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Special Article

Accelerated Partial Breast Irradiation: Executive summary for the update of an ASTRO Evidence-Based Consensus Statement

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Abstract

Purpose: To update the accelerated partial breast irradiation Consensus Statement published in 2009 and provide guidance on use of intraoperative radiation therapy (IORT) for partial breast irradiation in early-stage breast cancer, based on published evidence complemented by expert opinion.

Methods and materials: A systematic PubMed search using the same terms as the original Consensus Statement yielded 419 articles; 44 articles were selected. The authors synthesized the published evidence and, through a series of conference calls and e-mails, reached consensus regarding the recommendations.

Supplementary material for this article (doi:10.1016/j.prro.2016.09.007) can be found at www.practicalradonc.org.

Conflicts of interest: 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, Virginia, 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.BDS receives research funding from Varian Medical Systems. MCL 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 followed by extreme hypofractionation to whole breast with IMRT in postmenopausal women. AT is a site principal investigator for the Targeted Intraoperative Radiotherapy (TARGIT-A) trial and coauthor for the resulting publication. EEH is the writing committee member for the TARGIT-A trial and a coauthor for the resulting publication; she is also a principal investigator for the NRG institutional and committee member for the NRG Breast Cancer Working Group. JW receives research funding from the 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. CC is a steering committee member of the Early Breast Cancer Trialists Collaborative Group (EBCTCG). None of the relationships disclosed was viewed as having any substantive impact upon the consensus statement.

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Results: The new recommendations include lowering the age in the "suitability group" from 60 to 50 years and in the "cautionary group" to 40 years for patients who meet all other elements of suitability (Table 1). Patients with low-risk ductal carcinoma in situ, as per Radiation Therapy Oncology Group 9804 criteria, were categorized in the "suitable" group. The task force agreed to maintain the current criteria based on margin status. Recommendations for the use of IORT for breast cancer patients include: counseling patients regarding the higher risk of ipsilateral breast tumor recurrence with IORT compared with whole breast irradiation; the need for prospective monitoring of long-term local control and toxicity with low-energy radiograph IORT given limited follow-up; and restriction of IORT to women with invasive cancer considered "suitable."
Conclusion: These recommendations will provide updated clinical guidance regarding use of accelerated partial breast irradiation for radiation oncologists and other specialists participating in the care of breast cancer patients.

Introduction

Accelerated partial breast irradiation (APBI) is a localized form of radiation delivered after lumpectomy to only the part of the breast where the tumor was removed. This procedure requires close collaboration between the surgeon and the radiation oncologist. When compared with whole breast irradiation (WBI), APBI offers several benefits, including reducing treatment time and sparing healthy tissue. Initial research indicates APBI can be as effective as WBI in terms of survival and controlling local recurrences in select patients. 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 radiographs or electrons, most commonly delivered at the time of surgery.

The American Society for Radiation Oncology (ASTRO) consensus statement on APBI was originally published in 2009. The Board of Directors approved the proposal to partially update consensus statement in January 2015. This update addresses key question (KQ) 1 from the original guideline: Which patients may be considered for APBI outside of a clinical trial? It also considers a new KQ: Which patients may be considered for intraoperative partial breast irradiation (PBI)? This update is endorsed by the Society of Surgical Oncology.

Methods

For information on the literature review, the grading of the recommendations and evidence, and the consensus methodology, please see the full version (supplementary materials at www.practicalradonc.org).

Results

KQ1: 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," 100% Agreement).
B. Patients who are aged 40 to 49 years and who meet all other elements of suitability are considered "cautionary" (lower quality of evidence, recommendation rated as "Weak," 100% Agreement).
C. Retain patients with age younger than 40 years or those who are 40 to 49 years without meeting other elements of suitable in the "unsuitable" group (no evidence rating, recommendation rated as "Weak," 100% Agreement).

Three randomized trials evaluating APBI versus WBI have been published or updated since the original ASTRO consensus statement. In the Groupe Européen de Curiethérapie of the European Society for Radiotherapy and Oncology (GEC-ESTRO) trial, 1184 patients were enrolled in a phase 3, noninferiority trial and were randomized to WBI plus a tumor bed boost or APBI delivered with multicatheter interstitial brachytherapy.[1] The 5-year risk of ipsilateral breast tumor recurrence (IBTR) was less than 2% in both treatment arms, and the study concluded that APBI was not inferior to WBI. In addition, there were no differences in toxicity through 5 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.[1] In the National Institute of Oncology Budapest trial in which 128 received primarily multicatheter brachytherapy APBI, 23% of patients were younger than age 50. In this trial, patients younger than age 40 were excluded after 2001 because of an early analysis that reported unacceptably high IBTR risk in these patients.[2] At a median follow-up of 10.2 years, 5.5% had an in-breast recurrence, but no further analysis by age was done.[3] In the University of Florence trial, 15.8% of the 260 randomized to intensity modulated radiation therapy (IMRT) APBI were <50 years old. With a median follow-up of 5 years, 1.5% had an in-breast recurrence and age was not a significant factor associated with recurrence.[4] In each trial, roughly 90% or more of enrolled patients had T1, N0 and hormone-sensitive disease. Data from other large randomized phase 3 trials evaluating APBI, including the National Surgical Adjuvant Breast and Bowel Project B39/Radiation Therapy Oncology Group (RTOG) 0413 trial[5] and Randomized Trial of Accelerated Partial Breast Irradiation trials,[6] 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.[7] In this phase 2 study of 274 stage I, hormone-sensitive breast cancer patients who received multicatheter APBI, 5-year local recurrence for patients <50 years of age was 7.5%, and for patients ≥50 years was 1.1% ($P = .030$). 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 estrogen receptor(-) status were significantly associated with the development of in-breast recurrence.[8] In the Massachusetts General Hospital phase 2 trial of 3-dimensional (3D) conformal radiation therapy (3D-CRT) APBI, an IBTR occurred in 2 of 15 women aged 40 to 49 (14% actuarial risk) compared with 3 of 83 in those age ≥50 years (3% actuarial risk), with median follow-up 71 months, although this difference was not statistically significant.[9] The 2 patients less than 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 MammoSite registry trial final analysis, although in ductal carcinoma in situ (DCIS) patients, the 5-year IBTR rate was 19% in those aged <50 compared with 5.8% for aged >50 years.[10]

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," 75% Agreement).

Pure DCIS

Recommendation statement:

A. Include patients with low-risk DCIS as per RTOG 9804 criteria (ie, screen-detected, low to intermediate nuclear grade, less than or equal to 2.5 cm size, resected with margins negative at ≥3 mm), in the "suitable" group (MQE, recommendation rated as "Weak," 100% Agreement).

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.[11] With a median follow-up of 7.2 years, risk of IBTR was 6.7% risk in the observation arm compared with 0.9% in the WBI arm. Similar results were noted in the initial publication of the Eastern Cooperative Oncology Group (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.[12,13] 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 5-year risk of an IBTR of 0%.[14] The 5-year rate of IBTR among all 194 DCIS patients in the MammoSite registry was 3.4%.[15] A pooled analysis of 300 women with DCIS from the MammoSite registry and a single institution similarly showed a 2.6% 5-year risk of IBTR.[16] In addition, a single-institution study evaluating 99 DCIS patients treated with either balloon brachytherapy, interstitial brachytherapy, or 3D-CRT external beam radiation therapy (EBRT) APBI demonstrated a 1.4% 5-year risk of IBTR.[17] 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% 5-year IBTR risk among 32 women with DCIS treated with multicatheter brachytherapy.[18]

In contrast, one single-institution investigation reported a trend toward higher risk of time to IBTR among pure DCIS tumors compared with invasive ductal carcinomas at 4 years after MammoSite (hazard ratio, 3.57; $P = .06$).[19] One prospective multicenter trial using MammoSite in 41 DCIS patients showed a 9.8% 5-year risk of IBTR, all outside the treatment field.[20]

Data from randomized trials of APBI versus WBI 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 PBI?

Recommendation statements:

A. Patients interested in cancer control equivalent to that achieved with WBI postlumpectomy for breast conservation should be counseled that in 2 clinical trials the risk of IBTR was higher with IORT (high quality of evidence, recommendation rated as "Strong," 87.5% Agreement).

Table 1 Comparison of patient groups in original and updated consensus statements

Patient group	Risk factor	Original	Update
Suitability	Age	≥60 y	≥50 y
	Margins	Negative by at least 2 mm	No change
	T stage	T1	Tis or T1
	DCIS	Not allowed	If all of the below: • Screen-detected • Low to intermediate nuclear grade • Size ≤2.5 cm • Resected with margins negative at ≥3 mm
Cautionary	Age	50-59 y	• 40-49 y if all other criteria for "suitable" are met • ≥50 y if patient has at least 1 of the pathologic factors below and does not have any "unsuitable" factors *Pathologic factors:* • Size 2.1-3.0 cm [a] • T2 • Close margins (<2 mm) • Limited/focal LVSI • ER(-) • Clinically unifocal with total size 2.1-3.0 cm [b] • Invasive lobular histology • Pure DCIS ≤3 cm if criteria for "suitable" not fully met • EIC ≤3 cm
	Margins	Close (<2 mm)	No change
	DCIS	≤3 cm	≤3 cm and does not meet criteria for "suitable"
Unsuitable	Age	<50 years	• <40 y • 40-49 y and do not meet the criteria for cautionary
	Margins	Positive	No change
	DCIS	>3 cm	No change

[a] The size of the invasive tumor component.
[b] 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.

B. Electron beam IORT should be restricted to women with invasive cancer considered "suitable" for PBI (Table 1) based on the results of a multivariate analysis with median follow-up of 5.8 years (MQE recommendation rated as "Strong," 100% Agreement).
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, recommendation rated as "Weak").

Clinical trials

Two large phase 3 trials, the Intraoperative radiotherapy with electrons (ELIOT) trial and the TARGIT trial, compared WBI with IORT PBI using either electron beam (ELIOT)[21] or low-energy x-rays (Intrabeam device, TARGIT).[22] Both trials reported increased risk of IBTR after IORT. In ELIOT, the 5-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.[23] Among these patients, the 5-year occurrence of IBTR was approximately 1.5%, pointing out the importance of patient selection.[23]

In TARGIT, the 5-year IBTR risk was 3.3% (23/3375) in the low-energy x-ray IORT arm compared to 1.3% (11/3375), (P = .042) in the WBI arm.[22] The overall median follow up for TARGIT is 2.4 years (n = 3451). The task force acknowledges that 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 prepathology subgroup (2.1% (10 of 2234) with IORT vs 1.1% (6 of 2234) with WBI),[22] the task force thought greater weight should be placed on evaluation of the efficacy of IORT in the prespecified primary analysis population that included all patients. The task force also noted concerns from the chair of the TARGIT Data Monitoring Committee

regarding misuse of the noninferiority criterion and the responses from the authors.[24,25] For these reasons, the task force felt low-energy x-ray IORT should continue to be used within the context of a prospective registry or clinical trial to ensure 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 are no data on the use of IORT with DCIS, the task force recommended 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[26,27] was increased with IORT, whereas skin side effects were lower.[24,26] Mild breast fibrosis[26,28,29] occurred with electron beam radiation on ELIOT, with no significant difference compared with WBI in the ELIOT trial.[26] IORT techniques may allow improved critical organ sparing compared with WBI. Lung fibrosis in the ELIOT trial[30] and deaths from cardiovascular causes in the TARGIT trial were lower in the IORT groups.[8]

In some studies, low-energy radiographs followed by WBI was associated with double the risk of breast fibrosis (to 37.5%), increased patient-reported pain, and decreased patient-reported quality of life compared with WBI alone.[30-33] 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 EBRT boost.[33-35] As such, the task force felt the combination of IORT and WBI should be used only with caution and limited to women with higher risk features on final pathology.

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, likely at least 10 years. 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 EBRT 3D-CRT or IMRT. Most important, the Randomized Trial of Accelerated Partial Breast Irradiation trial randomized 2135 patients to WBI or 3D-CRT APBI.[6] 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 3 trial reported that IMRT APBI resulted in improved physician-rated cosmetic outcome compared with WBI.[4] Single-arm studies have also reported higher rates of fair to poor cosmetic outcomes in approximately 20% of patients treated with EBRT-based APBI.[29,36,37] However, other clinical series of APBI delivered with 3D-CRT or IMRT reported acceptable cosmetic outcomes.[9,38-45] 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.[46-48] In light of ongoing research, particularly the National Surgical Adjuvant Breast and Bowel Project B-39/RTOG 0413 trial,[5] 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 more than 1000 patients over the past 10 years. These trials show that, in properly selected breast cancer patients, APBI has provided outcomes similar to WBI. In light of new literature, the suitability criteria for APBI have now been updated, as summarized in Table 1. 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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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

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