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The American Brachytherapy Society consensus statement for accelerated partial breast irradiation

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ABSTRACT

PURPOSE: To develop clinical guidelines for the quality practice of accelerated partial breast irradiation (APBI) as part of breast-conserving therapy for women with early-stage breast cancer.
METHODS AND MATERIALS: Members of the American Brachytherapy Society with expertise in breast cancer and breast brachytherapy in particular devised updated guidelines for appropriate patient evaluation and selection based on an extensive literature search and clinical experience.
RESULTS: Increasing numbers of randomized and single and multi-institution series have been published documenting the efficacy of various APBI modalities. With more than 10-year followup, multiple series have documented excellent clinical outcomes with interstitial APBI. Patient selection for APBI should be based on a review of clinical and pathologic factors by the clinician with particular attention paid to age (≥50 years old), tumor size (≤3 cm), histology (all invasive subtypes and ductal carcinoma *in situ*), surgical margins (negative), lymphovascular space invasion (not present), and nodal status (negative). Consistent dosimetric guidelines should be used to improve target coverage and limit potential for toxicity following treatment.
CONCLUSIONS: These guidelines have been created to provide clinicians with appropriate patient selection criteria to allow clinicians to use APBI in a manner that will optimize clinical outcomes and patient satisfaction. These guidelines will continue to be evaluated and revised as future publications further stratify optimal patient selection. © 2013 Published by Elsevier Inc. on behalf of American Brachytherapy Society.

Keywords: Breast cancer; Partial breast irradiation; Brachytherapy; Guidelines; Breast-conserving therapy

Introduction

Breast-conserving therapy (BCT) represents one of the seminal treatment breakthroughs in the management of breast cancer. With more than 20-year followup, multiple randomized trials have found comparable outcomes between BCT and mastectomy, allowing women to choose to preserve their breast without compromising their ability to be cured of their cancer (1–3). Beyond simply preserving the breast, BCT has been associated with improved quality of life, including social functioning, body image, and physical functioning, compared with mastectomy (4). Radiation therapy (RT) represents an integral part of BCT as multiple trials have documented increased rates of ipsilateral breast tumor recurrence (IBTR) in women undergoing breast-conserving surgery (BCS) without RT; even among women considered at low risk for IBTR, RT has been associated with a significant reduction in IBTR (Table 1) with a meta-analysis confirming these findings and identifying a breast cancer mortality benefit (1, 5–9). One factor that often prevents women from receiving BCS followed by adjuvant RT is the length of treatment

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Table 1
Breast-conserving therapy with or without RT

Trial	Number of patients	Trial randomization	Followup (mo)	Limiting factors	Local recurrence	
					RT (%)	No RT (%)
NSABP B-06 (1)	1851	Lumpectomy ± RT	248		14	39
NSABP B-21 (5)	1009	Lumpectomy + tamoxifen ± RT	87	T < 1 cm	3	16
Canadian Multi-Institutional (6)	769	Tamoxifen ± RT	66	>50 y old	.6	7.7
CALGB 9343 (7)	636	Tamoxifen ± RT	126	>70 y old	1	7
Milan (8)	580	Quadrantectomy ± RT	109	T ≤ 2.5 cm	5.8	23.5

RT = radiation therapy; NSABP = National Surgical Adjuvant Breast and Bowel Project; CALGB = Cancer and Leukemia Group B; T = tumor size.

required. Traditional whole-breast irradiation (WBI) typically requires 5–6 ½ weeks with studies demonstrating that 25% or more of women fail to receive adjuvant radiation after BCS (10, 11). Accelerated partial breast irradiation (APBI) represents a technique that allows for the delivery of adjuvant therapy after BCS in 1 week or less with multiple techniques available at this time to deliver APBI; intraoperative partial breast irradiation is an another alternative that delivers a single fraction of RT in the perioperative period. APBI allows for women who may otherwise forgo adjuvant RT the ability to complete treatment in an efficient manner and is increasingly being used with a 10-fold increase noted between 2002 and 2007 (12).

With the increased use of APBI, evidence-based guidelines are necessary to guide clinicians with regard to appropriate patient evaluation and selection. Although the American Brachytherapy Society (ABS) has previously provided guidelines for APBI, these guidelines have been updated to reflect the significant increase in published data and changes in clinical practice since the previous publication (13).

Methods and materials

The ABS guidelines for APBI were composed by members of the ABS with expertise in breast cancer and in particular breast brachytherapy. The goals of this effort were to update the previous guidelines based on a review of new data addressing the efficacy and toxicity of APBI. Clinical guideline development was initiated with a systematic review of the literature with a focus on randomized trials, multi-institution series, and single institution reports addressing clinical outcomes and toxicities. Five randomized trials were identified along with 41 nonrandomized studies (Phase I/II, single institution, and multi-institution). Although randomized trials were evaluated, because of the short followup of more recent trials, outdated or nonstandard techniques of older trials, and a lack of power in several trials, focus was placed on nonrandomized data when creating the final guidelines. Current recommendations or guidelines previously published (by other societies) were evaluated as well. Following a discussion of the literature, the revised guidelines were established by consensus among the authors based on the review of the literature on the topic and their expert opinions. When evaluating the data available and establishing guidelines, the study design and limitations of studies were also taken into consideration. Furthermore, guidelines were made with the knowledge that current guidelines may be changed moving forward based on future published data, in particular data from randomized trials.

Evaluation of specific guideline recommendations

With regard to age criteria for the application of APBI, this guideline remains unchanged because of a lack of significant new data supporting a change in the recommendation. Specifically, no APBI studies were identified that conclusively established age as risk factor for an increased risk of IBTR when applying the technique beyond that already identified when using BCT in general with standard WBI.

When evaluating tumor size, the threshold was kept at 3 cm, consistent with the previous ABS guidelines and other consensus guidelines and inclusion criteria for randomized trials. No data were identified to suggest that APBI should or could be applied after neoadjuvant chemotherapy for patients with tumors >3 cm. Similarly, when evaluating nodal status, only node-negative patients were included consistent with the previous ABS guidelines and other consensus guidelines.

For surgical margins, the recommendation was based on recently published data and confirmed with other consensus guidelines. Specifically, very few published studies were identified that conclusively established (or suggested) that APBI could be applied safely in other clinical settings (i.e., focally positive margins, etc.). The exclusion of lymphovascular space invasion (LVSI) was based on a combination of recently published APBI data and consensus agreement with previously published guidelines.

For histology, a change was made to incorporate all invasive subtypes and ductal carcinoma *in situ* (DCIS) because no new data were identified establishing any other subtype that resulted in a higher risk of IBTR. Specifically, the inclusion of DCIS was based on a large number of new publications supporting the clinical efficacy of APBI in patients with DCIS. With regard to the invasive lobular carcinomas (ILC), although there still remains limited data regarding APBI and lobular carcinomas, the guideline was modified to include lobular carcinomas based on (*1*) the

publication of two series confirming the efficacy of APBI in this population, (*2*) a lack of any modern APBI study finding increased recurrences with ILCs treated with APBI, and (*3*) extrapolation from series evaluating treatment of ILCs with standard BCT using WBI.

With regard to estrogen receptor status, there was significant discussion regarding the inclusion of estrogen receptor–negative patients based on recently published data; however, these data are consistent with multiple other series in patients treated with mastectomy or BCT with WBI that have found that estrogen receptor negativity is associated with higher rates of local recurrence (LR). As such, it was felt that the biology of the tumor rather than the treatment modality (i.e., limiting RT to the vicinity of the lumpectomy cavity) is responsible for the higher rates of LR, and thus, the guideline was made to include estrogen receptor–negative patients. Finally, this report was reviewed and approved by the Board of Directors of the ABS.

Results

Prior published guidelines

In an effort to guide clinicians, guidelines or consensus statements have been previously published by groups, including the American Society for Radiation Oncology, Groupe Europeen de Curietherapie-European Society for Therapeutic Radiology and Oncology, American Society of Breast Surgeons (ASBS), and aforementioned ABS guidelines (13–16).

Clinical outcomes

Clinical outcomes by technique are presented in Table 2 (17–64). The top of this table focuses on the published randomized trials to date; although there is a paucity of randomized data, multiple randomized Phase III trials are currently accruing or are recently closed and an increasing number of prospective, multi-institution, and single institution retrospective series are being published at this time.

Interstitial APBI represents the technique with the longest followup to date. Multiple series have reported outcomes with more than 10-year followup to date (22–39). A randomized trial from Hungary randomized 258 women with T1N0-1mi, Grades 1–2 nonlobular breast cancer with negative surgical margins to WBI or partial breast irradiation (high-dose rate, HDR, accelerated [36.4 Gy/7 fx, 69% of patients] or electrons standard fractionation to a limited field [50 Gy/25 fx, 31% of patients]). At 5 years, no difference in LR was noted (3.4% vs. 4.7%), and rates of excellent/good cosmesis were significantly improved with HDR-based APBI compared with electrons (81% vs. 70%) (19). Ten-year results have recently been presented, and the key findings remain unchanged. Although a few smaller and older series have published poor outcomes or cosmesis, multiple more recent and larger series have demonstrated excellent outcomes including a nonrandomized matched-pair analysis which found no difference in IBTR, regional recurrence (RR), or survival between patients undergoing interstitial APBI or WBI at 12 years (22, 27, 28, 40). The Radiation Therapy Oncology Group (RTOG) trial 9517 was a Phase I/II trial of 99 patients undergoing interstitial APBI with either HDR or low-dose-rate brachytherapy. At 5/10 years, the rates of IBTR were 4.7%/5.9%, with 3–9% rates of Grades 3 and 4 toxicity (34).

Balloon-based APBI emerged with the introduction of the MammoSite applicator (Hologic, Inc, Bedford, MA). A prospective trial of 70 patients at 5 years showed no LRs developed, and more than 80% of patients had excellent/good cosmesis. These outcomes have been confirmed by the larger ASBS Cancer MammoSite Registry Trial of 1440 women. This study, with 54-month followup, found the 5-year actuarial rate of IBTR to be 3.8% with 90.6% of patients reporting excellent/good cosmesis at 60 months (49, 50). A retrospective multi-institutional analysis of nearly 500 patients with 24-month followup demonstrated a 1.2% IBTR with more than 90% of patients having excellent/good cosmesis (48). Although there are no published randomized comparisons of balloon APBI with WBI, a retrospective matched-pair analysis comparing outcomes from the ASBS Registry with those of WBI patients from the SEER database found no difference in rates of RR or survival at 5 years (65).

External beam RT has also been developed as a method to deliver APBI. Two older randomized trials from the United Kingdom found increased rates of LR with partial breast techniques that are inconsistent with today's standard techniques (17, 18). A more recent prospective trial from Italy found reduced rates of acute toxicities with intensity-modulated RT–based APBI (21). RTOG 0319 was a Phase I/II trial of 52 patients undergoing external beam RT APBI and found the 4-year rate of IBTR to 6%, with only 4% of patients developing Grade 3 toxicity. Although two recent series have documented increased rates of toxicity and poor cosmesis, an interim analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39/RTOG 0413 trial evaluating the 1386 patients receiving three-dimensional conformal radiotherapy APBI found no significant toxicity issues at 41 months with a 3% rate of Grade 3 or more fibrosis (52, 53, 66). On the contrary, recent analysis of the Randomized Trial of Accelerated Partial Breast Irradiation Trial comparing external beam APBI and WBI found that this form of APBI was associated with an increased rate of adverse cosmesis and Grade ½ toxicities with short-term followup (67).

Intraoperative therapy, although included in Table 2 as a partial breast technique, should not be grouped with other APBI modalities in terms of outcomes, toxicities, and guidelines recommendations because of significant differences in the technique. Although initial outcomes from a randomized noninferiority trial comparing intraoperative

Table 2
Series evaluating clinical outcomes by partial breast technique

Trial	Year published	Number of patients	APBI technique	Followup (mo)	Findings
Randomized					
Christie Hospital (17)	1993	708	EBRT	65	LR 15% limited field vs. 11% WBI and increased LR with ILC and limited field
United Kingdom (18)	2005	174	EBRT		Trend toward increased LR with APBI (12% vs. 4%)
Hungary (19)	2007	258	Interstitial/electron	66	No difference in LR (4.7% vs. 3.4%) and HDR associated with improved cosmesis
TARGIT (20)	2010	2232	Intraoperative		No difference in LR between intraoperative therapy and WBI; recent update demonstrates increase in IBTR for IORT cohort
Florence (21)	2010	259	EBRT (IMRT)		Grade ½ skin toxicity 41% WBI vs. 5.8% APBI
Nonrandomized					
Guy's Hospital (22)	1996	27	Interstitial (HDR)	72	37% IBTR at 8 y
Oschner Clinic (23)	2000	50	Interstitial (HDR)	75	No difference in outcomes and toxicities between APBI and EBRT cohort
University of Kansas (24)	2001	24	Interstitial (HDR)	47	0% IBTR at 4 y
Virginia Commonwealth (25)	2003	44	Interstitial (HDR/LDR)	42	0% LR at 4 y, 80% excellent/good cosmesis, and 90% with HDR
Ontario (26)	2003	39	Interstitial (HDR)	91	5-y IBTR 16.2% and 5% in-field
Guys' Hospital (27)	2004	50	Interstitial (HDR-Cs)	75	18% IBTR, 7/9 IBTR in-field, and 80% excellent/good
Hungary (28)	2004	70	Interstitial (^{60}Co)	144	27/34 Disease free and 50% poor cosmesis
Czech Republic (29)	2005	25	Interstitial (HDR)	11	0% IBTR at 1 y
Australia (30)	2006	7	Interstitial (HDR)	43	No LR
Tufts University (31)	2007	32	Interstitial (HDR)	70.5	5-y IBTR 6.1% and beyond 5 y 90% excellent cosmesis
University of Wisconsin (32)	2008	273	247-Interstitial (HDR), 26 MammoSite	48.5	5-y LR 2.2% low risk vs. 6.4% high risk (<50 y, ER−, and LN+)
Spain (33)	2008	26	Interstitial (HDR)	53	6-y LR 0% and 87.5% excellent/good cosmesis
RTOG 9517 (34)	2008	99	Interstitial (HDR/LDR)	73	5-y IBTR 3% (HDR) and 6% (LDR) 3%/9% Grade ¾ toxicity with HDR/LDR
Sweden (35)	2009	50	Interstitial (PDR)	86	7-y LR 4% and 56% excellent/good cosmesis
Japan (36)	2009	45	Interstitial (HDR)		4% LR
Hungary (37)	2010	45	Interstitial (HDR)	133	12-y IBTR 9.3% and 78% excellent/good cosmesis
MGH (38)	2011	50	Interstitial (LDR)	134	12-y LR 15%
German–Austrian (39)	2011	274	Interstitial (HDR/PDR)	63	5-y LR 2% and 90% excellent/good cosmesis
William Beaumont (40)	2011	199	Interstitial (HDR)	126	No difference in LR between APBI (5.0%) and WBI (3.8%) at 12 y
St. Vincent (41)	2004	32	Balloon	11	86% Excellent/good cosmesis and 25% acute erythema/desquamation
Rush (42)	2004	112	Balloon	<1 y	Well tolerated and 4/112 punctured or ruptured balloon
Kaiser Permanente (43)	2006	51	Balloon	16	0% LR and 95.6% excellent/good cosmesis
Multi-Institution (44)	2006	44	Balloon	14	82% Skin discoloration/inflammation and 18% telangiectasias
Germany (45)	2006	32	Balloon	20	26% Telangiectasias, 56% hyperpigmentation, and 91% erythema
MammoSite Initial Trial (46)	2007	70	Balloon		5-y LR 0% and 83.3% excellent/good cosmesis
William Beaumont (47)	2007	80	Balloon	22	3-y IBTR 2.9%, 88.2% excellent/good cosmesis, and decreased cosmesis with <7 mm spacing
Multi-Institution (48)	2008	483	Balloon	24	1.2% IBTR and 91% excellent/good cosmesis
ASBS Registry (49, 50)	2011	1440	Balloon	54	5-y IBTR 2.6%, 5.4%, and 5.3% by risk group and 90.4% excellent/good cosmesis
Rocky Mountain (51)	2007	55	EBRT (IMRT)	10	0% LR and 54/64 excellent/good cosmesis
Tufts University (52)	2009	60	EBRT	15	10% Moderate/severe late toxicity, 25% Grades 2–4 fibrosis, and 81.7% excellent/good cosmesis
University of Michigan (53)	2010	34	EBRT (IMRT)	24	7/32 Unacceptable cosmesis
RTOG 0319 (54)	2010	52	EBRT	54	4-y IBTR 6% and 4% Grade 3 toxicity

William Beaumont (55)	2010	94	EBRT	50	4-y IBTR 1.1% and 89% excellent/good cosmesis
NYU (56)	2012	97	EBRT (prone)		92% Grade ½ dermatitis and IMRT reduces acute toxicity vs. 3D-CRT
Italy (57)	2006	47	Intraoperative	48	4-y LR 0%
Memorial Sloan-Kettering (58, 59)	2007	50	Intraoperative		No LR and volume <47 cm^3 associated with improved cosmetic outcomes
Milan (60)	2010	1822	Intraoperative	36	3-y LR 2.3%
University of North Carolina (61)	2011	71	Intraoperative	42	3-y LR 5.2% and IBTR 8%
Baton Rouge (62)	2011	67	Intraoperative		0% LR, 11/67 required WBI, and 4/67 mastectomy
MGH (63)	2006	20	Protons	12	No LRs, 100% excellent/good cosmesis at 12 mo, 79% moderate/severe skin color change, and 22% moist desquamation
Loma Linda (64)	2011	50	Protons	48	5-y LR 0% and reduction in dose to contralateral breast, heart, and lungs

APBI = accelerated partial breast irradiation; EBRT = external beam radiation therapy; LR = local recurrence; WBI = whole-breast irradiation; ILC = invasive lobular carcinoma; HDR = high-dose rate; TARGIT = targeted intraoperative radiotherapy; IMRT = intensity-modulated radiation therapy; IBTR = ipsilateral breast tumor recurrence; LDR = low-dose rate; RTOG = Radiation Therapy Oncology Group; PDR = pulsed dose rate; MGH = Massachusetts General Hospital; ASBS = American Society of Breast Surgeons; NYU = New York University; 3D-CRT = three-dimensional conformal radiotherapy.

radiation therapy (IORT) with WBI found no difference in outcomes at 4 years, a more recent update suggested a 2% higher rate of IBTR compared with WBI, whereas updates from the Milan trial have found higher than the expected rates of IBTR (20, 68, 69).

Patient evaluation

Patient evaluation for APBI should be a multidisciplinary approach that incorporates the breast surgeon, radiation oncologist, and medical oncologist. Ideally, the patient should be evaluated by a radiation oncologist before or within a few days of surgery. A detailed history should be performed to rule out absolute/relative contraindications for BCT in general or APBI including pregnancy, prior RT to the breast or chest, connective tissue disease, or strong family history (potentially requiring genetic testing). Breast examination should be performed to help guide clinicians as to whether a patient will be a good candidate for APBI. Mammograms should be reviewed and evaluated for multifocality or multicentricity and diffuse calcifications. Pathology reports from the biopsy and excision should be reviewed to assess tumor size, histology, grade, receptor status, margin status, presence of LVSI, presence of extensive intraductal component (EIC), and nodal status as all these factors can help to guide clinicians in recommending appropriate adjuvant therapy for their patients. Patients with calcifications associated with their disease should have a postoperative mammogram (70).

Patient selection

The following section provides a review of the literature used to guide patient selection criteria. Based on these studies and the consensus of the panel, the ABS acceptable criteria are presented in Table 3 .

Histology

To date, most randomized and prospective trials limited patient inclusion to ductal histologies with limited numbers of patients with lobular carcinoma (ILC) or DCIS treated on the initial studies.

With regard to lobular histology, these patients were excluded from the randomized Hungarian and intraoperative

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

Criteria	
Age	≥50 y old
Size	≤3 cm
Histology	All invasive subtypes and DCIS
Estrogen receptor	Positive/negative
Surgical margins	Negative
Lymphovascular space invasion	Not present
Nodal status	Negative

DCIS = ductal carcinoma *in situ*.

radiotherapy trials but included in the Christie Hospital trial. This randomized trial which used electrons to deliver APBI found that in patients with ILC, APBI was associated with increased rates of LR (42% vs. 17%) and was confirmed by a smaller Swedish study (17, 35). However, the data from the Christie trial are difficult to interpret in light of the outdated technique for target delineation, a treatment delivery technique that is no longer routinely used, and a lack of modern image guidance during treatment delivery. However, the more recent German–Austrian trial found no difference rates of LR between ILC and invasive duct carcinoma (IDC) patients (39). The largest reported series comes from William Beaumont Hospital (WBH), which evaluated 16 ILC patients and found no difference in LR compared with IDC patients (0% vs. 2.5%) (71).

DCIS remains a controversial topic because of limited data and its exclusion from the initial APBI trials. However, recent data from the ASBS MammoSite Registry Trial evaluated the 194 patients with DCIS treated and found a 5-year LR rate of only 3.4% (72). Also, data from WBH and Bryn Mawr Hospital have confirmed excellent results albeit with small numbers of patients (73, 74). A recent pooled analysis of 300 DCIS patients treated with APBI found a 5-year IBTR rate of 2.6%; furthermore, this analysis identified no difference in IBTR between DCIS patients and suitable risk invasive patients (75). *ABS Guideline: All invasive subtypes and DCIS are acceptable*.

Discussion. Previous ABS guidelines and other recommendations and trials have limited recommendations to only IDC. However, over the past several years, there have been a significant number of publications that allow for a change in the guideline. With regard to DCIS, more than five publications have now documented the efficacy of APBI in patients with DCIS including a pooled analysis of 300 patients. In light of these findings, DCIS has been included in acceptable histologies. Implicit in this recommendation is the acknowledgment that further data from phase III trials will be needed to conclusively establish the efficacy of APBI in patients with pure DCIS. Nonetheless, with no recent data documenting an increased risk of IBTR in these patients when treated with APBI, the panel felt that the inclusion of DCIS was appropriate.

With regard to lobular histology, there remains a paucity of data specifically addressing the use of APBI in patients with this invasive carcinoma subtype. However, over the past few years, two small series have been published addressing the role of APBI in these patients (no series larger than 50 patients). Because no modern series have been published documenting higher rates of IBTR for ILCs and multiple series using WBI have found comparable outcomes between IDCs and ILCs, it was the consensus opinion that lobular carcinomas should be considered acceptable for treatment (76–79). Again, implicit in this recommendation is the acknowledgment that further data from Phase III trials (and other prospective data) will be needed to conclusively establish the efficacy of APBI in patients with ILC.

Nodal status

To date, limited data remain available on patients with node-positive disease treated with APBI despite node-positive patients being included in the Yorkshire Breast Cancer Group Trial, RTOG 9517, RTOG 0319, Oschner Clinic experience, University of Wisconsin experience, Kaiser Permanent experience, and intraoperative radiotherapy trial. Data from older series have confirmed that without axillary lymph node sampling, increased rates of locoregional recurrence can be expected in patients undergoing APBI (17, 18). Furthermore, a series of three patients from Tufts University found that two of three patients that were node positive treated with APBI subsequently developed an IBTR (31). A retrospective review of 39 node-positive patients treated with APBI at WBH found no difference in IBTR at 5 years compared with node-negative patients with increased rates of RR and distant metastases (DM) in node-positive patients (80). Also, data from the high-risk series from the University of Wisconsin that included node-positive patients found no difference in outcomes compared with a low-risk cohort (32). *ABS Guideline: Off-protocol, patients should be node negative*.

Discussion. At this time, there remains insufficient evidence to support treatment of node-positive patients with APBI (even with limited nodal involvement). Older series have identified higher rates of failure and the largest modern series consists of only 39 patients. Furthermore, in light of the recently reported randomized Phase III trial (MA.20) demonstrating improvements in disease-free survival with the addition of regional irradiation to whole-breast treatment, node-positive patients should not be offered APBI off-protocol (81). Although currently accruing trials have included patients with limited nodal disease, it will be several years before mature data are available.

Tumor size

Although tumor size has been used in the past to risk stratify BCT patients, recent data suggest that it may not be associated with IBTR in patients undergoing APBI (82, 83). An analysis of more than 1800 patients treated with BCT and WBI found pathologic tumor size to be associated with IBTR and DM; however, a recent pooled analysis of outcomes from the ASBS Registry and WBH did not find tumor size to be associated with IBTR, with nearly 2000 patients evaluated (83). *ABS Guideline: Tumor size should be less than or equal to 3 cm (including pure DCIS)*.

Discussion. To date, limited research has been performed to determine the ideal tumor size criteria for patients undergoing APBI. As noted previously, because of paucity of data available, limited conclusions can be drawn. Furthermore, because of selection bias, published studies are of

limited value with a preponderance of subcentimeter tumors. Based on these findings, and consistent with previously published consensus criteria and guidelines along with clinical trial inclusion criteria, the guideline remains 3 cm. In addition, the panel does not believe that APBI should be applied off-protocol in the neoadjuvant setting.

Age

Previous randomized trials of women undergoing BCT have documented increased rates of IBTR with younger women (8). An analysis of the Christie Hospital randomized trial with partial breast irradiation did not find age to be associated with breast recurrence on multivariate analysis (84). However, the pooled analysis previously discussed found a trend for increased rates of IBTR for patients under 50 years old (83). *ABS Guideline: Patients should be 50 years or older.*

Discussion. To date, limited research has been completed to determine the ideal age criteria for patients undergoing APBI. As noted previously, because of paucity of data available, limited conclusions can be drawn but in light of the pooled analysis finding a trend for increased rates of IBTR in patients under age 50 years and similar data seen in patients undergoing WBI, the guideline has been left at 50 years old. The panel did not believe that there were sufficient data to specifically exclude younger patients from being treated with APBI but felt that caution was still warranted. Nonetheless, implicit in this recommendation is the acknowledgment by the panel that further data from Phase III trials will be needed to conclusively establish the efficacy of APBI in younger patients. Although no recent data documenting an increased risk of IBTR in these patients when treated with APBI (beyond that seen when WBI is used) have been conclusively identified, the panel felt that the inclusion of women less than age 50 years was not appropriate at this time.

Receptor status

Increasing data have suggested that estrogen receptor negativity is associated with IBTR in women undergoing APBI. As previously mentioned, a pooled analysis of the ASBS registry and data from WBH found that the only factor associated with IBTR was estrogen receptor negativity (83). Also, a review of 106 patients with cautionary features (including estrogen receptor negativity) found that receptor negativity was associated with a higher rate of IBTR (11.8% vs. 2.2%) (74). An analysis of high-risk patients including estrogen receptor–negative patients from the University of California Irvine also found that estrogen receptor negativity was associated with a decrease in recurrence-free survival (85). This has also been noted in older women who traditionally have excellent outcomes; analysis of the 537 women from the ASBS registry over age 70 years found that estrogen receptor–negative patients had higher rates of LR and decreased survival compared with estrogen receptor–positive patients (86). *ABS Guideline: Estrogen receptor may be positive or negative.*

Discussion. As noted previously, there are increasing numbers of small series identifying higher rates of IBTR in estrogen receptor–negative patients undergoing APBI compared with estrogen receptor–positive patients undergoing APBI. Although these studies suggest that estrogen receptor negativity is associated with higher rates of local failure, similar findings have been seen with WBI and mastectomy and therefore may be indicative of the biology of an estrogen receptor–negative tumor and not the treatment modality (87–89). To date, there are no data comparing local outcomes in estrogen receptor–negative patients receiving mastectomy, WBI, and APBI, and therefore, no data to suggest that rates of IBTR are higher in estrogen receptor–negative patients receiving APBI compared with those who receive WBI.

Margins

Although margin status has been associated with IBTR in patients undergoing WBI after BCS, limited data are available for patients undergoing APBI (90). A recent analysis of the MammoSite Registry found that close and positive margins were associated with a trend for increased rates of IBTR (83). Furthermore, a series of 48 patients prospectively treated with multicatheter brachytherapy from Korea did find that recurrence was associated with patients with close surgical margins (<2 mm) (91). *ABS Guideline: Surgical margins should be negative*.

Discussion. Although limited, the evidence presented to date suggests that close/positive margins are associated with higher rates of IBTR in patients undergoing APBI. These findings are consistent with large studies of patients undergoing WBI, and as such, the guideline remains consistent with previous consensus statements and guidelines recommending negative surgical margins. Because of differences in pathologic assessment of surgical margins, a lack of consistent data identifying that a certain ''ideal'' margin exits, and the fact that NSABP continues to use a definition of ''no tumor on ink,'' the panel finds that the guideline should remain a negative margin.

Other

Factors often associated with IBTR include LVSI and multifocality. However, limited data exist examining these factors in APBI patients. A review of 106 cautionary risk patients did not find focal LVSI to be associated with IBTR, RR, or DM (74). Recent data from WBH evaluated patients with and without LVSI and found that LVSI was associated with increased rates of RR and DM and a decrement in disease-free survival with no impact on IBTR or survival (92). The same series evaluated the impact of EIC and multifocality and found no difference in rates of IBTR based on

either factor; however, EIC was associated with higher rates of RR (92).

With regard to tumor grade, the Early Breast Cancer Trialists Collaborative Group meta-analysis has found that in women undergoing BCT, tumor grade was associated with recurrence risk at 10 years; also, the European Organisation for Research and Treatment of Cancer (EORTC) boost trial found tumor grade to be one of the most important factors associated with LR (9, 93). With regard to APBI, the Christie Hospital trial initially suggested that grade was associated with higher rates of breast recurrence (84). More recently, data from the ASBS registry found increasing grade to be associated with higher rates of RR (94). *ABS Guideline: LVSI should not be present (because of differences in pathologic assessment for LVSI, the presence of LVSI [focal or diffuse] is a contraindication).*

Discussion. LVSI has been found to be associated with IBTR in patients undergoing WBI; although small series evaluating the impact of LVSI in patients undergoing APBI have not found that LVSI impacts IBTR, only two reports have been published to date. Therefore, it is the consensus opinion that LVSI not be present. With regard to other factors including tumor grade and multifocality, limited data are available regarding these factors in patients treated with APBI and similarly when examining the literature on these features in patients undergoing WBI, controversy continues to exist; as such, they were not included in the guideline. With respect to EIC, data extrapolated from WBI series have confirmed that in negative surgical margin cases, that EIC is not a factor associated with IBTR (95). As such, EIC was not included in the consensus guidelines at this time as the panel believes that it is not a factor that should be used to stratify patient in light of negative surgical margins.

Technical guidelines

Previous guidelines have been published with regard to dosimetric guidelines. Previously published guidelines had focused on target coverage (≥90% dose received by ≥90% target volume, V_{150} <70 cm^3 [interstitial]/50 cm^3 [balloon], V_{200} <20 cm^3 [interstitial]/10 cm^3 [balloon], and dose homogeneity index ≥0.75) and skin dose–volume histogram parameters (maximum ≤100% [interstitial], <145% [balloon] consistent with the constraints of the NSABP B-39 protocol) (13, 14). With the development of multilumen balloon catheters and novel external beam techniques including intensity-modulated RT and protons, dosimetric guidelines should be revised to reflect the improvements in target coverage and normal tissue constraints possible with these new techniques. Before treatment, all patients should undergo CT-based planning. Based on clinical experience, expansions of 1–2 cm should be used to expand the seroma cavity to an appropriate planning target volume. Target margins may be individualized based on treatment technique and pathologic features (e.g., surgical margin status). Prescriptions have varied in the literature, but the most common prescriptions used are 34 Gy in 10 fractions twice daily for interstitial and intracavitary treatment and 38.5 Gy in 10 fractions twice daily for external beam–based treatment. A comprehensive review of each technique and the corresponding formal dosimetric recommendations are beyond of the scope of this review, but for reference, the NSABP B-39 guidelines and those presented by Wazer *et al.* may be used (14, 96).

It should also be noted that although the focus of these guidelines is APBI as a sole modality of treatment, that in appropriately selected cases, brachytherapy remains an excellent modality for boost following WBI as well. Brachytherapy for boost treatment is a well-documented and efficacious modality of treatment having been used in the EORTC randomized trial comparing mastectomy and BCT and the EORTC boost trial (2, 93). Furthermore, studies have demonstrated excellent long-term clinical outcomes with respect to tumor control and toxicities with multiple forms of brachytherapy boost; a recently published Phase II trial with 10-year followup had a 96% local control rate with 93% of patients having excellent/good cosmesis (97–99). Although brachytherapy boost has documented excellent clinical, toxicity, and cosmetic results with interstitial HDR and low-dose-rate brachytherapy, because of the technical challenges of performing interstitial brachytherapy, noninvasive image-guided breast brachytherapy (NIBB) has been developed recently. This technique, which consists of breast immobilization and mild compression, mammography-guided target delineation using ^{192}Ir brachytherapy with specialized surface applicators, results in highly collimated photon emissions. A dosimetric study from Tufts University found improved dosimetric outcomes including lower skin $V_{100}/D_{90}/D_{50}$ and reduced chest wall/lung dose using NIBB compared with electrons or three-dimensional conformal radiotherapy; these findings were confirmed by a multi-institutional registry study which documented no acute or late Grade 3 toxicities and 100% excellent/good cosmesis in a series of 146 patients (100, 101). This has led to the activation of a multi-institutional study to evaluate NIBB for APBI (102). Although future studies are required to further evaluate NIBB, the role of brachytherapy as a boost technique has sufficient data available to support its continued use.

Conclusions

These guidelines have been updated to provide clinicians with appropriate patient selection criteria to allow APBI to be used in a manner that will optimize clinical outcomes and patient satisfaction. The panel recommends that the application of APBI in any of these settings should still be approached carefully (on a case-by-case basis) with the understanding that until mature Phase III trial results are

available, patients and clinicians need to be cognizant of the limited long-term data establishing the efficacy of this treatment approach.

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