1346.

[8] EBCTCG (2011). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10801 women in 17 randomized trials. Lancet, 378, 1707-1716.

[9] EBCTCG. (2014). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual data for 8135 women in 22 randomized trials. Lancet, 383, 2127-2135.

[10] Hughes, K. S., Schnaper, L. A., Bellon, J. R., et al. (2013). Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer: long term follow-up of CALGB 9343. J. Clin. Oncol., 31, 2382-2387

[11] Kunkler, I. H., Williams, L W., Jack, W., et al. (2013). The PRIME II trial wide local excision and adjuvant hormonal therapy ± postoperative whole breast irradiation in women ≥ 65-years with early breast cancer managed by breast conservation. San Antonio Breast Cancer Symposium. Abstract S2-01. Presented 11 December 2013.

[12] Hershman, D. L, Wang, X., McBride, R., et aL (2006). Delay initiating adjuvant radiotherapy following breast conservation surgery and its impact on survival Int. J. Radial. Oncol. Biol. Phys., 65, 1353-1360

[13] Vujovic O., Yu E., Cherian A., et al. (2006). Eleven-year follow-up results in the delay of breast irradiation after conservative breast surgery in node-negative breast cancer patients. Int. J. Radiat. Oncol Biol Phys., 64, 760-764
[14] Livi L, Borghesi S, Saivea C et al. (2009). Radiotherapy, timing in 4, 820 patients with breast cancer: University of Florence experience. Int. J. Radiat. Oncol. Biol. Phys., 73, 365-369
[15] Karlsson R, Gole B., Colleoni M. et al. (2011). Timing of radiotherapy and outcome in patients receiving adjuvant endocrine therapy. Int. J. Radiat. Oncol. Biol. Phys., 80, 398-402,
[16] Haviland J.S., Owen J.R., Dewar J.A. et al. (2013). The UK standardization of breast radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomized controlled trials. Lancet Oncol, 14, 1086-1094.
[17] FAST trialists group, Agrawal, R. K., Alhasso, A., et al. (2011). First results of the randomized UK FAST Trial of radiotherapy hypofractionation for treatment of early breast cancer (CRUKE/04/015). Radiother. Oncol, 100, 93-100.
[18] Brunt AM, Yarnold J, Wheatley D, et al (2013). Acute skin toxicity reported in the FAST-Forward trial (HTA 09/01/47): a phase III randomised trial of 1-week whole breast radiotherapy compared to standard 3 weeks in patients with early breast cancer. Presented at: 10th National Cancer Research Institute Cancer Conference; 2014 Nov 2-5; Liverpool, UK.
[19] Vaidya JS, Wenz F, Bulsara M, et al .(2012). Targeted intraoperative radiotherapy for early breast cancer: TARGIT-A trial- updated analysis of local recurrence and first analysis of survival. Cancer Res:72-100s.
[20] Vaidya J., Wenz E., Bukara M., et al. (2014). Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomized trial. Lancet, 383, 603-613.
[21] Olivotto I., Whelan T., Parpia, S. et al. (2013). Interim cosmetic and toxicity results from RAPID: a randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. J, Clin. Oncol, 31, 4038-4045.
[22] Veronesi U., Orrechia R., Maisonncuve P. et al. (2013). Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomized controlled equivalence trial. Lancet Oncol., 14, 1269-1277.