Accelerated partial-breast irradiation: An emerging standard of care

Timothy D. Smile, BS; Naveen Karthik, Kyle Reilly, BS; Erick Westerbeck, BS; Radhika Takiar, BS; Ramya Vajapey, BS; Rahul Tendulkar, MD; Chirag Shah, MD

Breast-conserving therapy, consisting of breast-conserving surgery (BCS) followed by adjuvant radiation therapy, represents a mainstay in the treatment of early stage breast cancer.[1-3] Traditionally, radiation therapy following BCS has consisted of standard whole-breast irradiation (SWBI) followed by a tumor bed boost with a 5-7 week duration of treatment. However, the length of treatment is one factor associated with noncompliance with adjuvant radiation therapy following BCS.[4,5] To reduce treatment duration, decrease healthcare resource utilization, and potentially limit toxicity, alternatives to SWBI have been developed including accelerated whole-breast irradiation (AWBI) and accelerated partial-breast irradiation (APBI). AWBI represents a standard of care treatment option based on 4 randomized trials that have demonstrated comparable clinical outcomes and toxicity as compared to SWBI with long-term follow-up.[6-9] APBI can be delivered with anmultiple techniques including interstitial brachytherapy, applicator brachytherapy, and external-beam techniques. With the publication of 7 randomized trials, a large amount of data supports APBI as a standard-of-care treatment option following BCS in appropriately selected patients; however, data demonstrates that APBI remains underutilized despite the potential benefits for patients.[10] Therefore, the purpose of this review is to evaluate data supporting APBI and examine questions clinicians face regarding APBI.

***Mr. Smile, Mr. Karthik, Mr. Reilly, Mr. Westerbeck, Ms. Takiar**, and **Ms. Vajapey** are medical students; **Dr. Tendulkar** is an associate professor; and **Dr. Shah** is associate staff and director of clinical research, Cleveland Clinic, Taussig Cancer Institute, Department of Radiation Oncology, Cleveland, OH.*

Randomized Trials

At this time, 7 randomized trials comparing APBI with SWBI and/or AWBI have been published in abstract or manuscript form with five (National Institute of Oncology-Hungary, GEC-ESTRO, University of Florence, IMPORT LOW, and Hospital de la Esperanza) publishing clinical outcomes while two (RAPID, NSABP B-39) presented only toxicity data (Table 1).

Interstitial brachytherapy represents the oldest modern APBI technique and, as such, the randomized trial with the longest follow-up utilized this technique. The National Institute of Oncology in Hungary performed a randomized trial of 258 women with early stage breast cancer (T1N0-1mi, Grade 1-2, nonlobular, negative margins), with patients receiving either SWBI (50 Gy/25 fractions) or PBI (interstitial 36.4 Gy/7 fractions or electrons 50 Gy/25 fractions). With 10-year follow-up, no difference in the rates of local recurrence were noted (5.1% SWBI vs. 5.9% PBI) with improved cosmesis for partial-breast patients (81% vs. 63% excellent/good cosmesis).[11] This trial was followed by the GEC-ESTRO trial, which was a multi-institutional randomized noninferiority trial comparing SWBI and APBI delivered with interstitial brachytherapy (high dose or pulsed dose rate). A total of 1,184 patients (pTis, pT1-2a ($\leq$ 3 cm), pN0/N1mi, margins $\geq$ 2 mm, age $\geq$ 40) were enrolled and, at 5 years, no difference in rates of local recurrence (0.9% SWBI vs. 1.4% APBI) were noted. Additionally, APBI was associated with a trend for improved late grade 2-3 skin toxicity and breast pain.[12]

With respect to external-beam APBI, several randomized trials have been published. The Randomized Trial of Accelerated Partial Breast Irradiation using Three-Dimensional Conformal External Beam Radiation Therapy (RAPID) trial randomized 2,135 patients (tumor < 3 cm, node negative, nonlobular, margins negative, age > 40) to SWBI/AWBI or APBI delivered with 3-dimensional conformal radiation therapy (3D-CRT) (38.5

Table 1. Randomized studies evaluating accelerated partial-breast irradiation

	Years of accrual	APBI technique	Number of patients	Follow-up (months)	Clinical outcomes	Toxicity
National Institute of Oncology	1998-2004	HDR multi-catheter interstitial BT (n=88) and limited electron field (n=40)	258	122	Local recurrence: 5.9% (PBI) vs. 5.1% (WBI) 10-y survival: 79.7% (PBI) vs. 82.1% (WBI)	Improved excellent/good cosmetic outcome with PBI (81% vs.63%), HDR patients had improved cosmetic compared to WBI with 6-9 MV photons (85% vs. 67%)
GEC-ESTRO	2004-2009	Multicatheter interstitial BT (HDR/PDR)	1,184	78	Local recurrence 1.4% (APBI) vs 0.9% (WBI) 5-y Survival: 97.3% (APBI) vs. 95.6% (WBI)	Trend for reduced late grade 2-3 skin toxicity with APBI (3.2% vs. 5.7%, p=0.08)
Barcelona	Not specified	3D-CRT	102	60	Local recurrence: 0% (PBI) vs. 0% (WBI)	APBI reduced acute skin toxicity, similar late toxicity and cosmetic outcomes
University of Florence	2005-2013	IMRT	520	60	Local recurrence: 1.5% (PBI) vs. 1.5% (WBI) 5-y survival: 99.4% (APBI) vs. 96.6% (WBI)	APBI fewer acute & late skin toxicity compared to WBI (p = 0.0001, p = 0.004, respectively); APBI improved physician-rated cosmesis (p = 0.05)
IMPORT LOW	2007-2010	IMRT	2,018	68	Local recurrence: 0.2% (SIB) vs. 0.5% (APBI) vs. 1.1% (WBI)	Reduced change in breast appearance with APBI compared to AWBI
Toxicity Only						
RAPID	2006-2011	3D-CRT	2,135	36	N/A	Grade 1 and 2 toxicities increased with APBI (p < 0.001), worse cosmetic outcomes with APBI, grade 3 toxicities rare for both arms
NSABP B-39	2005-2013	3D-CRT*	1,386	41	N/A	Fibrosis: grade 2 ≤ 12%, grade 3 ≤ 3%, grade 4-5 0%

APBI = accelerated partial breast irradiation, AWBI= accelerated whole-breast irradiation, HDR = high dose rate, PBI = partial-breast irradiation, WBI= whole-breast irradiation, GEC-ESTRO = Groupe Europeen de Curietherapie European Society for Radiotherapy and Oncology, PDR = pulsed dose rate, 3D-CRT = 3-dimensional conformal radiotherapy, IMRT = intensity-modulated radiation therapy, SIB = simultaneous integrated boost
*cohort presented

Gy/10 fractions, twice daily). Interim analysis demonstrated worse cosmetic outcomes with APBI as well as rates of grade 1/2 toxicity.[13] However, these findings are inconsistent with an analysis of the NSABP B39 3D-CRT cohort, which demonstrated 0% Grade 4/5 toxicity and < 3% Grade 3 toxicity, and a smaller randomized study from Barcelona that demonstrated reduced acute toxicity with 3D-CRT APBI.[14,15] More recently, a randomized trial of 520 patients (tumor < 2.5 cm, margins > 5 mm, age > 40) from the University of Florence compared SWBI with APBI, delivered with IMRT (30 Gy/5 fractions, every other day). At 5 years, no difference in the rates of local recurrence were noted (1.5% SWBI vs.

Table 2a. Randomized studies evaluating 3-dimensional conformal radiotherapy accelerated partial-breast irradiation

	Years of accrual	APBI technique	Number of patients	Follow-up (months)	Clinical outcomes	Toxicity
RAPID	2006-2011	Randomized	2,135	36	N/A	Grade 1 and 2 toxicities increased with APBI ($p < 0.001$), worse cosmetic outcomes with APBI, grade 3 toxicity rare for both arms
NSABP B-39	2005-2013	Randomized	1,386	41	N/A	Fibrosis: grade 2 ≤ 12%, grade 3 ≤ 3%, grade 4-5 0%
Barcelona	Not specified	Randomized	102	60	Local recurrence: 0% (PBI) vs. 0% (WBI)	APBI reduced acute skin toxicity, similar late toxicity and cosmetic outcomes

APBI = accelerated partial-breast irradiation

Table 2b. Nonrandomized studies evaluating 3-dimensional conformal radiotherapy accelerated partial-breast irradiation

	Years of accrual	APBI technique	Number of patients	Follow-up (months)	Clinical outcomes	Toxicity
RTOG 0319	2003-2004	Phase II	52	63	6% ipsilateral breast failure	82% excellent/good cosmesis at 1 year, 64% at 3 years; adverse events: grade 1 = 36.5%, grade 2 = 50%, grade 3 = 5.8%
William Beaumont Hospital	2000-2011	Single institution-retrospective	192	56	Local recurrence: 0% Overall survival: 92%	81% excellent/good cosmesis, 7.5% grade 3 fibrosis
University of Michigan	2004-2007	Prospective	32	60	Local Recurrence: 3%	Fibrosis: grade 2 = 3.3%, grade 3 = 0%; excellent/good cosmesis 73%
Tufts University	2004-2007	Single institution-retrospective	60	15	—	Subcutaneous fibrosis: grade 2-4 = 25%, grade 3-4 = 8.3%; excellent/good cosmesis 82%

1.5% APBI) with improved cosmetic outcomes as well as reduced acute/chronic toxicity with APBI.[16] Similarly, the IMPORT LOW trial has been presented as an abstract; the trial compared AWBI (40 Gy/15 fractions) with APBI (40 Gy/15 fractions) and AWBI with a boost to the tumor bed (36 Gy/15 fractions whole breast, 40 Gy/15 fractions partial breast). The trial enrolled 2,018 patients (tumor < 3 cm, N0-1, margins > 2 mm, age ≥ 50) and found no difference in rates of local recurrence at 5 years (1.1% AWBI vs. 0.5% APBI vs. 0.2% simultaneous integrated boost). Additionally, APBI was associated with decreased breast appearance changes as compared to AWBI.[17] Taken together, several key conclusions can be drawn: 1) randomized data supports that there is no difference in local control with APBI as compared to SWBI, 2) randomized trials with multiple techniques have demonstrated consistent findings, and 3) toxicity data supports no difference in outcomes between interstitial APBI and SWBI, while data with external-beam

APBI favors IMRT or daily radiation compared to the 3D-CRT technique. At this time, there is limited ability to directly compare different APBI techniques, as the trials above used a single APBI technique (with the exception of the National Institute of Oncology trial). However, with the anticipated publication of mature outcomes from NSABP B-39, clinicians should have data to directly compare clinical outcomes and toxicity profiles between techniques.

Clinical Questions

What is the data supporting applicator-based brachytherapy?

The initial randomized trial evaluating APBI primarily used interstitial brachytherapy, a technically challenging modality used in a limited number of centers. However, with the advent of the single-entry balloon applicator, brachytherapy-based APBI became available and its use increased.[10,18] The MammoSite Registry included 1,449 cases treated with single-lumen applicators; with 5-year follow-up, the rate of ipsilateral breast tumor recurrence was 3.8% with 91% of patients having excellent/good cosmesis.[19,20] These findings are consistent with smaller applicator-based brachytherapy series and confirm excellent clinical outcomes with the technique.[21,22] Additionally, since the initial studies evaluating single-lumen applicators, multilumen and strut applicators have been developed, which have been shown to improve target coverage and reduce dose to organs at risk, potentially further improving outcomes.[23,24] It should be noted that interstitial and applicator-based brachytherapy use slightly different expansions, with applicator brachytherapy traditionally using a 1-cm expansion around the cavity, compared to 2 cm with interstitial brachytherapy.[11,12,25] More data is expected as applicator-based brachytherapy was included on NSABP B-39; in the interim, applicator-brachytherapy remains a standard APBI option for appropriate patients, with data supporting excellent clinical and toxicity outcomes.

Are there toxicity-related concerns regarding brachytherapy-based APBI?

Over the past few years, several observational studies demonstrated that while the incidence of brachytherapy increased, its use was associated with higher rates of subsequent mastectomy (reasons unclear), as well as infectious and noninfectious toxicity compared to WBI.[26, 27] However, despite the large number of patients in these studies, significant limitations exist including the retrospective nature, short follow-up, use of billing codes as surrogates for clinical outcomes, and concerns regarding reproducibility.[28,29] Additionally, the years evaluated occurred before the widespread use of multi-lumen applicators and included only patients 66 years or older. It is important to note that data from randomized and prospective studies have failed to validate these concerns and brachytherapy-based APBI remains a mainstay approach as noted by evidence-based guidelines from multiple societies.[30,31]

What external-beam approaches should be used?

Clinicians can consider several external-beam APBI approaches. The initial modern external technique was described by Baglan et al and delivered a dose of 38.5 Gy in 10 fractions twice daily using noncoplanar beams to a tumor volume that included a 1.5-cm clinical target volume expansion along with an additional 1 cm for internal target volume and planning target volume.[33] This technique was found to have excellent clinical outcomes and toxicity profiles in the William Beaumont Hospital experience.[32] Unfortunately, concerns regarding the toxicity profile with this technique have emerged, including outcomes from the RAPID trial, RTOG 0319 as well as data from Tufts University and the University of Michigan.[13,34-36] However, analysis of the 3D-CRT cohort from NSABP B39 and data from a Spanish randomized trial have failed to confirm these findings; as such, this remains an area of further study and is summarized in Tables 2a and b.[14,15] In the interim, alternatives to this technique have emerged. The first is the use of intensity-modulated radiation therapy (IMRT). This technique was evaluated by Lei et al and found to have low rates of local recurrence, 88%-90% excellent/good cosmesis, and low rates of toxicity using the same 38.5 Gy/10 fraction regimen.[37] An alternative IMRT approach used by Livi et al featured an every-other-day approach (30 Gy/5 fractions), with 1-cm CTV, and a 1-cm PTV expansion. Data from the randomized study demonstrated reduced toxicity with APBI IMRT compared to SWBI, and improved cosmesis.[16] Alternatively, instead of switching external beam techniques, one can switch the dose and fractionation from 38.5 Gy/10 fractions delivered twice daily to daily regimens such as the Florence regimen or a more protracted course of 40 Gy/15 fractions, which was utilized in the IMPORT LOW trial.[16,17] At this time, external APBI should still be considered for patients; while further data on the 3D-CRT technique will emerge from NSABP B-39/RTOG 0413, physicians should consider IMRT or daily fractionation to minimize toxicity risk and improve cosmetic outcomes.

What is the data surrounding proton therapy to deliver APBI?

Proton therapy represents an alternative external-beam technique, compared to 3D-CRT or IMRT, which use photons. Initial studies evaluating proton APBI demonstrated high rates of skin toxicity as well as subacute toxicity;[38] long-term follow-up confirmed these findings with increased rates of late toxicity and poor cosmetic outcomes.[39]

However, the technique has been refined, and phase II data from Korea (30 Gy/5 fractions) has demonstrated excellent clinical outcomes and low toxicity rates, although cosmetic outcomes appear to be lower than those seen with traditional APBI techniques and follow-up remains short.[40] Similarly, data from Loma Linda Medical Center included 100 patients and, with 5-year follow up, toxicity rates were low, with 90% of patients having excellent/good cosmetic outcomes.[41] Although recent data is promising and studies have shown proton APBI to be comparable in cost to some techniques and less expensive than others, the limited number of patients treated and lack of long-term outcomes suggest that proton APBI should continue to be used only on-protocol.[42]

How does intraoperative radiation therapy fit in the context of APBI?

Intraoperative radiation therapy (IORT) is a form of partial-breast irradiation in that it treats a target smaller than the whole breast, delivering treatment to the lumpectomy cavity. However, despite the promise of IORT as a way to complete local therapy in one visit, it should not be considered a form of APBI and the data available does not support IORT to be used off protocol at this time.[43] IORT differs from APBI with respect to 1) dose delivery to a margin beyond the lumpectomy cavity, 2) failure to have consistent image-guidance protocols, and 3) confirmation of dose with formal treatment planning.[44,45] Additionally, two randomized studies comparing SWBI and IORT have found increased rates of local recurrence with IORT with short follow-up, something not seen in the randomized APBI trials. The ELIOT trial used intraoperative electrons following BCS and randomized 1,305 patients (tumor $\leq$ 2.5 cm, age 48-75) to SWBI or IORT. With 5-year follow-up, the study found increased rates of local recurrence with IORT (4.4% vs. 0.4%, $p < 0.0001$); a unique feature of this trial was that patients did not receive remedial WBI.[46] In contrast, the TARGIT trial randomized 3,451 patients (invasive ductal, age $\geq$ 45) to SWBI or IORT with remedial WBI for some IORT patients (15% of all patients; 22% pre-pathology, 4% post-pathology). However, the study also demonstrated increased rates of local recurrence with IORT (3.3% vs. 1.3%, $p = 0.04$), although they were within the allowed noninferiority threshold except for the post-pathology cohort (5.4% vs. 1.7%, $p = 0.07$).[47] Significant controversy regarding the methodology of the TARGIT trial and the role of IORT exists; however, given the data, IORT should not be recommended off-protocol at this time, which is consistent with updated American Society for Radiation Oncology (ASTRO) guidelines put forth for review.[43,48-50]

What are the cost concerns?

With an increased focus on value-based healthcare, it is important to consider the costs associated with adjuvant radiation therapy. APBI 3D-CRT represents an APBI technique that is less costly than SWBI or AWBI and would be expected to have comparable cost to AWBI when using a daily regimen over 15 days similar to IMPORT LOW.[42,51] While brachytherapy-based APBI is more costly (based on reimbursement) than WBI or AWBI delivered with 3D-CRT, it has been found to be cost-effective when accounting for indirect costs and outcomes, and is less expensive than SWBI delivered with IMRT.[52] However, a recent study using time-driven, activity-based costing found increased costs associated with brachytherapy-based APBI.[53]

With respect to other APBI techniques, while proton APBI remains investigational, recent cost studies have demonstrated comparable cost for protons compared to 3D-CRT SWBI and alternative APBI techniques (brachytherapy), while finding protons more expensive than 3D-CRT AWBI and 3D-CRT APBI.[42] IORT has been heralded as a means to reduce the cost of adjuvant radiotherapy;[54] however, when factoring in the costs of supplemental WBI, increased OR time, and management of recurrences, SWBI, AWBI, and APBI are considered cost-effective.[55] Moving forward, to properly evaluate APBI cost-effectiveness, studies must move beyond absolute reimbursement and use techniques that incorporate patient costs associated with treatment duration, as well as the impact on quality of life and toxicity profiles.

What about patient selection?

One of the greatest challenges facing clinicians is determining which patients are appropriate for APBI. One way of assessing eligibility is to use the inclusion criteria from published randomized trials to guide selection. However, concerns exist, as data that evaluates outcomes for subsets within these trials is limited. Additionally, several societies have released consensus guidelines for treatment off-protocol, including ASTRO, the American Brachytherapy Society, Groupe Europeen de Curiethrapie-European Society of Therapeutic Radiology and Oncology, and the American Society of Breast Surgeons.[29,30,56,57] As data continues to emerge, these guidelines will evolve; however, the current ASTRO groupings have failed to correlate with risk of local recurrence. As such, further study is required.[58,59] At this time, ideal candidates for APBI include those 50 years or older with T1-2N0 tumors ($\leq$ 3 cm)/DCIS ($\leq$ 3 cm) and negative surgical margins without lymphovascular space invasion.

Where does APBI stand as a treatment option?

APBI is a standard-of-care treatment option for appropriately selected patients with early stage breast cancer. The basis of this recommendation is the publication of 5 randomized clinical tri-

als demonstrating no difference in rates of local recurrence compared to SWBI or AWBI with mature follow-up. Similarly, randomized data has demonstrated acceptable toxicity profiles for interstitial and IMRT APBI, while prospective data has demonstrated the safety and efficacy of applicator APBI. While the data has limitations, it justifies routine use of APBI in appropriate patients, with future data expected to refine treatment techniques and selection criteria rather than focus on APBI validation.

Future Directions

APBI continues to evolve as a technique with novel strategies to reduce treatment duration. Data from William Beaumont Hospital evaluated the feasibility of applicator-based APBI delivered in 2 days (28 Gy/4 fractions); with 4-year follow-up, no local recurrences were noted, with 98% of patients demonstrating excellent/good cosmesis, and 3 rib fractures noted in a cohort of 45 patients.[60] This study was performed using single-lumen applicators, and additional studies (eg, the TRIUMPH trial) are evaluating 2-day fractionation with multilumen and strut applicators.[61] Additionally, studies are investigating intraoperative-like, single-fraction APBI, providing the convenience of IORT with a technique that is image-guided, covers appropriate target depth, and allows for pathologic confirmation prior to treatment.[62]

Conclusions

With the publication of 7 randomized trials and availability of long-term outcomes, APBI represents a standard-of-care treatment approach following breast-conserving surgery. Patients eligible for SWBI and AWBI should be considered for APBI in light of significant overlap in eligibility criteria. Studies are underway to further shorten the treatment duration of APBI, thereby reducing the burden of adjuvant treatment for women with early stage breast cancer.

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