Accelerated Partial-Breast Irradiation: Outcomes and Future Perspectives

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Abstract

Accelerated partial-breast irradiation (APBI) is an adjuvant radiotherapy technique that allows for the completion of radiation therapy (RT) in 1 week or less for women undergoing breast conservation. Traditionally delivered using interstitial brachytherapy, APBI can also be performed using newer techniques that include applicator-based brachytherapy and external-beam techniques (3D-conformal RT, intensity-modulated RT). Long-term outcomes with APBI encompass data from randomized trials, prospective data, and single-institution series, which have highlighted the efficacy as well as comparable recurrence risks compared with whole-breast irradiation (WBI). Prospective randomized comparisons of APBI with WBI have demonstrated similar rates of tumor control, although toxicity results vary based on the technique used with the potential for improved toxicity with brachytherapy based techniques. Moving forward, studies are under way to evaluate shorter courses of APBI, with evidence-based guidelines evolving to the increasing literature supporting the technique.

Key Words: breast cancer, radiation therapy, breast-conserving therapy, accelerated partial-breast irradiation, brachytherapy

Introduction

Breast-conserving therapy (BCT) represents one of the most significant advances in breast cancer treatment over the past several decades. With more than 20 years of follow-up, BCT has been shown to have equivalent rates of local control and overall survival (OS) compared with mastectomy, with improvements in patient quality of life.[1-5] Randomized trials comparing BCT and mastectomy have consistently utilized whole-breast irradiation (WBI) with or without a tumor bed boost. Whole-breast irradiation typically requires 5 to 6 1/2 weeks of adjuvant radiotherapy (RT) for its completion. This lengthy duration of therapy is one factor responsible for many women failing to undergo adjuvant RT following breast-conserving surgery (BCS), despite the improvement in breast cancer mortality associated with RT.[4,6]

Over the past 2 decades, alternatives to standard WBI have emerged, including hypofractionated WBI (15–16 fractions) and accelerated partial-breast irradiation (APBI). Accelerated partial-breast irradiation is a technique that treats only the lumpectomy cavity plus a small area surrounding the surgical bed (margin of tissue), rather than the whole breast. This concept is based upon patterns of failure data demonstrating that the majority of ipsilateral breast failures occur in close proximity to the lumpectomy cavity.[7,8] The purpose of this review is to examine the data supporting the utilization of APBI, as well as clinical guidelines and future directions to help clinicians decide on appropriate adjuvant RT techniques for their patients with early stage breast cancer.

Results of Clinical Trials

Clinical Outcomes

The earliest technique utilized to deliver APBI was interstitial brachytherapy (IB). This was initially used as either a boost following WBI or as the sole radiation modality; consequently, it represents the technique with the most mature data. A randomized study of 258 women from Hungary compared WBI with APBI delivered with either IB or electrons. At 10 years of follow-up, no difference in clinical outcomes, including local recurrence (5.1% vs 5.9%), was noted. Improvement in cosmetic outcomes compared with WBI was seen for those women treated with IB (81% vs 63%).[9] These findings were consistent with a prospective study of 45 patients from the same institution: 12-year outcomes demonstrated a 9% rate of local recurrence, 78% excellent/good cosmesis, and low rates of toxicity, including a 2% rate of grade 3 fibrosis.[10]

A large, multi-institutional phase 3, noninferiority randomized trial compared IB-based APBI to WBI, randomizing 1184 patients with low-risk, early stage breast cancer and was recently published. With a median follow-up of 6.6 years, there was no difference in the 5-year rates of local recurrence (1.44% with APB–I vs 0.92% with WBI; P = 0.42) and no difference in the rates of regional recurrences, distant metastases, disease-free survival, breast cancer mortality, or OS was noted. With respect to toxicity, WBI was associated with increased grade 2–3 breast

pain (1.1% APBI vs 3.2% WBI; P = 0.04) and a trend for increased grade 2–3 late skin side effects (3.2% APBI vs 5.7% WBI, p = 0.08) with no difference in the rates of grade 2–3 subcutaneous late side effects (7.6% vs 6.3%) and grade 3 fibrosis (0% vs 0.2%).[11]

In the United States, the RTOG 95-17 phase II trial[12] evaluated IB with either a high-dose rate (HDR; n = 66) or low-dose rate (LDR; n = 33) implant. Ninety-nine patients were enrolled, and at 5 years, low rates of local recurrence were noted (3% HDR/6% LDR). With longer follow-up (12 years), cosmetic outcomes remained stable, with 66% reporting excellent/good cosmesis and a 13% rate of grade 3 toxicity.[13]

Similar findings were noted in a prospective protocol published by Hattangadi et al,[14] in which 50 patients received interstitial APBI via an LDR technique on a dose-escalation protocol. At 12 years, a 15% local recurrence rate was noted, with 67% of patients having excellent/good cosmesis. Toxicity outcomes demonstrated that 54% of patients had moderate/severe fibrosis, 35% had fat necrosis, and 34% had telangiectasias.These studies demonstrating fair/poor cosmesis rates of 30% to 35% may be secondary to the rates of fibrosis and fat necrosis that can impact cosmesis.

A total of 199 patients treated with interstitial HDR APBI at William Beaumont Hospital were compared via a matched-pair analysis (age, tumor size, nodal status, receptor status, hormonal therapy) to patients treated with WBI; 12-year outcomes demonstrated no differences in rates of local recurrence, regional recurrence, or survival.[15] The **Table** presents key clinical studies by APBI technique.

Although IB provided a technique with excellent clinical outcomes and low rates of toxicity, the technical complexity and need for multiple catheters limited the scope and interest for its use. However, with the development of single-entry applicators, brachytherapy became a technique more readily available to patients and continues to evolve with the introduction of second-generation multilumen and strut devices. Initial studies with the single-lumen MammoSite applicator confirmed the feasibility of the technique, with 5-year outcomes from the initial study demonstrating no recurrences and low toxicity rates; importantly, a correlation between cosmesis and skin distance was noted with the initial data, which served as a guideline for clinicians using the single-lumen devices.[16]

This initial success led to a prospective registry study of 1449 patients who were all treated with single-lumen devices, receiving 34 Gy over 5 days with twice-daily treatment. Five-year outcomes from this study demonstrated a 5-year local recurrence rate of 3.8%, with more than 90% of patients having excellent/good cosmesis.[17] Over the past few years, multilumen and strut-based devices have been developed with improved dosimetric outcomes noted (improved target coverage with reduced skin, normal breast tissue, and chest wall/rib doses).[18-20] It is anticipated that in light of these improvements, long-term outcomes with this new generation of devices will demonstrate lower rates of toxicity and the potential for improved cosmetic outcomes.

Recently, two observational studies were performed evaluating toxicity with brachytherapy-based APBI. Smith et al[21] evaluated a cohort of Medicare beneficiaries and found higher rates of subsequent mastectomy and infectious and noninfectious complications with brachytherapy-based APBI; a recent analysis by the same group found higher rates of mastectomy in younger patients with endocrine receptor–negative disease.[22] Similarly, Presley et al[23] evaluated a cohort of Medicare beneficiaries and found higher rates of complications with brachytherapy-based APBI, including wound and skin complications. These studies both had significant limitations, including their use of billing codes rather than true clinical assessment, evaluation of brachytherapy prior to widespread clinical implementation with multilumen applicators, failure to evaluate clinical/pathologic features, and short follow-up, as well as the fact that the increase in mastectomy noted may not be clinically significant. It should be noted that final analysis of the American Society of Breast Surgeons Registry trial[10] demonstrated low rates of toxicity and that cosmesis data from the randomized Hungarian trial has favored brachytherapy, as did recent toxicity data from the GEC-ESTRO trial.[11,24] Multiple prospective and retrospective series of studies also have failed to confirm the findings of these observational studies, although smaller numbers of patients may limit the ability to detect small differences seen in large observational studies.[13,16,18,20]

Following surgery, some patients prefer to avoid an additional invasive procedure. External-beam RT (EBRT) APBI was developed to allow for shorter-duration treatment without the need for an additional procedure; however, studies have shown that in order to account for patient motion, larger target volumes are needed, leading to higher doses to normal breast tissue.[25] Initial studies of the technique from William Beaumont Hospital demonstrated excellent clinical outcomes in 192 patients with no local recurrences at 5 years and an 80% rate of excellent/good cosmesis.[26] These findings were supported by a report from the RTOG 0413/NSABP B-39 phase III trial that found no concerns regarding toxicity with the 3-dimensional conformal RT (3D-CRT) technique.[27] However, studies from Tufts University and the University of Michigan (study utilized intensity modulated radiation therapy) have raised concerns regarding toxicity and poor cosmesis, with increased rates of grade 3 or greater fibrosis (8%) and suboptimal cosmesis.[28,29]

These findings were confirmed by the RAPID randomized trial,[29] a study that included 2135 patients over age 40 with invasive ductal carcinoma/ductal carcinoma in situ (DCIS), negative margins, pathologically node-negative, and tumors less than 3 cm. The study compared 3D-CRT APBI (38.5 Gy/10 fractions twice daily) with WBI (42.5 Gy/16 fractions (82%) or 50 Gy/25 fractions (18%), 21% boost) and found that APBI was associated

TABLE. Key Accelerated Partial-Breast Irradiation Studies

	Study Type	Patients (n)	Median Follow-Up (months)	Technique	Local Recurrence	Toxicity
Interstitial						
National Institute of Oncology, Hungary	Randomized	258	122	HDR (n=88)/ electrons (n=40)	10-year LR (5.1% WBI vs. 5.9% PBI, NS)	Improved excellent/good cosmesis with partial breast 81% vs 63%
GEC-ESTRO	Randomized	1184	78	HDR/PDR	5 year LR (0.9% WBI vs. 1.4% APBI, NS)	Reduced breast pain and trend for reduced grade 2-3 late skin toxicity with APBI
RTOG 9517	Prospective	99	73	HDR (n=66)/ LDR (n=33)	5-year LR 3%/6% (HDR/LDR)	13% grade 3 skin toxicity, 37% skin dimpling, 45% fibrosis, 45% telangiectasias, 15% symptomatic fat necrosis, 66% excellent/good cosmesis
Harvard University	Prospective	50	134	LDR (dose-escalation)	12-year LR 15%	67% excellent/good cosmesis, 35% fat necrosis, 34% telangiectasias, 22% grade 3/4 skin toxicity
William Beaumont Hospital	Matched-Pair Analysis	199	127	HDR	12-year LR (3.8% WBI vs 5% APBI, NS), no difference in RR, DFS, CSS, OS	
Applicator						
MammoSite Initial Trial	Prospective	70 (43 treated)	65 (n=36)	Single-Lumen	5-year LR 0%	9.3% infection, 33% seroma, 12% symptomatic seroma, 4 patients with fat necrosis, 83% excellent/good cosmesis
MammoSite Registry	Prospective	1449	63	Single-Lumen	5-year LR 3.8% (3.7% invasive, 4.1% DCIS)	91% excellent/good cosmesis, 9.6% infection, symptomatic seroma 13%, 13% telangiectasias, 2.5% fat necrosis
External Beam						
NSABP B-39/RTOG 0413; 2011	Randomized	1367	37	3D-CRT		3% Grade 3+ fibrosis
RAPID	Randomized	2135	36	3D-CRT		Increased adverse cosmesis with APBI, Grade 3 toxicity 1.4%, increased grade 1/2 toxicity with APBI
University of Florence	Randomized	520	60	IMRT	5-year IBTR 1.5%, no difference with WBI	Reduced acute and chronic toxicity with APBI, improved cosmetic outcome with APBI
RTOG 0319	Prospective	52	63	3D-CRT	4-year LR 6%	64% excellent/good cosmesis at 3 years, 5.8% grade 3 toxicity
William Beaumont Hospital	Retrospective	192	56	3D-CRT	5-year LR 0%	81% excellent/good cosmesis, 7.5% grade 3 fibrosis, 7.6% telangiectasias
Tufts University	Retrospective	60	15	3D-CRT		8% grade 3/4 fibrosis, 82% excellent/ good cosmesis
University of Michigan	Prospective	34	60	3D-CRT	5-yr LR 3%	73% excellent/good cosmesis, 0% grade 3 fibrosis

APBI=accelerated partial-breast irradiation; CRT= conformal radiotherapy; CSS=cancer-specific survival; DCIS=ductal carcinoma in situ; DFS=disease-free survival; HDR=high dose rate; IBTR= ipsilateral breast tumor recurrence; IMRT=intensity-modulated radiotherapy; LDR=low dose rate; LR=local recurrence; NS=nonsignificant; OS=overall survival; PBI=partial-breast irradiation; RR=regional recurrence; 3D-CRT=3-dimensional conformal radiotherapy; WBI=whole-breast irradiation.

with higher rates of grade 1 and 2 toxicity; cosmesis was evaluated by trained nurses and physicians reviewing photographs as well as patients, and APBI was associated with adverse cosmesis with each (29% vs 17%, 35% vs 17%, and 26% vs 18%, respectively).[30] Similarly, RTOG 0319[31] evaluated the 3D-CRT APBI technique and found that although initial toxicity outcomes were low, cosmesis deteriorated with longer follow-up, with only 64% of patients having excellent/good cosmesis and a 5.8% rate of grade 3 or greater toxicity at 3 years.

In light of these concerns, new EBRT techniques are being developed that include intensity-modulated RT (IMRT), with initial results demonstrating lower rates of toxicity, although further follow-up is needed.[32] A randomized study from the University of Florence compared APBI (30 Gy/ 5 fractions daily) with WBI (50 Gy/25 fractions with 10 Gy boost); with a median follow-up of 5 years, no difference in local recurrence was noted, with improved acute and chronic toxicity and cosmesis using APBI.[33] Whereas a previous IMRT study (University of Michigan) found higher rates of poor cosmesis, the improved cosmesis may be due to an alternative dose fractionation scheme in this trial.

Evidence-Based Guidelines

Multiple evidence-based guidelines exist to assist clinicians in determining which patients are appropriate for APBI (off clinical trial) based on clinicopathologic criteria.[34-37] The most recent set of guidelines were published by the American Brachytherapy Society (ABS) and support APBI for patients aged 50 or older, with tumors 3 cm or less, all invasive cancers and DCIS histologies, negative margins, no lymphovascular space invasion (LVSI), and negative lymph nodes.[34] Previously, Smith et al[35] had published American Society for Therapeutic Radiology and Oncology (ASTRO) consensus guidelines for APBI in 2009 that included age, *BRCA* status, tumor size, margins, LVSI, estrogen receptor status, multifocality/centricity, histology, nodal status, and receipt of neoadjuvant chemotherapy. However, several studies evaluating these guidelines failed to demonstrate a correlation between ASTRO groupings and local recurrence; further, additions to the literature have provided more clarity regarding certain cautionary factors (eg, DCIS).[38-41] With the expected publication of mature data from several randomized trials in the years to come, it is anticipated that these guidelines will continue to evolve and may include tumor genetics, as well.

Future Directions

As APBI continues to advance as an adjuvant RT technique, future directions will focus on further shortening the duration of treatment and providing alternative methods to deliver RT. With regard to reducing the length of treatment, data have been published on schedules shorter than the traditional 5-day, twice-daily schedule. A prospective study from William Beaumont Hospital enrolled 45 patients to receive APBI via a single-lumen applicator with a dose of 28 Gy delivered in 4 fractions over 2 days. With a median follow-up of 3.7 years, no ipsilateral breast tumor recurrences (IBTRs) were noted, with 4-year disease-free survival, cancer-specific survival, and OS of 96%, 100%, and 93%, respectively. Toxicity rates were low, with the only grade 1 or 2 toxicities being fat necrosis (18%) or asymptomatic seroma (42%). Three patients developed rib fractures.[42] Further studies are under way to examine the long-term clinical efficacy and toxicity profiles with this fractionation scheme.[43]

One technique that is considered to be a form of PBI is intraoperative RT (IORT); however, significant differences exist compared with traditional APBI techniques, including differences in the physics, biology, and a lack of image guidance.[44,45] Two randomized trials have been performed evaluating IORT. The ELIOT trial[46] randomized 1305 patients to IORT (electrons) or WBI and found that with a median follow-up of 5.8 years, IORT was associated with higher rates of IBTR (4.4% vs 0.4%), with no difference in survival noted. WBI was associated with higher rates of skin toxicity, although events remained low, while IORT was associated with higher rates of fat necrosis.

Similarly, the TARGIT trial[47] randomized 3451 patients to IORT (delivered with a low-energy x-ray source; 15.2%-21.6% received supplementary WBI) or WBI . The 5-year risk of local recurrence (although follow-up was only 29 months) was significantly higher with IORT (3.3% vs 1.3%), with no difference in survival noted. Importantly, the difference in local recurrence in the post-pathology stratum (5.4% vs 1.7%) exceeded the 2.5% noninferiority threshold of the trial. Much controversy has been raised by these results, with significant concerns regarding the methodology raised by several authors.[48,49] In light of the higher local recurrence rates, lack of long-term follow-up, and methodological concerns regarding the TARGIT trial, IORT should not be considered to be equivalent to WBI or APBI techniques and should not be used off-protocol at this time.

Preoperative PBI also has been evaluated using an intraoperative technique in a phase II study from North Carolina. With a 69-month follow-up, the actuarial rate of IBTRs was 15% in 53 enrolled patients. The authors expressed concerns regarding the higher rates of local recurrence, particularly in the cautionary-risk group.[50]

Conclusions

At this time, APBI represents an appropriate treatment option for appropriately selected women with early stage breast cancer. Mature results from randomized trials and prospective series have consistently demonstrated comparable clinical and survival outcomes with low rates of toxicity with brachytherapy-based APBI. Although observational studies have raised concerns regarding increased toxicity with brachytherapy-based APBI, these findings are not supported by randomized and prospective data and are further limited by the deficiencies of observational stud-

ies. With the advent of multilumen devices, toxicity rates are expected to continue to decline with brachytherapy APBI. In light of recent data, EBRT APBI techniques continue to evolve with the aim of reducing toxicity and improving cosmesis. Evidence-based guidelines have been created to assist clinicians in determining appropriate candidates for APBI and continue to evolve with emerging data. Intraoperative RT, while particularly convenient for patients and highly publicized recently, should not be considered a standard treatment option off-protocol at this time, with data demonstrating higher local recurrence rates with relatively short follow-up. We await the published results of other large, randomized phase III trials that have completed accrual comparing APBI to WBI to determine efficacy of this treatment and its associated side-effect profile.

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