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Cosmetic Results and Side Effects of Accelerated Partial-Breast Irradiation Versus Whole-Breast Irradiation for Low-Risk Invasive Carcinoma of the Breast: The Randomized Phase III IRMA Trial

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abstract

PURPOSE The results in terms of side effects vary among the published accelerated partial-breast irradiation (APBI) studies. Here, we report the 5-year results for cosmetic outcomes and toxicity of the IRMA trial.

METHODS We ran this randomized phase III trial in 35 centers. Women with stage I-IIA breast cancer treated with breast-conserving surgery, age ≥ 49 years, were randomly assigned 1:1 to receive either whole-breast irradiation (WBI) or external beam radiation therapy APBI (38.5 Gy/10 fraction twice daily). Patients and investigators were not masked to treatment allocation. The primary end point was ipsilateral breast tumor recurrence. We hereby present the analysis of the secondary outcomes, cosmesis, and normal tissue toxicity. All side effects were graded with the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer Radiation Morbidity Scoring Schema. Analysis was performed with both intention-to-treat and as-treated approaches.

RESULTS Between March 2007 and March 2019, 3,309 patients were randomly assigned to 1,657 WBI and 1,652 APBI; 3,225 patients comprised the intention-to-treat population (1,623 WBI and 1,602 APBI). At a median follow-up of 5.6 (interquartile range, 4.0-8.4) years, adverse cosmesis in the APBI patients was higher than that in the WBI patients at 3 years (12.7% *v* 9.2%; $P = .009$) and at 5 years (14% *v* 9.8%; $P = .012$). Late soft tissue toxicity (grade ≥ 3: 2.8% APBI *v* 1% WBI, $P < .0001$) and late bone toxicity (grade ≥ 3: 1.1% APBI *v* 0% WBI, $P < .0001$) were significantly higher in the APBI arm. There were no significant differences in late skin and lung toxicities.

CONCLUSION External beam radiation therapy-APBI with a twice-daily IRMA schedule was associated with increased rates of late moderate soft tissue and bone toxicities, with a slight decrease in patient-reported cosmetic outcomes at 5 years when compared with WBI, although overall toxicity was in an acceptable range.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Breast-conserving surgery (BCS) followed by whole-breast irradiation (WBI) is the standard of care for early-stage breast cancer.[1] Despite the well-documented equivalence of BCS with postoperative WBI compared with mastectomy alone,[2,3] mastectomy rates vary significantly among patients suitable for breast conservation.[4,5] One of the reasons for underutilization of breast-conserving treatment is the additional time required to undergo fractionated WBI.[6,7]

Accelerated partial-breast irradiation (APBI) has been suggested as a potentially more convenient and less toxic treatment option for patients with early-stage breast cancer.

Advances in radiation therapy (RT) technology allowed us to perform partial-breast irradiation noninvasively, using external beam radiation therapy (EBRT).[8-10] Potential advantages of postoperative EBRT include the availability of the full pathologic information, reduced operator dependence, and reduced upfront capital expenditures.[11] On the basis of these developments, we started the IRMA Trial in 2007, to our knowledge the largest international randomized study, using only EBRT.

CONTEXT

Key Objective

Several randomized trials addressing different techniques of accelerated partial-breast irradiation (APBI) have been published, showing conflicting results regarding late side effects and cosmetic outcomes. We report cosmetic outcomes and normal tissue toxicity of the IRMA trial, comparing them with other reports.

Knowledge Generated

To our knowledge, IRMA is the largest international multicentric randomized study, using only external beam radiotherapy, evaluating APBI versus whole-breast irradiation. APBI delivered with twice-daily fractions of external beam radiation therapy increases the rate of moderate late soft tissue toxicity and results in a slightly inferior cosmetic outcome when compared with whole-breast irradiation. As no data regarding bone toxicity had ever been provided in any of the other randomized clinical APBI trials, to our knowledge, our analysis is the first to report a small but measurable increase in severe (grade 3-4) late bone toxicity in the APBI arm.

Relevance *(B.G. Haffty)*

This study demonstrates that this twice-daily external beam fractionation scheme over 1 week for partial-breast radiation results in increased toxicity and inferior cosmetic outcomes compared with whole-breast radiation. These results should be considered in clinical decision making regarding the selection of external beam partial-breast radiation schedules.*

*Relevance section written by *JCO* Deputy Editor Bruce G. Haffty, MD.

We report the 5-year results for cosmetic outcomes and normal tissue toxicity.

METHODS

Study Design and Patients

IRMA recruited patients at 35 centers in five countries.

Patients were eligible if they had histologically confirmed invasive breast cancer treated with BCS with clear margins ($\geq$ 2 mm), a maximum tumor diameter $\leq$ 3 cm, negative axillary lymph nodes (pN0) or metastases in 1-3 axillary lymph nodes (pN1), and a clinical target volume that was $<$ 30% of the whole breast volume (see the Protocol [online only] and the Data Supplement [online only] for detailed inclusion/exclusion criteria).

Ethics approval and written informed consent were obtained. The study was registered at ClinicalTrials.gov (identifier: NCT01803958).

Random Assignment and Masking

Patients were randomly assigned/stratified as specified in the Protocol. Patients and investigators were not masked to treatment allocation.

Procedures

All patients received lumpectomy plus sentinel node biopsy and/or axillary lymph node dissection. Patients received adjuvant systemic therapy according to institutional guidelines.

RT was planned using computed tomography scans acquired in supine position with both arms elevated.

For patients allocated to the WBI group, tangential opposing megavoltage ($\geq$ 4 MV) photon beams were used to treat the whole breast up to a total dose of 50-50.4 Gy/25-28 fractions (Fr) or 42.56 Gy/16 Fr or 45 Gy/18 Fr or 40 Gy/15 Fr. Fractionation was selected by each center according to local guidelines. A boost of 10-16 Gy was allowed in centers where this was part of the standard treatment. The dose was prescribed according to the ICRU-50 criteria.

Patients allocated to APBI were treated with four to five noncoplanar conformal fields or with intensity-modulated techniques. The prescribed dose was 38.5 Gy in 10 Fr administered twice daily over 5 days with a minimum interfraction interval of 6 hours. Boost was not permitted in the APBI arm. The dose was prescribed according to the ICRU-50 criteria; to ensure uniformity in dose distribution, $>$ 90% of the planning tumor volume for dose distribution evaluation (PTV_eval; see the Protocol for detailed definition) was required to be covered by at least the 90% isodose line. Organ-at-risk dose constraints and target volume definition are outlined in the Protocol.

Follow-up was scheduled at 6 weeks, 3 months, 6 months, and 12 months in the first year; every 6 months in years 2-3; and then annually for $\geq$ 10 years.

Outcome End Points

The primary end point of the IRMA trial was ipsilateral breast tumor recurrence. Secondary end points were incidence and severity of acute and late side effects, cosmesis, and survival end points, which are reported here.

All acute and late side effects were prospectively tracked and graded with the Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer Acute and Late Radiation Morbidity Scoring Schema[12] by a treating physician.

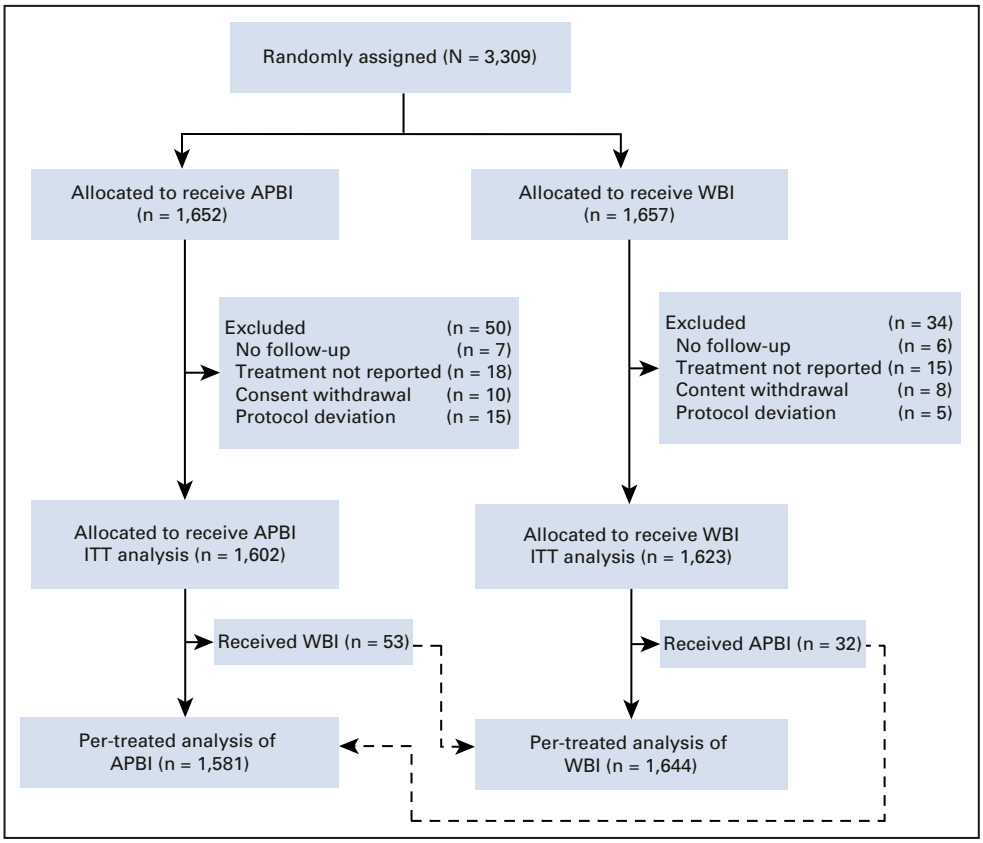

FIG 1. CONSORT diagram. APBI, accelerated partial-breast irradiation; ITT, intention-to-treat; WBI, whole-breast irradiation.

Cosmetic results were assessed by a physician using the Harvard criteria.[13] Before the start of RT and during follow-up visits, the patient was also instructed by the clinician about the criteria to evaluate the patient's cosmetic result with a four-point scale system as detailed in the Protocol and was asked to score it.

Statistical Analysis

This study was designed to test the hypothesis that APBI was not inferior to WBI in terms of incidence of ipsilateral recurrence. To assess the association between safety/toxicity and the two treatment paradigms, we performed the analysis of toxicity end points with both intention-to-treat and as-treated approaches.

Comparisons between APBI and WBI were performed regarding both acute and late toxicities. The acute toxicity regarded those events occurring between the beginning of the irradiation treatment and up to 3 months after the end of treatment. Late toxicity events included those between 3 months and 10 years after the end of treatment.

These incidences were compared stratifying them for the five levels of grade (0, 1, 2, 3, and 4) and dichotomized for two-level groups (0-2 and 3-4).

The first occurrence of grade 3-4 late toxicity was compared between groups by using the log-rank test and was represented by using Kaplan-Meier curves. Hazard ratio (HR) and its 95% CI were also estimated by using the Cox model. The HR was obtained by dividing the hazard rate of the events observed in the APBI group by the hazard rate of those observed in the WBI arm.

Prevalence of toxicity at different grades between groups was also compared at 1, 3, and 5 years.

The differences between APBI and WBI were also assessed for cosmetic outcomes. Comparisons were performed by using the chi-square test.

Results were considered statistically significant if their P value was $< .05$.

RESULTS

Between March 2007 and March 2019, 3,309 patients were randomly assigned, 1,657 to WBI and 1,652 to APBI. After random assignment, 50 patients assigned to the APBI arm and 34 to the WBI arm were excluded from intention-to-treat analysis because of consent withdrawal, protocol deviation (misinterpretation of the eligibility criteria), or loss to follow-up. After random assignment, a limited number of patients declined the assigned treatment and received the other study treatment, resulting in 1,581 patients being treated with APBI and 1,644 with

TABLE 1. Characteristics of Patients (intention-to-treat)

Characteristic	APBI (n = 1,602)	WBI (n = 1,623)
Age at random assignment, years		
49-60	468 (29.2)	489 (30.1)
60-70	690 (43.1)	644 (39.7)
≥ 70	444 (27.7)	490 (30.2)
Median (25th and 75th percentiles)	65 (58-70)	65 (58-71)
Mean (SD)	64.4 (8.0)	64.7 (8.3)
T stage		
T1	1,479 (92.3)	1,483 (91.4)
T2	121 (7.6)	136 (8.4)
Missing	2 (0.1)	4 (0.3)
N stage		
N0	1,478 (92.3)	1,501 (92.5)
N1	121 (7.6)	119 (7.3)
Missing	3 (0.2)	3 (0.2)
Tumor grade		
I	453 (28.3)	450 (27.7)
II	896 (55.9)	908 (56.0)
III	224 (14.0)	231 (14.2)
Unknown	17 (1.1)	11 (0.7)
Missing	12 (0.8)	23 (1.4)
Histologic type		
Ductal invasive	1,345 (84.0)	1,370 (84.4)
Lobular invasive	136 (8.5)	118 (7.3)
Tubular	39 (2.4)	40 (2.5)
Ductal and lobular	15 (0.9)	23 (1.4)
Others	59 (3.6)	66 (4.1)
Unknown	8 (0.5)	5 (0.3)
Missing	0 (0)	1 (0.1)
Hormone receptor		
ER+/PR+	1,366 (85.3)	1,382 (85.2)
ER+/PR–	166 (10.4)	161 (9.9)
ER–/PR+	1 (0.1)	5 (0.3)
ER–/PR–	53 (3.3)	66 (4.1)
Unknown	1 (0.4)	0 (0.0)
Missing	15 (0.9)	9 (0.6)
HER2-neu		
Positive	71 (4.4)	71 (4.4)
Negative	1,344 (83.9)	1,378 (84.9)
Unknown/missing	187 (11.7)	174 (10.7)
Nodal assessment		
Sentinel node biopsy	1,500 (93.6)	1,516 (93.4)
Axillary dissection	100 (6.3)	77 (6.4)
Missing	2 (0.1)	3 (0.2)
Adjuvant chemotherapy		
Yes	170 (10.6)	163 (10.0)
No	1,432 (89.4)	1,457 (89.8)
Missing	0 (0.0)	3 (0.2)
Endocrine therapy		
Yes	951 (59.4)	949 (58.5)
No	651 (40.6)	671 (41.3)
Missing	0 (0.0)	3 (0.2)

NOTE. Data are No. (%).

Abbreviations: APBI, accelerated partial-breast irradiation; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; SD, standard deviation; WBI, whole-breast irradiation.

WBI; these patients were included in the as-treated analyses (Fig 1).

Patient and tumor characteristics were similar between arms (Table 1).

The overall median follow-up for the whole group was 5.6 (interquartile range [IQR], 4.0-8.4) years; for the APBI group, it was 5.8 (IQR, 4.0-8.5) years, and for the WBI group, 5.5 (IQR, 3.9-8.4) years.

The 5-year overall survival was 97.17% (96.19-97.9) in the WBI group and 97.44% (96.48-98.14) in the APBI group.

The cosmetic outcome at baseline and at years 1, 2, 3, and 5 according to the treatment arm are reported in Table 2.

Cosmetic score assessed by the patients at baseline was not different between the two arms, but a slightly higher proportion of APBI patients had adverse cosmesis than patients in the WBI arm at 3 years (12.7% *v* 9.2%, respectively; $P = .009$) and at 5 years (14% *v* 9.8%, respectively; $P = .012$). Of note, in the APBI arm, the percentage of patients with adverse cosmesis at 5 years is only slightly higher than that at baseline (14% *v* 12.2%, respectively), indicating that there were no relevant further changes after the baseline assessment and the absolute difference between treatment arms was small in any case. Similar results were observed for cosmesis when assessed by the physicians, but the proportions of patients with self-reported adverse cosmesis were lower than adverse cosmesis reported by physicians in both arms. More details about cosmetic outcomes are given in the Data Supplement.

We also performed an analysis of the effect of boost irradiation among patients treated with WBI. At 5 years, no difference was found between the two groups (10.6% of patients without a boost had adverse cosmesis *v* 8.9% of

TABLE 2. Cosmetic Results According to Treatment (intention-to-treat)

	Patients' Assessment			Physicians' Assessment		
Cosmetic Outcome	**APBI**	**WBI**	***P***	**APBI**	**WBI**	***P***
Baseline						
Excellent to good	1,315/1,498 (87.8)	1,319/1,500 (87.9)	.900	1,288/1,523 (84.6)	1,282/1,522 (84.2)	.797
Fair to poor	183/1,498 (12.2)	181/1,500 (12.1)		235/1,523 (15.4)	240/1,522 (15.8)	
1-Year follow-up						
Excellent to good	1,201/1,336 (89.9)	1,141/1,277 (89.4)	.648	1,169/1,343 (87.0)	1,088/1,274 (85.4)	.222
Fair to poor	135/1,336 (10.1)	136/1,277 (10.6)		174/1,343 (13.0)	186/1,274 (14.6)	
3-Year follow-up						
Excellent to good	953/1,092 (87.3)	950/1,046 (90.8)	.009	892/1,085 (82.2)	908/1,040 (87.3)	.001
Fair to poor	139/1,092 (12.7)	96/1,046 (9.2)		193/1,085 (17.8)	132/1,040 (12.7)	
5-Year follow-up						
Excellent to good	682/793 (86.0)	661/733 (90.2)	.012	640/778 (82.3)	623/724 (86.0)	.045
Fair to poor	111/793 (14.0)	72/733 (9.8)		138/778 (17.7)	101/724 (14.0)	

NOTE. Data are No./n (%).
Abbreviations: APBI, accelerated partial-breast irradiation; WBI, whole-breast irradiation.

patients who received a boost; $P = .452$), but at baseline, a higher proportion of patients without a boost had adverse cosmesis than patients treated with boost (14.1% *v* 8.4%; $P = .001$; Data Supplement).

Any acute skin toxicity (≥ grade 1) was observed in 44.7% (713 of 1,596) of the patients in the APBI arm and in 71% (1,147 of 1,615) of the patients allocated to the WBI arm. Aggregated grade 3-4 acute skin toxicity was higher in patients allocated to WBI than to APBI (21 [1.3%] of 1,615 patients treated with WBI *v* two [0.1%] of 1,596 patients treated with APBI; $P < .0001$). Only one patient in the WBI arm experienced grade 4 acute skin toxicity, and none in the APBI arm. Grade 1 and grade 2 acute skin toxicities were registered in 40.7% (649 of 1,596) and 3.9% (62 of 1,596) of the patients in the APBI arm versus 49.8% (805 of 1,615) and 19.9% (321 of 1,615) of the patients in the WBI arm, respectively ($P < .01$).

Grade 4 late toxicity was very low for each assessed end point in both arms, except for bone (Data Supplement). Fourteen (0.9%) of the 1,602 patients in the APBI arm and zero of the 1,623 patients in the WBI arm had grade 4 late bone toxicity. No grade 4 late skin and lung toxicities were registered in both arms. No patients in the APBI arm versus one (0.1%) in the WBI arm experienced grade 4 late soft tissue toxicity. In addition, grade 3 late toxicity was low in both arms (Data Supplement). Forty-five (2.8%) of the 1,602 patients in the APBI arm and 15 (0.9%) of the 1,623 patients in the WBI arm experienced grade 3 late soft tissue toxicity ($P < .01$).

There were no significant differences in late skin and lung toxicities aggregated to two levels (grade 0-2 *v* grade ≥ 3), but late soft tissue toxicity (grade ≥ 3: 45 [2.8%] APBI *v* 16 [1%] WBI, $P < .0001$) and late bone toxicity (grade ≥ 3: 17 [1.1%] APBI *v* 0 [0%] WBI, $P < .0001$) were significantly higher in patients assigned to the APBI arm (Table 3).

A decrease in the prevalence of late skin toxicity was observed between the first year and the third year, and afterward, a plateau was reached that persisted until the fifth observation year in both treatment arms (Table 4). Late soft tissue toxicity decreased in the WBI arm at years 1, 3, and 5, but was slightly increased in the APBI arm between the first year and the third year while afterward remaining stable until the fifth year (Table 4).

The 5-year cumulative risk of grade 3-4 late skin toxicity was low in both arms and did not differ significantly: 0.42% (95% CI, 0.18 to 0.93) for patients assigned to the APBI arm versus 0.42% (0.19 to 0.95) for WBI patients (difference 0% [95% CI, –0.47 to 0.47]; HR, 1.15 [95% CI, 0.42 to 3.17]; $P = .79$; Fig 2).

The cumulative risk of grade 3-4 late soft tissue toxicity at 5 years was significantly higher in the APBI arm (2.83%; 95% CI, 2.06 to 3.89) than in the WBI arm (0.9%; 0.52 to 1.55; difference 1.93% [95% CI, 0.9 to 2.96]; HR, 2.85 [95% CI, 1.61 to 5.05]; $P < .001$; Fig 3).

The cumulative 5-year risk for developing symptomatic (grade ≥ 3) late bone toxicity differed significantly between arms: 1.2% (95% CI, 0.75 to 1.95) for patients allocated to the APBI arm versus 0% for patients assigned to the WBI arm ($P < .001$; Data Supplement).

Similar results were found in the as-treated analyses. Details are given in the Data Supplement.

DISCUSSION

The 5-year results of the multicenter randomized IRMA trial demonstrate that APBI with EBRT is feasible

TABLE 3. Incidence of Late Toxicity (dichotomization into two toxicity grade groups; intention-to-treat)

Late Toxicity	APBI	WBI	*P*
Skin			.7810
Grade 0-2	1,591/1,599 (99.5)	1,608/1,615 (99.6)	
Grade 3-4	8/1,599 (0.5)	7/1,615 (0.4)	
Soft tissue			< .0001
Grade 0-2	1,554/1,599 (97.2)	1,597/1,613 (99.0)	
Grade 3-4	45/1,599 (2.8)	16/1,613 (1.0)	
Lung			.6630
Grade 0-2	1,597/1,599 (99.9)	1,613/1,616 (99.8)	
Grade 3-4	2/1,599 (0.1)	3/1,616 (0.2)	
Bone			< .0001
Grade 0-2	1,581/1,598 (98.9)	1,614/1,614 (100.0)	
Grade 3-4	17/1,598 (1.1)	0/1,614 (0.0)	

NOTE. Data are No./n (%).

Abbreviations: APBI, accelerated partial-breast irradiation; WBI, whole-breast irradiation.

with an overall acceptable toxicity profile. Compared with WBI, twice-daily APBI was associated with a reduced rate of acute toxicity, but with an increased rate of moderate late soft tissue and bone toxicities; twice-daily APBI resulted in a slightly inferior cosmetic outcome. The results regarding the primary end point (ipsilateral breast recurrence) will be reported in a future study, because of an ongoing in-depth investigation to distinguish true and elsewhere ipsilateral local recurrence. However, the identically excellent overall survival in both treatment arms excludes that survival differences affect toxicity data, which therefore can be considered extremely reliable.

The rate of severe acute skin toxicity was very low, but significantly higher in the WBI arm, in line with radiobiologic evidence suggesting that acute toxicity depends more on total dose and volume than dose per fraction. This is comparable with what was observed in other partial breast irradiation (PBI) trials reporting acute skin toxicity (ie, GEC-ESTRO,[14] Florence trial,[8] RAPID,[9] and ELIOT[15]).

Late soft tissue toxicity incidence, instead, was higher in patients treated with APBI, mostly because of an increase in grade 2-3 toxicity, although the grade 3 toxicity was rare in both arms.

The fact that 5-year late toxicity prevalence was lower than the 5-year cumulative incidence means that in some patients, side effects tend to resolve over time, a phenomenon that was recently reported by others.[16]

A limitation of our analysis is that the toxicity was evaluated using only clinician-based outcomes, whereas other trials

TABLE 4. Prevalence of Skin, Soft Tissue, and Bone Toxicities of Grade 0, 1-2, and 3-4 at 1, 3, and 5 Years (intention-to-treat)

	1 Year		3 Years		5 Years	
Grade	APBI	WBI	APBI	WBI	APBI	WBI
Skin						
0	1,369 (89.3)	1,285 (83.9)	1,228 (93.0)	1,197 (91.5)	924 (92.9)	885 (92.5)
1-2	161 (10.5)	245 (16.0)	93 (7.0)	111 (8.5)	70 (7.0)	70 (7.3)
3-4	3 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.2)
Total	1,533 (100.0)	1,531 (100.0)	1,321 (100.0)	1,308 (100.0)	995 (100.0)	957 (100.0)
P	< .001		.166		.805	
Soft tissue						
0	1,012 (66.0)	1,019 (66.6)	833 (63.1)	963 (73.7)	643 (64.7)	748 (78.1)
1-2	516 (33.6)	506 (33.1)	472 (35.7)	338 (25.9)	338 (34.0)	207 (21.6)
3-4	6 (0.4)	5 (0.3)	16 (1.2)	6 (0.5)	13 (1.3)	3 (0.3)
Total	1,534 (100.0)	1,530 (100.0)	1,321 (100.0)	1,307 (100.0)	994 (100.0)	958 (100.0)
P	.901		< .001		< .001	
Bone						
0	1,517 (98.9)	1,526 (99.7)	1,312 (99.3)	1,306 (99.9)	993 (99.8)	955 (99.6)
1-2	10 (0.7)	4 (0.3)	5 (0.4)	1 (0.1)	1 (0.1)	4 (0.42)
3-4	7 (0.5)	0 (0.0)	4 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Total	1,534 (100.0)	1,530 (100.0)	1,321 (100.0)	1,307 (100.0)	995 (100.0)	959 (100.0)
P	.008		.037		.237	

NOTE. Data are No. (%).

Abbreviations: APBI, accelerated partial-breast irradiation; WBI, whole-breast irradiation.

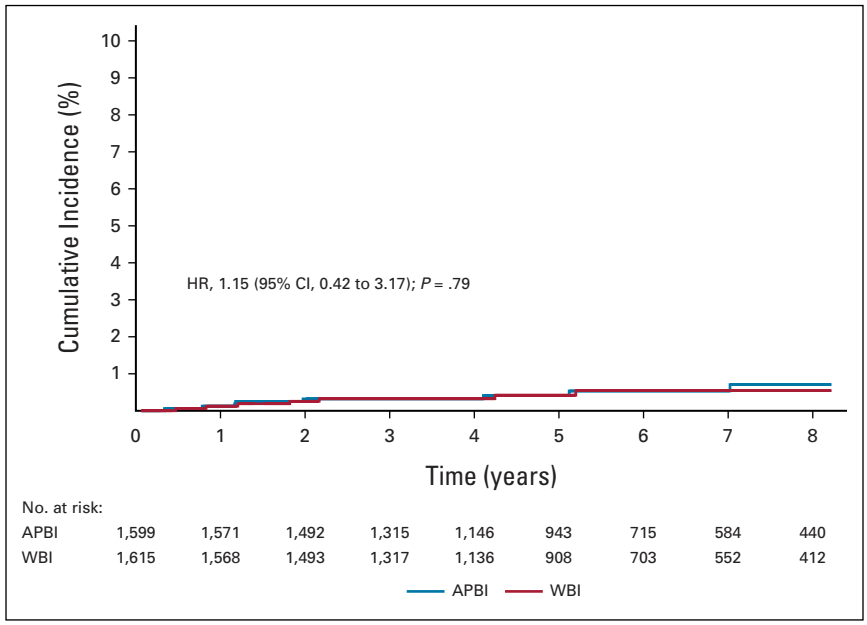

FIG 2. First occurrence of grade 3-4 late skin toxicity (intention-to-treat). APBI, accelerated partial-breast irradiation; HR, hazard ratio; WBI, whole-breast irradiation.

have also reported patient-related outcomes.[17] However, the analysis of the START trial found that both approaches ensure a coherent estimate of the relative treatment effects between arms.[18]

Cosmetic outcomes were good in most patients in both arms at each analyzed time point. A slightly higher proportion of APBI patients had adverse cosmesis than patients treated with WBI at 3 years and 5 years. This difference was primarily due to a different trend, over time, of the development of adverse cosmesis. Cosmesis improved between baseline (postsurgery cosmesis) and 1 year in both arms, but after the first year in the APBI group, there was a trend to worsen, where in WBI patients, it was stable. As a result, in APBI patients, the prevalence of adverse cosmesis at 5 years is higher than that in WBI patients but only slightly higher than that at baseline.

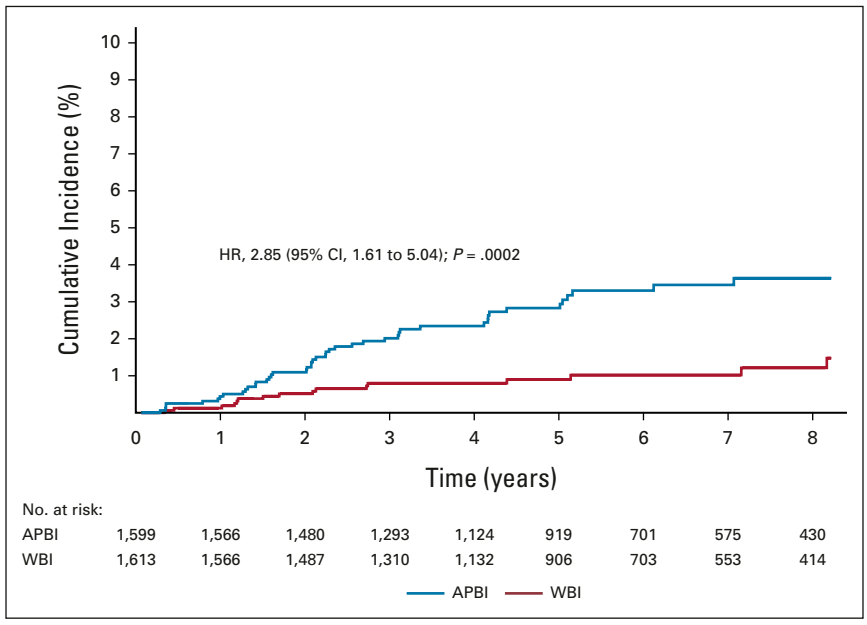

FIG 3. First occurrence of grade 3-4 soft tissue late toxicity (intention-to-treat). APBI, accelerated partial-breast irradiation; HR, hazard ratio; WBI, whole-breast irradiation.

Cosmetic outcomes were not centrally masked using digital photos. This is a limitation, but a digital photography-based documentation before treatment and during follow-up was, however, performed, and a masked analysis will be made in the future.

There are several potential explanations for the increase in late toxicity and the slightly worse cosmesis observed in the APBI arm. In addition to the relatively high fraction size in the APBI arm that already translates into an equivalent dose in 2 Gy that might already be higher, assuming low α/β values, than that for the used WBI schedules, radiobiologic models suggest that a 6-hour interfraction interval may be insufficient to permit complete repair of normal tissue damage.[19] Data from the CHART head-and-neck trial showed that the recovery halftime for fibrosis may be around 4.4 hours.[20] Bentzen and Yarnold,[19] using this recovery halftime, estimated that the APBI schedule used in IRMA would translate into an equivalent dose in 2 Gy of 64.9 Gy for fibrosis as the end point. This also explains why studies of APBI with 24 hours or more interfraction intervals reported less late toxicity than trials with two-daily fractions.

In IMPORT LOW,[21] RT was administered once daily for 3 weeks. Similar adverse effects were registered in the PBI and WBI arms for analyzed end points, and the frequencies of a change in breast appearance and a harder/firmer breast were significantly lower in the PBI arm ($P = .007$). In the Florence trial,[8] APBI was administered in five nonconsecutive once-daily fractions. In the APBI arm, late adverse events were significantly lower than those in the WBI arm. Similar results were observed for cosmetic outcomes. Recently, Boutrus et al,[22] in a prospective randomized single institutional trial, compared patients treated with a once-daily versus a twice-daily APBI schedule. All patients received 38.5 Gy in 10 Fr. A decrease in the incidence of grade 3 late skin and subcutaneous toxicities and a significantly lower proportion of patients with poor/fair cosmesis were reported in patients treated with once-daily fractionation.

In RAPID,[9] NSABP B-39/RTOG 0413,[10] and IRMA, conversely, patients in the APBI arm received 10 twice-daily fractions over 1 week.

Despite the use of the same RT schedule, the results in terms of late side effects differed among the studies. In RAPID, an increase in late soft tissue toxicity and skin telangiectasia was observed in patients treated with APBI. The rate of grade ≥ 3 fibrosis was 2.9% in the APBI arm versus 0.5% in the WBI arm. These data are very similar to the rate of late subcutaneous tissue toxicity observed in IRMA, but the results regarding late skin toxicity, without an immediately obvious explanation, differ between RAPID and IRMA. In NSABP B-39/RTOG 0413, finally, adverse events were similar between the two groups (although a detailed report has not yet been provided). Consequently, no clear pattern of a correlation of toxicity and treatment paradigm emerges, and therefore, the differences in late side effects between these three trials are equivocal and cannot be explained only by the twice-daily schedule used in some of the trials.

One factor that may act as a possible confounder and might explain these observations is the use of a tumor-bed boost in WBI patients. Boost irradiation has been correlated with a higher toxicity and worse cosmesis.[23,24] This also seems to emerge from our post hoc analysis. In NSABP B-39/RTOG 0413, 80% of WBI patients were treated with boost, whereas only 21% and 33% of WBI patients received boost in RAPID and IRMA, respectively. This higher proportion of WBI patients treated with boost in NSABP B-39/RTOG 0413 could have counterbalanced the differences in late side effects between the two arms. The use of brachytherapy in NSABP B-39/RTOG 0413 may also be important. According to GEC-ESTRO-trial,[25] toxicity/cosmetic results are similar in patients treated with brachytherapy APBI or conventional WBI. In NSABP B-39/RTOG 0413, 27% of APBI patients were treated with brachytherapy, which could have counterbalanced the differences in late side effects between the two arms.

Another limitation of our analyses is the lack of data regarding body mass index and bra cup size. Weng et al[26] found that an elevated body mass index and large bra cup size were risk factors for worse patient-reported outcomes across many domains, including cosmesis and physician-rated cosmesis. However, because of our study design, these characteristics should be balanced between arms.

Finally, we also observed an increase in severe (grade 3-4) late bone toxicity in the APBI arm (0% WBI *v* 1.1% APBI). No data regarding bone toxicity were provided in any of the other randomized clinical APBI trials, except for IMPORT LOW. Coles et al,[21] in the Data Supplement, reported data on symptomatic rib fracture. The rate of this event, overall, was equally infrequent as in the IRMA trial, but no differences were found between the three study arms in IMPORT LOW. Additional detailed analyses linking individual dosimetric data to clinical bone toxicity end points may further elucidate this issue.

In conclusion, EBRT-APBI with a twice-daily IRMA schedule was associated with an increased rate of moderate late soft tissue and bone toxicities and a slight decrease in patient-reported cosmetic outcomes at 5 years when compared with WBI although overall toxicity was in an acceptable range. Nevertheless—although available data are not unequivocal—given its likely slightly better toxicity profile among the currently available APBI data sets, once-daily fractionation should currently be the preferred regimen for APBI. The relative merit of APBI in comparison with short WBI schedules such as FAST and FAST-FORWARD is still to be defined.

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REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group, Darby S, McGale P, et al: Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 378:1707-1716, 2011
2. van Maaren MC, de Munck L, de Bock GH, et al: 10 Year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: A population-based study. Lancet Oncol 17:1158-1170, 2016
3. Lagendijk M, van Maaren MC, Saadatmand S, et al: Breast conserving therapy and mastectomy revisited: Breast cancer-specific survival and the influence of prognostic factors in 129,692 patients. Int J Cancer 142:165-175, 2018
4. Showalter SL, Grover S, Sharma S, et al: Factors influencing surgical and adjuvant therapy in stage I breast cancer: A SEER 18 database analysis. Ann Surg Oncol 20:1287-1294, 2013
5. Gu J, Groot G, Boden C, et al: Review of factors influencing women's choice of mastectomy versus breast conserving therapy in early stage breast cancer: A systematic review. Clin Breast Cancer 18:e539-e554, 2018
6. Lam J, Cook T, Foster S, et al: Examining determinants of radiotherapy access: Do cost and radiotherapy inconvenience affect uptake of breast-conserving treatment for early breast cancer? Clin Oncol (R Coll Radiol) 27:465-471, 2015
7. Nattinger AB, Kneusel RT, Hoffmann RG, et al: Relationship of distance from a radiotherapy facility and initial breast cancer treatment. J Natl Cancer Inst 93: 1344-1346, 2001

8. Meattini I, Marrazzo L, Saieva C, et al: Accelerated partial-breast irradiation compared with whole-breast irradiation for early breast cancer: Long-term results of the randomized phase III APBI-IMRT-Florence trial. J Clin Oncol 38:4175-4183, 2020
9. Whelan TJ, Julian JA, Berrang TS, et al: External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): A randomised controlled trial. Lancet 394:2165-2172, 2019
10. Vicini FA, Cecchini RS, White JR, et al: Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: A randomised, phase 3, equivalence trial. Lancet 394:2155-2164, 2019
11. Formenti SC: External-beam partial-breast irradiation. Semin Radiat Oncol 15:92-99, 2005
12. Cox JD, Stetz J, Pajak TF: Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 31:1341-1346, 1995
13. Harris JR, Levene MB, Svensson G, et al: Analysis of cosmetic results following primary radiation therapy for stages I and II carcinoma of the breast. Int J Radiat Oncol Biol Phys 5:257-261, 1979
14. Ott OJ, Strnad V, Hildebrandt G, et al: GEC-ESTRO multicenter phase 3-trial: Accelerated partial breast irradiation with interstitial multicatheter brachytherapy versus external beam whole breast irradiation: Early toxicity and patient compliance. Radiother Oncol 120:119-123, 2016
15. Veronesi U, Orecchia R, Maisonneuve P, et al: Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): A randomised controlled equivalence trial. Lancet Oncol 14:1269-1277, 2013
16. Poortmans PM, Struikmans H, De Brouwer P, et al: Side effects 15 years after lymph node irradiation in breast cancer: Randomized EORTC trial 22922/10925. J Natl Cancer Inst 113:1360-1368, 2021
17. Bhattacharya IS, Haviland JS, Kirby AM, et al: Patient-reported outcomes over 5 years after whole- or partial-breast radiotherapy: Longitudinal analysis of the IMPORT LOW (CRUK/06/003) phase III randomized controlled trial. J Clin Oncol 37:305-317, 2019
18. Haviland JS, Hopwood P, Mills J, et al: Do patient-reported outcome measures agree with clinical and photographic assessments of normal tissue effects after breast radiotherapy? The experience of the standardisation of breast radiotherapy (START) trials in early breast cancer. Clin Oncol (R Coll Radiol) 28:345-353, 2016
19. Bentzen SM, Yarnold JR: Reports of unexpected late side effects of accelerated partial breast irradiation—Radiobiological considerations. Int J Radiat Oncol Biol Phys 77:969-973, 2010
20. Bentzen SM, Saunders MI, Dische S: Repair halftimes estimated from observations of treatment-related morbidity after CHART or conventional radiotherapy in head and neck cancer. Radiother Oncol 53:219-226, 1999
21. Coles CE, Griffin CL, Kirby AM, et al: Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-Year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. Lancet 390:1048-1060, 2017
22. Boutrus RR, El Sherif S, Abdelazim Y, et al: Once daily versus twice daily external beam accelerated partial breast irradiation: A randomized prospective study. Int J Radiat Oncol Biol Phys 109:1296-1300, 2021
23. 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 25:3259-3265, 2007
24. King MT, Link EK, Whelan TJ, et al: Quality of life after breast-conserving therapy and adjuvant radiotherapy for non-low-risk ductal carcinoma in situ (BIG 3-07/TROG 07.01): 2-Year results of a randomised, controlled, phase 3 trial. Lancet Oncol 21:685-698, 2020
25. Polgár C, Ott OJ, Hildebrandt G, et al: Late side-effects and cosmetic results of accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: 5-Year results of a randomised, controlled, phase 3 trial. Lancet Oncol 18:259-268, 2017
26. Weng JK, Lei X, Schlembach P, et al: Five-year longitudinal analysis of patient-reported outcomes and cosmesis in a randomized trial of conventionally fractionated versus hypofractionated whole-breast irradiation. Int J Radiat Oncol Biol Phys 111:360-370, 2021

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Cosmetic Results and Side Effects of Accelerated Partial-Breast Irradiation Versus Whole-Breast Irradiation for Low-Risk Invasive Carcinoma of the Breast: The Randomized Phase III IRMA Trial

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