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Original Article

Accelerated Partial Breast Irradiation Using 3D Conformal Radiation Therapy versus Whole Breast Irradiation in Patients with Early Breast Cancer

Moawad M., Abdelhakim K.N., Gobran N.S., Gaballah A., Elebrashi M*.

Clinical Oncology and Nuclear Medicine Department, Faculty of medicine, Ain Shams University

ABSTRACT

Purpose/Objective(s): Accelerated partial breast irradiation (APBI) is an approach that treats only the lumpectomy bed plus 1-2 cm margin rather than the whole breast. By increasing the radiation fraction size and decreasing the target volume. APBI may be as effective as whole breast treatment, allowing shorter treatment courses and reducing side effects. Comparing ABPI vs whole breast irradiation (WBI) helps us to evaluate the efficacy, toxicity and cosmetic outcome after breast conserving treatment (BCT) with APBI using 3D conformal external beam radiation therapy (EBRT).

Materials/Methods: This is a phase III prospective randomized clinical trial including 62 women with early stage breast cancer, 31 of them received APBI using EBRT with a regimen of 4 Gy/ fraction, BID, 9 fractions /one week to a total dose of 36 Gy while the other 31 received conventional WBI during the period between August 2015 to December 2016, with a median follow up period of 18 months The patients' age ranged between 45 to 83 years with mean age 65.59±8.01 years. 59.6% of our cases (37 patients) of all the study cases had left sided breast cancer, while 21 patients (40.4%) had right sided breast cancer. Most of our cases 72.5 % of all the cases were Invasive ductal carcinoma, most of the patients (67.7%) were GII, with a median tumor size of 0.90 (0.1-2.70), only 4.8% were classified as T2. Data were analyzed with SPSS version 21. The normality of data was first tested with one-sample Kolmogorov-Smirnov test.

Results: The median follow up period for all patients was of 18 months, our results showed that there was no significant difference between the two study groups as regards cosmetic outcome, excellent cosmetic outcome was found in 7 patients in each group, good outcome in 17 in the APBI group vs 19 patients in the whole breast irradiation group, so we had 84% with good to excellent cosmetic outcome in the APBI group, fair in 4 vs 6 patients, while poor cosmetic outcome in 1 patient in each group, only 3.2% of the patients had grade 3 toxicities. There was no significant difference between the two study groups regarding local recurrence. There was a significant difference in the heart mean dose between the two groups, it was much less in the APBI group (P=0.008). Other factors as age, tumor pathology and type of systemic treatment were not significant

Conclusion: These data are consistent with the fact that breast cancer and the dose-limiting normal tissues respond similarly to change in radiotherapy fraction size. The study regimen of 36 Gy in 9 fractions was similar to the control regimen of 50 Gy in 25 fractions in terms of Loco-regional tumor control, skin toxicities, breast cosmetic outcome.

Keywords
Accelerated partial breast irradiation
3D conformal radiation
Whole breast irradiation
Early breast cancer

INTRODUCTION

Standard of care for early stage breast cancer is breast conserving surgery (BCS) plus radiation (RT) for women under age 70 and, for those over age 70, BCS with or without RT[1-4]. For patients with small tumors, partial breast irradiation (PBI) may be as effective as whole breast treatment, allowing shorter treatment courses and the potential for reduced side effects[5].

There is a significant shortage of radiation therapy machines in most regions, so can we achieve local control with radiation therapy delivered only to the area at highest risk of recurrence, if so, radiation could be delivered in a significantly shortened period, thereby, potentially making the BCS option available and attracting to more women. This is the concept of accelerated partial breast irradiation[6].

Many studies reported that 44% to 86% of local recurrence occurs close to the tumor bed. An additional advantage to accelerated partial breast irradiation (APBI) is a decreased dose to normal tissue such as heart & lung[7]. Accelerated partial breast irradiation (APBI) is generally defined as radiation therapy that uses daily fraction doses greater than 2 Gy delivered in less than 5 weeks[8].

The goal of APBI is to irradiate disease in the tumor bed and immediately surrounding tissues, while minimizing and/or eliminating exposure of nearby normal tissues such as heart, lung, and normal breast tissue. Treating smaller target volumes also allows the possibility of fractionation schedules that can substantially reduce the overall time of treatment[9].

Accelerated partial breast irradiation is an approach that treats only the lumpectomy bed plus 1-2 cm margin rather than the whole breast[10]. By increasing the radiation fraction size and decreasing the target volume, this technique allows the treatment to be accomplished in a shorter period[11]. Shaitelman et al[12] showed increased utilization of APBI from 3.8% of breast cancer radiation in 2004 to 10.6% in 2011.

The primary objective of this study was to evaluate the efficacy, toxicity and cosmetic outcome of breast conserving treatment (BCT) with accelerated partial breast irradiation APBI using 3D conformal external beam radiation therapy and compare APBI versus WBI.

METHODS

Patients Selection

We performed a phase III prospective randomized clinical trial of early stage breast women who aged between 45 and 85 years with pathologically proved breast cancer after breast conservative surgery (invasive & DCIS), we included patients with tumor size less than or equal 4 cm with negative surgical margins and negative lymph node breast cancer. This trial was conducted in Clinical Oncology and Nuclear Medicine Department, Ain Shams University Hospitals during the period between August 2015 to December 2016, with a median follow up period of 18 months.

The study populations were divided into 2 subgroups each consist of equal number of patients, the APBI group (Group I) and WBI group (Group II). Group 1:Intervention group (31 patients), patients in this group were treated with APBI 36 Gy, 4 Gy per fraction delivered twice daily using 3D conformal radiotherapy in 9 fractions over 5 consecutive days. Group 2: Control group (31 patients) were treated by WBI 50 Gy delivered to the whole breast in daily fraction of 2 Gy per fraction for 5 consecutive days for 5 weeks, with 10 Gy boost to the tumor bed using 3D conformal radiotherapy.

Data collection and Endpoints

During treatment, Patients were weekly evaluated as regarding acute reactions during treatment according to RTOG Radiation Morbidity Scoring System. All patients were evaluated every 3 months for 18 months as the routine FU. During the follow-up visits, toxicity results and late radiation side effects will be graded according to the RTOG/EORTC scale.

Primary end points were development of radiation toxicity and its severity, while secondary end points were Loco-regional failure and distant failure, cosmetic outcome were assessed by Harvard scoring system. Harvard Scale [13] for cosmetic outcome, in which excellent outcome is that the treated breast nearly identical to the untreated breast, while good is that the treated breast slightly different than untreated breast, fair is the treated breast clearly different than untreated one but not seriously distorted, while poor is the treated breast seriously distorted.

Statistical Analysis

Data were analyzed with **SPSS** version 21. The normality of data was first tested with one-sample Kolmogorov-Smirnov test. Qualitative data were described using number and percent. Association between categorical variables was tested using Chi-square test while Fischer exact test was used when expected cell count less than 5. Continuous variables were presented as mean ± SD (standard deviation) for parametric data and median for non-parametric data. The two groups were compared with Student t test for parametric data and Mann Whitney test for non-parametric.

RESULTS

The age of patients included in this study ranged between 45 to 83 years with mean age 65.59±8.01 years. Our results showed that 21 patients (67.7%) of those who received APBI were left sided, while there were 16 patients (51.6%) in those who received WBI, 37 patients (59.6%) of all the study cases had left sided breast cancer, while 21 patients (40.4%) had right sided breast cancer. Most of our cases 72.5 % of all the cases were Invasive ductal carcinoma, most of the patients (67.7%) were GII, with a median tumor size of 0.90 (0.1-2.70), only 4.8% were classified as T2**. (Table 1)**

Table 1. Patient characteristics:

Variables	Group I (n=31)		Group II (n=31)		Test of significance	p-value
	No	%	No	%		
Age/years						
Mean ± SD	65.67±8.43		65.51±7.71		t=2.59	0.274
Min-Max	52.00-83.00		45.00-80.00			
BMI						
Mean ± SD	26.21±5.33		27.65±5.70		t=0.99	0.324
Min-Max	18.08-41.43		16.50-46.50			
Obesity						
Obese	7	22.6	8	28.6	c^2=0.28	0.598
Non-obese	24	77.4	20	71.4		
Comorbidities	23	74.2	18	58.1	1.80	0.180
HTN	13	41.9	14	45.2	0.066	0.798
DM	3	9.7	3	9.7	FET	1.0
Ex-Smoker	6	19.4	0	0	FET	0.024*
OCO	6	19.4	6	19.4	0.0	1.0
Hypothyroidism	5	16.1	7	22.6	0.413	0.520
Cardiac	4	12.9	4	12.9	FET	1.0
Tumor laterality						
Right	10	32.3	15	48.4	c^2=2.38	0.123
Left	21	67.7	16	51.6		
Biopsy pathology						
DCIS	2	6.5	6	19.4		
IDC	25	80.6	20	64.4	5.63	0.344
ILC	1	3.2	2	6.5		
Mixed invasive ductal &lobular	3	9.7	3	9.7		
Grade						
GI	10	32.3	8	25.8	0.317	0.853
GII	20	64.5	22	71.0		
GIII	1	3.2	1	3.2		
TNM						
TisN0M0	1	3.2	6	19.4		
T1aN0M0	4	12.9	1	3.2	5.75	0.218
T1bN0M0	13	41.9	13	41.9		
T1cN0M0	11	35.5	10	32.3		
T2N0M0	2	6.5	1	3.2		
Tumor size						
Median (Min-Max)	0.90 (0.10-2.20)	0.90 (0.1-2.70)	Z=0.401	0.688		

FET: Fischer exact test

Table 2. Adverse effects of radiotherapy and cosmetic outcome

Variables	Group I (n=31)		Group II (n=31)		c^2	p-value
	No	%	No	%		
Arm Lymphedema	10	32.3	11	35.5	0.072	0.788
Radiation Pneumonitis	0	0	1	3.2	FET	1.0
Skin reaction	25	80.6	25	80.6	-	-
G0	6	19.4	6	19.4		
G1	21	67.7	24	77.4	2.00	0.368
G2	4	12.9	1	3.2		
Cosmetic outcome						
Excellent	7	22.6	7	22.6		
Good	19	61.3	17	54.8	0.51	0.916
Fair	4	12.9	6	19.4		
Poor	1	3.2	1	3.2		

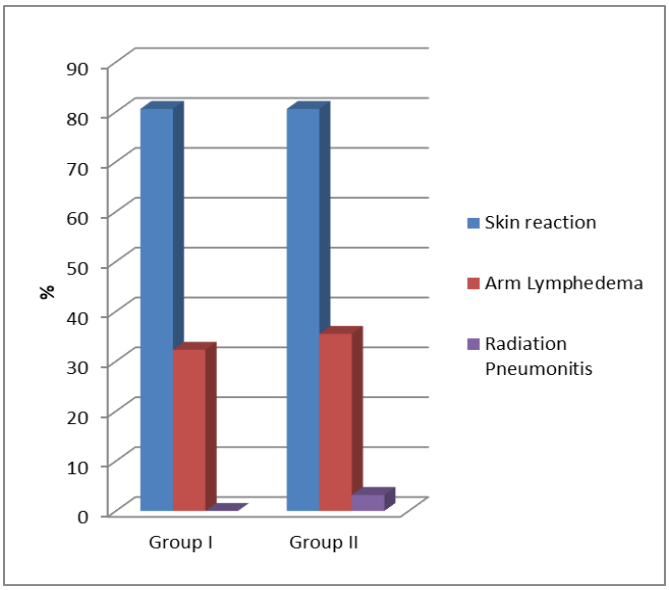

Figure 1. Adverse effects of radiotherapy.

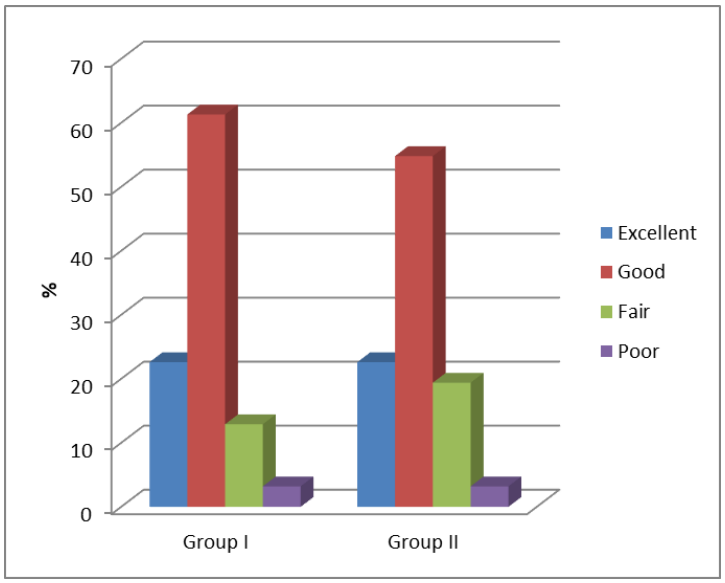

Figure 2. Cosmetic outcome

Table 3. Heart mean dose and Lung V20 in DVH

Variables	Study group (n=31)	Control group (n=31)	Z	p-value
DVH Heart mean dose	0.08 (0.00-1.00)	0.37 (0.00-1.24)	2.637	0.008*
Lung V20	0.38 (0.00-1.82)	0.38 (0.00-1.82)	0.289	0.773

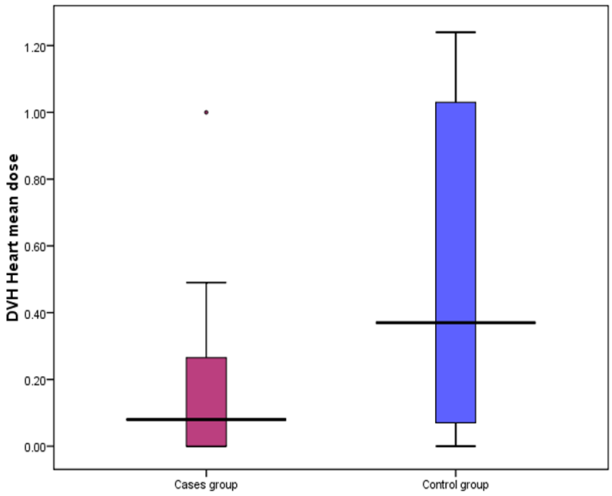

Figure 3. DVH Heart mean dose

Table 4. Local recurrence and distant metastasis

Variables	Group I (n=31)		Group II (n=31)		c^2	p-value
	No	%	No	%		
Local Recurrence						
Yes	0	0	1	3.2		
No	31	100	30	96.8	FET	1.0
Distant metastasis						
Yes	1	3.2	1	3.2		
No	30	96.8	30	96.8	FET	1.0

Of 62 patients, 10 patients who received APBI (32.3%) while 11 patients who received WBI developed arm lymphedema, 25 patients of the APBI group had different grades of skin reaction, 21 with G1 while 4 patients had G2 skin reaction, the same number of patients in the WBI group had skin reaction, 24 patients had G1 while only 1 patient had G2 skin reaction, 1 patient developed radiation pneumonitis in the WBI group. as regards cosmetic outcome, excellent cosmetic outcome was found in 7 patients in each group, good outcome in 17 in the APBI group vs 19 patients in the whole breast irradiation group, fair in 4 vs 6 patients, while poor cosmetic outcome in 1 patient in each group

Our results showed that there is a significant difference in the heart mean dose between the APBI group and the WBI group, as the heart received much lesser dose in the APBI group

There was no Local Recurrences in those who received APBI (group I), while only one patient in those who received WBI (had local recurrence. **Table 4** shows that there was no significant difference between the two study groups as regards local recurrence as well as regarding distant metastasis as each group had one patient who developed distant metastasis

DISCUSSION

In our study, we enrolled 62 patients with invasive or in situ breast cancer ≤ 4cm after BCS with negative margins and negative ALND or SLND. Women age was > 45 years with a mean age of 65.59±8.01 and the age ranged between 45 to 83 years and all cases were Postmenopausal at the time of diagnosis, In RAPID trial, they enrolled women of age > 40 years[10].

After a median follow up of 18 months, our results show that there was no significant difference between the two study groups as regards cosmetic outcome, excellent cosmetic outcome was found in 7 patients in each group, good outcome in 17 in the APBI group (group I) vs 19 patients in the whole breast irradiation group (group II), fair in 4 vs 6 patients, while poor cosmetic outcome in 1 patient in each group. In comparison to the RAPID trial the median follow-up was 36 months. Adverse cosmesis at 3 years was increased among those treated with APBI compared with WBI as assessed by trained nurses (29% v 17%; P < .001), by patients (26% v 18%; P = .0022), and by physicians reviewing digital photographs (35% v 17%; P < .001). Grade 3 toxicities were rare in both treatment arms (1.4% v 0%), but grade 1 and 2 toxicities were increased among those who received APBI compared with WBI (P < .001) [10]. This might be due to the smaller sample size in our study.

Three trials explored dose escalation using interstitial brachytherapy for APBI at the Careggi Hospital (Florence, Italy), Royal Devon and Exeter Hospital (Exeter, England), and, again, Guy's Hospital (London, United Kingdom). Similarly, these studies included patients with unknown or positive margins, resulting in high local recurrence rates [14]. Around the same time period, the Milan group reported a much lower local recurrence rate of 4.8% with WBI [15] In our study, there was no significant difference between the two study groups regarding local recurrence. This might be due to shorter follow up period as our patients were followed up for 18 months.

RTOG 0319, a phase I/II trial, the 4-year estimates of local recurrence, DFS, and OS were 6%, 84%, and 96%, respectively. Only 4% of patients suffered grade 3 toxicities [16] our results showed only 3.2% of the patients had grade 3 toxicities.

Bush et al.,[17] reported the 5 year results of a phase II trial using proton beam radiation to deliver APBI in patients with invasive non-lobular carcinoma, the 5-year actuarial rates of local recurrence, DFS, and OS were 97%, 94% and 95%, respectively. There was no grade 3 or higher acute skin reactions, and patient and physician reported that cosmetics outcome was good to excellent in 90%. In our study, we had 84% with good to excellent cosmesis.

In another study, the University of Florence (Florence, Italy) recently reported the result of a phase III randomized controlled trial comparing IMRT vs WBI. At a median follow-up of 5.0 years, the ipsilateral breast tumor recurrence rate was 1.5% in the APBI and WBI groups. The 5-year OS was 96.6% for the WBI group and 99.4% for APBI group. Patients treated with APBI demonstrated significantly less acute and late toxicity and better cosmetic outcome [18]. Our results showed that there was no significant difference between the two study groups regarding both cosmetic outcome and local recurrence.
Two hundred and forty-two patients between 2004 and 2014 with early breast cancer treated with APBI were compared to 59 matched patients treated with WBI from 2012 to 2014. They were evaluated with modified Functional Assessment of Chronic Illness Therapy breast quality of life questions which measured pain, lymphedema, energy level, self-consciousness, and breast cosmesis. Compared to APBI eligible patients treated with WBI, the APBI cohort experienced significantly better lymphedema (P = 0.0002), self-consciousness (P = 0.0004), and energy level (P = 0.009) scores during the first year after treatment. The APBI group reported significantly better breast cosmesis during the second year after treatment. There were no significant differences in the recurrence rates (P > 0.05)[19]. Moreover, analyses of late toxicities and cosmesis of patients treated with APBI on RTOG 0319 demonstrated good to excellent cosmesis in 82% and 64% of patients at 1 year and 3 years, respectively. When questioned at 3 years, 31 patients were satisfied with their treatment, 5 were not satisfied but would choose 3D-CRT again, and no patients would elect standard radiation therapy[20].

In addition, Chang etal,[21] reported results of prospective study of 30 patients treated with 3D conformal RT in equivalent 6 fractions delivered daily over 5 consecutive days. At 59 months of median follow-up, no patients had local or metastatic recurrence, and all patients were alive at the last follow-up. Qualitative physician cosmetic assessments of good to excellent were 69% at 3 years.

Other groups are investigating alternative external beam fractionation regimens. The ACCEL Trial (NCT0 2681107), sponsored by AHS Cancer Control Alberta, is a phase II study evaluating patients treated with EBRT APBI to a prescribed dose of 27 Gy over 5 fractions delivered daily. The Mayo Clinic is sponsoring a phase II trial evaluating APBI given in 3 fractions of 7.3 Gy using EBRT or 7 Gy using catheter-based brachytherapy. APBI has gained acceptance for appropriately selected cases of early stage breast cancer, as outlined by current guidelines.

In addition to all the benefits of APBI, it is important to consider other factors, such as socioeconomic issues. Shah et al[22] reported results of cost efficacy of multiple APBI techniques compared with WBI, their analyses included cost minimization, incremental cost-effectiveness ratio (ICER), and cost per quality adjusted life year (QALY) analyses

In conclusion, our data are consistent with the fact that breast cancer and the dose-limiting normal tissues respond similarly to change in radiotherapy fraction size. The study regimen of 36 Gy in 9 fractions was similar to the control regimen of 50 Gy in 25 fractions in terms of Loco-regional tumor control, skin tox-

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