

Breast/Soft Tissue

The American Brachytherapy Society consensus statement for accelerated partial-breast irradiation

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ABSTRACT

PURPOSE: Adjuvant radiation after breast-conserving surgery remains the standard-of-care treatment for patients with ductal carcinoma *in situ* and early-stage invasive breast cancer. Multiple alternatives to standard whole-breast irradiation exist including accelerated partial-breast irradiation (APBI). Therefore, the purpose of this APBI guideline is to provide updated data for clinicians as well as recommendations regarding appropriate patient selection and techniques to deliver APBI.

METHODS: Members of the American Brachytherapy Society with expertise in breast cancer and breast brachytherapy in particular created an updated guideline for appropriate patient selection based on an extensive literature search and clinical experience. In addition, data were evaluated with respect to APBI techniques and recommendations presented.

RESULTS: Appropriate candidates for APBI include patients aged 45 years or older, all invasive histologies and ductal carcinoma *in situ*, tumors 3 cm or less, node negative, estrogen receptor positive/negative, no lymphovascular space invasion, and negative margins. With respect to techniques, the strongest evidence is for interstitial brachytherapy and intensity-modulated radiation therapy APBI with moderate evidence to support applicator brachytherapy or three-dimensional conformal radiotherapy APBI. Intraoperative radiation therapy and electronic brachytherapy should not be offered regardless of technique outside of clinical trial.

CONCLUSIONS: The updated guidelines presented offer clinicians with a summary of data supporting APBI and guidelines for the appropriate and safe utilization of the technique. © 2017 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

Keywords:

Breast cancer; Partial-breast irradiation; Brachytherapy; Guidelines; Interstitial; Applicator

Introduction

Breast-conserving therapy (BCT) remains a standard of care in the management of early-stage breast cancer with long-term outcomes demonstrating equivalent local control and survival compared with mastectomy (1–3). Furthermore, multiple studies have confirmed that BCT offers the potential for improving quality of life, sexual, and social functioning compared with mastectomy (4–6). One of the traditional tenets of BCT is adjuvant radiation therapy after breast-conserving surgery (BCS), with randomized trials and meta-analyses demonstrating a reduction in local

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recurrence and breast cancer mortality with the addition of radiation therapy to BCS (7–9). However, traditional radiotherapy after BCS consisted of standard fractionated whole-breast irradiation (1.8–2.0 Gy/fx) (WBI), which requires 5–6.5 weeks of daily treatment. Such a protracted radiotherapy schedule is one reason why many patients may forgo adjuvant radiation therapy after BCS (10,11). Over the past several decades, alternative schedules have been developed including hypofractionated WBI and accelerated partial-breast irradiation (APBI) (12,13). Although hypofractionated WBI allows for the completion of radiation therapy in 3–4 weeks, APBI offers the ability to complete treatment in 1 week or less with multiple techniques available. In addition, although concerns were raised by population studies about the toxicities associated with APBI (particularly brachytherapy), these concerns appear to be unfounded with the publication of seven randomized trials supporting APBI as a standard-of-care option after BCS (14,15). In light of new data, updated evidence-based American Brachytherapy Society (ABS) guidelines are presented to provide clinicians with guidelines to assist in appropriate patient selection and technique utilization (16,17).

Methods

The ABS board of directors appointed a group of physicians with expertise in breast cancer and breast brachytherapy in particular to provide a consensus statement. The goals of the project were to update the previous guidelines based on review of new data addressing the efficacy and toxicity of APBI. A review of the literature with a focus on randomized trials, prospective studies, multi-institutional series, and single-institution reports addressing clinical outcomes and toxicities with APBI by technique was performed. After a discussion of the updated literature, the guidelines were reviewed and changes were made based on consensus among the authors (16,17). Before publication, the consensus statement was approved by the ABS board of directors.

Results

Previously published guidelines

Guidelines and consensus statements have been previously published including updated American Society for Radiation Oncology (ASTRO), the Groupe Européen de Curiétherapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO), and the American Society of Breast Surgeons (ASBS) as well as the previously noted ABS guidelines (16–20). These were reviewed as part of updating the ABS guidelines.

Clinical outcomes

Randomized trials. At this time, seven randomized trials evaluating APBI have been presented in either manuscript

or abstract form with two additional randomized trials evaluating intraoperative radiation therapy (IORT) published as well (Table 1) (21–29). The most mature results come from the Hungarian National Institute of Oncology randomized trial. This trial included 258 women (T1N0-1mi, Grades 1–2, nonlobular histology, negative margins) and randomized patients to WBI or APBI delivered with interstitial brachytherapy (36.4 Gy/7 fx, 69% of patients) or electrons (50 Gy/25 fx). Ten-year results have been reported, with no difference in rates of local recurrence (5.1% WBI vs. 5.9% APBI) noted and improved cosmetic outcomes with APBI (21). More recently, five-year outcomes from the GEC-ESTRO randomized noninferiority trial have been published. The study included 1184 women (Stage 0–IIA, negative margins) who were randomized to WBI or interstitial APBI (32 Gy/8 fx, 30.3 Gy/7 fx, twice daily). At 5 years, no difference in the rates of local recurrence was noted (0.9% WBI vs. 1.4% APBI) with reduced late Grade 2–3 skin toxicity with APBI (6.9% vs. 10.7%, $p = 0.02$) and a trend for reduced breast pain (22,23).

Over the past several years, four randomized trials evaluating external APBI have been published. The RAPID trial enrolled 2135 women (tumor ≤ 3 cm) to WBI or APBI (38.5 Gy/10 fx, twice daily) delivered via three-dimensional conformal radiotherapy (3D-CRT). Interim analysis of this trial, with 3-year followup found that 3D-CRT APBI was associated with increased rates of Grade 1 or 2 toxicity (Grade 3: 1.4%), mostly related to fibrosis. They also reported worse cosmetic outcomes based on patient, trained nurse, and physician evaluation (24). However, analysis of the 3D-CRT cohort of the NSABP B-39/RTOG 0413 trial found low rates of toxicity with 3D-CRT APBI, with a 3% rate of Grade 3 fibrosis and no Grade 4/5 toxicity at 41 months (25,26). Similar results were seen in a small randomized trial of 3D-CRT APBI that found no difference in cosmetic outcomes compared with WBI (27). More recently, randomized trials have evaluated external beam APBI delivered with intensity-modulated radiation therapy (IMRT). The University of Florence randomized trial (Livi *et al.*) enrolled 520 women to either WBI or IMRT APBI (30 Gy/5 fx, every other day). With a 5-year followup, no difference in the rates of local recurrence was noted (1.5% in both arms), with reduced acute and late toxicities as well as improved cosmetic outcomes with IMRT APBI (28). Finally, data from the intensity-modulated partial organ radiotherapy (IMPORT) LOW trial, which randomized 2018 patients to hypofractionated WBI, hypofractionated WBI with simultaneous integrated boost, or partial-breast irradiation (40 Gy/15 fx), has been published. With a 5-year followup, no difference in rates of local recurrence (1.1% vs. 0.2% vs. 0.5%) was noted with reduced breast appearance changes and breast firmness with APBI as compared to WBI (29).

Two randomized trials evaluating IORT have been performed. The TARGIT-A study randomized 3451 patients to either adjuvant WBI or IORT (50 kV, 20 Gy to surface)

Table 1
Randomized trial evaluating accelerated partial-breast irradiation

	Hungary	GEC-ESTRO	RAPID	NSABP B-39	University of Florence	IMPORT LOW	Barcelona
	Brachytherapy		External beam				
Technique	Interstitial/electron	Interstitial	3D-CRT	3D-CRT	IMRT	IMRT	3D-CRT
Number of patients	258	1184	2135	4300 (1386)	520	2018	102
Dose/fractionation	36.4 Gy/7 fx (HDR); 50 Gy/25 fx (electron)	32 Gy/8 fx, 30.2 Gy/7 fx (HDR); 50 Gy (PDR)	38.5 Gy/10 fx BID	38.5 Gy/10 fx BID	30 Gy/5 fx (QOD)	40 Gy/15 fx	37.5 Gy/10 fx BID
Followup	10.2	6.6	3.0	3.5	5.0	5.8	5.0
Local recurrence	5.1% WBI vs. 5.9% APBI	0.9% WBI vs. 1.4% APBI	–	–	1.5% WBI vs. 1.5% APBI	1.1% WBI vs. 0.2% SIB vs. 0.5% APBI	0% both arms
Survival	82% WBI vs. 80% APBI	96% WBI vs. 97% APBI	–	–	97% WBI vs. 99% APBI	–	No difference
Acute toxicity	–	–	Increased Grades 1–2 toxicity with APBI	–	APBI reduced any grade or Grade 2+	–	Lower acute skin toxicity with APBI
Chronic toxicity	–	Grade 3 skin toxicity: 2% WBI vs. <1% APBI, Grade 2+ toxicity 27% WBI vs. 23% APBI, increased Grades 2–3 skin toxicity with WBI	–	Grade 3 fibrosis 3%; no Grade 4/5	APBI reduced any grade	–	Lower late toxicity at 5 years with APBI, only Grade 1/2
Cosmesis	63% WBI vs. 81% PBI	Patient: 91% WBI vs. 92% APBI; physician: 90% WBI vs. 93% APBI	Worse cosmetic outcomes with APBI	–	APBI improved cosmesis	Similar photograph and clinician-assessed breast appearance vs. WBI, improved patient-reported breast appearance	No difference

GEC-ESTRO = Groupe Européen de Curiétherapie-European Society for Therapeutic Radiology and Oncology; IMPORT = intensity-modulated partial organ radiotherapy; 3D-CRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiation therapy; HDR = high dose rate; WBI = whole-breast irradiation; APBI = accelerated partial-breast irradiation; PDR = pulsed dose rate; QOD = every other day; SIB = simultaneous integrated boost; PBI = partial breast irradiation.

with a subset of IORT patients receiving supplemental WBI (21.6% prepathology, 3.6% postpathology) for features including margins < 1 mm, extensive intraductal component (EIC), or lobular carcinoma with individual centers able to add additional features. Patients were able to receive IORT as part of the prepathology cohort (IORT at time of lumpectomy) or postpathology cohort (wound reopened to deliver IORT). With a median followup of 29 months, 5-year rates of local recurrence were increased with IORT (3.3% vs. 1.3%, $p = 0.04$), which is within the noninferiority threshold despite a significant p -value. However, patients in the postpathology cohort had increased rates of local recurrence exceeding the noninferiority threshold (5.4% vs. 1.7%, $p = 0.07$), whereas the prepathology cohort still had a nonsignificant increase (2.1% vs. 1.1%) in local recurrences (30). The ELIOT trial randomized 1305 patients to WBI or IORT (electrons, 21 Gy) with no supplemental WBI offered. Five-year outcomes demonstrated increased rates of local recurrence with IORT (4.4% vs. 0.4%). Increased rates of local recurrence (>10%) were noted for patients with tumors > 2 cm, 4+ lymph nodes, estrogen receptor negativity, triple negative tumors, or Grade 3 disease (31).

Prospective studies. Multiple prospective studies have been performed to evaluate different APBI techniques with key studies presented in Table 2 (32–40). Long-term outcomes with interstitial brachytherapy come from a prospective Hungarian study. Forty-five patients (T1N0-N1mic, nonlobular breast cancer, no EIC, and negative surgical margins) received APBI with interstitial brachytherapy (30.3 or 36.4 Gy/7 fx). With 11-year followup, the 12-year rates of ipsilateral breast tumor recurrence (IBTR) were 9.3% with one case of Grade 3 fibrosis (2.2%) and 78% of patients having excellent/good cosmetic outcomes (32). RTOG 9517 was a prospective Phase II trial (Stage I/II unifocal breast cancer, <3 cm, negative margins, 0–3 positive nodes without

extracapsular extension) that evaluated interstitial APBI with either a high dose rate (34 Gy/10fx, twice daily) or a low dose rate (45 Gy over 3.5–5 days) technique. Updated results with 12-year followup demonstrated a 10-year IBTR of 5.2% without distant metastases (33,34). A Phase I/II prospective study from Harvard University enrolled 50 patients (Stage T1N0) to receive interstitial APBI via low-dose-rate brachytherapy on a dose escalation (50 Gy, 55 Gy, and 60 Gy) protocol. With 11-year followup, local control was 85% with 35% of patients developing fat necrosis and 34% developing telangiectasias over more than 1 cm² of the treated breast (41). Finally, a prospective Phase II multicenter study of 274 patients undergoing interstitial brachytherapy (64% pulsed-dose, 36% high dose rate) had a 5-year local recurrence rate of 2% with 90% of patients having excellent/good cosmesis. Toxicity rates were low with a 0.4% rate of Grade 3+ fibrosis and a 2.2% rate of Grade 3+ telangiectasias (42).

With respect to applicator brachytherapy (single-entry devices including balloon and strut devices), initial prospective data from Benitez *et al.* confirmed the feasibility and safety of the single-entry device with a balloon applicator (43). The largest source of data to date comes from the ASBS Registry. The registry enrolled 1444 patients (1449 cases) to receive APBI via a single-lumen applicator with patients receiving 34 Gy/10 fx, twice daily. With a median followup of 63 months, the 5-year rate of IBTR was 3.8% (3.7% for invasive cancers, 4.1% for ductal carcinoma *in situ* [DCIS]) with estrogen receptor negativity and tumor size associated with IBTR. Final toxicity analysis from the registry found low rates of toxicity with a 9.6% rate of infection, 13.4% symptomatic seromas, and 2.5% fat necrosis (35,36,44). More recently, results from the Contura registry trial of 342 patients identified a 2.2% rate of local recurrence at 3 years with 88% excellent/good cosmesis. Toxicity was low with an 8.5% rate of infection and 4.4% rate of symptomatic seromas (45).

Table 2
Key prospective trials evaluating brachytherapy-based accelerated partial-breast irradiation

	Hungary	RTOG 9517	ASBS	RTOG 0319	University of Michigan
Technique	Interstitial	Interstitial	Applicator	External beam	External beam
Number of patients	45	100	1444	52	34
Dose/fractionation	30.3 or 36.4 Gy/7 fx	34 Gy/10 fx or 45 Gy (LDR)	34 Gy/10 fx	38.5 Gy/10 fx	38.5 Gy/10 fx
Followup	11.1	12.1	5.3	8.0	5.0
Local recurrence	9.3%	5.2%	2.8%	7.7%	3%
Survival	88.9%	78%	91.7%	78.8%	—
Acute toxicity	—	3% (HDR)/9% (LDR)	24.2% rate of any complication at 1 year	Grade-3 dermatitis 2%	—
Chronic toxicity	2.2% Grade-3 fibrosis	13% Grade-3 skin	13.4% symptomatic seroma; 2.5% fat necrosis; 9.6% infection	Worst reported toxicity Grade 3 7.7%;	3.3% Grade-2 fibrosis
Cosmesis (excellent/good)	78%	66–68%	91%	64%	73.3%

RTOG = Radiation Therapy Oncology Group; ASBS = American Society of Breast Surgeons; LDR = low dose rate; HDR = high dose rate.

Several key prospective studies have been performed to evaluate external beam APBI (46). RTOG 0319 was a Phase I/II trial evaluating 3D-CRT APBI (38.5 Gy/10 fx, twice daily). A total of 58 patients were enrolled (52 treated) with a 7-year IBTR rate of 7.7% and a 7.7% rate of Grade 3 toxicity (37,38). However, a prospective study from the University of Michigan that enrolled 34 patients to receive IMRT APBI (38.5 Gy/10 fx, twice daily) was terminated because of poor cosmetic outcomes with a 73% rate of excellent/good cosmesis and 3.3% rate of Grade 2 toxicity and 0% grade 3 at last assessment (39,40). Finally, a prospective study evaluating IMRT APBI (38.5 Gy/10 fx, twice daily) from the Rocky Mountain Cancer Center enrolled 136 patients; with 4-year followup, the IBTR was 0.7% with 90% excellent/good cosmesis and low rates of toxicity noted (47).

Additional studies. To date, multiple prospective, retrospective, and single-institution studies have been reported documenting the safety and efficacy of interstitial APBI (48–60). Two key studies were analyses that compared interstitial APBI with WBI; 12-year results from the William Beaumont Hospital matched-pair analysis demonstrated no difference in rates of local recurrence or survival, whereas 5-year outcomes from Washington University demonstrated no difference in rates of local control (59,60). Finally, a pooled analysis of 1356 patients treated with interstitial brachytherapy and 6.9-year followup demonstrated a 10-year IBTR rate of 7.6% with 84% of patients having excellent/good cosmesis (61).

Similarly, a growing body of literature has been published demonstrating the safety and efficacy of applicator APBI (62–68). A matched-pair analysis of 3009 patients comparing brachytherapy APBI (interstitial and applicator) with WBI found no difference in 10-year rates of IBTR, survival, or excellent/good cosmesis with similar results seen from a comparison of the ASBS Registry single-lumen applicator APBI patients compared to Surveillance Epidemiology End Results WBI patients (69,70). In addition, a pooled analysis of the ASBS Registry Trial and data from William Beaumont Hospital not only demonstrated low rates of recurrence but found that estrogen receptor status was the only factor associated with IBTR (71).

With respect to external beam APBI, retrospective data evaluating 192 patients receiving 3D-CRT APBI at William Beaumont found no local recurrences at 5 years with 81% of patients having excellent/good cosmesis and a 7.5% rate of Grade 3 fibrosis (72). Hepel *et al.* reported on 60 patients receiving the technique and with short followup found similar results with an 8.3% rate of Grades 3–4 fibrosis and 82% of patients having excellent/good cosmetic outcomes (73).

Guidelines

An updated set of guidelines for appropriate selection of patients for APBI is presented in Table 3.

Table 3
American Brachytherapy Society acceptable criteria for accelerated-partial-breast irradiation

Criteria	
Age	≥45 years
Size	≤3 cm
Histology	All invasive subtypes and DCIS
Estrogen receptor	Positive/negative
Surgical margins	Negative (no tumor on ink for invasive, ≥2 mm for DCIS)
Lymphovascular space invasion	Not present
Nodal status	Negative

DCIS = ductal carcinoma *in situ*.

Histology. Most randomized, prospective, and retrospective studies evaluating APBI have predominantly included patients with invasive ductal carcinoma. However, growing literature exists supporting the use of APBI in DCIS and nonductal breast cancers. With respect to DCIS, multiple single-institution analyses and a pooled analysis have been published demonstrating low rates of local recurrence with APBI, with the exception of two small series (74–81). The largest series published to date comes from Vicini *et al.*; 300 patients (from the ASBS Registry and William Beaumont Hospital) with DCIS treated with APBI were evaluated with a 5-year IBTR rate of 2.6% noted. In addition, the rate of IBTR was not statistically different than the IBTR rates seen for suitable invasive cases and suitable/cautionary invasive cases based on the previous ASTRO guidelines (78). This is consistent with outcomes from the PROMIS study, which evaluated 240 DCIS patients treated with interstitial APBI and found a 5-year IBTR rate of 4% (74). In addition, patients with DCIS were eligible for the recently published GEC-ESTRO (6% of APBI patients, $n = 36$) and University of Florence (8.8% of APBI patients, $n = 23$) trials (22,28). Goyal *et al.* evaluated patients in the MammoSite Registry who matched the Eastern Cooperative Oncology Group (ECOG) trial criteria, omitting radiation therapy for selected DCIS patients; low-risk patients (low to intermediate grade, 0.3–2.5 cm, margins ≥ 3 mm margins, $n = 41$) had reduced rates of IBTR (0% APBI vs. 5.3% ECOG trial) as did high-risk patients (high grade, <1 cm, ≥3 mm margins, $n = 29$) (5.3% APBI vs. 15.3% ECOG) (82). Although recent APBI guidelines have suggested APBI is only appropriate for low-risk DCIS patients as defined by RTOG 9804, there are little data to support this distinction for patients undergoing APBI (18,83).

Patients with invasive lobular carcinomas (ILCs) remain underrepresented in trials evaluating APBI. Although older data suggested higher rates of local recurrence for patients with ILC treated with partial-breast irradiation, smaller studies using modern techniques have failed to demonstrate differences in rates of local recurrence by histology nor did the University of Florence trial find a difference by histology (28,42,76,84–86). However, a study from Cannon *et al.* did find lobular histology to be associated with locoregional

recurrence (87). Data from the PROMIS study found the 10-year IBTR to be 7.3% in a cohort of 55 lobular cancers (R. Kuske, personal communication, 2017). Furthermore, when evaluating outcomes for patients with ILC undergoing BCS and WBI, no difference in outcomes are noted with modern techniques (88). As such, APBI can be offered to patients with ILC.

ABS guideline: All invasive subtypes and DCIS are acceptable

Nodal status. To date, limited data are available on outcomes with APBI in lymph node–positive patients, and small numbers of such patients were included on trials. Additional data are expected from the NSABP B-39/RT0G 0413 trial in the years to come. One series reported on a cohort of 39 node-positive patients and found no difference in rates of recurrence compared with node-negative patients receiving APBI (89). A more recent study of 72 patients (59 N1a, 13 N1c) also found no difference in rates of local control with higher rates of distant metastases and lower cause-specific survival for node-positive patients undergoing APBI as compared to node-negative patients (90). Similarly, a subset analysis of ASTRO-unsuitable patients treated on the ASBS Registry failed to find an association between nodal positivity and IBTR (91). However, an analysis of 204 patients did find an association with nodal positivity and time to local failure (92). Although such data are promising because of the small numbers of patients evaluated and in light of level I data demonstrating a benefit with regional nodal irradiation in patients with limited nodal involvement and the insufficient data available, APBI should not be offered to node-positive patients off trial (93–95).

ABS guideline: Off-protocol, patients should be node negative

Receptor status. As noted in the previous ABS guideline, estrogen receptor negativity has been associated with increased rates of local recurrence for patients undergoing WBI and mastectomy (17,96,97). With respect to APBI, a pooled analysis has also identified increased rates of IBTR for estrogen receptor–negative patients, consistent with smaller analyses and a subset analysis of the PROMIS study, which found higher rates of local recurrence (13% at 5 years) for estrogen receptor–negative patients aged less than 50 years (71, 76,87,91,92,98,99). Randomized data from *Livi et al.* and prospective data from *Strnad et al.* did not find an association with estrogen receptor negativity and local recurrence although the number of patients and events remains small (28,42). With respect to breast cancer subtypes, *Anderson et al.* evaluated in a large group of patients undergoing interstitial APBI and found higher rates of IBTR with triple negative and HER2 subtypes, with *Wilkinson et al.*

finding no association (100,101). However, consistent with outcomes for patients undergoing mastectomy and WBI, triple negative disease does appear associated with higher rates of recurrence (100,102–104). At this time, the data available with respect to APBI are consistent with the literature for WBI or mastectomy in that estrogen receptor negativity is associated with higher rates of local recurrence than estrogen receptor–positive cases. However, no data suggest higher rates of local recurrence for estrogen receptor–negative patients treated with APBI compared with WBI; as such, the current recommendation is based on the data available and expert opinion and remains unchanged.

ABS guideline: Estrogen receptor may be positive or negative

Margin status. Since the publication of the previous ABS guidelines, two guidelines have been published with respect to appropriate margins after BCS (105,106). The Society of Surgical Oncology–ASTRO margin guidelines for invasive breast cancers included a meta-analysis with the finding that no tumor on ink should be considered an appropriate guideline for negative margins (105,107). However, the subsequent publication of the Society of Surgical Oncology–ASTRO guideline for DCIS recommended a 2 mm or greater margin with no definitive recommendation for those with 0–2 mm margins (106). Limited data are available with respect to margin status and outcomes in patients undergoing APBI, with a pooled analysis finding close/positive margins to have a trend for association with IBTR and a smaller analysis finding association with close margins (<2 mm) (108,109). *Kamrava et al.* also found an association between margins and IBTR (61). It should be noted that differences in assessment of margins exist, which make defining an optimal margin challenging. However, in light of current guidelines and limited data available supporting potentially higher rates of recurrence with inadequate margins, negative margins should be achieved before APBI.

ABS guideline: Surgical margins should be negative (no tumor on ink for invasive cancers, ≥ 2 mm for DCIS). In addition, alternative margins similar to the treating institution's margins used for patients receiving WBI can be considered.

Age

Since the previous ABS guideline, increasing data are available with respect to age and outcomes for patients undergoing APBI. Previously, increased rates of local recurrence have been noted in younger patients undergoing APBI including the Hungarian randomized trial, which was amended to include women aged over 50 years due to higher rates of IBTR seen in younger patients (110).

However, the GEC-ESTRO randomized trial included patients 40 years and older (15% < 50) with no difference in rates of IBTR noted (22). Similarly, the University of Florence randomized trial included patients 40 years and older (18.5% < 5) with age not associated with IBTR (28). In addition, final analysis of the ASBS MammoSite Registry did not find age to be associated with IBTR (although this was noted for DCIS patients), with a pooled analysis finding a trend for age < 50 and IBTR (35,71,91). Evaluation of the PROMIS pooled analysis found no association with age (45-year-old cutoff) and local recurrence on univariate or multivariate analysis (90). In light of increasing data in younger patients treated with APBI and a lack of data demonstrating that younger patients treated with APBI had higher rates of recurrence compared with those undergoing WBI, the current guidelines have switched from age 50 to age 45 (87). The expectation is that in the years to come, mature data from additional randomized trials will help further elucidate the optimal age criterion and may also help clarify if age should still be a criterion for treatment in the era of tumor biology/genetics.

ABS guideline: Patients should be aged 45 years or older

Tumor size. To date, limited data have suggested an association between IBTR and tumor size in patients undergoing APBI although previous data have suggested a relationship for patients undergoing WBI (111). Furthermore, when evaluating the data available, it is important to recognize that most patients treated with APBI to date have had T1 tumors. Kamrava *et al.* evaluated 1356 patients undergoing interstitial APBI and did not find tumor size to be associated with local recurrence, using a 2-cm cut point (90). Using the same cut point, a pooled analysis found no relationship between tumor size and IBTR nor did it find an association when tumor size was analyzed as a continuous variable consistent with the ASBS registry analysis (71,91). As such, it does not appear that there is a need to distinguish T1 tumors (≤ 2 cm) from 2 to 3 cm T2 tumors with respect to suitability for APBI (76,87). In addition, when faced with tumors greater than 3 cm, a concern is the larger cavities associated and therefore, the larger volume of normal breast tissue irradiated as well. Neoadjuvant therapy is not recommended to make an otherwise ineligible patient, eligible by size criterion based on tumor downstaging because of a paucity of data available and concerns about microscopic disease remaining in the original volume.

ABS guideline: Tumor size should be less than or equal to 3 cm (including pure DCIS)

Other. Previous data have found an association between lymphovascular space invasion (LVSI) and local recurrence

in patients undergoing mastectomy or BCT (112,113). To date, the University of Florence trial found no association with LVSI and IBTR nor did retrospective analyses from William Beaumont Hospital and the University of Wisconsin (28,76,114). However, an older randomized trial evaluating partial breast irradiation did find an association with LVSI and IBTR as did the study from Cannon *et al.* (87,115).

The association of grade and IBTR remains controversial for patients undergoing WBI and APBI (12,116). An older study evaluating partial breast irradiation did find an association with higher grade and IBTR as did a pooled study evaluating interstitial brachytherapy (90,115); however, analysis of the University of Florence trial did not confirm this relationship nor did the ASBS Registry (28,91). An analysis evaluating axillary recurrences from the ASBS Registry did, however, find a relationship between high grade and axillary recurrences (117).

Limited prospective data are available evaluating outcomes in patients with multifocal disease undergoing APBI due to patients with multifocality being excluded from many trials. Results from a single-institution analysis demonstrated no association between multifocality and IBTR although the number of patients was small and no events were noted (114).

Finally, with respect to EIC, data evaluating the impact on local recurrence in patients undergoing WBI have failed to confirm an association with local recurrence (118). However, an analysis of APBI patients from the University of Wisconsin did find an association with EIC and local recurrences, whereas a small retrospective analysis and the ASBS Registry did not (87,91,114). As such, the recommendation based on expert opinion and review of the data is that EIC is not considered a factor on which decisions for or against APBI should be based.

ABS guideline: Lymphovascular space invasion should not be present (due to differences in pathological assessment for LVSI, the presence of LVSI [focal or diffuse] is a contraindication). Multifocality should not be present. Grade and EIC are not factors to be used when assessing for APBI appropriateness; however, extent of disease in total (invasive + DCIS) should be ≤ 3 cm.

Partial-breast irradiation techniques

A summary of APBI techniques is presented in Table 4.

Interstitial brachytherapy. As noted previously, two randomized trials have evaluated interstitial brachytherapy as compared with WBI. The Hungarian randomized trial, with 10-year followup, has provided a long-term comparison to WBI with no difference in clinical outcomes noted (21). More recently, results of the GEC-ESTRO trial, which used interstitial brachytherapy, demonstrated equivalent clinical outcomes and improved rates of late

Table 4
Accelerated partial-breast irradiation technique summary and guidelines

	Pros	Cons	Recommendation	Utilization
Multicatheter interstitial brachytherapy	Long-term followup Randomized data Cost-effective	Technical complexity	Strong	Off and on protocol
External beam: IMRT	Randomized data—equivalent outcomes, lower toxicity	Increased cost vs. 3D-CRT APBI	Strong	Off and on protocol
Applicator brachytherapy	Ease of use Prospective data Low rates of toxicity	Cost Lack of randomized data	Moderate	Off and on protocol
External beam: 3D-CRT	Least costly APBI technique Noninvasive	Worse cosmesis Increased subcutaneous toxicity/fibrosis	Moderate	Off and on protocol
Proton therapy	Noninvasive Updated results show low rates of toxicities	Small number of patients treated High rates of acute toxicity in initial studies	Weak	On protocol
Intraoperative radiation therapy	Single treatment	Higher rates of local recurrence Up to 20% require whole-breast irradiation Low-energy: question of volume coverage	Weak	On protocol
Electronic brachytherapy	Single treatment	Small number of patients treated Lack of long-term clinical outcomes Lack of mature toxicity outcomes	Weak	On protocol

IMRT = intensity-modulated radiation therapy; 3D-CRT = three-dimensional conformal radiotherapy; APBI = accelerated partial-breast irradiation.

Grade 2–3 skin toxicity with APBI (22,23). These findings are consistent with prospective and single-institution studies as well as a recently published pooled analysis of 1356 patients which demonstrated the efficacy and safety of multicatheter interstitial brachytherapy (32–34,41,42,48–61).

ABS recommendation/guideline: Strong

In light of two randomized trials with mature followup demonstrating equivalent rates of local control and survival compared with WBI as well as the potential for reduced toxicity and improved cosmetic outcomes, interstitial brachytherapy is a strongly recommended APBI technique at this time.

Applicator brachytherapy

Prospective data from the MammoSite Registry has demonstrated low rates of local recurrence and acceptable toxicity profiles with single-lumen applicator APBI that has been confirmed by additional studies including a matched-pair analysis (35,36,68–70). More recently, multi-lumen and strut applicators have been used, allowing for improved target coverage and reduced dose to the skin, chest wall, and the remaining breast tissue (45,119,120). Results with these applicators have been published with excellent clinical outcomes and toxicity profiles to date (45,121–123). However, a lack of randomized data exists in evaluating applicator brachytherapy compared with WBI (although these patients were included in NSABP B-39) and differences in target volumes between applicator APBI and interstitial APBI limit direct extrapolation. Pathologic data do suggest, however, that the 1-cm expansion

used with applicator brachytherapy is appropriate with respect to microscopic disease (124).

ABS recommendation/guideline: Moderate

There are no randomized trials specifically evaluating applicator brachytherapy; however, large prospective series have validated clinical outcomes and toxicity profiles with single-lumen applicators. Multilumen applicators have demonstrated improved dosimetry compared to single-lumen applicators and the outcomes are promising.

Three-dimensional conformal radiotherapy

Three-dimensional conformal APBI was designed with the use of non-coplanar beams, and initial single institution outcomes were promising, as were the initial results of RTOG 0319, a German Phase II trial, and a prospective study from Harvard University (37,38,46,72,104,125). Additional series also supported the efficacy of the technique (126–129). However, with further followup, cosmetic outcomes in RTOG 0319 deteriorated to 64% excellent/good cosmesis compared with 82% at 1 year, with a 6% rate of Grade 3 toxicity with similar outcomes noted in two institutional series (39,40,73). More recently, results of two randomized studies have evaluated 3D-CRT APBI. The RAPID study, as previously noted, evaluated 3D-CRT APBI and found worse cosmesis and Grade 1–2 toxicities compared with WBI (24). However, a review of 1386 patients treated with 3D-CRT on NSABP B-39 found limited toxicity concerns with no Grade 4/5 toxicities and less than a 3% rate of Grade 3 fibrosis toxicities (25). Attempts to identify dosimetric parameters associated with toxicity have not identified consistent factors although the

volume of breast tissue receiving dose has been suggested (130–132). In addition, studies have found this technique to be the most cost-effective APBI modality (133,134). In light of these conflicting results, further mature results are required to clarify the role of 3D-CRT APBI.

ABS recommendation/guideline: Moderate

At this time, there are conflicting data with respect to 3D-CRT when comparing the RAPID and NSABP B-39 data. The data to date support the clinical efficacy of 3D-CRT APBI with some concern raised regarding cosmetic outcomes and fibrosis. However, the cosmesis rates remain on par with traditional and hypofractionated WBI, and as such, 3D-CRT APBI is given a moderate recommendation.

Intensity-modulated radiation therapy

As noted previously, the University of Florence used IMRT APBI to deliver 30 Gy in five fractions (every other day) compared with standard fractionated WBI. With 520 patients enrolled, the IMRT APBI arm was found to have equivalent clinical outcomes and reduced acute and chronic toxicities (28). Similarly, the IMPORT LOW trial evaluated APBI (40 Gy/15 fractions) and found no difference in the rates of local recurrence (29). These findings are consistent with a Phase II study from the Rocky Mountain Cancer Center; 136 patients were enrolled and treated with IMRT APBI (38.5 Gy/10 fractions BID) and with 4-year followup, there was a 0.7% local recurrence rate, 91% excellent/good cosmesis, and low rates of toxicity. These findings are consistent with other studies evaluating IMRT APBI (47,135,136). Furthermore, recent data have demonstrated that such an approach is cost-effective compared with hypofractionated WBI (137).

ABS recommendation/guideline: Strong

With randomized data demonstrating no difference in clinical outcomes and improved toxicity with the technique, APBI IMRT has strong data supporting its utilization at this time. Further study is required on the ideal dose and fractionation using this technique.

Proton therapy

At this time, multiple prospective studies evaluating proton-based APBI have been published (138–142). Initial studies evaluating proton APBI found significant acute toxicities with nearly 80% of patients having moderate to severe skin color changes at 3–4 weeks after treatment and 22% having moderate to severe desquamation at 6–8 weeks after treatment (138). Additionally, a Phase I study from Massachusetts General Hospital evaluated 98 patients treated with APBI (32 Gy/8 fractions BID) from 2003 to 2006, with patients receiving either protons ($n = 19$) or photons/mixed photon–electron ($n = 79$). With a median

followup of 83 months, similar clinical outcomes were noted with worse cosmesis and increased rates of telangiectasias, pigmentation changes, and late skin toxicity noted with proton therapy; however, this study was an early experience with proton therapy, and as such, newer techniques with multiple fields have been developed (139). A study of 100 patients treated with proton APBI at Loma Linda used a prescription of 40 Gy/10 fractions delivered once daily. With 5-year followup, 3% of patients developed a local recurrence with no Grade 3 or higher acute skin toxicity and 90% excellent/good cosmesis (140); similar results have been seen in additional institutional experiences as well (141,142). Recently, financial analyses have also demonstrated that the cost of proton APBI may be lower than previously expected (143).

ABS recommendation/guideline: Weak

Proton–APBI represents a technique that continues to evolve with recent data supporting outcomes on par with alternative APBI techniques. However, a limited number of patients have been treated with proton therapy using a variety of fractionation schedules and the total number of prospective patients evaluated remains low. As such, further study is required at this time and patients treated with protons should be considered for treatment on protocol.

Intraoperative radiation therapy

IORT can be delivered using a variety of techniques with the most common technique being low-energy x-rays (50 kV, TARGIT) or electrons (3–12 MeV, ELIOT) (144). Technical concerns exist regarding IORT including dose (particularly for low-energy IORT, with 5–7 Gy delivered at 1 cm), a lack of image guidance, and a lack of dosimetry (145–147). Two randomized trials have been performed comparing IORT with WBI. The TARGIT-A study used low-energy x-ray IORT and found that it was associated with an increase in local recurrences (3.3% vs. 1.3%). Although a non-statistically significant difference was noted in the prepathology cohort, this was not the primary end point for all patients in the trial but rather a stratified patient cohort (30). In addition, statistical concerns regarding the trial have further cast doubt on the conclusions (148). These findings are consistent with the TARGIT registry, which evaluated 935 patients and had a local recurrence rate of 2.3% with a median followup of only 23 months (149). The ELIOT study used electron IORT and found an increase in the rates of local recurrence (4.4% vs. 0.4%), consistent with the 2.3% recurrence rate at 3 years from a previous institutional analysis (31,150); however, an analysis from Leonardi *et al.* did suggest low rates of IBTR for electron IORT patients falling into the previous ASTRO suitable criteria (151). Additionally, it remains unclear at this time whether IORT is better than endocrine therapy alone with similar rates of local recurrence seen from trials omitting radiotherapy, although direct comparisons

are limited and patient populations may be different (152,153). Although there is controversy regarding interpretation of these studies, the findings of the two studies are inconsistent with other APBI techniques, which have not demonstrated higher rates of local recurrence with longer followup as compared to WBI (154,155). Proponents of IORT, particularly low-energy x-ray IORT, have attempted to make the case that IORT is a standard-of-care option (156); however, it is important to recognize that no difference in local recurrence has been noted with any of the seven APBI trials, while both trials evaluating IORT have demonstrated increased rates of local recurrence for the entire population (the primary end point), and as such, IORT is not a standard-of-care approach at this time. Future studies evaluating IORT must first demonstrate equivalent local control with WBI, HWBI, or validated APBI techniques with long-term followup before being considered a standard-of-care option. Furthermore, although IORT has been proposed as a cost-saving adjuvant radiotherapy option, when accounting for the increased rates of recurrences and costs associated, a cost-effectiveness study found alternative APBI techniques to be cost-effective (157,158). It does appear that IORT may have a role as a tumor-bed boost with mature data demonstrating low rates of recurrence and toxicity with such an approach (159–164). This may be valuable with the increased use of oncoplastic procedures, allowing for the tumor-bed boost to be delivered at the time of surgery.

ABS recommendation/guideline: Weak

IORT, including low-energy and electron techniques, should not be offered to patients outside prospective clinical trials in light of a lack of data demonstrating equivalent local control compared with WBI, something not seen with other partial-breast techniques.

Electronic brachytherapy

At this time, there are limited data evaluating electronic brachytherapy as an APBI technique. Epstein *et al.* evaluated 702 patients treated with electronic brachytherapy; overall, 21% of patients developed acute complications and 13% chronic toxicities with 4.6% of patients having significant complications (165). Data from the same group evaluated a series of 146 DCIS patients treated with the technique and found that 18% of patients had acute toxicities while 12% of patients had chronic toxicities and overall a 7.5% rate of significant complications (166).

ABS recommendation/guideline: Weak

With limited published data documenting safety, clinical outcomes, or mature toxicity results, electronic brachytherapy remains investigational and should only be used on prospective studies at this time.

Brachytherapy boost

Brachytherapy boost remains an appropriate and standard-of-care approach to boosting patients undergoing WBI with the technique included in randomized trials evaluating BCT and boost therapy (2,167). Multiple studies have been published demonstrating the safety and efficacy of the technique (168–170). Although alternative techniques including electrons and photons are available, brachytherapy may represent the ideal technique in some cases. For example, with deep-seated tumor beds, appropriate electron energies may not be available or can result in high skin doses, whereas photon boosts may lead to worse cosmetic outcomes or additional dose to the heart and lungs. Finally, brachytherapy boost may be an ideal option for women with augmented breasts and those undergoing oncoplastic surgery.

ABS recommendation/guideline: Strong

Brachytherapy boost is a well-studied technique to deliver a boost with WBI and should be considered in appropriately selected patients.

Special topics

APBI in the setting of permanent breast implants. WBI in the setting of permanent breast implants remains difficult with the potential for increased toxicity, particularly capsular contracture (171). APBI in the setting of an augmented breast can represent a technical challenge to the radiation oncologist. Kuske *et al.* have presented guidelines for interstitial brachytherapy using the “pinch view” insertion technique to avoid implant puncture (172). In a series of 250 patients treated with this technique, no implant ruptures were noted along with excellent target volume coverage. Less than 5% of patients experienced new onset capsular contracture (172). A case report from Bloom *et al.* evaluated the use of a single-entry applicator and was able to meet appropriate dosimetric parameters with limited acute or late toxicities noted (173). A report of 7 patients from the University of Texas Medical Branch evaluated using multilumen applicators in augmented patients. With a followup of 32 months, no recurrences were noted with 6 of 7 patients having excellent/good cosmetic outcomes. No late Grade 3 or 4 toxicities were noted (174,175). However, single-entry devices may not be feasible in many cases due to thin tissue planes with interstitial brachytherapy preferred. In cases where cavities are in the tail of the breast or more breast tissue is present in front of the implant, single-entry applicators can be considered.

Leonard *et al.* evaluated IMRT APBI in a series of 4 patients with breast augmentation finding that 3 of 4 patients had excellent/good cosmetic outcomes. Dosimetric constraints were met with low rates of late toxicity to date (176). An update from the group, which included 16

patients, demonstrated 81% excellent/good cosmetic outcomes with 6% of patients having moderate breast/chest wall pain with 24-month followup (177).

ABS recommendation/guideline:

Brachytherapy-based APBI should be considered for appropriate patients with permanent breast implants.

Noninvasive breast brachytherapy

Noninvasive breast brachytherapy (NIBB) represents an alternative non-invasive APBI technique (178). The technique uses mammography-guided target delineation, allowing for breast immobilization via compression. Iridium-192 surface applicators are used to deliver the dose with data from Sioshansi *et al.* demonstrating the dosimetric feasibility of the technique (179). An initial study evaluating NIBB to provide tumor-bed boost included 146 women and with 6-month followup, no Grade 4 toxicities were noted, with all patients having excellent/good cosmesis. Delivery of NIBB before WBI was also associated with less discomfort for patients (180). A multi-institutional analysis of 518 patients receiving NIBB boost found 97.4% excellent/good cosmesis with 12-month followup (181). A subsequent analysis comparing NIBB with external beam boost found reduced rates of skin/subcutaneous toxicity and a trend for reduced Grade 2+ desquamation with NIBB (182). NIBB has been evaluated as an APBI technique with initial studies identifying a dose and fractionation of 36 Gy in 10 fractions with future studies evaluating outcomes with the technique as monotherapy (178,183,184,185).

Novel fractionation

Traditionally, APBI has been delivered in 7–10 fractions, delivered twice daily over 1 week or less. However, novel fractionation schemes have been developed. Once-daily regimens have demonstrated promise with external beam APBI based on data from the University of Florence randomized trial (every other day, 2-week duration) and the IMPORT LOW trial (once daily, 3 weeks) (28,29). However, shorter fractionation regimens have also been evaluated. Four-year outcomes from a prospective study at William Beaumont demonstrated no recurrences in a series of 45 patients treated with 2-day fractionation (28 Gy/4 fx, twice daily) using a single-lumen applicator. Toxicity rates were low, although 7% of patients did develop rib fractures, and excellent/good cosmetic outcomes were noted in 98% of patients (185). The “Overnight Trial” planned to treat three cohorts of 30 patients each to doses of 7 Gy \times 4, 8.25 Gy \times 3, and 9.5 Gy \times 2. Preliminary results from the first cohort were reported and demonstrated dosimetric feasibility and expected low toxicity (186). The trial accrued to the second cohort but was then terminated because of loss of sponsor support. The successor to this effort is the ongoing TRIUMPH-T protocol evaluating

three fractions of 7.5 Gy after BCS, which has completed accrual as of July 2017, with additional studies evaluating novel fractionation schemes (187–190).

Conclusions

APBI represents a standard-of-care treatment option for appropriately selected patients with early-stage breast cancer. Acceptable patients for APBI include 45 years of age or older, tumors 3 cm or less, node negative, all invasive histologies/DCIS, estrogen receptor positive/negative, negative surgical margins, and no LVSI. The techniques with the strongest data supporting their utilization include interstitial brachytherapy and IMRT (strong recommendations) as well as applicator brachytherapy (moderate recommendation). IORT and electronic brachytherapy should not be used off clinical trial.

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