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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.

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 cm^2 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/RTOG 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 N1ic) 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, multilumen 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 Brach 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 × 4, 8.25 Gy × 3, and 9.5 Gy × 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.

References

[1] Fisher B, Anderson S, Bryant J, *et al*. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002;347:1233−1241.

[2] Van Dongen JA, Voogd AC, Fentiman IS, *et al*. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. *J Natl Cancer Inst* 2000;92:1143−1150.

[3] Veronesi U, Cascinelli N, Mariani L, *et al*. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002; 347:1227−1232.

[4] Arndt V, Stegmaier C, Ziegler H, *et al*. Quality of life over 5 years in women with breast cancer after breast-conserving therapy versus mastectomy: A population-based study. *J Cancer Res Clin Oncol* 2008;134:1311−1318.

[5] Aerts L, Christiaens MR, Enzlin P, *et al*. Sexual functioning in women after mastectomy versus breast conserving therapy for early-stage breast cancer: A prospective controlled study. *Breast* 2014;23:629−636.

[6] Sun Y, Kim SW, Heo CY, *et al*. Comparison of quality of life based on surgical technique in patients with breast cancer. *Jpn J Clin Oncol* 2014;44:22−27.

[7] Fisher B, Bryant J, Dignam JJ, *et al*. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. *J Clin Oncol* 2001;20:4141−4149.

[8] Fyles AW, McCready DR, Manchul LA, *et al*. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. *N Engl J Med* 2004;351:963−970.

[9] Early Breast Cancer Trialists' Collaborative Group (EBCTG) Darby S, McGale P, Correa C, *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 on 10,801 women in 17 randomised trials. *Lancet* 2011;378:1707−1716.

[10] Morrow M, White J, Moughan J, *et al*. Factors predicting the use of breast-conserving therapy in stage I and II breast carcinoma. *J Clin Oncol* 2001;19:2254−2262.

[11] Voti L, Richardson LC, Reis I, *et al*. The effect of race/ethnicity and insurance in the administration of standard therapy for local breast cancer in Florida. *Breast Cancer Res Treat* 2006;95:89−95.

[12] Whelan TJ, Pignol JP, Levine MN, *et al*. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010; 362:513−520.

[13] Haviland JS, Owen JR, Dewar JA, *et al*. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomized controlled trials. *Lancet Oncol* 2013;14:1086–1094.

[14] Smith GL, Xu Y, Buchholz TA, *et al*. Association between treatment with brachytherapy vs whole-breast irradiation and subsequent mastectomy, complications, and survival among older women with invasive breast cancer. *JAMA* 2012;307:1827–1837.

[15] Presley CJ, Soulos PR, Herrin J, *et al*. Patterns of use and short-term complications of breast brachytherapy in the national Medicare population from 2008-2009. *J Clin Oncol* 2012;30:4302–4307.

[16] American Brachytherapy Society: Breast Brachytherapy Task Group. Breast Brachytherapy. Available at: http://www.americanbrachytherapy.org/guidelines/abs_breast_brachytherapy_taskgroup.pdf. Accessed May 22, 2017.

[17] Shah C, Vicini F, Wazer DE, *et al*. The American Brachytherapy Society consensus statement for accelerated partial breast irradiation. *Brachytherapy* 2013;12:267–277.

[18] Correa C, Hariss 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;l7:73–79.

[19] Polgar C, Van Limbergen E, Potter R, *et al*. Patient selection for accelerated partial-breast irradiation (APBI) after breast conserving surgery: Recommendations of the Groupe Europeen de Curietherapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009). *Radiother Oncol* 2010;94:264–273.

[20] The American Society of Breast Surgeons. Consensus Statement for Accelerated Partial Breast Irradiation. Available at: https://www.breastsurgeons.org/statements/PDF_Statements/APBI.pdf. Accessed May 12, 2017.

[21] Polgar C, Fodor J, Major T, *et al*. Breast-conserving therapy with partial or whole breast irradiation: Ten-year results of the Budapest randomized trial. *Radiother Oncol* 2013;108:197–202.

[22] 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.

[23] Polgar 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* 2017;18:259–268.

[24] Olivotto I, Whelan TJ, Parpia S, *et al*. Interim cosmetic and toxicity results from RAPID: A randomized trial of accelerated partial breast irradiation using 3D conformal external beam radiation therapy. *J Clin Oncol* 2013;31:4038–4045.

[25] Julian TB, Constantino JP, Vicini FA, *et al*. Early toxicity results with 3D conformal external beam (CEBT) from the NSABP B-39/RTOG 0413 accelerated partial breast irradiation (APBI) trial. *J Clin Oncol* 2011;29:S1011.

[26] RTOG 0413 Protocol Information. Available at: https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0413. Accessed May 22, 2017.

[27] Rodriguez 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.

[28] 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.

[29] Coles C, 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* 2017;390:1048–1060.

[30] Vaidya JS, Wenz F, Bulsara M, *et al*. Risk-adapted targeted intraoperative radiotherapy versus whole-beast radiotherapy for breast cancer: 5-year results of local control and overall survival from the TARGIT-A randomized trial. *Lancet* 2014;383:603–613.

[31] Veronesi U, Orecchia R, Maisonneuve P, *et al*. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): A randomized controlled equivalence trial. *Lancet Oncol* 2013;14:1269–1277.

[32] Polgar C, Major T, Fodor J, *et al*. Accelerated partial-breast irradiation using high-dose-rate interstitial brachytherapy: 12-year update of a prospective clinical study. *Radiother Oncol* 2010;94:274–279.

[33] White J, Winter K, Kuske RR, *et al*. Long-term outcomes from Study NRG Oncology/RTOG 9517: A phase 2 study of accelerated partial breast irradiation with multicatheter brachytherapy after lumpectomy for early-stage breast cancer. *Int J Radiat Oncol Biol Phys* 2016;95:1460–1465.

[34] Rabinovitch R, Winter K, Kuske R, *et al*. RTOG 95-17, a Phase II trial to evaluate brachytherapy as the sole method of radiation therapy for Stage I and II breast carcinoma- year-5 toxicity and cosmesis. *Brachytherapy* 2014;13:17–22.

[35] Shah C, Badiyan S, Ben Wilkinson J, *et al*. Treatment efficacy with accelerated partial breast irradiation (APBI): Final analysis of the American Society of Breast Surgeons MammoSite breast brachytherapy trial. *Ann Surg Oncol* 2010;20:3279–3285.

[36] Shah C, Khwaja S, Badiyan S, *et al*. Brachytherapy-based partial breast irradiation is associated with low rates of complications and excellent cosmesis. *Brachytherapy* 2013;12:278–284.

[37] Rabinovitch R, Moughan J, Vicini F, *et al*. Long-term update of NRG Oncology RTOG 0319: A Phase 1 and 2 trial to evaluate 3-dimensional conformal radiation therapy confined to the region of the lumpectomy cavity for Stage I and II breast carcinoma. *Int J Radiat Oncol Biol Phys* 2016;96:1054–1059.

[38] Chafe S, Moughan J, McCormick B, *et al*. Late toxicity and patient self-assessment of breast appearance and satisfaction on RTOG 0319: A phase 2 trial of 3-dimensional conformal radiation therapy-accelerated partial breast irradiation following lumpectomy for stages I and II breast cancer. *Int J Radiat Oncol Biol Phys* 2013;86:854–859.

[39] Jagsi R, Ben-David MA, Moran JM, *et al*. Unacceptable cosmesis in a protocol investigating intensity-modulated radiotherapy with active breathing control for accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys* 2010;76:71–78.

[40] Liss A, 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.

[41] Hattangadi JA, Powell SN, Macdonald SM, *et al*. Accelerated partial breast irradiation with low-dose-rate interstitial implant brachytherapy after wide local excision: 12-year outcomes from a prospective trial. *Int J Radiat Oncol Biol Phys* 2012;83:791–800.

[42] Strnad V, Hildebrandt G, Potter R, *et al*. Accelerated partial breast irradiation: 5-year results of the German-Austrian multicenter phase II trial using interstitial multicatheter brachytherapy alone after breast-conserving surgery. *Int J Radiat Oncol Biol Phys* 2011;80:17–24.

[43] Benitez PR, Keisch ME, Vicini F, *et al*. Five-year results: The initial clinical trial of MammoSite balloon brachytherapy for partial breast irradiation in early-stage breast cancer. *Am J Surg* 2007;194:456–462.

[44] Vicini FA, Keisch M, Shah C, *et al*. Factors associated with optimal long-term cosmetic results in patients treated with accelerated

partial breast irradiation using balloon-based brachytherapy. *Int J Radiat Oncol Biol Phys* 2012;83:512−518.

[45] Cuttino LW, Arthur DW, Vicini F, *et al*. Long-term results from the Contura multilumen balloon breast brachytherapy catheter phase 4 registry trial. *Int J Radiat Oncol Biol Phys* 2014;90:1025−1029.

[46] Baglan KL, Sharpe MB, Jaffray D, *et al*. Accelerated partial breast irradiation using 3D conformal radiation therapy (3D-CRT). *Int J Radiat Oncol Biol Phys* 2003;55:302−311.

[47] Lei RY, Leonard CE, Howell KT, *et al*. Four-year clinical update from a prospective trial of accelerated partial breast intensity-modulated radiotherapy (APBIMRT). *Breast Cancer Res Treat* 2013;140:119−133.

[48] King TA, Bolton JS, Kuske RR, *et al*. Long-term results of wide-field brachytherapy as the sole method of radiation therapy after segmental mastectomy for T(is,1,2) breast cancer. *Am J Surg* 2000;180:299−304.

[49] Krishnan L, Jewell WR, Tawfik OW, *et al*. Breast conservation therapy with tumor bed irradiation alone in a selected group of patients with stage I breast cancer. *Breast J* 2001;7:91−96.

[50] Arthur DW, Koo D, Zwicker RD, *et al*. Partial breast brachytherapy after lumpectomy: Low-dose-rate and high-dose-rate experience. *Int J Radiat Oncol Biol Phys* 2003;56:681−689.

[51] Perera F, Yu E, Engel J, *et al*. Patterns of breast recurrence in a pilot study of brachytherapy confined to the lumpectomy site for early breast cancer with six years' minimum follow-up. *Int J Radiat Oncol Biol Phys* 2003;57:1239−1246.

[52] Johansson B, Karlsson L, Liljegren G, *et al*. Pulsed dose rate brachytherapy as the sole adjuvant radiotherapy after breast-conserving surgery of T1-2 breast cancer: First long time results from a clinical study. *Radiother Oncol* 2009;90:30−35.

[53] Yoshida K, Nose T, Masuda N, *et al*. Preliminary result of accelerated partial breast irradiation after breast-conserving surgery. *Breast Cancer* 2009;16:105−112.

[54] Stevens MJ, Cooper SG, Cross P, *et al*. Accelerated partial breast irradiation using interstitial high dose rate iridium brachytherapy: Early Australian experience and review of the literature. *Australas Radiol* 2006;50:143−151.

[55] Kaufman SA, DiPetrillo TA, Price LL, *et al*. Long-term outcome and toxicity in a Phase I/II trial using high-dose-rate multicatheter interstitial brachytherapy for T1/2 breast cancer. *Brachytherapy* 2007;6:286−292.

[56] Patel RR, Christensen ME, Hodge CW, *et al*. Clinical outcome analysis in "high-risk" versus "low-risk" patients eligible for national surgical adjuvant breast and bowel B-39/radiation therapy oncology group 0413 trial: Five-year results. *Int J Radiat Oncol Biol Phys* 2008;70:970−973.

[57] Gomez-Iturriaga A, Pina L, Cambeiro M, *et al*. Early breast cancer treated with conservative surgery, adjuvant chemotherapy, and delayed accelerated partial breast irradiation with high-dose-rate brachytherapy. *Brachytherapy* 2008;7:310−315.

[58] Slampa P, Soumarova R, Ruzickova J, *et al*. Pilot study of sole conformal perioperative interstitial brachyradiotherapy of early stage breast carcinoma using high-dose rate afterloading. *Neoplasma* 2005;52:292−296.

[59] Shah C, Antonucci JV, Wilkinson JB, *et al*. Twelve-year clinical outcomes and patterns of failure with accelerated partial breast irradiation versus whole-breast irradiation: Results of a matched-pair analysis. *Radiother Oncol* 2011;100:210−214.

[60] Ferraro DJ, Garsa AA, Dewees TA, *et al*. Comparison of accelerated partial breast irradiation via multicatheter interstitial brachytherapy versus whole breast irradiation. *Radiat Oncol* 2012;7:53.

[61] Kamrava M, Kuske RR, Anderson B, *et al*. Outcomes of breast cancer patients treated with accelerated partial breast irradiation via multicatheter interstitial brachytherapy: The Pooled Interstitial Sites (PROMIS) experience. *Ann Surg Oncol* 2015;22:s404−s411.

[62] Richards GM, Berson AM, Rescigno J, *et al*. Acute toxicity of high-dose-rate intracavitary brachytherapy with the MammoSite applicator in patients with early-stage breast cancer. *Ann Surg Oncol* 2004;11:739−746.

[63] Dowlatshahi K, Snider HC, Gittleman MA, *et al*. Early experience with balloon brachytherapy for breast cancer. *Arch Surg* 2004;139:603−607.

[64] Tsai PI, Ryan M, Meek K, *et al*. Accelerated partial breast irradiation using the MammoSite device: Early technical experience and short-term clinical follow-up. *Am Surg* 2006;72:929−934.

[65] Niehoff P, Ballardini B, Polgar C, *et al*. Early European experience with the MammoSite radiation therapy system for partial breast brachytherapy following breast conservation operation in low-risk breast cancer. *Breast* 2006;15:319−325.

[66] Niehoff P, Polgar C, Ostertag H, *et al*. Clinical experience with the MammoSite radiation therapy system for brachytherapy of breast cancer: Results from an international phase II trial. *Radiother Oncol* 2006;79:316−320.

[67] Chao KK, Vicini FA, Wallace M, *et al*. Analysis of treatment efficacy, cosmesis, and toxicity using the MammoSite breast brachytherapy catheter to deliver accelerated partial-breast irradiation: The William Beaumont Hospital experience. *Int J Radiat Oncol Biol Phys* 2007;69:32−40.

[68] Cuttino LW, Keisch M, Jenrette JM, *et al*. Multi-institutional experience using the MammoSite radiation therapy system in the treatment of early-stage breast cancer: 2-year results. *Int J Radiat Oncol Biol Phys* 2008;71:107−114.

[69] Wobb JL, Shah C, Chen PY, *et al*. Brachytherapy-based accelerated partial breast irradiation provides equivalent 10-year outcomes to whole breast irradiation: A matched-pair analysis. *Am J Clin Oncol* 2016;39:468−472.

[70] Shah C, Wilkinson JB, Lyden M, *et al*. Comparison of survival and regional failure between accelerated partial breast irradiation and whole breast irradiation. *Brachytherapy* 2012;11:311−315.

[71] Shah C, Wilkinson JB, Lyden M, *et al*. Predictors of local recurrence following accelerated partial breast irradiation: A pooled analysis. *Int J Radiat Oncol Biol Phys* 2012;82:e825−e830.

[72] Shah C, Wilkinson JB, Lanni T, *et al*. Five-year outcomes and toxicities using 3-dimensional conformal external beam radiation therapy to deliver accelerated partial breast irradiation. *Clin Breast Cancer* 2013;13:206−211.

[73] Hepel JT, Tokita M, MacAusland SG, *et al*. Toxicity of three-dimensional conformal radiotherapy for accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys* 2009;75:1290−1296.

[74] Kuske R, Kamrava M, Chen P, et al. Interstitial multi-catheter brachytherapy for select DCIS with 5 year follow-up: A multi-institutional study PROMIS: Pooled registry of multicatheter interstitial sites. American Society of Breast Surgeons Annual Meeting, May 2014, Las Vegas, Nevada.

[75] Shah C, McGee M, Wilkinson JB, *et al*. Clinical outcomes using accelerated partial breast irradiation in patients with ductal carcinoma in situ. *Clin Breast Cancer* 2012;12:259−263.

[76] Stull TS, Goodwin M, Gracely EJ, *et al*. A single-institution review of accelerated partial breast irradiation in patients considered "cautionary" by the American Society for Radiation Oncology. *Ann Surg Oncol* 2012;19:553−559.

[77] Benitez PR, Streeter O, Vicini F, *et al*. Preliminary results and evaluation of MammoSite balloon brachytherapy for partial breast irradiation for pure ductal carcinoma in situ: A phase II clinical study. *Am J Surg* 2006;192:427−433.

[78] Vicini F, Shah C, Wilkinson JB, *et al*. Should ductal carcinoma-in-situ (DCIS) be removed from the ASTRO consensus panel cautionary group for off-protocol use of accelerated partial breast irradiation (APBI)? A pooled analysis of outcomes for 300 patients with DCIS treated with APBI. *Ann Surg Oncol* 2013;12:91−98.

[79] McHaffie DR, Patel RR, Adkison JB, *et al*. Outcomes after accelerated partial breast irradiation in patients with ASTRO consensus statement cautionary features. *Int J Radiat Oncol Biol Phys* 2011;81:46−51.

[80] Abbott AM, Portschy PR, Lee C, *et al*. Prospective multicenter trial evaluating balloon-catheter partial-breast irradiation for ductal carcinoma in situ. *Int J Radiat Oncol Biol Phys* 2013;87:494−498.

[81] Zauls AJ, Watkins JM, Wahlquist AE, *et al*. Outcomes in women treated with MammoSite brachytherapy or whole breast irradiation stratified by ASTRO accelerated partial breast irradiation consensus statement groups. *Int J Radiat Oncol Biol Phys* 2012;82:21−29.

[82] Goyal S, Vicini F, Beitsch PD, *et al*. Ductal carcinoma in situ treated with breast-conserving surgery and accelerated partial breast irradiation comparison of the MammoSite registry trial with intergroup study E5194. *Cancer* 2011;117:1149−1155.

[83] McCormick B, Winter K, Hudis C, *et al*. RTOG 9804: A prospective randomized trial for good-risk ductal carcinoma in situ comparing radiotherapy and observation. *J Clin Oncol* 2015;33:709−715.

[84] Ribeiro GG, Magee B, Swindell R, *et al*. The Christie Hospital breast conservation trial: An update at 8 years from inception. *Clin Oncol* 1993;5:278−283.

[85] Shah C, Wilkinson JB, Shaitelman S, *et al*. Clinical outcomes using accelerated partial breast irradiation in patients with invasive lobular carcinoma. *Int J Radiat Oncol Biol Phys* 2011;81:e547−e551.

[86] Shaikh AY, LaCombe MA, Du H, *et al*. Accelerated partial breast irradiation using once-daily fractionation: Analysis of 312 cases with four years median follow-up. *Radiat Oncol* 2012;7:17.

[87] Cannon DM, McHaffie DR, Patel RR, *et al*. Locoregional recurrence following accelerated partial breast irradiation fore early-stage invasive breast cancer: Significance of estrogen receptor status and other pathological variables. *Ann Surg Oncol* 2013;20:3346−3352.

[88] Moran MS, Yang Q, Haffty BG, *et al*. Yale University experience of early-stage invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC) treated with breast conservation treatment (BCT): Analysis of clinical-pathologic features, long-term outcomes, and molecular expression of COX-2, Bcl-2, and p53 as a function of histology. *Breast J* 2009;15:571−578.

[89] Shah C, Wilkinson JB, Shaitelman S, *et al*. Impact of lymph node status on clinical outcomes after accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys* 2012;82:e409−e414.

[90] Kamrava M, Kuske RR, Anderson B, *et al*. Outcomes of node-positive breast cancer patients treated with accelerated partial breast irradiation via multicatheter interstitial brachytherapy: The pooled registry of multicatheter interstitial sites (PROMIS) experience. *Am J Clin Oncol* 2016;. [Epub ahead of print].

[91] Beitsch P, Vicini F, Keisch M, *et al*. Five-year outcome of patients classified in the "unsuitable" category using the American Society of Therapeutic Radiology and Oncology (ASTRO) consensus panel guidelines for the application of accelerated partial breast irradiation: An analysis of patients treated on the American Society of Breast Surgeons MammoSite Registry Trial. *Ann Surg Oncol* 2010;17:219−225.

[92] Wilder RB, Curcio LD, Khanijou RK, *et al*. Preliminary results with accelerated partial breast irradiation in high-risk breast cancer patients. *Brachytherapy* 2010;9:171−177.

[93] Whelan TJ, Olivotto IA, Parulekar WR, *et al*. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med* 2015;373:307−316.

[94] Donker M, van Tienhoven G, Straver ME, *et al*. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): A randomised, multicenter, open-label, phase 3 non-inferiority trial. *Lancet Oncol* 2014;15:1303−1310.

[95] Tendulkar RD, Rehman S, Shukla ME, *et al*. Impact of postmastectomy radiation on locoregional recurrence in breast cancer patients with 1-3 positive lymph nodes treated with modern systemic therapy. *Int J Radiat Oncol Biol Phys* 2012;83:e577−e581.

[96] Lowery AJ, Kell MR, Glynn RW, *et al*. Locoregional recurrence after breast cancer surgery: A systematic review by receptor phenotype. *Breast Cancer Res Treat* 2012;133:831−841.

[97] Truong PT, Sadek BT, Lesperance MF, *et al*. Is biological subtype prognostic of locoregional recurrence risk in women with pT1-2N0 breast cancer treated with mastectomy? *Int J Radiat Oncol Biol Phys* 2014;88:57−64.

[98] Kuske RR, Demanes J, Anderson BM, *et al*. Discrepancies in accelerated partial breast irradiation (APBI) treatment outcomes in younger women when using claims versus a database (PROMIS) with actual recurrence rates. *Int J Radiat Oncol Biol Phys* 2016;96:e53−e54.

[99] Khan AJ, Vicini FA, Beitsch P, *et al*. Local control, toxicity, and cosmesis in women > 70 years enrolled in the American Society of Breast Surgeons Accelerated Partial Breast Irradiation Registry Trial. *Int J Radiat Oncol Biol Phys* 2012;84:323−330.

[100] Anderson BM, Kamrava M, Wang PC, *et al*. Locoregional recurrence by molecular subtype after multicatheter interstitial accelerated partial breast irradiation. Results from the pooled registry of multicatheter interstitial sites research group. *Brachytherapy* 2016;15:788−795.

[101] Wilkinson JB, Shah C, Amin M, *et al*. Outcomes according to breast cancer subtype in patients treated with accelerated partial breast irradiation. *Clin Breast Cancer* 2017;17:55−60.

[102] Jwa E, Shin KH, Kim JY, *et al*. Locoregional recurrence by tumor biology in breast cancer patients after preoperative chemotherapy and breast conservation treatment. *Cancer Res Treat* 2016;48:1363−1372.

[103] Tseng YD, Uno H, Hughes ME, *et al*. Biologic subtype predicts risk of locoregional recurrence after mastectomy and impact of postmastectomy radiation in large national database. *Int J Radiat Oncol Biol Phys* 2015;93:622−630.

[104] Pashtan IM, Recht A, Ancukiewicz M, *et al*. External beam accelerated partial-breast irradiation using 32 Gy in 8 twice-daily fractions: 5-year results of a prospective study. *Int J Radiat Oncol Biol Phys* 2012;84:e271−e277.

[105] Moran MS, Schnitt SJ, Giuliano AE, *et al*. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stage I and II invasive breast cancer. *J Clin Oncol* 2014;32:1507−1515.

[106] Morrow M, Van Zee KJ, Solin LJ, *et al*. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma in situ. *J Clin Oncol* 2016;34:4040−4046.

[107] Houssami N, Macaskill P, Marinovich ML, *et al*. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: A meta-analysis. *Ann Surg Oncol* 2014;21:717−730.

[108] Shah C, Wilkinson JB, Keisch M, *et al*. Impact of margin status on outcomes following accelerated partial breast irradiation using single-lumen balloon-based brachytherapy. *Brachytherapy* 2013;12:91−98.

[109] Yeo SG, Kim J, Kwak GH, *et al*. Accelerated partial breast irradiation using multicatheter brachytherapy for select early-stage breast cancer: Local control and toxicity. *Radiat Oncol* 2010;5:56.

[110] Polgar C, Major T. Current status and perspectives of brachytherapy for breast cancer. *Int J Clin Oncol* 2009;14:7−24.

[111] Kunkler IH, Kerr GR, Thomas JS, *et al*. Impact of screening and risk factors for local recurrence and survival after conservative surgery and radiotherapy for early breast cancer: Results from a large series with long-term follow-up. *Int J Radiat Oncol Biol Phys* 2012;83:829−838.

[112] Katz AM, Strom EA, Buchholz T, *et al*. The influence of pathologic tumor characteristics on locoregional recurrence rates following mastectomy. *Int J Radiat Oncol Biol Phys* 2001;50:735−742.

[113] Jobsen J, van der Palen J, Riemersma S, *et al*. Pattern of ipsilateral breast tumor recurrence after breast-conserving surgery. *Int J Radiat Oncol Biol Phys* 2014;89:1006−1014.

[114] Jawad MS, Wilkinson JB, Shah C, *et al*. Impact of lymphovascular space invasion, extensive intraductal component, and multi-focality

following accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys* 2012;84:s1049.

[115] Magee B, Swindell R, Harris M, *et al*. Prognostic factors for breast recurrence after conservative breast surgery and radiotherapy: Results from a randomised trial. *Radiother Oncol* 1996;39:223−227.

[116] Braunstein LZ, Taghian AG, Niemierko A, *et al*. Breast-cancer subtype, age, and lymph node status as predictors of local recurrence following breast-conserving therapy. *Breast Cancer Res Treat* 2017;161:173−179.

[117] Aburabia M, Roses RE, Kuerer HM, *et al*. Axillary failure in patients treated with MammoSite accelerated partial breast irradiation. *Ann Surg Oncol* 2011;18:3415−3421.

[118] Leong C, Boyages J, Jayasinghe UW, *et al*. Effect of margins on ipsilateral breast tumor recurrence after breast conservation therapy for lymph node-negative breast carcinoma. *Cancer* 2004;100:1823−1832.

[119] Arthur DW, Vicini FA, Todor DA, *et al*. Contura multi-lumen balloon breast brachytherapy catheter: Comparative dosimetric findings of a phase 4 trial. *Int J Radiat Oncol Biol Phys* 2013;86:264−269.

[120] Shah C, Ghilezan M, Arthur D, *et al*. Initial clinical experience with multilumen brachytherapy catheters for accelerated partial breast irradiation. *Brachytherapy* 2012;11:369−373.

[121] Yashar C, Attai D, Butler E, *et al*. Strut-based accelerated partial breast irradiation: Report of treatment results for 250 consecutive patients at 5 years from a multicenter retrospective study. *Brachytherapy* 2016;15:780−787.

[122] Rehman S, Agarwal R, Ochoa L, *et al*. Prospective analysis of toxicity in patients treated with strut-adjusted volume implant for early-stage breast cancer. *Brachytherapy* 2016;15:625−630.

[123] Bitter SM, Heffron-Cartwright P, Wennerstrom C, *et al*. WBRT vs. APBI: An interim report of patient satisfaction and outcomes. *J Contemp Brachytherapy* 2016;8:17−22.

[124] 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.

[125] Ott OJ, Strnad V, Stillkrieg W, *et al*. Accelerated partial breast irradiation with external beam radiotherapy: First results of the German phase 2 trial. *Strahlenther Onkol* 2017;193:55−61.

[126] Horst KC, Fasola C, Ikeda D, *et al*. Five-year results of a prospective clinical trial investigating accelerated partial breast irradiation using 3D conformal radiotherapy after lumpectomy for early stage breast cancer. *Breast* 2016;28:178−183.

[127] Mozsa E, Meszaros N, Major T, *et al*. Accelerated partial breast irradiation with external beam three-dimensional conformal radiotherapy. Five-year results of a prospective phase II clinical study. *Strahlenther Onkol* 2014;190:444−450.

[128] Formenti SC, Hsu H, Fenton-Kerimian M, *et al*. Prone accelerated partial breast irradiation after breast-conserving surgery: Five-year results of 100 patients. *Int J Radiat Oncol Biol Phys* 2012;84:606−611.

[129] Vera R, Trombetta M, Mukhopadhyay ND, *et al*. Long-term cosmesis and toxicity following 3-dimensional conformal radiation therapy in the delivery of accelerated partial breast irradiation. *Pract Radiat Oncol* 2014;4:147−152.

[130] Shateilman SF, Kim LH, Grills IS, *et al*. Predictors of long-term toxicity using three-dimensional conformal external beam radiotherapy to deliver accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys* 2011;81:788−794.

[131] Leonard KL, Hepel JT, Hiatt JR, *et al*. The effect of dose-volume parameters and interfraction interval on cosmetic outcome and toxicity after 3-dimensional conformal accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys* 2013;85:623−629.

[132] Mellon EA, Sreeraman R, Gebhardt BJ, *et al*. Impact of radiation treatment parameters and adjuvant systemic therapy on cosmetic outcomes after accelerated partial breast irradiation using 3-dimensional conformal radiation therapy technique. *Pract Radiat Oncol* 2014;4:e159−e166.

[133] Shah C, Lanni TB, Saini H, *et al*. Cost-efficacy of accelerated partial-breast irradiation compared with whole breast irradiation. *Breast Cancer Res Treat* 2013;138:127−135.

[134] Shah C, Lanni T, Wilkinson JB, *et al*. Cost-effectiveness of 3-dimensional conformal radiotherapy and applicator-based brachytherapy in the delivery of accelerated partial breast irradiation. *Am J Clin Oncol* 2014;37:172−176.

[135] Reeder R, Carter DL, Howell K, *et al*. Predictors of clinical outcomes after accelerated partial breast intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2009;74:92−97.

[136] Lewin AA, Derhagopian R, Saigal K, *et al*. Accelerated partial breast irradiation is safe and effective using intensity-modulated radiation therapy in selected early-stage breast cancer. *Int J Radiat Oncol Biol Phys* 2012;82:2104−2110.

[137] Shah C, Ward M, Tendulkar R, *et al*. *Evaluating the cost efficacy of image guided partial breast irradiation compared to hypofractionated whole breast irradiation. Varian Research Symposium*. Chicago: Illiniois in May; 2017.

[138] Kozak KR, Smith BL, Adams J, *et al*. Accelerated partial-breast irradiation using proton beams: Initial clinical experience. *Int J Radiat Oncol Biol Phys* 2006;66:691−698.

[139] Galland-Girdet S, Pasthan I, MacDonald SM, *et al*. Long-term cosmetic outcomes and toxicity of proton beam therapy compared with photon-based 3-dimensional conformal accelerated partial breast irradiation: A phase 1 trial. *Int J Radiat Oncol Biol Phys* 2014;90:493−500.

[140] Bush DA, Do S, Lum S, *et al*. Partial breast radiation therapy with proton beam: 5-year results with cosmetic outcomes. *Int J Radiat Oncol Biol Phys* 2014;90:501−505.

[141] Chang JH, Lee NK, Kim JY, *et al*. Phase II trial of proton beam accelerated partial breast irradiation in breast cancer. *Radiother Oncol* 2013;108:209−214.

[142] Strom EA, Ovalle V. Initial clinical experience using protons for accelerated partial-breast irradiation: Longer-term results. *Int J Radiat Oncol Biol Phys* 2014;90:506−508.

[143] Ovalle V, Strom EA, Godby J, *et al*. Proton partial-breast irradiation for early-stage breast cancer: Is it really so costly? *Int J Radiat Oncol Biol Phys* 2016;95:49−51.

[144] Shah C, Harris EE, Holmes D, *et al*. Chapter 51: Partial breast irradiation: Accelerated and intraoperative. In: Bland K, Copeland E, Klimberg VS, *et al*, editors. *The Breast*. 5th ed. New York: Elsevier; 2017.

[145] Khan AJ, Arthur DW, Vicini FA. On the road to intraoperative radiotherapy: More proceed with caution signs. *Oncology* 2013;27:113−114.

[146] Shah C, Khan AJ, Arthur D, *et al*. Intraoperative radiation therapy: Not ready for prime time. *Ann Surg Oncol* 2014;21:351−353.

[147] Shah C, Wobb J, Khan A. Intraoperative radiation therapy: Still not ready for prime time. *Ann Surg Oncol* 2016;23:1796−1798.

[148] Cuzick J. Radiotherapy for breast cancer, the TARGIT-A trial. *Lancet* 2014;383:1716.

[149] Valente SA, Tendulkar RD, Cherian S, *et al*. TARGIT-R (retrospective): North American experience with intraoperative radiation therapy using low-kilovoltage x-rays for breast cancer. *Ann Surg Oncol* 2016;23:2809−2815.

[150] Veronesi U, Orecchia R, Luini A, *et al*. Intraoperative radiotherapy during breast conserving surgery: A study on 1,822 cases treated with electrons. *Breast Cancer Res Treat* 2010;124:141−151.

[151] Leonardi MC, Maisonneuve P, Mastropasqua MG, *et al*. How do the ASTRO consensus statement guidelines for the application of accelerated partial breast irradiation fit intraoperative radiotherapy? A retrospective analysis of patients treated at the European Institute of Oncology. *Int J Radiat Oncol Biol Phys* 2012;83:806−813.

[152] Hughes KS, Schnaper LA, Bellon JR, *et al*. Lumpectomy plus tamoxifen with or without irradiation on women age 70 years or

older with early breast cancer: Long-term follow-up of CALGB 9343. *J Clin Oncol* 2013;31:2382−2387.

[153] Kunkler IH, Williams LJ, Jack WJ, *et al*. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): A randomised controlled trial. *Lancet Oncol* 2015;16:266−273.

[154] Hepel J, Wazer DE. A flawed study should define a new standard of care. *Int J Radiat Oncol Biol Phys* 2015;91:255−257.

[155] Vaidya JS, Bulsara M, Wenz F, *et al*. Pride, prejudice, or science. Attitudes towards the results of the TARGIT-A trial of targeted intraoperative radiation therapy for breast cancer. *Int J Radiat Oncol Phys* 2015;92:491−497.

[156] Small W Jr, Thomas TO, Alvarado M, *et al*. Commentary on ''accelerated partial breast irradiation consensus statement: Update of an ASTRO evidence-based consensus statement''. *Pract Radiat Oncol* 2017;7:e159−e163.

[157] Alvarado MD, Mohan AJ, Esserman LJ, *et al*. Cost-effectiveness analysis of intraoperative radiation therapy for early-stage breast cancer. *Ann Surg Oncol* 2013;20:2873−2880.

[158] Shah C, Badiyan S, Khwaja S, *et al*. Evaluating radiotherapy options in breast cancer: Does intraoperative radiotherapy represent the most cost-efficacious option? *Clin Breast Cancer* 2014;14:141−146.

[159] Vaidya JS, Baum M, Tobias J, *et al*. Long-term results of targeted intraoperative radiotherapy (TARGIT) boost during breast-conserving surgery. *Int J Radiat Oncol Biol Phys* 2011;81:1091−1097.

[160] Fastner G, Sedlmayer F, Mertz F, *et al*. IORT with electrons as boost strategy during breast conserving therapy in limited stage breast cancer: Long term results of an ISIORT pooled analysis. *Radiother Oncol* 2013;108:279−286.

[161] Blank E, Kraus-Tiefenbacher U, Weizel G, *et al*. Single-center long-term follow-up after intraoperative radiotherapy as a boost during breast-conserving surgery using low-kilovoltage x-rays. *Ann Surg Oncol* 2010;17:352−358.

[162] Fastner G, Reitsamer R, Ziegler I, *et al*. IOERT as anticipated tumor bed boost during breast-conserving surgery after neoadjuvant chemotherapy in locally advanced breast cancer-results of a case series after 5-year follow-up. *Int J Cancer* 2015;136:1193−1201.

[163] Forouzannia A, Harness JK, Carpenter MM, *et al*. Intraoperative electron radiotherapy boost as a component of adjuvant radiation for breast cancer in the community setting. *Ann Surg* 2012;78:1071−1074.

[164] Wong WW, Pockaj BA, Vora SA, *et al*. Six-year outcome of a prospective study evaluating tumor bed boost with intra-operative electron irradiation followed by whole-breast irradiation for early-stage breast cancer. *Breast J* 2014;20:125−130.

[165] Epstein M, Silverstein M, Lin K, *et al*. Acute and chronic complications in breast cancer patients treated with intraoperative radiation therapy. *Ann Surg Oncol* 2016;23:3304−3309.

[166] Epstein MS, Silversten MJ, Lin K, *et al*. Acute and chronic complications in patients with ductal carcinoma in situ treated with intraoperative radiation therapy. *Breast J* 2016;22:630−636.

[167] 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* 2007;25:3259−3265.

[168] Guinot JL, Tortajada MI, Carrascosa M, *et al*. Ten-year results of a phase II study with single fraction of high-dose-rate brachytherapy (FAST-boost) after whole breast irradiation in invasive breast carcinoma. *Clin Transl Oncol* 2012;14:109−115.

[169] Schroeder TM, Liem B, Sampath S, *et al*. Early breast cancer with positive margins: Excellent local control with an upfront brachytherapy boost. *Breast Cancer Res Treat* 2012;134:719−725.

[170] Pan Q, Calitschi E, Otmezguine Y, *et al*. Long term results of exclusive radiotherapy and brachytherapy of breast cancer. *Cancer Radiother* 2012;16:674−680.

[171] Kuske RR. Chapter 24: Breast conservation therapy without capsular contracture in augmented women using interstitial brachytherapy. In: Arthur DAW, Vicini FA, Wazer DE, *et al*, editors. *Short Course Breast Radiotherapy: A comprehensive review of hypofractionation, partial breast, and intra-operative irradiation*. 1st ed. New York: Springer; 2016. p. 373−386.

[172] Kuske R. Breast conservation therapy without capsular contracture in young augmented women using interstitial brachytherapy. *J Contemp Brachytherapy* 2014;6:231−235.

[173] Bloom ES, Kirsner S, Mason BE, *et al*. Accelerated partial breast irradiation using strut-adjusted volume implant single-entry hybrid catheter in brachytherapy for breast cancer in the setting of breast augmentation. *Brachytherapy* 2011;10:178−183.

[174] Akhtari M, Pino R, Scarboro SB, *et al*. Dosimetric considerations and early clinical experience of accelerated partial breast irradiation using multi-lumen applicators in the setting of breast augmentation. *J Contemp Brachytherapy* 2015;7:423−429.

[175] Akhtari M, Nitsch PL, Bass BL, *et al*. Long-term outcome of accelerated partial breast irradiation using a multilumen balloon applicator in a patient with existing breast implants. *Brachytherapy* 2015;14:289−292.

[176] Leonard CE, Johnson T, Tallhamer M, *et al*. Accelerated partial breast intensity-modulated radiotherapy in women who have prior breast augmentation. *Clin Breast Cancer* 2011;11:184−190.

[177] Lei RY, Leonard CY, Howell KT, *et al*. External beam accelerated partial breast irradiation yields favorable outcomes in patients with prior breast augmentation. *Front Oncol* 2014;4:154.

[178] Hepel JT, Hiatt JR, Sha S, *et al*. The rationale, technique, and feasibility of partial breast irradiation using noninvasive image-guided breast brachytherapy. *Brachytherapy* 2014;13:493−501.

[179] Sioshansi S, Rivard MJ, Hiatt JR, *et al*. Dose modeling of noninvasive image-guided breast brachytherapy in comparison to electron beam boost and three-dimensional conformal accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys* 2011;80:410−416.

[180] Hamid S, Rocchio K, Arthur D, *et al*. A multi-institutional study of feasibility, implementation, and early clinical results with noninvasive breast brachytherapy for tumor bed boost. *Int J Radiat Oncol Biol Phys* 2012;83:1374−1380.

[181] Schuster J, Chipko C, Kasper M, *et al*. Updated feasibility and reproducibility results of a multi-institutional study of noninvasive breast tumor bed boost. *Brachytherapy* 2016;15:804−811.

[182] Leonard KL, Hepel JT, Styczynski JR, *et al*. Breast boost using noninvasive image-guided breast brachytherapy vs. external beam: A 2:1 matched-pair analysis. *Clin Breast Cancer* 2013;13:455−459.

[183] Leonard KL, Rivard MJ, Wazer DE, *et al*. Prescription dose evaluation for APBI with noninvasive image-guided breast brachytherapy using equivalent uniform dose. *Brachytherapy* 2015;14:496−501.

[184] Hepel JT, Leonard KL, Sha S, *et al*. Non-invasive image-guided breast brachytherapy (NIBB) to deliver accelerated partial breast irradiation (APBI): Analysis of acute toxicity and early outcomes. *Int J Radiat Oncol Biol Phys* 2014;90:S136.

[185] Wilkinson JB, Martinez AA, Chen PY, *et al*. Four-year results using balloon-based brachytherapy to deliver accelerated partial breast irradiation with a 2-day dose fractionation schedule. *Brachytherapy* 2012;11:97−104.

[186] Khan AJ, Vicini FA, Brown S, *et al*. Dosimetric feasibility and acute toxicity in a prospective trial of ultrashort-course accelerated partial breast irradiation (APBI) using a multi-lumen balloon brachytherapy device. *Ann Surg Oncol* 2013;20:1295−1301.

[187] Accelerated Partial Breast Radiation Therapy Using High-Dose Rate Brachytherapy in Treating Patients with Early Stage Breast

Cancer After Surgery (TRIUMPH-T). Available at: https://clinicaltrials.gov/ct2/show/NCT02526498. Accessed May 22, 2017.

[188] Showalter SL, Petroni G, Trifletti DM, *et al*. A novel form of breast intraoperative radiation therapy with CT-guided high-dose rate brachytherapy: Results of a prospective Phase I clinical trial. *Int J Radiat Oncol Biol Phys* 2016; 96:46−54.

[189] Rahimi A, Thomas K, Spangler A, *et al*. Preliminary results of a Phase I dose escalation trial for early-stage breast cancer using 5-fraction stereotactic body radiation therapy for partial-breast irradiation. *Int J Radiat Oncol Biol Phys* 2017;98:196−205.

[190] Horton JK, Blitzblau RC, Yoo S, *et al*. Preoperative single-fraction partial breast radiation therapy. A novel Phase 1, dose-escalation protocol with radiation response biomarkers. *Int J Radiat Oncol Biol Phys* 2015;92:846−855.