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Scientific Article

Patterns of Recurrence Among Higher-Risk Patients Receiving Daily External Beam Accelerated Partial-Breast Irradiation to 40 Gy in 10 Fractions

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Abstract

Purpose: The 2016 American Society for Radiation Oncology consensus guidelines for the use of accelerated partial-breast irradiation (APBI) define "suitable," "cautionary," and "unsuitable" populations for this adjuvant breast radiation therapy technique. We sought to determine whether patients in the cautionary group exhibited adverse outcomes after APBI compared with their suitable counterparts.

Methods and Materials: We identified 252 consecutively treated patients from a single institution with in situ or early-stage invasive breast cancer who underwent APBI between 2008 and 2017. Treatment technique was uniform throughout the population, consisting of 3-dimensional conformal radiation therapy to 40 Gy administered in 10 daily fractions.

Results: One hundred seventy-eight patients (70%) were classified as suitable, 69 (27%) as cautionary, and 5 (2.0%) as unsuitable. Because unsuitable patients were few and had no recurrences, they were excluded from analysis. At a median follow-up time of 3.9 years, 97.2% of patients were free of recurrence. Four patients (1.5% overall; 3 suitable and 1 cautionary) experienced ipsilateral in-breast recurrences, and 1 cautionary patient developed an ipsilateral regional recurrence in an axillary lymph node. There was no significant difference in the rate of ipsilateral breast recurrence (2.4% vs 1.0%) between cautionary and suitable groups.

Conclusions: Local recurrences are rare among guideline-defined cautionary patients with in situ or invasive breast cancer treated with APBI delivered via daily 3-dimensional conformal radiation therapy to 40 Gy. At a median follow-up of 3.9 years, no significant differences in local control were noted between cautionary and suitable patient groups. Further study is needed to characterize long-term disease outcomes among various risk groups.

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Introduction

Breast-conserving surgery followed by adjuvant radiation therapy (RT) is the preferred definitive regimen for most women with early-stage in situ or invasive breast cancer.[1,2] Historically, RT has consisted of up to 6 weeks of daily treatment to the whole breast. In recent decades, however, data have supported adoption of accelerated partial-breast irradiation (APBI), in which larger fractions may be delivered more rapidly over 1 to 3 weeks, targeting only the tumor bed rather than the whole breast.[3] Moreover, several trials show that APBI may afford similar local control to whole-breast radiation among appropriately selected patients.[4-9]

APBI techniques include external beam radiation therapy (3-dimensional conformal or intensity modulated RT), brachytherapy (intracavitary or interstitial), and intraoperative radiation therapy.[10] Brachytherapy-based techniques have the longest follow-up data, with largely favorable long-term outcomes.[4,11,12] Improvements in tumor bed demarcation along with 3-dimensional planning techniques have enabled adoption of external beam APBI using extant technologies and expertise. Indeed, the practical advantages of noninvasive APBI have led many institutions to deprecate their breast brachytherapy programs. We adopted an external beam APBI regimen consisting of 4 Gy delivered once daily in 10 fractions to a total dose of 40 Gy. This regimen differs from the twice-daily fractionation to 34 to 38.5 Gy used by the National Surgical Adjuvant Breast and Bowel Project B39 and RAPID trials.[8,9] The selection of this dosing scheme was based on excellent preliminary tolerability and efficacy data from our institution[13,14] and others[15] and robust patient preference for the convenience of a once-daily fractionation scheme compared with twice-daily (70% vs 30%).[16] We expect local control with this convenient daily regimen to be similar to twice-daily fractionation with more putatively improved cosmesis than seen with twice-daily fractions, based on radiobiologic priniciples.[17]

The identification of appropriate candidates for APBI remains an active area of research. The American Society for Radiation Oncology (ASTRO) has issued 2 consensus statements regarding criteria for employing APBI outside of a clinical trial. The original guidelines in 2009 were based on early literature demonstrating low event rates among a highly selected group of patients.[18] These recommendations were updated in 2016 to incorporate additional evidence, largely expanding the application of APBI to include patients studied on 3 randomized trials.[19]

The APBI consensus guidelines now classify patients as suitable, cautionary, or unsuitable candidates based on age and salient disease parameters. These categories are based on prior study populations in which more than 90% of patients had T1N0 with estrogen receptor (ER)-positive disease and more than 80% were >50 years old. Having routinely employed external beam APBI within our institution before wide implementation of the consensus guidelines, we sought to determine whether our patients who were retrospectively classified as cautionary exhibited adverse outcomes in comparison to their suitable counterparts.

Methods and Materials

Patient selection and classification

We identified 252 consecutive patients who were treated with adjuvant APBI after breast-conserving surgery at our center between 2008 and 2017. The 2016 ASTRO consensus guidelines for APBI were retrospectively applied.[19] In brief, suitable patients were those age $\geq$50 with T_{is} cancer <2.5 cm or T1 cancer and margins for invasive cancer negative by $\geq$ 2 mm ($\geq$3 mm for ductal carcinoma in situ [DCIS]). Suitable patients with DCIS must have also had screen-detected disease and low to intermediate nuclear grade. Cautionary patients were those age 40 to 49 and meeting all other suitable criteria or age $\geq$50 with 1 of the following pathologic risk factors: invasive tumor size 2.1 to 3.0 cm, close margins for invasive cancer (<2 mm), limited or focal lymphovascular invasion, ER negativity, microscopically multifocal disease with a total size of 2.1 to 3.0 cm, invasive lobular histology, pure DCIS $\leq$3 cm but not all "suitable" criteria met, or an extensive intraductal component <3 cm. Unsuitable patients were those age <40, age 40 to 49 and not meeting the cautionary criteria, positive margins, or DCIS >3 cm.

Radiation simulation, planning, and delivery

All patients underwent computed tomography simulation in the supine position. The lumpectomy cavity and tumor bed were then identified, and a clinical target volume was contoured based on the presence of surgical clips or seroma. An isotropic margin of 1.5 to 2 cm was added to generate the planning target volume (PTV). Margin expansion anteriorly was limited to within 5 mm of the skin

Table 1 Overall characteristics of the patient population treated with partial-breast radiation

	N = 252 (%)
Median age, y (range)	63 (39-90)
Median tumor size, cm (range)	0.9 (0.1-3.8)
Histology	
DCIS	36 (14.3)
Invasive ductal	180 (71.4)
Invasive lobular	13 (5.2)
Mucinous	11 (4.4)
Papillary	2 (0.8)
Tubular	10 (4)
Grade (invasive)	
1	38 (15.1)
2	59 (23.4)
3	113 (44.8)
Grade (DCIS)	
Low	4 (1.6)
Intermediate	25 (9.9)
High	7 (2.8)
Side	
Left	130 (51.6)
Right	122 (48.4)
Estrogen receptor	
Positive	233 (92.5)
Negative	8 (3.2)
Progesterone receptor	
Positive	199 (79)
Negative	28 (11.1)
Her2 receptor	
Positive	6 (2.4)
Negative	246 (97.6)
Close margins*	14 (5.6)
LVI-positive	14 (5.6)
Received chemotherapy	28 (11.1)
Received hormone therapy	204 (81)

Abbreviations: DCIS = ductal carcinoma in situ; LVI = lymphovascular invasion.

* *Close margins* are defined as <2 mm for invasive cancer and <3 mm for DCIS per consensus guidelines.

surface and posteriorly by the chest wall (the anterior rib surface). A dose of 40 Gy in 10 daily fractions, 5 days per week, was prescribed to the PTV and delivered with a combination of photon beams (energy ≥6 MV) with or without an electron beam contribution (see contouring and planning parameters at http://econtour.org/cases/108).[14]

Dosimetric constraints were set to limit 50% of the uninvolved ipsilateral breast (ipsilateral breast minus PTV) to <50% of the prescription dose. Ipsilateral lung volume receiving 20 Gy (V20) was limited to ≤3%; V10 was ≤10%; and V5 was ≤20%. Maximum heart and liver dose were limited to <90% of the prescription dose.

RT was initiated 2 weeks after simulation and typically 4 to 12 weeks postsurgery, or 2 to 6 weeks after completion of chemotherapy. kV imaging with alignment of surgical cavity clips was used for daily setup.

Statistics

Demographic and clinical features were compared across cautionary and suitable groups. The Wilcoxon rank sum test and Fisher exact test were employed for continuous and categorical variables, respectively. Cumulative incidence of local recurrence was assessed using a competing risk model with a competing risk of death without local recurrence.

Results

Patient characteristics

The cohort included 252 consecutively treated female patients with in situ or early-stage invasive breast cancer who were treated with APBI between 2008 and 2017 (Table 1). Mean patient age was 63 (range, 39-90), and the most common histologies were invasive ductal carcinoma (73%) and DCIS (13%). Nearly all tumors were ER-positive (93%) and HER2-negative (98%), and nearly half of invasive tumors were high-grade (45%). Thus, most invasive tumors were classified as luminal A (ER + or progesterone receptor−positive, HER2−, and grade 1-2; n = 96) or luminal B (ER + or progesterone receptor−positive, HER2−, and grade 3; n = 102).[20] In turn, 88% of ER + patients received antiestrogen therapy, whereas 11% of the overall cohort received chemotherapy that was typically driven by molecular subtype (triple-negative or HER2−amplified) or elevated Oncotype DX score.

Patient stratification by ASTRO APBI consensus guidelines

Of the 252 patients, 178 (70%) were retrospectively classified by consensus guidelines as suitable for APBI and 69 (27%) were classified as cautionary. Five patients were classified as unsuitable owing to age <40 (N = 1), age 40 to 49, and not otherwise meeting the suitable criteria (N = 3), or large tumor size (N = 1). Because the number of unsuitable patients was small and no recurrences occurred in this group (local, regional, or distant), they were excluded from further analysis.

Young age was the most common cautionary feature, with 32% of patients in the cautionary group being <50 years old (Table 2). The second most common reason for a cautionary designation was close margin status, defined as <2 mm for invasive cancer and <3 mm for in situ disease (20% of patients, Table 2). In addition, 9% of patients in the cautionary group had >1 cautionary risk factor.

Table 3 contrasts the aggregate characteristics of the cautionary and suitable patient groups. Characteristics significantly different between the 2 subgroups included histologic subtype (largely driven by the inclusion of invasive lobular carcinomas exclusively in the cautionary

Table 2 Tabulation of "cautionary" risk factors among the cohort per 2016 consensus guidelines

Risk factor	Patient number (%)*
Age 40-49	22 (31.8)
Large tumor size†	2 (5.8)
Lobular histology	13 (18.8)
High-grade DCIS	6 (8.7)
ER-negative	7 (10.1)
Close margins‡	14 (20.3)
LVI	12 (17.4)

Abbreviations: DCIS = ductal carcinoma in situ; ER = estrogen receptor; LVI = lymphovascular invasion.

* Although the total number of patients in this group was 69, 6 patients had more than 1 cautionary risk factor (hence aggregate percentages exceed 100%).

† *Large tumor size* is defined as >2.0 cm for invasive cancer and >2.5 cm for DCIS.

‡ *Close margins* are defined as <2 mm for invasive cancer and <3 mm for DCIS per consensus guidelines.

group), grade of DCIS (10% high grade vs 0%, respectively; $P = .001$), close margins (20% vs 0%; $P < .001$), lack of estrogen receptor expression (10% ER−vs 0%; $P < .001$), and presence of lymphovascular invasion (17% vs 0%; $P < .001$). The groups did not differ significantly with respect to age, tumor size, invasive histologic grade, HER2/neu amplification, or treatment with either chemotherapy or hormone therapy.

Outcomes

At a median follow-up time of 47 months, 97% of patients remained free of any breast cancer recurrence. Five patients (2% overall; n = 3 suitable; n = 2 cautionary) experienced ipsilateral locoregional recurrence: 4 within the treated breast and 1 isolated axillary recurrence. No significant differences were observed in the rates of locoregional recurrence between cautionary and suitable groups (Fig 1). The 4-year local recurrence rate was 2.4% among cautionary patients and 1% among suitable patients.

Of the 4 patients with ipsilateral breast recurrences, none required a mastectomy and all were able to undergo salvage lumpectomy. Three of the 4 received salvage whole-breast radiation to a reduced dose (45-46.8 Gy in 25-26 fractions); 1 patient received an additional boost of 12.5 Gy in 5 fractions to the second lumpectomy cavity. One patient with an axillary nodal recurrence underwent salvage dissection followed by chemotherapy and salvage radiation to the whole breast and nodes, with reduced dose administered to the area that received the prior partial-breast radiation.

One patient (0.4%) classified as suitable developed distant metastases shortly after therapy and succumbed to disseminated disease. An additional suitable patient developed contralateral breast cancer and is currently free of disease after breast-conserving therapy.

Table 3 Comparison of the suitable and cautionary groups of patients treated with APBI, as stratified by 2016 ASTRO consensus guidelines

	N = 69 (%)	N = 178 (%)	*P* value
Age, y (range)	62 (40-90)	63 (50-88)	.122
Tumor size, cm (range)	0.9 (0.1-2.7)	0.9 (0.1-2)	.988
Histology			<.001
DCIS	13 (18.8)	21 (11.8)	
Invasive ductal	37 (53.6)	141 (79.2)	
Invasive lobular	13 (18.8)	0 (0)	
Other	6 (8.7)	16 (9.0)	
Grade (Invasive)			.078
1	9 (13.0)	29 (16.2)	
2	9 (13.0)	50 (28.0)	
3	34 (49.2)	76 (42.7)	
Grade (DCIS)			.001
Low	0 (0)	4 (2.2)	
Intermediate	7 (10.1)	17 (9.6)	
High	6 (8.7)	0 (0)	
Side			.068
Left	32 (46.4)	97 (54.5)	
Right	37 (53.6)	81 (45.5)	
ER-positive	60 (87)	169 (94.9)	<.001
Her2-positive	4 (5.8)	2 (1.1)	.053
Close margins*	14 (20.3)	0 (0)	<.001
LVI-positive	12 (17.4)	0 (0)	<.001
Received chemotherapy	10 (14.5)	17 (9.6)	.264
Received hormone therapy	52 (75.4)	150 (84.3)	.14

Abbreviations: APBI = accelerated partial-breast irradiation; ASTRO = American Society for Radiation Oncology; DCIS = ductal carcinoma in situ; ER = estrogen receptor; LVI = lymphovascular invasion.

* *Close margins* are defined as <2 mm for invasive cancer and <3 mm for DCIS per consensus guidelines.

Figure 2 illustrates the pertinent clinical details among the 5 patients who developed locoregional recurrence, including variations in subtype, histology, and anatomy between primary (1°) and recurrent (2°) lesions. The time from diagnosis of the primary tumor to development of recurrence ranged from 1.8 to 5.2 years, and all women were >60 years old at time of initial diagnosis.

Discussion

By retrospectively applying ASTRO consensus definitions to this early experience with daily fractionation external beam APBI, we demonstrate limited distinction in locoregional risk outcomes between suitable and cautionary patients. Of 252 patients, only 5 recurrences were noted with no appreciable differences at this early time point between the 2 risk strata.

ASTRO has issued 2 consensus guidelines for APBI spanning several decades of clinical investigation.[18,19]

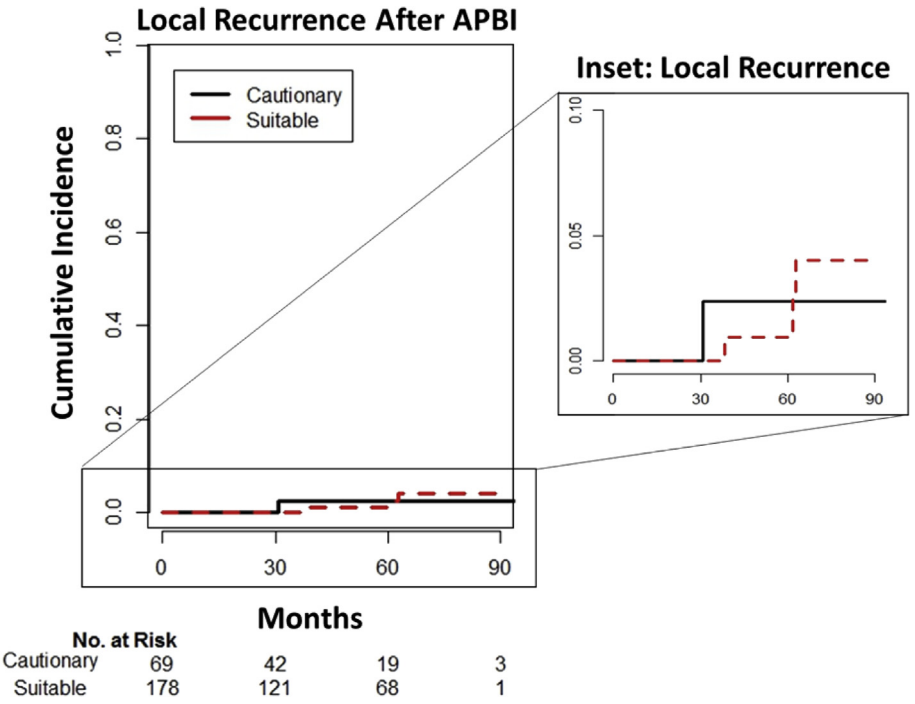
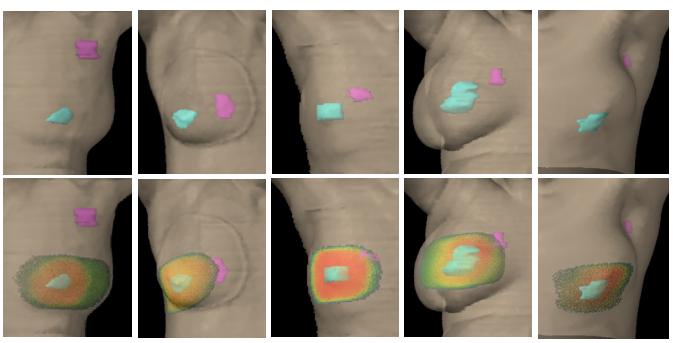


Figure 1 Cumulative incidence of ipsilateral breast recurrences after accelerated partial-breast irradiation. The rate of incidence is very low, as further illustrated from the zoomed-in inset. There was no significant difference in the rate of ipsilateral recurrence between cautionary and suitable groups.

Abbreviations:
IDC, invasive ductal carcinoma
Multi, multifocal
Mic, microinvasive
Papil, invasive papillary
ER, estrogen receptor
PR, progesterone receptor
LVI, lymphovascular invasion
CMF, cyclophosphamide + methotrexate + fluorouracil
AC-T, doxorubicin + cyclophosphamide + paclitaxel
AI, aromatase inhibitor
Tam, tamoxifen



	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5	
ASTRO PBI Category	Suitable		Suitable		Suitable		Cautionary		Cautionary	
	1°	2°	1°	2°	1°	2°	1°	2°	1°	2°
Tumor Size (cm)	1.4	1.2	0.9	0.4	1.4	0.7	0.6	Multi	0.8	2.2
Histology	IDC	IDC	IDC	IDC	Papil	Papil	IDC	Mic	IDC	IDC
Histology Grade	3	3	3	3	3	3	3	N/A	3	3
Receptor (ER/PR/Her2)	+/-/-	+/-/-	+/+/-	+/+/-	+/+/-	+/+/-	-/-/-	-/-/-	+/+/-	+/-/-
Close Margins	No	No	No	No	No	No	No	No	Yes	No
LVI	No	No	No	No	No	No	No	No	No	Yes
Lymph Nodes	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Pos
Chemo?	CMF	T	CMF	No	No	No	CMF	A-T	CMF	AC-T
Hormonal Therapy?	AI	Tam	AI	Tam	No	AI	No	No	Tam	Yes

Figure 2 Pertinent clinical details of the 5 patients who developed locoregional recurrences. Upper panels depict the locations of primary tumors (cyan) and ipsilateral recurrences (magenta) in 4 patients who experienced local recurrence and 1 who experienced regional recurrence after accelerated partial-breast irradiation treatment. Lower panels depict the isodose distribution of the initial definitive accelerated partial-breast irradiation regimen, from the 50% dose level to the plan maximum dose (ranging up to 107.5%-115%). Planning target volume expansions were 2 cm for 4 out of 5 patients and 1.5 cm for patient 4. Clinicopathologic features are listed for primary (1°) and recurrent (2°) lesions. Close margins are defined as <2 mm for invasive cancer and <3 mm for ductal carcinoma in situ per consensus guidelines.

With increasing reports on the safety and efficacy of APBI, updated guidance significantly expanded patient selection criteria, reclassifying many previously cautionary patients as suitable. Even among this contemporary higher-risk cautionary cohort, our study suggests that external beam APBI remains feasible with an exceedingly low recurrence rate.

An anatomic analysis of patterns of failure among our cohort yields an interesting observation: of the 5 patients with ipsilateral locoregional recurrence, 3 of the recurrences arose in the dose fall-off region and could be considered "marginal" recurrences. Two marginal recurrences were in suitable patients, and 1 was in a cautionary patient. Of all 5 patients with locoregional recurrences, PTV expansions on the seroma cavity and clips were 2 cm for 4 patients and 1.5 cm for 1 patient. One patient with a recurrence in the dose fall-off region was both in the cautionary cohort and was treated with 1.5 cm margins. It is unclear whether a whole-breast RT approach would have mitigated these events. Because it is known that local recurrence risk decreases with distance from the tumor bed,[21-23] the immediate region around the initial tumor would be the predicted location of most recurrences regardless of whether partial- or whole-breast radiation was used. Given the low rate of events among this cohort, the RT treatment margins of 1.5 to 2 cm appear adequate.[24]

It also bears noting that of the 5 patients with ipsilateral locoregional recurrences, 4 received chemotherapy (80%). In contrast, only 11% of the entire 252-patient cohort received chemotherapy. This finding may represent the higher-risk nature of patients receiving chemotherapy (due to high Oncotype DX score, ER negativity, or other factors typically considered for systemic therapy). Further study is needed to determine whether prior chemotherapy has implications for APBI suitability.

Our findings appear consistent with other institutional reports and larger prospective studies. Shah et al reported on 290 patients treated with a more prolonged partial-breast irradiation regimen to 43.2 Gy in 16 fractions.[25] At a median follow-up of 8 years, there was no difference in ipsilateral breast recurrences between suitable, cautionary, and unsuitable patients, although recurrence after partial-breast irradiation did outpace whole-breast RT recurrences, highlighting the importance of appropriate patient selection. Jawad et al published a study on a larger cohort of 690 patients treated with a variety of APBI techniques (interstitial brachytherapy, balloon brachytherapy, and 3-dimensional conformal external beam radiation).[26] Among these, local recurrences were not significantly different among the 3 risk strata ($P = .58$). In a third study comprising 238 patients who underwent exclusively balloon-based techniques, the 4-year rate of in-breast recurrences was again similar among ASTRO consensus groups.[27] In aggregate, these reports suggest that the current stratification criteria do not robustly identify the patients most likely to experience recurrence when treated with APBI. Longer follow-up among these cohorts with relatively indolent disease will be informative.

Results from 2 landmark studies of twice-daily external beam APBI versus whole-breast irradiation support the continued feasibility of this approach. The RAPID trial reported that APBI was noninferior to whole-breast irradiation in preventing local recurrences at 8 years (3.0% vs 2.8%),[9] whereas the National Surgical Adjuvant Breast and Bowel Project B-39 and Radiation Therapy Oncology Group 0413 trial failed to meet its prespecified noninferiority endpoint for APBI, although the absolute difference in ipsilateral breast control was <1% (95.2% control in the APBI arm vs 95.9% in the whole-breast irradiation arm).[8] Notably, RAPID demonstrated increased adverse cosmesis with APBI (32% vs 16%), and B39 showed a slight increase in grade 3 toxicity as well (9.6% vs 7.1%). These reports provide a framework for studying a daily fractionation scheme that is hypothesized to yield favorable cosmesis, as we have previously reported.[14] Additional analysis to further characterize efficacy and cosmetic endpoints is needed.

Strengths of our study include a uniformity of technique and dosing, allowing these conclusions to be applied to a single practicable technique that is easily implemented (as noted above, typically using opposed partial-breast tangents with an en face electron contribution to a total dose of 40 Gy over 10 daily fractions). Moreover, the size of this cohort is relatively large considering the recent development of external beam APBI techniques. We observed a low event rate among both suitable and cautionary cohorts, supporting the low-risk nature of these groups after daily external beam APBI, yet precluding robust statistical comparison of risk factors in the setting of limited events. While longer follow-up will provide more definitive evidence for this regimen, local recurrences among ER-negative subtypes tend to occur early, and we identified no safety concerns among patients who were ER-negative in these early data.

Conclusions

As the relevant literature has grown in recent years, APBI rates increased from 3.8% in 2004 to 10.6% in 2011.[28] APBI utilization will likely continue to increase, given the practical convenience of abbreviated noninvasive adjuvant therapy. Our study provides additional supportive evidence that APBI affords excellent rates of in-breast tumor control among appropriately selected patients with cautionary risk profiles. Longer follow-up studies will further elucidate the appropriateness of this treatment paradigm among various risk strata.

References

1. McGuire KP, Santillan AA, Kaur P, et al. Are mastectomies on the rise? A 13-year trend analysis of the selection of mastectomy versus breast conservation therapy in 5865 patients. *Ann Surg Oncol*. 2009; 16:2682-2690.
2. Habermann EB, Abbott A, Parsons HM, Virnig BA, Al-Refaie WB, Tuttle TM. Are mastectomy rates really increasing in the United States? *J Clin Oncol*. 2010;28:3437-3441.
3. Hickey BE, Lehman M, Francis DP, See AM. Partial breast irradiation for early breast cancer. *Cochrane Database Syst Rev*. 2014:CD007077.
4. Strnad V, Ott OJ, Hildebrandt G, et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: A randomised, phase 3, non-inferiority trial. *Lancet*. 2016;387:229-238.
5. Polgár C, Fodor J, Major T, Sulyok Z, Kásler M. Breast-conserving therapy with partial or whole breast irradiation: Ten-year results of the Budapest randomized trial. *Radiother Oncol*. 2013;108:197-202.
6. Livi L, Meattini I, Marrazzo L, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. *Eur J Cancer*. 2015;51:451-463.
7. Rodríguez N, Sanz X, Dengra J, et al. Five-year outcomes, cosmesis, and toxicity with 3-dimensional conformal external beam radiation therapy to deliver accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys*. 2013;87:1051-1057.
8. Vicini F, Cecchini R, White J, et al. Abstract GS4-04: Primary results of NSABP B-39/RTOG 0413 (NRG Oncology): A randomized phase III study of conventional whole breast irradiation (WBI) versus partial breast irradiation (PBI) for women with stage 0, I, or II breast cancer. *Cancer Res*. 2019;79:GS4-04-GS04-04.
9. Whelan T, Julian J, Levine M, et al. Abstract GS4-03: RAPID: A randomized trial of accelerated partial breast irradiation using 3-dimensional conformal radiotherapy (3D-CRT). *Cancer Res*. 2019; 79:GS4-03-GS04-03.
10. Njeh CF, Saunders MW, Langton CM. Accelerated partial breast irradiation (APBI): A review of available techniques. *Radiat Oncol*. 2010;5:90.
11. 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*. 2016;120:119-123.
12. Polgar C, Major T, Mangel L, et al. 48 Sole HDR-brachytherapy after breast conserving surgery: 4 year results of a pilot study and initial findings of a randomized phase III trial. *Radiother Oncol*. 2000;55:31.
13. Cahlon O, Ho A, Siu C, et al. A phase II study of once a day partial breast irradiation (PBI) for early-stage or noninvasive breast cancer: early toxicity outcomes. *Int J Radiat Oncol Biol Phys*. 2015;93:E15.
14. Braunstein LZ, Thor M, Flynn J, et al. Daily fractionation of external beam accelerated partial breast irradiation to 40Gy is well tolerated and locally effective. *Int J Radiat Oncol Biol Phys*. 2019.
15. Trovo M, Roncadin M, Polesel J, et al. Toxicity and cosmesis following partial breast irradiation consisting of 40 Gy in 10 daily fractions. *Breast*. 2013;22:744-747.
16. Hoopes DJ, Kaziska D, Chapin P, et al. Patient preferences and physician practice patterns regarding breast radiotherapy. *Int J Radiat Oncol Biol Phys*. 2012;82:674-681.
17. Liss AL, Ben-David MA, Jagsi R, et al. Decline of cosmetic outcomes following accelerated partial breast irradiation using intensity modulated radiation therapy: Results of a single-institution prospective clinical trial. *Int J Radiat Oncol Biol Phys*. 2014;89:96-102.
18. Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *Int J Radiat Oncol Biol Phys*. 2009;74:987-1001.
19. Correa C, Harris EE, Leonardi MC, et al. Accelerated partial breast irradiation: Executive summary for the update of an ASTRO evidence-based consensus statement. *Pract Radiat Oncol*. 2017;7:73-79.
20. Goldhirsch A, Wood WC, Coates AS, et al. Strategies for subtypes—dealing with the diversity of breast cancer: Highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. *Ann Oncol*. 2011;22:1736-1747.
21. Dirbas APFM, Jeffrey DSS, Goffinet DDR. The evolution of accelerated, partial breast irradiation as a potential treatment option for women with newly diagnosed breast cancer considering breast conservation. *Cancer Biother Radiopharm*. 2004;19:673-705.
22. Fisher ER, Anderson S, Tan-Chiu E, Fisher B, Eaton L, Wolmark N. Fifteen-year prognostic discriminants for invasive breast carcinoma. *Cancer*. 2001;91:1679-1687.
23. Smith TE, Lee D, Turner BC, Carter D, Haffty BG. True recurrence vs. new primary ipsilateral breast tumor relapse: An analysis of clinical and pathologic differences and their implications in natural history, prognoses, and therapeutic management. *Int J Radiat Oncol Biol Phys*. 2000;48:1281-1289.
24. Vicini FA, Kestin LL, Goldstein NS. Defining the clinical target volume for patients with early-stage breast cancer treated with lumpectomy and accelerated partial breast irradiation: A pathologic analysis. *Int J Radiat Oncol Biol Phys*. 2004;60:722-730.
25. Shah S, Kyrillos A, Kuchta K, et al. A single institution retrospective comparison study of locoregional recurrence after accelerated partial breast irradiation using external beam fractionation compared with whole breast irradiation with 8 years of follow-up. *Ann Surg Oncol*. 2017;24:2935-2942.
26. Jawad MS, Shah C, Wilkinson JB, et al. Seven-year outcomes following accelerated partial breast irradiation stratified by ASTRO consensus groupings. *Am J Clin Oncol*. 2017;40:483-489.
27. Christoudias MK, Collett AE, Stull TS, Gracely EJ, Frazier TG, Barrio AV. Are the American Society for Radiation Oncology Guidelines accurate predictors of recurrence in early stage breast cancer patients treated with balloon-based brachytherapy? *Int J Surg Oncol*. 2013;2013:7.
28. Shaitelman SF, Lin HY, Smith BD, et al. Practical implications of the publication of consensus guidelines by the American Society for Radiation Oncology: Accelerated partial breast irradiation and the National Cancer Data Base. *Int J Radiat Oncol Biol Phys*. 2016;94: 338-348.