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Scientific Article

Long-Term Clinical and Cosmetic Outcomes of Once-Daily Accelerated Partial Breast Irradiation in Early Breast Cancer

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Purpose: Accelerated partial breast irradiation (APBI) is one of the standard treatment options in early-stage node negative breast cancer in selected patients. However, the optimal dose fractionation schedule still represents a challenge. We present the 12-year follow up results of clinical and cosmetic outcomes of once daily APBI with external beam radiation therapy which provides an APBI radiation dose equivalent to the whole breast radiation with a boost.

Methods and Materials: From July 2008 to August 2010, we enrolled 34 patients with T1, T2 (< 3cm) N0 to receive once daily APBI with three dimensional conformal radiation therapy (3D-CRT) to a total dose of 49.95 Gy over 15 single daily fractions over 3 weeks at 3.33 Gy per fraction. Ipsilateral breast tumor recurrence (IBTR), acute toxicity, late toxicity and cosmesis was analyzed. The median follow-up for all patients is 144 months (12 years).

Results: The median age of the patients was 61 years (range 46-83). Nine patients had ductal carcinoma in situ (DCIS) and 25 patients had invasive cancer. The median size of the tumor with DCIS pathology was 0.5 cm, while median size of the tumor with invasive cancer pathology was 1.0 cm. All of the patients had negative margins and negative nodes. Two IBTR was observed (5.8%). One patient had DCIS at recurrence and other had invasive recurrence. Two patients died due to non-cancer cause. The 12-year actuarial ipsilateral breast recurrence free survival was 93.5% and the 12-year actuarial overall survival was 93.2%. Late Grade 2 toxicity was observed in 6 patients and late grade 3 toxicity was seen in 1 patient. 91% of the patients had excellent to good cosmesis.

Conclusions: This novel APBI dosing schema is based on an equivalent dose compared to whole breast radiation plus a tumor bed boost. This once daily APBI scheme is well-tolerated and demonstrates good to excellent cosmetic outcome and low rates of late complications on long term follow-up.

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Introduction

Accelerated partial breast irradiation (APBI) is one of the standard treatment options in patients with early-stage node-negative breast cancer in selected cases.[1] Various treatment techniques and radiation doses have been used in APBI.[2] Most of the studies have shown an equivalent treatment result with APBI in carefully selected patients; however, the optimal schedule to obtain the best balance between patient preference, local control, toxicity, and cosmesis still represents a challenge.

In 2008, we designed a single-arm, prospective trial (CINJ 040801; NCT00749437) investigating once-daily APBI using 3-dimensional conformal radiation therapy (3D-CRT). Patients were treated with a novel, hypofractionated once-daily APBI regimen of 3.33 Gy for 15 fractions over 3 weeks. Three year clinical and cosmetic results were previously presented.[3] We hereby present the long-term results (12-year follow-up) of the local control, acute toxicity, late toxicity, and cosmesis of a once-daily fractionation scheme for APBI using 3D-CRT in patients with early-stage, node-negative breast cancer.

Methods and Materials

Study population

We performed the single-arm prospective trial of APBI with 3D-CRT between July 2008 to August 2010. Preoperative eligibility criteria included age ≥45 years, ductal carcinoma in situ or invasive histology, clinical tumor size ≤3 cm, and clinically node negative. Forty-five patients consented for the study and underwent definitive surgical resection with fiducial marker placement. Axillary evaluation was performed for all patients with invasive histology. Patients received 4 to 6 gold fiducial markers (CIVCO Medical Solutions, Kalona, IA) during the definitive surgical procedure. Each gold fiducial marker is 2 mm in diameter and is attached to 2/0 prethreaded proline suture; these were sutured to the superior, inferior, medial, lateral, and posterior walls of the surgical cavity. Patients were enrolled on trial if the final pathologic review was appropriate (n = 34). Additional final eligibility criteria included negative margins as defined by the National Surgical Adjuvant Breast and Bowel Project (NSABP), pathologically node-negative, unifocal disease, delivery of APBI before any systemic therapy, simulation between 14 and 60 days from date of last surgery, and initiation of radiation within 15 to 80 days of date of last surgery. Patients with positive margins underwent re-excision to obtain clear margins and underwent additional placement of gold markers. The CONSORT diagram and trial profile are summarized in Fig. 1.

Radiation planning

All patients received radiation therapy to their breast based on the established partial breast guidelines set forth by the Radiation Therapy Oncology Group (RTOG), and these details were thoroughly described in previous reports.[3,4] Briefly, the seroma cavity was defined on computed tomography (CT) scan and an expansion of 1.5 cm was added to form the clinical target volume. The clinical target volume was then restricted to within the lung-chest

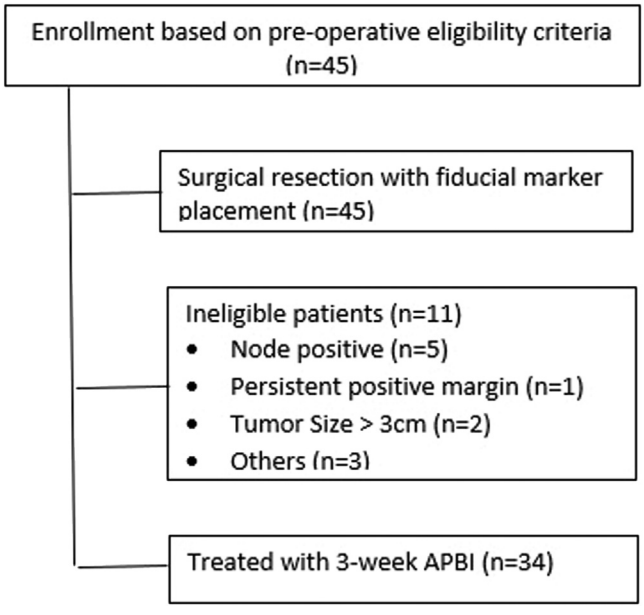

Figure 1 Consort diagram. *Abbreviation*: APBI = accelerated partial breast irradiation.

Table 1 EQD2 (Gy) across various fractionation schemes

	Standard WBI with boost	START pilot WBI with boost	START B WBI with boost	Canadian WBI with boost	Present study
Dose (Gy)/fractions	50/25 +16/8	42.9/13 +14/7	40/15+10/5	42.5/16+10/4	49.95/15
Tumor control (α/β = 4.0 Gy)	66	66.2	54.5	58.1	61
Acute effects (α/β = 10 Gy)	66	61.5	52.3	55.3	55.5
Late effects (α/β = 3 Gy)	66	68.1	55.4	59.2	63.2

Abbreviations: EQD2 =equivalent dose in 2 Gy fractions ; WBI = whole-breast irradiation.

Table 2 EQD2 (Gy) across various APBI fractionation schemes

	IMPORT LOW	RAPID	FLORENCE	Present study
Dose (Gy)/fractions	40/15	38.5/10	30/5	49.95/15
Tumor control (α/β = 4.0 Gy)	44.4	50.4	50	61
Acute effects (α/β = 10 Gy)	44.2	44.4	40	55.5
Late effects (α/β = 3 Gy)	45.3	52.7	54	63.2

Abbreviations: APBI = accelerated partial breast irradiation; EQD2 = equivalent dose in 2 Gy fractions.

wall interface and 5 mm of the skin surface; an additional 1.0 cm margin was provided to form the planning target volume. The planning target volume then excluded the pectoralis muscles, chest wall, and the first 5 mm beneath the skin to form the planning target volume-evaluation. Normal structures delineated included the thyroid, ipsilateral whole breast, contralateral whole breast, lungs, and heart. Typically, 3-, 4-, or 5-field noncoplanar photon beams were used; electrons were used to supplement dose in 2 patients given the medial location of the seroma cavity in their left breast. The following dosimetric constraints were used to evaluate plans: <60% of the whole-breast reference volume received ≥50% of the prescribed dose and <35% of the whole-breast reference volume received the prescribed dose. The contralateral breast reference volume received <3% of the prescribed dose to any point. Less than 15% of the ipsilateral lung received 30% of the prescribed dose while less than 15% of the contralateral lung received 5% of the prescribed dose. For right-sided lesions, <5% of the heart received 5% of the prescribed dose, and for left-sided lesions, <40% of the heart received 5% of the prescribed dose. The mean heart dose in all patients was 0.95 Gy (range, 0.07-4.69 Gy). The maximum dose to the thyroid was 3% of the prescribed dose.

Radiation therapy fractionation design

Patients were treated using a APBI fractionation scheme: 49.95 Gy over 15 single daily fractions. This fractionation has already been used in hypofractionated whole-breast irradiation (WBI) and post mastectomy radiation with 5-year results reported in the literature.[5-7] This was based on the hypofractionated WBI regimen in START pilot study with 42.9 Gy over 13 fractions followed by a 14 Gy tumor bed boost in 7 fractions.[8] Thus, this dose fractionation regimen included the tumor bed boost radiation dose. Assuming an a/b ratio of 4 Gy for tumor kill, 10 Gy for acute effects and 3 Gy for late effects, the equivalent dose in 2 Gy fractions (EQD2) doses for the study regimen was comparable with other popular hypofractionated whole-breast radiation schedules with inclusion of the tumor bed boost radiation component (Table 1). The EQD2 doses for the commonly used APBI regimens are compared and tabulated in Table 2 and shows that the present study has slightly higher EQD2 as compared with other APBI regimens. This higher EQD2 resulted because this dose was equivalent to the WBI followed by tumor bed boost radiation, which is a very common clinical practice.[9,10]

Follow-up

Adjuvant systemic treatment was prescribed following the institutional policy during the trial enrollment period. Patients were evaluated weekly during the course of radiation therapy, 3 to 4 weeks after completion of treatment, and then at 3- to 6-month intervals thereafter. Clinical examination was performed at each follow-up visit, mammography was performed annually, and other diagnostic examinations were requested in case of suspect symptoms. To gather information regarding locoregional toxicities and recurrences, charts were reviewed for clinical information before, during, and after radiation therapy. Patients were also called if the chart lacked information or if a patient relocated and was receiving care at another

institution. The long-term clinical and cosmetic outcomes were analyzed.

Endpoints

Ipsilateral breast tumor recurrence (IBTR) was defined as any reappearance of breast cancer in the ipsilateral breast. Locoregional tumor recurrence included any recurrence in the ipsilateral axillary, supraclavicular or internal mammary nodal regions. Distant metastasis was defined as any recurrence to distant organs. Acute and late toxicities were scored using the Common Terminology Criteria for Adverse Events. The Harvard Cosmesis Scale was used to determine the cosmetic outcome of the treated breast. Contralateral breast tumor recurrence rates, overall survival (OS), and breast cancer specific survival were calculated.

Statistical methods

Standard statistical methods using version 29 of the SPSS statistical software package was used to analyze all data. Descriptive analyses were used to show the proportion of patients with grade 0, grade 1, and grade 2+ events at each follow-up visit. Survival analyses were performed in relation to specific events: IBTR, locoregional tumor recurrence, distant metastasis, and death. Time to events was measured from the date of diagnosis to the date of the specific event. Patients who were lost to follow-up were considered censored at their date of last follow-up. All tests were declared statistically significant if the calculated P value was $<.05$.

Results

Patient characteristics

A total of 45 patients underwent lumpectomy and gold fiducial placement between July 2008 and August 2010. Eleven patients were ineligible due to node positivity (5 patients), large tumor size (2 patients), persistent positive margin (1 patient), and other reasons (3 patients; Fig. 1). Thus, 34 patients were enrolled in the study. The patient characteristics of enrolled patients are summarized in Table 3. The median age of the patients was 61 years (range, 46-83). Nine patients had ductal carcinoma in situ (DCIS) and 25 patients had invasive cancer. The median size of the tumor with DCIS pathology was 0.5 cm (range, 0.3-1.9 cm), while the median size of the tumor with invasive cancer pathology was 1.0 cm (range, 0.1-2.0 cm). All of the patients had negative margins (at least 2 mm for invasive cancer and at least 3 mm for DCIS) and negative nodes. Most of the patients had a favorable breast cancer histologic profile with estrogen

Table 3 Patient characteristics

Feature	No.
Age, y	
≤50	3
>50	31
Race	
White	33
Black	1
Pathologic stage	
DCIS	9
Invasive	25
Tumor size (DCIS), cm	
Mean	0.65
Median	0.50
Range	0.30-1.90
Tumor size (invasive), cm	
Mean	1.06
Median	1.00
Range	0.10-2.00
Grade (DCIS)	
Low	1
Int	4
High	4
Grade (invasive)	
G1	4
G2	15
G3	6
LVI	
Negative	28
Positive	6
Margins	
Negative	34
Positive	0
Pathologic N stage	
N0	34
ER status	
Negative	4
Positive	30
PR status	
Negative	4
Positive	30
Her2 status	
Negative	30
Positive	4
Composite hormonal profile	
ER+ PR+ Her−	29
ER+ PR+ Her+	1
ER− PR− Her+	3
ER− PR− Her−	1
ASTRO criteria	
Suitable (invasive/DCIS)	19 (15/4)
Cautionary (invasive/DCIS)	15 (10/5)

Abbreviations: ASTRO = American Society for Radiation Oncology; DCIS = ductal carcinoma in situ; ER = estrogen receptor; LVI = lymphovascular invasion; PR = progesterone receptor.

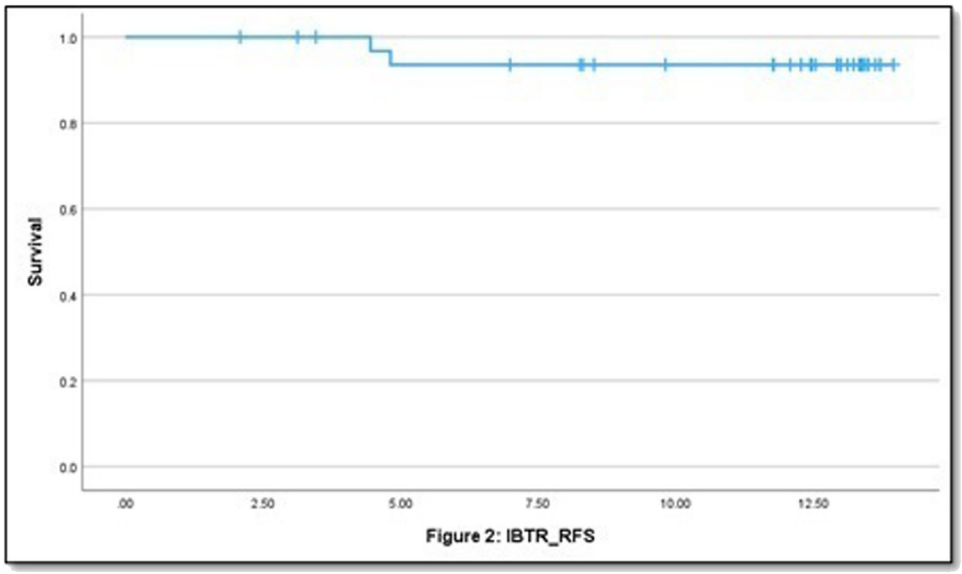

Figure 2 Kaplan-Meier analysis showing ipsilateral breast tumor recurrence (recurrence-free survival). *Abbreviations*: IBTR = ipsilateral breast tumor recurrence; RFS = recurrence-free survival.

receptor (ER) positive/progesterone receptor (PR) positive and Her-2 negative disease. As per the updated American Society for Radiation Oncology (ASTRO) APBI criteria, 19 patients were in suitable category while 15 patients were in cautionary category. The factors present in the 15 patients in cautionary category were age less than 50 years (3 patients), ER negative (4 patients), focal lymphovascular invasion (6 patients), and high nuclear grade DCIS (4 patients), with 2 patients having a combination of factors. All patients completed the planned treatment without any treatment breaks. The median follow-up for all patients is 144 months (12 years).

Treatment efficacy

A total of 2 IBTRs was observed (5.8%). One patient had invasive recurrence and she was initially treated for invasive cancer with APBI followed by hormonal therapy. She was in suitable category at presentation with negative margins and no other adverse features. The other recurrence patient was in cautionary category at presentation due to high nuclear grade DCIS. She had no other adverse features and was treated with APBI alone. She refused hormonal therapy and had ipsilateral DCIS at recurrence. The mean ipsilateral breast recurrence-free survival of the entire cohort was 13.34 years, whereas the 12-year actuarial ipsilateral breast recurrence-free survival was 93.5% (Fig. 2). Both recurrences were salvaged with surgery, and they did not have any other recurrence in long term. None of the patient had regional failure or distant metastases.

Contralateral breast tumor recurrence was seen in 5 patients (14.7%). Two patients had invasive tumor, and 3 patients had DCIS. Three patients had nonbreast second malignancy (non-hodgkin lymphoma, rectal carcinoid, and meningioma). Two patients died due to noncancer causes (neurologic, 1 and vascular, 1). The mean OS of the entire cohort was 13.55 years, and the 12-year actuarial overall survival was 93.2%.

Acute toxicity

Grade 1 radiation dermatitis was seen in 32 patients and only 2 patients had grade 2 radiation dermatitis. No patients had grade 3 to 4 acute skin toxicity. Overall, 70% of patients had grade 1 pigmentation at 1 month after treatment completion. There were no cases of fibrosis, breast edema, symptomatic seroma, or fat necrosis during or within 1 month of radiation therapy. There was 1 case of radiation pneumonitis 6 weeks after radiation, which resolved with steroid treatment.

Late toxicity

Overall, grade 2 late toxicity was seen in 6 patients and grade 3 late toxicity was seen in 1 patient. Of these, 2 patients had grade 2 late skin toxicity (moderate telangiectasia), which persisted for long-term until the last follow-up. One patient had grade 2 subcutaneous toxicity and one has grade 3 subcutaneous toxicity consisting of moderate fibrosis at 3 months follow-up. The grade 2 subcutaneous toxicity resolved with physical therapy; however, the patient with grade 3 subcutaneous toxicity developed breast edema, which persisted on longer follow-up.

Table 4 APBI EBRT studies

	APBI	WBI	Notes
NSABP B 39/RTOG 0413 38.5 Gy/10 fraction/5 d	IBTR 4.6% Late ≥ G3 10%	IBTR 3.9% Late ≥ G3 7%	73% of APBI were 3D-CRT
RAPID 38.5 Gy/10 fraction/5 d	IBTR 3.0% Late ≥ G2 32% Fair/poor cosmesis 36%	IBTR 2.8% Late ≥ G2 13% Fair/poor cosmesis 19%	More late effects and adverse cosmesis in APBI due to bid treatment
Boutrus et al (BID APBI) 38.5 Gy/10 fraction/5 d	Late 11.7% Fair/poor cosmesis 26.7%	NA	OD APBI has better late toxicity and cosmetic outcomes compared with BID APBI
Boutrus et al (OD APBI) 38.5 Gy/10 fraction/10 d	Late ≥ G2 3.8% Fair/poor cosmesis 7.5%	NA	
FLORENCE 30 Gy/5 fractions/every other day	IBTR 3.7% Late ≥ G2 0% Fair/poor cosmesis 0.8%	IBTR 2.5% Late ≥ G2 2.7% Fair/poor cosmesis 14.6%	Overall treatment duration is 1.5 2 wk
IMPORT LOW 40 Gy/15 fraction/3 wk	IBTR 0.5%	IBTR 1.1%	Lower late effects and better cosmesis with APBI
Present study 49.95 Gy/15 fraction/3 wk	IBTR 5.8% Fair/poor cosmesis 9%	NA	The total dose is equivalent to WBI + boost

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; APBI = accelerated partial breast irradiation; BID = twice daily; EBRT = external beam radiation therapy; IBTR = ipsilateral breast tumor recurrence; OD = once daily; RTOG = Radiation Therapy Oncology Group; WBI = whole-breast irradiation.

Three patients developed small fat necrosis, 2 were asymptomatic, and only 1 had painful symptoms which resolved after excision. There was no significant dosimetric feature in radiation planning which could be attributed to fat necrosis.

Two patients developed chest wall pain at 3-month follow-up, which resolved with physical therapy. One patient had symptomatic rib fracture at 1 year after blunt trauma force. One patient developed persistent and symptomatic seroma requiring multiple aspirations, up to 2 years after radiation therapy. None of the patients developed arm stiffness, brachial plexopathy, radiation recall, breast infection, or pericarditis.

In all, 36% of the patients developed grade 1 fatigue at the completion of treatment and 83% patients who developed grade 1 fatigue at the completion of treatment experienced resolution of fatigue by 1 month. All patients reported resolution of fatigue at 1 year post treatment.

Cosmesis

On long-term follow-up of 34 patients, 91% of the patients had excellent (44%) to good (47%) cosmetic outcome. Fair cosmesis was seen in 2 patients and 1 patient had poor cosmesis.

Discussion

APBI is one of the standard recommended radiation treatment options in carefully selected patients with early-stage breast cancer with very good local control rates and good cosmesis.[11] Various modalities like interstitial brachytherapy, Mammosite, intraoperative radiation therapy and external beam radiation therapy (EBRT) all have been used to deliver APBI with a widely variable different dose fractionation.[12] The external beam partial breast is a noninvasive approach and radiation can be delivered with standard 3D-CRT or intensity modulated radiation therapy techniques (Table 4).

NSABP B39/Radiation Therapy Oncology Group 0413 trial compared WBI with APBI and used different modalities to deliver APBI with 73% of patients in APBI arm received EBRT with 3D-CRT.[13] The EBRT APBI dose was 38.5 Gy in 10 fractions over 5 treatment days. At median follow-up of 10.2 years, the IBTR with APBI was 4.6% versus 3.9% in WBI, favoring WBI (P = NS). The late grade 3 toxicity rates with APBI were comparable to WBI (10% vs 7%).

The RAPID trial used similar EBRT APBI regimen (38.5 Gy in 10 fractions over 5 treatment days) with WBI and showed that APBI was noninferior to WBI.[14] The 8-year IBTR was 3.0% with APBI versus 2.8% in WBI. There was less acute toxicity with APBI but had increased late toxicity (32% vs 13%) with APBI. The 7-year fair/poor cosmesis was higher with APBI (36% vs 19%), probably due to twice-daily fractionation. In comparison, the long-term fair/poor cosmesis in the present study is 9% only, even with higher EQD2 doses. This emphasizes the effect of once-daily fractionation with cosmetic outcomes.

Hoopes et al[15] showed that 70% of women preferred once-daily radiation over 10 days to the breast compared

with twice-daily radiation over 5 days. Once-daily verses twice-daily fractionation with EBRT APBI (38.5 Gy in 10 fractions) was explored in a randomized trial of 113 patients by Boutrus et al.[16] Once-daily fractionation had similar local control and acute toxicities with statistically significant reduction in late skin toxicity (3.8% vs 11.7%; $P = .001$). The 2-year fair/poor cosmesis was lower with once-daily fractionation (7.5% vs 26.7%) compared with twice-daily fractionation. This result is similar to the once-daily fractionation regimen as in our study.

The FLORENCE trial compared APBI using intensity modulated radiation therapy (30 Gy in 5 fractions once daily, every other day) with WBI and 10-year results showed similar IBTR of 3.7% in APBI versus 2.5% in WBI ($P = .40$). The 10-year OS and breast cancer specific survival were similar in both arms.[17] The APBI arm showed significantly less acute and late toxicity with improved cosmetic outcome.

IMPORT LOW study compared hypofractionated WBI with hypofractionated APBI using same radiation dose (40 Gy in 15 fractions over 3 weeks).[18] This PBI regimen is simple, well tolerated and noninferior clinically with IBTR of 0.5% in APBI arm compared with 1.1% in WBI arm. The late effects were lower in the PBI arm with better cosmesis with APBI. Our study is similar to IMPORT LOW study in terms of once-daily fractionation over 3 weeks; however, the EQD2 dose is slightly higher in the present study as it included the tumor bed boost radiation dose.

The present study used EBRT APBI with 49.95 Gy in 15 once-daily fractions over 3 weeks. This APBI dosing schema is novel as it is based on an equivalent dose compared with whole-breast radiation plus a tumor bed boost, as addition of boost is a very widely accepted clinical practice.[9] The addition of tumor bed boost after whole-breast radiation has shown to improve the long-term local control in young patients and in high-grade tumors.[19] Hypothetically, this regimen with high EQD2 can be more pragmatic in patients in ASTRO cautionary category who can receive equivalent dose as with whole-breast radiation plus a tumor bed boost. This regimen was well tolerated with no occurrences of acute G3/4 skin toxicity as in other APBI regimens. Our 12-year actuarial ipsilateral breast recurrence free survival of 93.5% was also comparable with published contemporary APBI literature. The present study had very low late toxicity and 91% of the patients had excellent to good cosmesis. This is probably due to once-daily fractionation as seen in other once-daily fractionation schedules as in IMPORT LOW, FLORENCE, and Boutrus et al.[16-18] Fifteen patients (44%) fell into the cautionary category as per the updated ASTRO guidelines; however, the long-term clinical outcomes were acceptable overall.

The strengths of this study are an APBI dose regimen, which is equivalent to WBI followed by tumor bed boost, once-daily fractionation APBI regimen, and 12-year follow-up of clinical and cosmetic outcomes. The limitations of the study are being single-arm phase 2 study and the small number of patients.

Conclusion

Our accelerated partial breast fractionation scheme of 15 once-daily fractions of 3.33 Gy (49.95 Gy total) is a remarkably well-tolerated regimen of 3D-CRT—based APBI. In addition, limited long-term follow-up demonstrates good to excellent cosmetic outcome and acceptable rates of late complications for patients treated with this fractionation schedule. This regimen may be considered as an option in APBI in future clinical trials and practice, especially in patients in the ASTRO cautionary category.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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