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

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ABSTRACT

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

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

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

CONCLUSIONS: The updated guidelines presented offer clinicians with a summary of data supporting APBI and guidelines for the appropriate and safe utilization of the technique.

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

Introduction

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

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

Methods

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

Results

Previously published guidelines

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

Clinical outcomes

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

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

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