SUPPLEMENTAL MATERIAL

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Accelerated Partial Breast Irradiation: Update of an ASTRO Evidence-Based Consensus Statement

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Conflict of Interest Disclosure Statement

Before initiation of this update, all members of the Update Task Force were required to complete disclosure statements. These statements are maintained at the American Society for Radiation Oncology (ASTRO) Headquarters in Arlington, VA, and pertinent disclosures are published with this report. The ASTRO Conflict of Interest Disclosure Statement seeks to provide a broad disclosure of outside interests. Where a potential conflict is detected, the disclosure and any remedial measures to address potential conflicts are taken and noted in the consensus statement.

Benjamin D. Smith, MD receives research funding from Varian Medical Systems. Maria Cristina Leonardi, MD holds position of the National Coordinator of IORT Working Group on behalf of the Italian Society of Radiation Oncology and is the co-investigator in an ongoing boost IORT

She is also the author of three and co-author of twelve papers on IORT. Alastair M. Thompson, MD is a site principal investigator for the TARGIT- A trial and co-author for the resulting publication. Eleanor E. Harris, MD is the writing committee member for the TARGIT-A trial and a co - author for the resulting publication. She is also a principal investigator for the NRG institutional and committee member for the NRG Breast Cancer Working Group. Julia White, MD receives research funding from Susan G. Komen foundation and IntraOp Medical and paid travel expenses and research funding from Qfix. She is also a member of the National Cancer Institute (NCI) Breast Cancer Steering Group and a member-liaison of the NCI Breast Cancer Local Disease Task Force. Candace Correa, MD is a steering committee member of the Early Breast Cancer Trialists Collaborative Group (EBCTCG). None of the relationships disclosed were viewed as having any substantive impact upon the consensus statement.

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This document was prepared by the Accelerated Partial Breast Irradiation Update task force. ASTRO guidelines present scientific, health, and safety information and may to some extent reflect scientific or medical opinion. They are made available to ASTRO members and to the public for educational and informational purposes only. Any commercial use of any content in this guideline without the prior written consent of ASTRO is strictly prohibited.

Adherence to this guideline will not ensure successful treatment in every situation. Furthermore, this guideline should not be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all circumstances presented by the individual patient. ASTRO assumes no liability for the information, conclusions, and findings contained in its guidelines. In addition, this guideline cannot be assumed to apply to the use of these interventions performed in the context of clinical trials, given that clinical studies are designed to evaluate or validate innovative approaches in a disease for which improved staging and treatment are needed or are being explored.

This guideline was prepared on the basis of information available at the time the task force was conducting its research and discussions on this topic. There may be new developments that are not reflected in this guideline update, and that may, over time, be a basis for ASTRO to consider revisiting and updating the guideline.

Introduction

Accelerated Partial Breast Irradiation (APBI) is a localized form of radiotherapy in which focused radiation is delivered after lumpectomy to the tumor bed. Several options exist for delivery of APBI, including brachytherapy using either intracavitary or interstitial approaches, and external beam radiation (EBRT) using either three-dimensional conformal radiotherapy (3D-CRT), intensity modulated radiation therapy (IMRT), or proton radiation. Recently, interest has also grown in intraoperative radiation therapy (IORT), which treats the partial breast with a single dose of radiation using either low-energy x-rays or electrons, most commonly delivered at the time of surgery. These different modalities are likely to have certain tradeoffs with regard to their effectiveness and toxicity profiles, although these tradeoffs have yet to be completely described in the existing literature.

When compared with whole breast irradiation (WBI), all APBI and IORT for PBI strategies offer several benefits, including reduced treatment time and sparing of uninvolved tissue. In 2009, the American Society for Radiology Oncology (ASTRO) published a consensus statement on use of APBI outside of clinical trial enrollment.[1] Subsequently, the ASTRO guidelines subcommittee enacted a formal process to review and update existing guidelines as new evidence becomes available which is consistent with the American Society of Clinical Oncology (ASCO) approach.[2] This manuscript provides the results of applying this process to update the ASTRO APBI consensus statement, with a focus on selection criteria for APBI and IORT for PBI outside of a clinical trial. This update is endorsed by the Society of Surgical Oncology.

Methods and Materials

Process

In April 2014, a work group was formed to review the available evidence and recommend whether the APBI Consensus Statement should be updated. The work group included three coauthors of the original Consensus Statement (BDS, JW, JRH), a breast cancer expert not involved in the initial Consensus Statement (AGT), and three members of the ASTRO guidelines subcommittee (EH, CC, BDS). After a review of the literature, the work group recommended a partial update of the Consensus Statement including: (1) Revising the inclusion criteria of the "suitable" and "cautionary" patient groups, with regard to age, margins, and pure DCIS; and (2) Creating a new key question regarding the use IORT for PBI in early-stage breast cancer outside of a clinical trial. Other aspects of the prior guideline were felt to still be current and thus not in need of updating. The work group also proposed adding two IORT experts; a surgeon (AMT- TARGIT) and a radiation oncologist (MCL- ELIOT). In January 2015, the ASTRO Board of Directors approved the proposal to partially update the Consensus Statement.

Through a series of communications by conference calls and emails between March 2015 and May 2016, the task force, with ASTRO staff support, completed the systematic review created literature tables, and formulated the recommendation statements and narratives. The initial draft was reviewed by four expert reviewers (see acknowledgements) and ASTRO legal counsel. A revised draft was placed on the ASTRO Web site in February 2016 for public comment. Following integration of the feedback, the document was submitted for approval to the ASTRO Board of Directors July 2016. The ASTRO guidelines subcommittee will reevaluate this update when necessary.

Literature Review

A systematic literature review in PubMed formed the basis of the guideline using the same terms as the original Consensus Statement. The searches identified English-language studies between May 2008 and March 2014 that evaluated patients 18 and older with stage I/II breast cancer who received accelerated radiotherapy following breast conserving surgery. Due to the complexity of the topic and the length of time to the completion of the paper, the literature search was extended to March 2016. A total of 419 articles that included the following key words were identified: Breast neoplasms/radiotherapy, accelerated, balloon, brachytherapy, catheter, implant, implantation, interstitial, intraoperative, limited, partial, Savi, Contura, TARGIT, Intrabeam, Xoft, Clearbeam, IOERT, IORT, and Mobitron. The electronic searches were supplemented by hand searches and articles suggested by the chair. The search ultimately yielded 19 randomized trials, 24 prospective studies, and 1 meta-analysis, all of which were abstracted into literature tables and made available to the task force during discussions. Retrospective studies were also discussed and cited when they provided novel information relevant to the subject matter.

Grading of Evidence and Recommendations and Consensus Methodology

The task force consensus on the statements was evaluated through a modified Delphi approach. The task force members independently rated their agreement with each recommendation on a five-point Likert scale, from strongly disagree to strongly agree using an electronic survey. A pre-specified threshold of greater than or equal to 75% “agree” or “strongly agree” responses indicated consensus was achieved.[2] A total of four survey rounds, with revision

as needed after each survey, were conducted to ascertain consensus on all the recommendation statements. For each statement, the strength of the recommendation and supporting evidence were rated using the American College of Physicians (ACP) process (see Appendix).[3] In determining recommendation strength, balance of risks and benefits was assessed. The chair initially assigned the ratings, which the task force later approved. A strong recommendation was defined as the benefit of the intervention outweighs the risk, or vice versa, with uniform consensus. A weak recommendation was defined as the benefit of the intervention equals the risk, or vice versa, with uniform or non-uniform consensus

Results

KQ 1: Which patients may be considered for APBI outside of a clinical trial?

Age

Recommendation Statements:

A. Include age greater than or equal to 50 years in the "suitable" group **(moderate quality of evidence (MQE), recommendation rated as "Weak").**
B. Patients who are aged 40-49 years and who meet all other elements of suitability are considered "cautionary" **(lower quality of evidence (LQE), recommendation rated as "Weak").**
C. Retain patients with age less than 40 years or those who are 40 – 49 years without meeting other elements of suitable in the "unsuitable" group **(No evidence rating, recommendation rated as "Weak").**

Young age is a consistently documented risk factor for ipsilateral breast cancer tumor recurrence (IBTR) following WBI post-lumpectomy.[4,5] The choice in the original Consensus

Statement of age 60 as the lower limit to be "suitable" was influenced by three main factors: 1) The median age of women treated with APBI in available prospective data was >60 years;[1] 2) The 2005 Early Breast Cancer Trialists' Collaborative Group (EBCTCG)[6] meta-analysis supported that women >60 years had lower IBTR risk and less survival benefit from post-lumpectomy radiotherapy; and 3) Most existing APBI clinical experience had < 5 years follow-up, raising concerns that this underestimated the event rate, particularly in younger women.

Among other published trial, the Groupe Européen de Curiethérapie of the European Society for Radiotherapy and Oncology (GEC-ESTRO) recommended criteria for "low risk" includes women age >50 years as good candidates for brachytherapy APBI.[7] Their justification cites the European Organisation for Research and Treatment of Cancer (EORTC)[5] and Budapest boost trials,[8] both showed greater benefit of a boost in women under age 50, suggesting the APBI biologically equivalent dose of 50 Gy is inadequate for the younger age group, in whom a conventional dose of 60 Gy or higher is warranted to maximize local control.

Three randomized trials evaluating APBI versus whole breast irradiation have been published or updated since the original ASTRO consensus statement. In the GEC-ESTRO trial, 1184 patients were enrolled in a phase III, non-inferiority trial and were randomized to WBI plus a tumor bed boost or APBI delivered with multi-catheter interstitial brachytherapy. The five-year risk of IBTR was less than 2% in both treatment arms, and the study concluded that brachytherapy APBI was not inferior to WBI. In addition, there were no differences in toxicity through five years. The lower limit of age on the GEC-ESTRO trial was 40 years, and there was no evidence of increased risk of IBTR with APBI for women in their 40s. However, only 14% of women enrolled were < 50 years of age.[9] In the National Institute of Oncology, Budapest trial in which 128 received primarily multi-catheter brachytherapy APBI, 23% of patients were under

the age of 50. In this trial, patients less than age 40 were excluded after 2001 due to an early analysis that reported unacceptably high IBTR risk in these patients.[10] At a median follow up of 10.2 years, 5.5% had an in-breast recurrence, but no further analysis by age was done.[10] In the University of Florence trial, 15.8% of the 260 randomized to IMRT APBI were < 50 years old. With a median follow up of five years, 1.5% had an in-breast recurrence and age was not a significant factor associated with recurrence.[11] In each trial, roughly 90% or more of enrolled patients had T1, N0 and hormone sensitive disease. Data from other large randomized phase III trials evaluating APBI, including the NSABP B39/RTOG 0413[12] and RAPID trials,[13] are pending.

Updates to institutional prospective studies of APBI cited in the original Consensus Statement have also been reviewed. The Austrian Multi Institutional study has reported its findings specifically for age.[14] In this phase II study of 274 stage I, hormone sensitive breast cancer patients who received multicatheter APBI, five-year local recurrence for patients < 50 years of age was 7.5%, and for patients $\geq$ 50 years was 1.1% (p = 0.030). Younger women were more likely to have received chemotherapy, and those with chemotherapy less likely to have had anti-hormone therapy (AHT). Five-year local recurrence for hormone-sensitive patients (n = 264) with AHT was 1.1%, and without AHT was 12% (0.0087). In an analysis from 3 prospective trials studying mostly brachytherapy delivery of APBI at William Beaumont Hospital, the lack of adjuvant tamoxifen therapy use, age < 50, and ER (-) status were significantly associated with the development of in-breast recurrence.[15] In the Massachusetts General Hospital phase II trial of 3D-CRT APBI, an IBTR occurred in 2 of 15 women aged 40-49 (14% actuarial risk) compared to 3 of 83 in those age $\geq$ 50 years (3% actuarial risk), with median follow-up 71

months, although this difference was not statistically significant.[16] The two patients <50 years of age who had an IBTR both had triple negative disease.

Among APBI registry studies that have updated results, Shah reported no difference by age in invasive ductal patients treated with APBI in the American Society of Breast Surgeons (ASBS) Mammosite registry trial final analysis, although in DCIS patients, the five -year IBTR rate was 19% in those aged < 50 compared to 5.8% for aged >50 years.[17]

Margins

Recommendation Statement:

A. Maintain the current selection criteria for "suitable", "cautionary" and "unsuitable" patients based on margin status **(No evidence rating, recommendation rated as "Weak").**

Both ASTRO[1] and GEC-ESTRO[7] currently recommends surgical margins of ≥2 mm for the "suitable" or "low risk" groups. Close margins, defined as negative, but <2 mm, were considered "cautionary" or "intermediate risk" and positive margins, defined as "ink on tumor," were designated "unsuitable" or "high risk" for APBI. The criteria for negative surgical margins differ between APBI studies addressing EBRT (including IMRT) and range from "no ink on tumor" to 1 mm to 5 mm clear margins.[13,18-24]

For intracavitary brachytherapy, the largest series available is the ASBS Mammosite registry study.[17] An analysis assessing association of margin status and outcome did not show a statistically significant difference by margin status for invasive cancer. For patients with pure DCIS, the IBTR rate was 17.6% and 4.2% for close and negative margins, respectively (p=0.004). There were only 2 DCIS patients with positive margins, neither had IBTR. It should

be noted that among patients with close/positive margins, 80% of IBTRs were elsewhere recurrences and likely secondary to the high rate of elsewhere recurrences in DCIS patients.

It is currently unclear whether the ASBS data apply to patients receiving interstitial implant or 3D-CRT APBI. While the NSABP-RTOG trial might shed light on the suitability of "no ink on tumor" definition for invasive and pure DCIS patients to receive APBI using the different techniques, it will take several more years to be reported and published. It was also noted that the recently published Society of Surgical Oncology-ASTRO guideline on margin width recommended that "no tumor on ink" be adopted as the accepted standard to establish margin negativity in patients receiving whole breast irradiation.[25] However, this guideline was not intended to apply to patients undergoing APBI given the limited clinical literature to inform this issue. Considering the available evidence, the task force recommends that the Consensus Statement remain unchanged with regard to margin status.

Pure Ductal Carcinoma In Situ (DCIS)

Recommendation Statement:

A. Include patients with low-risk DCIS as per RTOG 9804 criteria (i.e. screen-detected, low to intermediate nuclear grade, less than or equal to2.5 cm size, resected with margins negative at ≥ 3 mm), in the "suitable" group **(Moderate quality of evidence (MQE), recommendation rated as "Weak").**

The RTOG 9804 randomized clinical trial included women with screen-detected DCIS, low to intermediate nuclear grade, ≤ 2.5 cm size, resected with margins negative at ≥ 3 mm.[26] With a median follow up of 7.2 years, risk of IBTR was 6.7% risk in the observation arm compared to 0.9% in the whole breast irradiation arm. Similar results were noted in the initial

publication of the ECOG 5194 trial among patients meeting similar criteria, with observation yielding a 6.1% risk of IBTR at 6.7 years median follow up and 14.4% risk at 12 years.[27,28] These inclusion criteria therefore define a group of patients with low-risk DCIS for whom observation confers a low absolute risk of IBTR and for whom the addition of WBI confers a small but measurable absolute benefit in prevention of IBTR. When applied to APBI, 41 patients in the MammoSite registry met the low-risk enrollment criteria for the ECOG 5194 study and experienced a five-year risk of an IBTR of 0%.[29] The five-year rate of IBTR among all 194 DCIS patients in the MammoSite registry was 3.4%.[30] A pooled analysis of 300 women with DCIS from the MammoSite registry and a single institution similarly showed a 2.6% five-year risk of IBTR.[31] In addition, a single institution study evaluating 99 DCIS patients treated with either balloon brachytherapy, interstitial brachytherapy, or 3D-CRT EBRT APBI demonstrated a 1.4% five-year risk of IBTR.[32] When analyzed by the ECOG 5194 risk criteria, the risk was 2% for patients meeting these low-risk criteria. Other series similarly showed a 0% five-year IBTR risk among 32 women with DCIS treated with multicatheter brachytherapy.[33]

In contrast, one single institution investigation reported a trend towards higher risk of time to IBTR among pure DCIS tumors compared to invasive ductal carcinomas at four years after MammoSite (HR=3.57 and p=0.06).[34] One prospective multicenter trial using MammoSite in 41 DCIS patients showed a 9.8% five- year risk of IBTR, all outside the treatment field.[35]

Data from randomized trials of APBI versus whole breast irradiation with selection criteria including patients with DCIS are pending. However, given the low risk of IBTR in low-risk DCIS with wide local excision alone, coupled with favorable results following APBI for low-risk DCIS in several series, the task force recommends inclusion of low-risk DCIS patients

in the "suitable" group. The work group notes that hormonal therapy alone or observation may also be appropriate therapy for certain patients in this favorable subset.

New key question: Which patients may be considered for intraoperative partial breast irradiation?

Recommendation statements:

A. Patients interested in cancer control equivalent to that achieved with whole breast irradiation post lumpectomy for breast conservation should be counseled that in two clinical trials the risk of IBTR was higher with IORT. **(High quality of evidence (HQE), recommendation rated as "Strong").**
B. Electron beam IORT should be restricted to women with invasive cancer considered "suitable" for partial breast irradiation (Table 1) based on the results of a multivariate analysis with median follow up of 5.8 years. **(Moderate quality of evidence (MQE), recommendation rated as "Strong").**
C. Low-energy x-ray IORT for PBI should be used within the context of a prospective registry or clinical trial, per ASTRO Coverage with Evidence Development (CED) statement. When used, it should be restricted to women with invasive cancer considered "suitable" for partial breast irradiation (Table 1) based on the data at the time of this review. **(Moderate quality of evidence (MQE), recommendation rated as "Weak").**

Clinical Trials

Two large phase 3 trials, the ELIOT trial and the TARGIT trial, compared WBI to IORT PBI using either electron beam (ELIOT)[18] or low-energy x-rays (Intrabeam device, TARGIT).[36] Both trials reported increased risk of IBTR after IORT. In ELIOT, the five-year IBTR risk was

4.4% (35/651) after IORT versus 0.4% (4/654) after WBI. ELIOT has a median of 5.8 years follow up (n =1305). However, ELIOT patients with invasive cancer fitting the "suitability" criteria had a very low rate of IBTR.[37] Among these patients, the five –year occurrence of IBTR was approximately 1.5% (3/294), pointing out the importance of patient selection [37]

In TARGIT, the five-year IBTR risk was 3.3% (23/3375) in the low energy x-ray IORT arm compared to 1.3% (11/3375), (p=0.042) in the WBI arm.[36] The overall median follow up for TARGIT is 2.4 years (n = 3451). The task force acknowledges the initial 1222 patients have a median follow up of five years, however, notes the five-year IBTR risk is based on the overall short follow up of the TARGIT trial, which limits precision of the five-year risk estimates. Although there was no statistically significant difference in IBTR risk for patients treated with IORT versus WBI in the TARGIT pre-pathology subgroup (2.1% (10 of 2234) with IORT vs. 1.1% (6 of 2234) with WBI),[36] the task force thought that greater weight should be placed on evaluation of the efficacy of IORT in the pre-specified primary analysis population, which included all patients. The task force also noted concerns from the Chair of the TARGIT Data Monitoring Committee regarding misuse of the non-inferiority criterion and the responses from the authors.[38,39] For these reasons, the task force felt that low-energy x-ray IORT should continue to be used within the context of a prospective registry or clinical trial, per the ASTRO CED statement, to ensure that long-term local control and toxicity outcomes are prospectively monitored. Further, given the increased risk of IBTR, the task force advised that low-energy x-ray IORT, when used, be confined to patients with the lowest risk of IBTR, specifically those in the "suitable" group (Table 1). Since there is no data on the use of IORT with DCIS, the task force recommended that its use be limited to patients with invasive breast cancer. These

statements will be reconsidered and revised as appropriate when important new evidence warrants modification of the recommendation.

Adverse effects

Adverse effects are different after IORT compared with WBI. In the available trials, fat necrosis[19,40] was increased with IORT, while skin side effects were lower.[19,38] Mild breast fibrosis [19,41,42] occurred with electron beam radiation on ELIOT, with no significant difference compared to WBI in the ELIOT trial.[19] IORT techniques may allow improved critical organ sparing compared to WBI. Lung fibrosis in the ELIOT trial[43] and deaths from cardiovascular causes in the TARGIT trial were lower in the IORT groups.[15]

In some studies, breast fibrosis was problematic for the combination of low-energy x-rays followed by WBI.[43,44] For example, the use of low-energy x-ray IORT followed by WBI, compared to WBI alone, was associated with double the risk of breast fibrosis (to 37.5%), increased patient-reported pain, and decreased patient-reported quality of life.[43-46] In contrast, other studies have reported outcomes with IORT followed by WBI that appear acceptable and comparable to either WBI alone or WBI with a conventional external beam boost.[46-48] As such, the task force felt that the combination of IORT and WBI should be used only with caution and limited to women with higher risk features on final pathology.

Clinicopathologic selection criteria

ELIOT[18] enrolled women aged 48-75 years and found no impact of age on five-year IBTR, yet women under 50 accounted for only 7% of the study cohort. TARGIT randomized women greater than or equal to 45 years of age, with median 63 years, and has not yet reported

the relationship of age to IBTR.[36] A lower age limit of ≥ 50 years for IORT PBI, as for other ABPI, was therefore recommended.[37] The majority of cancers treated with IORT were < 2 cm (87% in TARGIT and 88% in ELIOT). Tumors ≥ 2 cm were associated with significantly increased risk of IBTR[18] in the ELIOT trial. For both electron beam[18] and low-energy x-ray[36] IORT, a 1 mm margin has generally been accepted, but wider margins (2-5 mm)[49,50] might be required according to local guidelines. Patients with positive resection margins underwent repeat resection[49-51] and 21.6% of patients having close or involved margins or other indications at the time of initial resection received low energy x-ray IORT with additional WBI.[36] In the ELIOT trial,[18] positive margins (0.3% in the IORT arm) did not undergo re-excision and were associated with increased risk of IBTR. High-grade (grade 3) was associated with increased risk of IBTR with electron IORT in ELIOT[18,37,41] the small proportion of high grade cancers in TARGIT (15%, 450 patients) precluded subset analysis.[36] Lymphovascular invasion was either an exclusion criterion[36,49] or, if identified, required subsequent 45 Gy in 25 fractions WBI.[36] In the ELIOT trial, it was not associated with increased risk of IBTR.[11] Tumor subtype impacted IBTR risk following electron IORT, with luminal A subtype associated with lower risk of IBTR.[18] A similar analysis has not been performed for subtype within TARGIT, where 82% of cancers were estrogen receptor positive.[36]

The majority of patients in IORT trials have been node negative as an entry criterion[36,49,52] or received 45 Gy in 25 fractions WBI.[36] For ELIOT patients, involvement of 4 or more nodes was associated with double the risk of IBTR, whereas isolated tumor cells, micrometastasis,[50] or 1-3 macrometastases did not appear to increase IBTR risk compared to node negative patients.[18,41]

Neoadjuvant therapy, multicentric invasive cancer, DCIS, or EIC (extensive intraductal component) have been excluded from most reports. Lobular histology (excluded from TARGIT) has been associated with increased risk of IBTR.[37]

Additional Considerations

Patients meeting criteria for treatment with IORT generally have a low absolute risk of IBTR, yet this risk persists over a long period of time, likely at least 10 years. Given these biologic considerations, coupled with the current follow up reported from the ELIOT and TARGIT trials, it is recommended that patients treated with IORT undergo routine long-term follow up for at least a 10 years to screen for IBTR.

Comment on External Beam APBI

Since 2009, several key studies have provided important new data on the complication profile of APBI delivered with external beam radiation therapy (3D-CRT) or intensity modulated radiation therapy [IMRT]). Most importantly, the RAPID trial randomized 2,135 patients to whole breast irradiation or 3D-CRT APBI. [13] Although the IBTR risk has not yet been reported, cosmetic outcome as assessed separately by patients, nurses, and physician panels was consistently worse at 3 and 5 years in patients randomized to 3D-CRT APBI.[15] In contrast, the University Florence phase III trial reported that IMRT APBI resulted in improved physician rated cosmetic outcome compared to whole breast irradiation.[11] Single-arm studies have also reported higher rates of fair - poor cosmetic outcomes in approximately 20% of patients treated with EBRT-based APBI[24,42,53] while other clinical series of APBI delivered with 3D-CRT or IMRT reported acceptable cosmetic outcomes.[16,21-23,54-58] These conflicting studies raise the

hypothesis that subtle variations in planning techniques and/or dose constraints may substantially modify the therapeutic ratio of EBRT-based APBI.[59-61] In the light of ongoing research, particularly the NSABP B-39/RTOG 0413 trial,[12] which has yet to report cosmetic outcomes for patients treated with 3D-CRT APBI, the task force opted not to make a specific recommendation either for, or against, the use of EBRT-based APBI at this time.

Conclusion

APBI has been tested in a limited number of trials with over 1000 patients over the last 10 years. These trials show that in properly selected breast cancer patients, APBI has provided outcomes similar to WBI. In the light of the new literature, the suitability criteria for APBI have now been updated, as summarized in Tables 1-3. Table 4 provides the overall summary of the new recommendations, including the level of agreement amongst the writing panel and the strength of the evidence and recommendations. It is hoped that this update will provide ongoing direction for radiation oncologists and other specialists participating in the care of breast cancer patients.

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Table 1. Patients "suitable" for APBI if all criteria are present

Factor	*Criterion*
Patient Factors	
Age	**≥ 50 y**
BRCA1/2 mutation	not present
Pathologic factors	
Tumor size	≤2 cm*
T stage	**Tis** or T1
Margins	Negative by at least 2 mm
Grade	Any
LVSI	No†
ER status	Positive
Multicentricity	Unicentric only
Multifocality	Clinically unifocal with total size ≤2 cm‡
Histology	Invasive ductal or other favorable subtypes§
Pure DCIS	**Allowed if screen-detected, low to intermediate nuclear grade, ≤ 2.5 cm size, and resected with margins negative at ≥ 3 mm**
EIC	Not allowed
Associated LCIS	Allowed
Nodal factors	
N stage	pN0 (i-,i+)
Nodal surgery	SN Bx or ALND‖
Treatment factors	
Neoadjuvant therapy	Not allowed

Bolded items reflect changes made to the prior Consensus Statement.

* The size of the invasive tumor component.

† The finding of possible or equivocal LVSI should be disregarded.

‡ Microscopic multifocality allowed, provided the lesion is clinically unifocal (a single discrete lesions by physical examination and ultrasonography/mammography) and the total lesion size (including foci of multifocality and intervening normal breast parenchyma) does not exceed 2 cm

§ Favorable subtypes include mucinous, tubular, and colloid

‖ Pathologic node staging is not required for DCIS

APBI = accelerated partial-breast irradiation; LVSI = lymph-vascular space invasion; ER = estrogen receptor; DCIS = ductal carcinoma in situ; EIC = extensive intraductal component; LCIS = lobular carcinoma in situ; SN Bx = sentinel lymph node biopsy; ALND = axillary lymph node dissection

Table 2. Patients "cautionary" for APBI if any of these criteria are present*

Factor	*Criterion*
Patient Factors	
Age	**40-49 y if all other criteria for "suitable" are met**
Age	**50 or higher if patient has at least one of the pathologic factors below and does not have any "unsuitable" factors**
Pathologic factors	
Tumor size	2.1-3.0 cm†
T stage	T2
Margins	Close (<2 mm)
LVSI	Limited/focal
ER status	Negative
Multifocality	Clinically unifocal with total size 2.1-3.0 cm‡
Histology	Invasive lobular
Pure DCIS	
	≤3 cm if criteria outlined in "suitable" table are not fully met
EIC	≤3 cm

Bolded items reflect changes made to the prior Consensus Statement.

* Caution and concern should be invoked when considering these patients for APBI.

† The size of the invasive tumor component

‡ Microscopic multifocality allowed, provided the lesion is clinically unifocal (a single discrete lesion by physical examination and ultrasonography/ mammography) and the total lesion size (including foci of multifocality and intervening normal breast parenchyma) falls between 2.1 and 3.0 cm.

APBI = accelerated partial-breast irradiation; LVSI = lymph-vascular space invasion; ER = estrogen receptor; DCIS = ductal carcinoma in situ; EIC = extensive intraductal component

Table 3. Patients "unsuitable" for APBI outside of a clinical trial if any of these criteria are present

Factor	*Criterion*
Patient factors	
Age	**<40 y**
BRCA1/2 mutation	Present
Pathologic factors	
Tumor size*	>3 cm
T stage	T3-4
Margins	Positive
LVSI	Extensive
Multicentricity	Present
Multifocality	If microscopically multifocal > 3 cm in total size or if clinically multifocal
Pure DCIS	If >3 cm in size
EIC	If >3 cm in size
Nodal factors	
N stage	pN1, pN2, pN3
Nodal surgery	None performed
Treatment factors	
Neoadjuvant therapy	If used

Bolded items reflect changes made to the prior Consensus Statement.

* The size of the invasive tumor component.

APBI = accelerated partial-breast irradiation; LVSI = lymph-vascular space invasion; ER = estrogen receptor; DCIS = ductal carcinoma in situ; EIC = extensive intraductal component

Table 4. Grading Evidence, Recommendations and Consensus Methodology

Guidelines statements	Strength of evidence	Strength of recommendation	Percent (%) Agreement
KQ1. Which patients may be considered for APBI outside of a clinical trial? • *Age*			
A. Include age greater or equal to 50 years in the "suitable" group.	MQE	Weak	100%
B. Patients who are aged 40-49 years and who meet all other elements of suitability are considered cautionary	LQE	Weak	100%
C. Retain patients with age less than 40 years or those who are 40 – 49 years without meeting other elements of suitable in the "unsuitable" group.	N/A	Weak	100%
KQ1. Which patients may be considered for APBI outside of a clinical trial? • *Margins*			
A. Maintain the current selection criteria for "suitable", "cautionary" and "unsuitable" patients based on margin status.	N/A	Weak	75%
KQ1. Which patients may be considered for APBI outside of a clinical trial? • *Pure Ductal Carcinoma In Situ (DCIS)*			
A. Include patients with low-risk DCIS as per RTOG 9804 criteria (i.e. screen-detected, low to intermediate nuclear grade, less than or equal to 2.5 cm size, resected with margins negative at greater than or equal to 3 mm), in the "suitable" group.	MQE	Weak	100%
New key question. Which patients may be considered for intraoperative partial breast irradiation?			
A. Patients interested in cancer control equivalent to that achieved with whole breast irradiation post lumpectomy for breast conservation should be counseled that in two clinical trials the risk of IBTR was higher with IORT.	HQE	Strong	87.5%
B. Electron beam IORT should be restricted to women with invasive cancer considered "suitable" for partial breast irradiation (Table 1) based on the results of a multivariate analysis with median follow up of 5.8 years.	MQE	Strong	100%
C. Low-energy x-ray IORT for PBI should be used within the context of a prospective registry or clinical trial, per ASTRO Coverage with Evidence Development (CED) statement. When used, it should be restricted to women with invasive cancer considered "suitable" for partial breast irradiation (Table 1) based on the data at the time of this review.	MQE	Weak	87.5%

HQE = high quality of evidence; MQE = moderate quality of evidence; LQE = low quality of evidence; N/A= not applicable, information only.