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Scientific Article

Comparison of Toxicity and Cosmetic Outcomes After Accelerated Partial Breast Irradiation or Whole Breast Irradiation Using 3-Dimensional Conformal External Beam Radiation Therapy

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Abstract

Purpose: To compare rates of acute and late skin toxicities and cosmetic outcomes after accelerated partial breast irradiation (APBI) or whole breast irradiation (WBI) using 3-dimensional conformal external beam radiation therapy in women with breast cancer after breast conservation surgery (BCS).

Methods and Materials: Women >35 years of age with invasive or noninvasive breast cancer ≤4 cm treated by BCS were randomized to 3D-CRT APBI (34 Gy/10 fractions/5 days) or WBI (40 Gy/16 fractions/3 weeks ± boost irradiation). The primary outcome was ipsilateral breast tumor recurrence. Important secondary outcomes were skin toxicities using Radiation Therapy Oncology Group scores, Late Effects Normal Tissue Task Force and Subjective, Objective, Management, Analytic scales, and adverse cosmetic outcome. This interim analysis focuses on the secondary endpoints of radiation toxicities and cosmesis. Patient and tumor characteristics and rates of adverse cosmetic outcomes and skin toxicities were compared using Fisher exact tests. All statistical tests were 2 sided, with $P < .05$ considered statistically significant.

Results: Between June 2011 and December 2015, 133 women with breast cancer were randomized to 3D-CRT APBI or WBI. Patient and tumor characteristics were balanced between the 2 arms. Median follow-up was 60 months (range, 12-93 months). Grade 4 late toxicity was not seen in either of the treatment arms, and grade 3 toxicity was very low for each endpoint assessed in both the groups. The rates of grade ≥2 acute dermatitis were 8% and 15%, respectively, for APBI and WBI ($P = .18$). Rates of grade ≥1 late radiation toxicities were higher in the WBI arm compared with the APBI arm for breast shrinkage ($P = .008$), pigmentation ($P = .028$), fibrosis ($P = .040$), induration ($P = .048$), and edema ($P = .33$). Adverse cosmesis at last follow-up was significantly higher in patients treated with WBI: 33% compared with 6% with APBI ($P < .001$).

Conclusions: In women with breast cancer after BCS, APBI was associated with better cosmetic outcome and fewer late radiation toxicities than WBI.

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Introduction

Breast conservative therapy (BCT) has been proven as effective as mastectomy in patients with early breast cancer.[1,2] Adjuvant whole breast irradiation (WBI) is an important part of BCT. Accelerated partial breast irradiation (APBI) is an alternative to WBI in selected patients with breast cancer after breast conservation surgery (BCS). It is delivered to the primary tumor cavity with a uniform 3-dimensional (3-D) margin of normal breast tissue. The rationale is that most breast cancer local relapses occur within a few centimeters of the primary tumor within the breast. It is one of the shortest hypofractionation radiation therapy schedules in patients with breast cancer after BCS and is delivered in 5 days.

Many studies with different APBI techniques and dose fractionations have been published in the past decade.[3-24] Brachytherapy is one of the oldest APBI techniques introduced in selected patients with breast cancer, but it is invasive and resource intensive and requires additional expertise for its application.[14,25] Other modalities of APBI have produced debatable outcomes (TARGIT [targeted intraoperative radiotherapy; inadequate dose] and ELIOT [electron intraoperative radiotherapy; improper patient selection]).[26,27] Intraoperative radiation therapy, which is delivered within a cavity, may also produce dose heterogeneity within the irradiated volume. There could also be implant inconsistency, and the gradient with brachytherapy is very sharp. The strain to the tissue during applicator insertion and trauma from catheter and needle insertion is likely to heal with fibrosis, which may compromise the cosmetic outcome of BCT. Long-term outcomes with low-dose-rate APBI have produced high rates of severe late complications (moderate to severe fibrosis, fat necrosis, and telangiectasias in >50%, 35%, and 35% of patients, respectively).[28]

Three-dimensional conformal external beam radiation therapy (3D-CRT) is widely available and can also be used for APBI. APBI with 3D-CRT is usually delivered 4 to 6 weeks after surgery. By this time the surgical cavity is filled and there is no air, so dose distribution is homogenous within the breast tissue. 3D-CRT APBI complications decrease with time, but the brachytherapy APBI complication rate increases. If an optimal schedule of 3D-CRT APBI is delivered, it may lead to best outcomes in select women with breast cancer. There are good data on APBI with interstitial techniques, but data with 3D-CRT are lacking. APBI with 3D-CRT is noninvasive and linear accelerator based, delivered with modern techniques, and may be less costly. Different studies have reported outcomes with APBI,[7-13] and few have reported unfavorable outcomes for cosmesis.[16-19]

This study was designed to compare APBI with WBI after BCS in women with breast cancer. The primary endpoint was ipsilateral breast tumor recurrence. Our hypothesis was that local recurrence rates, toxicity, cosmetic outcomes, and disease-free and overall survival would be similar between a 10-fraction APBI schedule and WBI in 16 fractions. At the time of this analysis, there were insufficient numbers of patients with documented local recurrences to perform a definitive analysis of the primary endpoint. Therefore, this interim report focuses on the secondary endpoints of acute and late skin toxicities and cosmetic outcomes.

Materials and Methods

The trial protocol was approved by the institutional ethics committee, and informed consent was obtained from all patients. Eligibility criteria were as follows: invasive ductal carcinoma; age >35 years; unifocal tumor; primary tumor size ≤4 cm (pT2); cN0, pN0-1 axillary nodes; and any histologic grade. Exclusion criteria were previous ipsilateral or contralateral breast cancer; bilateral breast cancer; synchronous or other prior malignancies; lobular histology (in situ or invasive); presence of an extensive intraductal component; microscopically positive or close (2 mm) surgical margins; multicentric disease; concurrent or neoadjuvant chemotherapy; and seroma collection that required repeated aspirations.

Patients were randomized using a computer-generated randomized list to receive 3D-CRT APBI (34 Gy in 10 fractions given twice daily) or WBI (40 Gy in 16 fractions given once daily ± boost irradiation). The boost dose was 10 to 16 Gy in 5 to 8 fractions over 1 to 1.5 weeks in sequence with WBI.

Radiobiologic rationale

From clinical data we know that the radiobiological parameter of α/β ratio for breast cancer is low. For acute skin effects the α/β is 10, and for late skin effects the α/β is 3; the biological effective dose (BED) of APBI in 34 Gy/10 fractions/5 days for acute and late skin effects is 45.5 Gy and 72.5 Gy_3, respectively. BED of WBI in 40 Gy/16 fractions/3 weeks for acute and late skin effects is 50 Gy and 73.3 Gy_3. With boost of 10 Gy/5 fractions/5

days, it is 62 Gy and 89.9 Gy_3; for 16 Gy/8 fractions/1.5 weeks, it will be 69.2 Gy and 99.9 Gy_3, respectively.

Simulation and treatment planning

All patients underwent noncontrast computed tomography (CT) simulation on a breast board in supine position for treatment planning and delivery. Radiopaque wires were used to outline the borders of the breast as marked by the radiation oncologist. CT images were then taken at 2.5-mm slice thickness from the mandible to the lung bases. The breast volume was defined as the tissue bounded by the cranial and caudal and medial and lateral wires, the skin, and 5 mm anterior to the lung–chest wall interface on each CT slice. A wire was also used to mark the scar.

The contouring was done by 1 radiation oncologist to avoid interobserver variability. If surgical clips were placed, they were used to delineate the cavity. If clips were not placed, information from the mammography/ultrasound, patient and surgical notes, and imaging changes were used to contour the cavity. The clinical target volume (CTV) was defined by 1 cm margin from the cavity. CTV excluded 5 mm of skin and the chest wall muscles. The planning target volume (PTV) and organs at risk (OARs) were contoured on all CT slices. PTV was defined as a 1 cm margin from the CTV. The PTV excluded the first 5 mm of skin and chest wall muscles. The heart, lungs, contralateral breast, esophagus, and spinal cord were also contoured by a radiation oncologist.

The number of fields and angles were decided by of the radiation oncologist with the help of physicist and were determined by 3-D conformal planning to produce the optimal treatment plan according to volume definitions as described in the next paragraph. The treatment plan generated for individual patient was analyzed by dose-volume histogram of the PTV and OARs.

Dose-volume constraints

Manual optimization was done by adjusting beam weights to cover the PTV by the $\geq$95% isodose line while maintaining a hot spot of $<$105%. In the WBI arm, 40 Gy in 16 fractions was delivered to the whole breast in daily fractions of 2.5 Gy (5 fractions/week), with or without an additional 10 to 16 Gy in 5 to 8 fractions to the tumor bed in some cases (depending on risk factors for local recurrence), in a sequential manner. The plans were normalized such that 95% of the prescription dose (38 Gy and 47.5-53.2 Gy) was delivered to at least 95% of the $PTV_{breasteval}$ and $PTV_{boosteval}$ with a maximum dose to the boost of 107% (53.5-59.92 Gy). In the APBI arm, the dose delivered was 34 Gy in 10 fractions over 5 days in 2 fractions per day at an interval of 6 hours.

Portal images of each beam and an orthogonal (anteroposterior) image were taken for the first and second fractions. Subsequent images were taken weekly. Additional individual portal images could be taken at the radiation oncologist's discretion.

Dosimetric values were recorded as per Radiation Therapy Oncology Group (RTOG) 0413/National Surgical Adjuvant Breast and Bowel Project (NSABP) B-29 protocol.[21,22] Less than 10% of the ipsilateral lung should receive 30% of the prescribed dose, and less than 10% of the contralateral lung should receive 5% of the prescribed dose. The contralateral breast should receive $<$3% of the prescribed dose to any point. For right-sided lesions, $<$5% of the heart should receive 5% of the prescribed dose. For left-sided lesions, the volume of the heart receiving 5% of the prescribed dose (V5) should be less than the V5 for treatment using conventional WBI with tangential fields. Less than 50% of the whole uninvolved normal breast should receive $\geq$50% of the prescribed dose, and $<$25% of the whole breast should receive the prescribed dose.

Follow-up, toxicity, and cosmesis

Follow-up visits were done by the treating radiation oncologist weekly for the first 4 weeks; at 1, 3, 6, and 12 months after completion of radiation therapy; and at yearly intervals thereafter. Mammography was performed yearly. Relevant investigations were performed if there was any symptom of local recurrence or distant metastases.

Radiation toxicities and cosmesis were assessed directly by a radiation oncologist at baseline and at each follow-up visit. The values presented are the patient's worst toxicity at any time point.

Acute and late radiation toxicities were assessed using the RTOG scores and Late Effects Normal Tissue Task Force and Subjective, Objective, Management, Analytic scales. The primary late toxicities of interest were pigmentation, fibrosis, breast shrinkage, induration, and edema.

Cosmetic outcomes were assessed using the Harvard/NSABP/RTOG scoring scale, a 4-point scale of breast cosmesis. The criteria for the scores are as follows:

I. Excellent: Compared with the untreated breast, there is minimal or no difference in the size or shape of the treated breast. The way the breasts feel (texture) is the same or slightly different. There may be thickening, scar tissue, or fluid accumulation within the breast, but not enough to change the appearance.
II. Good: There is a slight difference in the size or shape of the treated breast compared with the opposite breast or the original appearance of the

treated breast. There may be some mild reddening or darkening of the breast. The thickening or scar tissue within the breast causes only a mild change in the shape or size.

III. Fair: Obvious difference in the size and shape of the treated breast. This change involves one-quarter or less of the breast. There can be moderate thickening or scar tissue of the skin and the breast, and there may be obvious color changes.

IV. Poor: Marked change in the appearance of the treated breast involving more than one-quarter of the breast tissue. The skin changes may be obvious and detract from the appearance of the breast. Severe scarring and thickening of the breast, which clearly alter the appearance of the breast, may be found.

Fair or poor scores were considered adverse cosmetic outcomes.

Statistical considerations

The primary endpoint of this noninferiority study was local recurrence, defined as any histologically confirmed cancer tissue in the treated breast. It was hypothesized that the local recurrence rate for APBI would be noninferior to the local recurrence rate for WBI. It was assumed that the 5-year local recurrence rate for WBI would be approximately 5% and that any 5-year local rate less than 15% for APBI would be considered noninferior. If the distribution of time to local recurrence follows exponential distributions in each treatment arm, the noninferiority boundary (5-year local recurrence rates of 5% and 15%) corresponds to a hazard ratio of 3.168. A total of 19 local recurrences would need to be observed to have 80% power to reject the null hypothesis that APBI treatment is inferior to WBI treatment (nQuery, 2017; sample size and power calculation; Statsols, Statistical Solutions Ltd, Cork, Ireland). The target sample size was approximately 60 patients in each treatment. Follow-up would continue until at least 19 local recurrences had been observed.

Patient and tumor characteristics and rates of skin toxicities and adverse cosmetic outcomes were compared using Fisher exact tests. All statistical tests were 2-sided, with $P < .05$ considered statistically significant.

Results

Between June 2011 and December 2015, 133 women were randomized to receive 3D-CRT APBI or WBI. Patient and tumor characteristics were balanced between 2 arms (Table 1). Mean age was 50 years in both arms. One-third of the patients were <50 years of age in both the arms. Median follow-up was 60 months (range, 12-93 months). Chemotherapy was given in 35 (54%) and 51 (76%) patients in APBI and WBI arms, respectively.

Table 1 Patient and tumor characteristics

Characteristic	APBI (N = 65) n (%)	WBI (N = 67) n (%)	*P* value Fisher exact test
Age (y)			
Mean (range)	50 (32-75)	50 (27-67)	.16
≥50	42 (65)	37 (55)	
40-49	17 (26)	27 (40)	
<40	6 (9)	3 (4)	
T stage			
T1	34 (52)	36 (54)	1.00
T2	28 (43)	28 (42)	
T3	3 (5)	3 (4)	
N stage			
N0	57 (88)	58 (87)	1.00
N1	7 (11)	8 (12)	
N2	1 (2)	1 (1)	
Grade			
1	14 (22)	12 (18)	.92
2	37 (57)	39 (58)	
3	14 (22)	16 (24)	
Surgical margins			
Negative	60 (92)	60 (90)	.76
Positive	5 (8)	7 (10)	
Lymphovascular invasion			
No	56 (86)	55 (82)	.64
Yes	9 (14)	12 (18)	
Extracapsular extension			
No	64 (98)	65 (97)	1.00
Yes	1 (2)	2 (3)	
Estrogen receptor			
Positive	42 (69)	44 (68)	1.00
Negative	19 (31)	21 (32)	
Unknown	4	2	
Progesterone receptor			
Positive	38 (62)	39 (62)	1.00
Negative	23 (38)	24 (38)	
Unknown	4	4	
HER2-neu			
Positive	7 (12)	6 (10)	1.00
Negative	53 (88)	52 (90)	
Unknown	5	9	
Chemotherapy			
Yes	35 (54)	51 (76)	.09
No	30 (46)	16 (24)	
Hormone therapy			
Yes	49 (75)	48 (72)	.70
No	16 (25)	19 (28)	
Trastuzumab			
Yes	3 (43)	3 (50)	1.00
No	4 (57)	3 (50)	
Unknown	58	61	

Abbreviations: APBI = accelerated partial breast irradiation; WBI = whole breast irradiation.

Hormonal therapy was given in 49 (75%) and 48 (72%) patients in APBI and WBI arms, respectively. Trastuzumab was given to 3 patients in each arm. One patient each in the APBI and WBI arms also received nodal radiation, with a dose of 40 Gy in 16 fractions over 3 weeks.

Grade 4 toxicity was not seen in either of the treatment arms, and grade 3 toxicity was very low for each endpoint assessed in both the groups. Grade 3 acute skin toxicity was observed in only 1 patient (2%) in each group. The rates of acute grade ≥2 dermatitis were 8% and 15%, respectively, in the APBI and WBI arms ($P = .18$, Table 2).

There was only 1 grade 3 late toxicity with WBI. There was no late grade 3 toxicity with APBI. Rates of grades ≥1 late radiation toxicities were higher in the WBI arm compared with the APBI arm (Table 3). Grade ≥2 induration was significantly higher in the WBI arm (9 patients [13%]) compared with the APBI arm (3 patients [5%]; $P = .048$). Grade ≥1 edema was reported in 5 (8%) patients with APBI and in 10 (15%) patients with WBI ($P = .33$; Table 3). Grade 2 pigmentation was not seen in any patient treated with APBI compared with 6 patients (9%) with WBI ($P = .028$). Grade 2 fibrosis and breast shrinkage were reported in 2 (3%) versus 8 (12%) patients ($P = .040$) and 1 (2%) versus 5 (7%) patients in the APBI and WBI arms, respectively ($P = .008$). Grade 4 late toxicity was not seen in any of the treatment arms. Similarly, no fat necrosis was observed in the present study.

Adverse cosmesis at last follow-up was significantly higher in patients treated with WBI (22 patients [33%] compared with 4 patients [6%] with APBI; $P < .001$; Table 4). Excellent cosmesis was reported more often in patients with APBI compared with WBI. Excellent cosmesis was observed in 38 (58%) patients with APBI compared with 28 (42%) with WBI.

Table 2 Acute radiation toxicity

	APBI N = 65 n (%)	WBI N = 67 n (%)	*P* value Fisher exact test
None	44 (68)	38 (57)	.42
G1	16 (25)	19 (28)	.27
G2	4 (6)	9 (13)	
G3	1 (2)	1 (2)	
None/G1	60 (92)	57 (85)	
G2/G3	5 (8)	10 (15)	

Abbreviations: APBI = accelerated partial breast irradiation; WBI = whole breast irradiation.

Discussion

The present study showed that APBI might be an appropriate alternative to WBI in selected patients with breast cancer. At a median follow-up of 5 years, APBI was associated with better cosmetic outcome and fewer acute and late radiation toxicities compared with WBI. More patients in the APBI arm had excellent cosmesis compared with the WBI arm. More adverse cosmesis was seen in the WBI arm. The fractionation schedule used in this study was less per dose (3.4 Gy) and less total dose (34 Gy) than what was used in the external beam APBI regimens of RAPID[17] and NSABP B-39/RTOG 0413[19] at 38.5 Gy in 10 fractions twice daily; this may be the reason for fewer side effects than with WBI and in other published APBI external beam studies. Hence, if we later find noninferiority in efficacy of our regimen compared with WBI, it may be an appropriate alternative to WBI in selected patients with breast cancer.

In a similar study by Rodríguez et al, APBI reduced grade 2 acute dermatitis from 62.7% to 17.4% and reduced radiation doses to OARs in comparison to WBI ($P < .01$). Cosmetic outcomes at 5 years were reported to be excellent/good in >75% and >84% of patients in the APBI and the WBI arms, respectively. There was no grade 3 late skin toxicity in either group.[12] In the present study acute grade ≥2 dermatitis was reduced from 15% with WBI to 8% with APBI. Late grade 2 toxicities were also significantly less in the APBI arm in our study. A single-arm study of APBI with 3D-CRT by Chen et al reported 3% grade 3 fibrosis and 89% excellent or good

Table 3 Late skin toxicity

Toxicity	APBI (N = 65) n (%)	WBI (N = 67) n (%)	*P* value Fisher exact test
Induration			
None	49 (75)	37 (55)	.038
G1	13 (20)	21 (31)	
G2/G3	3 (5)	9 (13)	
Edema			
None	60 (92)	57 (85)	.31
G1	5 (8)	8 (12)	
G2	0	2 (3)	
Pigmentation			
None	59 (91)	52 (78)	.024
G1	6 (9)	9 (13)	
G2	0	6 (9)	
Fibrosis			
None	50 (77)	39 (58)	.44
G1	13 (20)	20 (30)	
G2	2 (3)	8 (12)	
Breast shrinkage			
None	52 (80)	37 (55)	.005
G1	12 (18)	25 (37)	
G2	1 (2)	5 (7)	

Abbreviations: APBI = accelerated partial breast irradiation; WBI = whole breast irradiation.

Table 4 Cosmesis

Cosmetic outcome	APBI (N = 65) n (%)	WBI (N = 67) n (%)	*P* value Fisher exact test
Excellent/good	61 (94)	45 (67)	<.001
Fair/poor	4 (6)	22 (33)	

Abbreviations: APBI = accelerated partial breast irradiation; WBI = whole breast irradiation.

cosmesis at 4 years. In the present study there was no grade 3 fibrosis, and grade 2 fibrosis was reported in only 3% of patients. This may be due to higher APBI dose used in these studies (38.5 Gy in 3.85 Gy per fraction). Median patient age was 62 years.[13] In contrast, we used a dose of 34 Gy in 3.4 Gy per fraction. Mean age in the present study was 50 years.

Other studies have also demonstrated similar outcomes with APBI compared with WBI. Polgar et al randomized 258 patients to APBI and WBI.[14] They reported grade 3 fibrosis in 2.2% of patients, whereas no grade 3 fibrosis was observed in the present study. The grade 2 induration rate of 5% in our study is also comparable with their study at 7% with partial breast radiation (PBI). Another study by the same authors reported grade 2 fibrosis in 6% patients with APBI, which is higher than the present study's rate of 3% only.[15] However, the excellent/good cosmetic outcome in the present study is better than in the PBI arm (77.6% vs 94%) of the study by Polgar et al. It is also better than the WBI arm with conventional fractionation by Polgar et al: 68% compared with 63% in our study with hypofractionated WBI.[15] This might be due to different modalities of APBI and dose fractionation schedules used in the studies.

In a study by Julian et al the reported rates of fibrosis—cosmesis and fibrosis—deep connective tissue toxicities were 12% grade ≤2 and 3% grade ≤3 with 3D-CRT.[16] Grade 2 fibrosis rates in our study were only 3%. There was no grade 3 fibrosis in the present study. Similarly, in the RAPID trial, APBI with 3D-CRT increased rates of adverse cosmesis from 17% to 29% at 3 years (P <.001) and increased late radiation toxicity compared with standard WBI.[17] In these studies, the total dose delivered was 38.5 Gy and the majority of women were >50 years of age, which might have contributed to these adverse cosmetic outcomes.[14,16] In the Innovazioni nella Radioterapia della Mammella (IRMA) trial, acute (1.4% vs 0%) and late toxicities (1.2% vs 1.5%) and adverse cosmesis (19% vs 20%) were comparable in both the arms with WBI of 50 Gy/25 fractions/5 weeks and APBI of 38.5 Gy/10 fractions/5 days, respectively.[18] The adverse cosmesis in this trial was also greater than in the present study; again, this may be explained on the basis of higher APBI dose used in the trial.

Recently 2 studies on APBI were presented at the San Antonio Breast Cancer Symposium (December 2018). The first study by Vicini et al (NSABP B-39/RTOG 0413) reported poor clinical outcomes with APBI compared with WBI.[19] They treated patients with both 3D-CRT and brachytherapy APBI. Overall poor outcomes with APBI occurred because patients treated with brachytherapy had a higher local recurrence rate (7.8% compared with 3.7% with 3D-CRT), which was comparable with 3.7% in WBI. From one of the recruitment centers, they included younger patients in the APBI with brachytherapy group; 10-year grade 3 toxicity was comparable (7.1% in the WBI arm and 9.6% in the APBI arm). This toxicity rate is higher than in the present study. There were no statistically significant differences between the 2 treatment arms for distant disease-free interval, disease-free survival, or overall survival. At 10 years there were only small differences in ipsilateral breast tumor recurrence (<1%) and relapse-free interval (1.5 %) between the 2 treatment arms, but the hazard ratio could not meet statistical equivalence. The second study by Whelan et al met the noninferiority endpoint but reported higher 3-year grade 3 late toxicities (4.5% vs 1%) and 7-year fair or poor cosmetic outcomes (31% vs 15%) in the patients treated with APBI. This might be due to the higher dose fractionation of 38.5 Gy in 10 fractions used in their study.[20] The other difference between these 2 trials was that the RAPID trial enrolled an older, low-risk population and treated all with 3D-CRT APBI (90%) compared it with the hypofractionation schedule than in the NSABP B-39/RTOG 0413 trial, where WBI arm used conventional fractionation. That may be one of the reasons it met the noninferiority endpoint.

Hypofractionation is unlikely to increase late toxicity if total prescribed dose is reduced. A dose of 38.5 Gy in 10 fractions will likely lead to more normal tissue biologic effect than standard WBI schedules; this may why it disproved the hypothesis that the decreased high-dose volume of APBI may make this dose fractionation tolerable. With hypofractionation there is a need to reduce the total dose, which we did in the present trial. The BED of 34 Gy/10 fractions/5 days for acute and late skin effects is 45.5 Gy and 72.5 Gy_3, respectively. The BED of 38.5 Gy/10 fractions/5 days for acute and late skin effects is 54 Gy and 88 Gy_3, respectively. There is a possibility that BED ≤50 Gy for acute effects in accelerated fractions with 2 fractions per day may lead to optimal local control and cosmetic outcomes comparable to those with WBI.

There is a steep dose gradient with brachytherapy and a relatively lower volume of normal breast is treated in comparison with the homogenous dose and large volume to address organ motion and day-to-day variation in 3D-CRT APBI. To adjust for this expected difference, a schedule of 38.5 Gy in 10 fractions was developed for 3D-CRT APBI as opposed to the 34 Gy in 10 fractions used for brachytherapy APBI. As a result, 3D-CRT APBI irradiates a larger volume of normal breast to a higher dose per fraction, which is likely to produce higher acute

and late toxicities and consequently higher adverse cosmesis; hence, there is need to reduce the total dose. This small dose reduction of 3 to 4 Gy can make a substantial difference in toxicities and has been seen in other studies as well. In the START A trial, 39 Gy in 13 fractions was better than 42.9 Gy in 13 fractions in terms of late toxicities with a difference of only 3.9 Gy between 2 arms.[23] Thus, a 10% dose reduction can make a significant difference in the late effects, as reported in different studies on APBI. The present study also suggests that the variations in toxicity results reported in different studies with 3D-CRT APBI may be due to this small difference in the dose.

The IMPORT low trial reported similar 5-year control rates and adverse cosmesis with WBI and PBI: 1.1% versus 0.5% and 23% versus 18%, respectively.[24] Similarly, a study from Italy reported similar 5-year control rates and adverse cosmesis with WBI and intensity modulated radiation therapy PBI: 1.4% versus 1.5% and 0.8% versus 0%, respectively.[24] The dose fractionation used in this study was 30 Gy in 5 fractions on alternate days with intensity modulated radiation therapy; treatment was completed in 2 weeks. Based on these studies, an alternate APBI schedule may be needed. A dose of 30 to 34 Gy in 10 fractions with 2 fractions per day may be optimal for APBI with 3D-CRT. As far as technique is concerned, 3D-CRT may be optimal because it is noninvasive, painless, and patient friendly; widely available; and technically simple, with no specialized training or equipment required. Economic and now level I evidence is also available.[19,20]

The other possible explanation for low toxicity rates in the WBI arm in different studies could be infrequent use of boost in the WBI arm. Boost is known to increase acute and late toxicity and is associated with adverse cosmesis. In our study, boost was delivered in 38 patients (56%) in the WBI group, and 16 patients (42%) were reported to have adverse cosmesis. Only 1 patient developed late grade 3 skin toxicity in the WBI arm, and this patient had also received boost. In the EORTC boost trial, boost was associated with moderate and severe fibrosis in 28% and 4.4% patients, respectively, at 10 years. In the no-boost arm, moderate and severe fibrosis rates were 1.6% and 1.3%, respectively. Thus, there is a possibility that more adverse cosmesis in patients in the WBI arm could be due to boost. In the RAPID trial, boost was delivered in 20% of patients compared with 80% in the NRG B39/0413 trial. The contrasting finding in the RAPID trial was that adverse cosmesis increased in the APBI arm from 19% at baseline to 36% at 7 years, but it increased marginally in the WBI arm from 17% at baseline to 19% at 7 years. This may be because only 20% patients in RAPID were given boost. It has been reported that with hypofractionation, adverse cosmesis tends to decrease with time.[23,24] There was no fat necrosis observed in our study. Higher rates of fat necrosis (15%) were reported with intraoperative radiation therapy in the ELIOT trial.[27]

Follow-up duration may be another factor affecting late and cosmetic effects of APBI. Few studies with limited patient numbers and short follow-up have reported higher toxicities and adverse cosmesis with APBI. In a study by Hepel et al, with a median follow-up of just 15 months, moderate to severe late toxicity and poor or fair cosmesis was reported in 10% and 18.4% of patients, respectively. Grade 2 to 4 fibrosis was observed in 25% of patients.[29] Similarly, Jagsi et al treated 34 patients with a dose of 38.5 Gy in 10 fractions with deep breath hold technique. At a median follow-up of 2.5 years they reported unacceptable cosmetic toxicity in 7 patients (20.5%), and the study was prematurely closed. In exploratory analysis they found that in patients who had adverse cosmesis, the mean breast V100% was higher than in those with good cosmesis (23.0% vs 15.5%; $P = .02$). Similarly, V50% mean was higher in the adverse cosmesis group ($P = .02$).[30] The dose used in this study was also higher than in our study. However, other studies with large numbers of patients and longer follow-up have shown favorable outcomes with 3D-CRT APBI. Julian et al, in their study with 1391 patients and 3 years of follow-up, observed grade $\geq$3 fibrosis in only 3% of patients in the APBI arm.[15] Shah et al observed minimal grade $\geq$2 toxicity and good or excellent cosmesis in 88% of patients at a follow-up of 3 years.[31]

To our knowledge this is the second study after RAPID on APBI with 3D-CRT in which the control arm (WBI) was treated with hypofractionated radiation therapy, although in the majority of other studies patients were treated with conventional fractionation. It is also unique because we have included patients between 35 and 40 years of age. That is why the mean age of the patients in our study is 50 years compared with >60 years in most studies. This is also one of the reasons why >50% of our patients received chemotherapy. Our findings cannot be compared with other techniques of APBI because of different dose fractionation, volume, conformity, and radiobiologic considerations.

A limitation of our study is the small sample size with few disease-related events at present. The primary endpoint will be reported once enough events (19 recurrences) have occurred. Toxicities in the present study were assessed solely by the physician but are quite consistent with other studies, which have also reported patient-related outcomes. To date, our results with respect to acute, late radiation toxicities and cosmesis are encouraging, and we will follow these patients to establish long-term safety and efficacy of 3D-CRT APBI in comparison to WBI. Proper dose selection, treatment technique, and follow-up duration may be of paramount importance in reporting outcomes with APBI. When all

these parameters are taken into consideration, 3D-CRT APBI may be noninferior to WBI.

Conclusions

In women with breast cancer after BCS, APBI was associated with better cosmetic outcome and fewer acute and late radiation toxicities than WBI. Our study provides further clinical safety evidence to use APBI with 3DCRT in selected patients with breast cancer after BCS with an appropriate dose fractionation schedule.

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