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**Accelerated partial breast irradiation: Past, present, and future**

Tann AW *et al*. Accelerated partial breast irradiation

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**Abstract**

Accelerated partial breast irradiation (APBI) focuses higher doses of radiation during a shorter interval to the lumpectomy cavity, in the setting of breast conserving therapy for early stage breast cancer. The utilization of APBI has increased in the past decade because of the shorter treatment schedule and a growing body of outcome data showing positive cosmetic outcomes and high local control rates in selected patients undergoing breast conserving therapy. Technological advances in various APBI modalities, including intracavitary and interstitial brachytherapy, intraoperative radiation therapy, and external beam radiation therapy, have made APBI more accessible in the community. Results of early APBI trials served as the basis for the current consensus guidelines, and multiple prospective randomized clinical trials are currently ongoing. The pending long term results of these trials will help us identify optimal candidates that can benefit from ABPI. Here we provide an overview of the clinical and cosmetic outcomes of various APBI techniques and review the current guidelines for selecting suitable breast cancer patients. We also discuss the impact of APBI on the economics of cancer care and patient reported quality of life.

**Key words:** Breast cancer; Accelerated partial breast irradiation; Interstitial brachytherapy; Intracavitary brachytherapy

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**Core tip:** Given that accelerated partial breast irradiation (APBI) is becoming increasingly utilized in the management of early breast cancer patients, it is crucial to address the evolution of studies that led to the current guidelines in identifying the suitable group of patients who obtain the most benefit clinically and cosmetically. We, herein, discuss the available clinical and cosmetic outcomes of different APBI techniques in addition to details of ongoing phase III randomized clinical trials. We also discuss the effects of APBI on breast cancer patient quality of life.

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**INTRODUCTION**

Breast conservation surgery (BCS) has been offered to newly diagnosed breast cancer patients as early as the 1950s[1]. BCS with adjuvant whole-breast irradiation (WBI), collectively referred to as breast conservation therapy (BCT), is one of the acceptable standard of cares. Numerous prospective randomized studies, with long term follow-up, have shown the equivalence of BCT to modified radical mastectomy in overall survival (OS) and disease-free survival (DFS)[2-5].

Standard WBI usually consists of 6-7 wk of daily radiation treatments to the whole breast with doses of 45 to 50 Gy. WBI typically includes a 10 to 16 Gy boost to the lumpectomy cavity for many patients to further reduce local recurrence. Local recurrence can also be reduced by tamoxifen or aromatase inhibitors in estrogen receptor positive breast cancer patients[6-9]. Hypofractionated WBI has recently been accepted as a treatment option in BCT, with local control (7.5% 10-year local recurrence rate)[10] and treatment toxicities comparable to conventional fractionation.

**Rationale for Accelerated Partial Breast Irradiation**

Accelerated partial breast irradiation (APBI) delivers radiation to the tumor bed at a higher dose per fraction. The radiobiologic model of the linear quadratic equation serves as the basis for APBI. A shorter radiation treatment course, given at higher dose per fraction, could achieve the same therapeutic effect as a longer treatment course, given at lower dose per fraction, based on the concept of radiobiologic equivalence. Ipsilateral breast tumor recurrences (IBTR) develop in and around the tumor bed in 44%-86% of cases[11-14], and treatment to the whole breast may be unnecessary. Therefore, by focusing the radiation to the area of potential recurrence, much of the surrounding tissues (including the lung, heart, uninvolved ipsilateral breast, contralateral breast, and skin) could be spared, reducing toxicity and improving cosmetic outcome[15-19].

**Early APBI Trials**

In the earliest prospective, randomized study, Christie Hospital (Manchester, United Kingdom) enrolled 708 patients, 355 of which were treated with wide-field (WF) irradiation and 353 treated with limited-field (LF) irradiation, from 1982 to 1987[20]. The study included patients younger than 70 years with tumor size ≤ 4 cm, and all women underwent tumorectomy “with gross or macroscopic clearance” only. The WF group received 40 Gy in 15 fractions over 21 d to the whole breast through parallel opposed tangent fields with a single matched anterior field covering the axillary, infraclavicular, and supraclavicular regions. The accelerated, partial breast LF group received 40 to 42 Gy in 8 fractions delivered over 10 d to the tumor bed only. At 8-year median follow-up, the survival in the two groups was the same (72%); however, the LF group showed a local recurrence rate of 25% *vs* 13% in the WF group (*P* = 0.00008)[21]. The authors concluded that APBI was possible, but would need more stringent selection of patients.

The next APBI trial was conducted by Guy’s Hospital (London, United Kingdom) beginning in the late 1980s and used low dose rate (LDR) brachytherapy to deliver focal radiation. Twenty-seven non-randomized patients received BCS and axillary clearance immediately followed by placement of brachytherapy needles in a multi-planar arrangement around the surgical cavity. Iridium-192 seeds were loaded into the needles to deliver 55 Gy over 5 d to a 2 cm margin around the tumor bed[22]. Results showed good to excellent cosmesis in 80%-96% of patients at 27 mo of median follow-up; however, 37% of patients suffered local regional failure at 72 mo of median follow-up[23]. The high rate of local regional recurrences was attributed to the inclusion of subjects with recognized risk factors, such as positive margins and node positive disease.

Three additional trials explored dose escalation using interstitial brachytherapy for APBI at the Careggi Hospital (Florence, Italy), Royal Devon and Exeter Hospital (Exeter, England), and, again, Guy’s Hospital (London, United Kingdom). Similarly, these studies included patients with unknown or positive margins, resulting in high local recurrence rates[24,25]. Around the same time period, the Milan group reported a much lower IBTR rate of 4.8% with WBI[26]. In summary, these studies demonstrated the feasibility of APBI and provided a basis for the design of subsequent APBI trials with young age, positive margin status, larger tumors, high nuclear grade, extensive ductal carcinoma *in situ*, invasive lobular carcinoma, involved nodes, and lymphovascular invasion (LVSI) established as risk factors for recurrence.

**Trials with Modern APBI Techniques**

***Brachytherapy***

**Multicatheter interstitial brachytherapy:** Investigators at Ochsner Medical Institutions conducted a pilot trial, enrolling 50 patients from January 1992 to October 1993 in a phase I/II study of multicatheter interstitial brachytherapy (MIB), after segmental mastectomy, for invasive or intraductal tumors ≤ 4 cm with negative inked margins and ≤ 3 involved axillary lymph nodes[27]. Patients were treated to the target volume with continuous LDR brachytherapy of 45 Gy over 4 d or fractionated HDR brachytherapy of 32 Gy in 8 fractions, given twice daily over 4 d. Cosmetic evaluation at median follow-up of 20 mo showed good to excellent cosmetic result in 75% of patients in both arms. At 75-mo median follow-up, there were 4 local-regional failures (8%). In another study, William Beaumont Hospital accrued patients between 1993 and 1999 for an APBI trial with stringent patient selection criteria: tumor size ≤ 3 cm, age ≥ 40 years, and no extensive DCIS or lobular histology[28]. All patients had lumpectomy and axillary node dissection with ≥ 2 mm clear microscopic margin of the lumpectomy cavity. Patients with 1-3 involved nodes were initially included but were later excluded. The early phase of the trial delivered 50 Gy of continuous LDR brachytherapy over 5 d with iodine-125 sources[29]. The later phase of the trial used HDR brachytherapy with iridium-192 to deliver 32 Gy in 8 twice daily fractions or 34 Gy in 10 twice daily fractions[30]. The planned treatment volume was the lumpectomy cavity with additional 1 to 2 cm margin. With 5.7 years of median follow-up, 90% (total 199 patients) of patients had good to excellent cosmesis with comparable complications to matched WBI treated patients. The 5-year actuarial recurrence rate was 1.2%. These studies, using multicatheter interstitial brachytherapy, were followed by other successful, non-randomized studies listed in Table 1, and ultimately led to multi-institutional trials.

Radiation Therapy Oncology Group (RTOG) 9517 was opened as a multi-institutional phase I/II MIB-based APBI trial, and enrolled patients with unifocal tumors < 3 cm, negative margins, and axillary lymph-node sampling, with involvement of ≤ 3 involved nodes with no extra-capsular extension[31]. One hundred patients were accrued between 1997 and 2000 and 99 patients were evaluated. Thirty-three patients received 45 Gy in 3.5-5 d with LDR, and 66 patients to 34 Gy in 10 twice-daily fractions with HDR. In both cases, the target volume was the lumpectomy cavity with 2 cm margin peripherally and 1 cm superficially and deep. The 5-year actuarial in-breast failure rates were 6% and 3% for LDR and HDR brachytherapy, respectively[32]. Acute toxicities, including pain, tenderness, erythema, edema, and infection, were followed, and 3 of 33 patients receiving LDR APBI and 2 of 66 patients receiving HDR APBI experienced grade 3 or 4 adverse effects. These rates of toxicity were similar to earlier single institution trials. Reported late toxicities included breast tenderness, skin thickening, and fibrosis, and the LDR group suffered more frequent late toxicities than the HDR group (18% *vs* 4%)[31].

The first phase III trial included patients treated with MIB-based APBI[33]. A total of 258 patients, with T1N0-1mi, grade 1-2 non-lobular breast cancer with negative resection margins and no extensive intraductal component, were randomized to partial breast irradiation (PBI) or WBI between 1998 and 2004. PBI included either LF external-beam irradiation of 50 Gy in 25 fractions for patients who were technically unsuitable for HDR MIB or HDR MIB of 5.2 Gy for 7 fractions. 133 patients were accrued in WBI group and 128 in PBI group (88 HDR MIB and 40 LF external-beam PBI). The 10-year actuarial local recurrence rate (5.9% PBI *vs* 5.1% WBI) was similar for the two arms (*P* = 0.77). The rates of good to excellent cosmetic outcome were 81% in the PBI groups together and 63% in the WBI group (*P* < 0.01). HDR MIB APBI demonstrated superior cosmesis compared to LF external-beam PBI, with 85% *vs* 72.5% good to excellent cosmesis[34].

A collaborative effort in Europe recently reported a phase III, randomized, non-inferiority trial, using solely MIB[35]. A total of 1184 patients between April 2004 and July 2009, with favorable invasive carcinoma and DCIS, were randomized to either WBI (551 patients) or MIB APBI (633 patients). The primary endpoint was local recurrence. Five patients in WBI group and 9 patients in APBI group had local recurrence at 5-year follow-up. The cumulative incidence of local recurrence of APBI was 1.44% *vs* 0.92% with WBI. The 5-year rate of grade 2-3 late toxicities to the skin was 5.7% with WBI *vs* 3.2% with APBI (*P* = 0.08), and the 5-year rate of grade 2-3 subcutaneous tissue late side-effects was 6.3% *vs* 7.6% (*P* = 0.53). The incidence of severe grade 3 fibrosis was 0.2% with WBI at 5 years and 0% with APBI (*P* = 0.46). There were no grade 4 late toxicities. The study concluded that the 5-year LC, DFS, and OS were similar for MIB APBI and WBI after BCS for patients with early breast cancer.

**Intracavitary brachytherapy (balloon and hybrid applicators):** The success of MIB APBI is highly dependent on center expertise; therefore, it is not easily accessible to the general population. This led to the development of a more user-friendly brachytherapy approach with flexible balloon catheter. The MammoSite® (Hologic Inc., Marlbourough, MA) intracavitary breast brachytherapy applicator was approved by the FDA in 2002 and simplified APBI administration. The deflated, single-channel balloon catheter is positioned into the lumpectomy cavity after resection at the time of surgery or post-operatively *via* a subsequent procedure. The balloon is then inflated with a mixture of saline and radio-opaque contrast to fill the lumpectomy cavity. CT imaging is used for assessment of catheter positioning and to assure appropriate skin spacing of at least > 5 mm or > 7 mm optimally. A computer-controlled remote after-loader is used to insert iridium-192 source into the balloon catheter to deliver 34 Gy in 10 twice daily fractions (prescribed to 1 cm from the balloon surface). The catheter is removed after the final fraction and deflation of the MammoSite® balloon.

The MammoSite® Breast Brachytherapy Registry Trial enrolled 1449 patients and had a median follow-up of 63.1 mo with 5-year actuarial rate of IBTR of 3.8%. Tumor size and the lack of estrogen receptor expression were found to be associated with IBTR. At 84 mo, 90.6% of patients had good to excellent cosmesis[36].

William Beaumont Hospital enrolled 45 patients in a phase I/II study using MammoSite balloon brachytherapy with an alternative fractionation schedule[37]. A total dose of 28 Gy in 4 fractions were given in 2 d. At ≥ 6 mo, 2% had grade 2 induration, radiation dermatitis, or hyperpigmentation and 2% grade 3 breast pain. There were 4 cases of fat necrosis. Cosmesis was good to excellent in 96% of cases. The investigators concluded that the 2-d dose schedule resulted in acceptable toxicity rates.

Efforts were made to improve the conformity of radiation delivered *via* balloon applicators with a multicatheter design. The SAVI® (Strut Assisted Volume Implant**)**, which was FDA approved in 2006, is a bundle of flexible, tiny catheters that can be expanded uniformly to conform to the size and shape of tumor cavity. Fisher *et al*[38] compared outcomes for 117 patients; 77 of whom received APBI *via* MammoSite® device and 40 patients *via* the SAVI® APBI device. None of the patients implanted with the SAVI device required explantation due to skin proximity. This compared to 57% of the patients implanted with the MammoSite® device, whose skin to target distance was < 7 mm, had explantation. The closest target-to-skin distance treated with the SAVI® device was 2 mm. Good to excellent cosmesis was reported in the 12 patients who had limited skin spacing treated with SAVI®. Contura, is another commercially available multilumen balloon breast brachytherapy catheter device, and investigators conducted a multi-institutional phase IV registry trial for this device, enrolling 342 evaluable patients between January 2008 and February 2011. The median follow-up was 36 mo, and the 3-year local recurrence-free survival was 97.8% and good to excellent cosmesis in 88% of the patients. The incidence of infection was 8.5% and 4.4% of patients suffered symptomatic seroma[39]. Patients treated at high-volume centers had a superior cosmetic outcome, with 95% of those patients with good to excellent overall cosmesis, indicating that cosmetic outcome is variable among centers.

***External beam radiation therapy***

External beam radiation therapy (EBRT) includes 3D-conformal radiation therapy (3D-CRT) and intensity modulated radiation therapy (IMRT) defined by the inverse planning of radiation fields. EBRT delivers radiation to a clinical target volume, which for APBI is the tumor bed with 10 to 15 mm. An additional 5 to 10 mm margin was added for set-up errors and target motion. Patients receiving APBI can be set up either supine or prone and are typically treated with four or five non-coplanar beams. A potential advantage of EBRT is that it is widely available. RTOG 0319, a phase I/II trial, sought to evaluate the efficacy and toxicity of 3D-CRT APBI. The trial enrolled 52 evaluable patients with tumors ≤ 3 cm, ≤ 3 positive nodes, and negative margins. Patients received 38.5 Gy in 10 twice daily fractions. With median follow-up of 4.5 years, the 4-year estimates of IBTR, DFS, and OS were 6%, 84%, and 96%, respectively. Only 4% of patients suffered grade 3 toxicities[40]. RTOG 0319 demonstrated the feasibility of 3D-CRT APBI, and the effectiveness of EBRT was further explored in subsequent trials.

The phase III study, NSABP B39/RTOG 0413 is the largest ongoing randomized trial of WBI *vs* APBI. The APBI techniques utilized in the trial are multicatheter brachytherapy (34 Gy), MammoSite (34 Gy), and EBRT (38.5 Gy), given twice daily for 10 fractions, with at least 6 hours in between.

While the oncology community waits for the results of NSABP B39/RTOG 0413, interim results from other randomized studies of EBRT APBI have been presented. The Ontario Clinical Oncology Group sponsored RAPID, a randomized trial of APBI using 3D-CRT *vs* WBI. The study enrolled 2135 patients between 2006 and 2011, and an interim cosmetic and toxicity report demonstrated increased adverse cosmesis at 3 years for patients receiving APBI as compared with WBI evaluated by trained personnel (29% vs 17%, *P* < 0.001), by patients (26% vs 18%, *P* = 0.0022), and by review of imaging by physicians (35% vs 17%, *P* < 0.001). Grade 3 toxicities were uncommon in the 2 treatment arms (1.4% for APBI vs 0% for WBI)[41]. In another study, the University of Florence (Florence, Italy) recently reported the result of a phase III randomized controlled trial comparing IMRT *vs* WBI. A total of 520 patients were randomized with 260 patients in each arm between March 2005 and June 2013[42]. At a median follow-up of 5.0 years, the IBTR rate was 1.5% in the APBI and WBI groups. The 5-year OS was 96.6% for the WBI group and 99.4% for APBI group. Patients treated with APBI demonstrated significantly less acute and late toxicity and better cosmetic outcome.

Other groups are investigating alternative external beam fractionation regimens. The ACCEL Trial (NCT02681107), sponsored by AHS Cancer Control Alberta, is a phase II study evaluating patients treated with EBRT APBI to a prescribed dose of 27 Gy over 5 fractions delivered daily. The Mayo Clinic is sponsoring a phase II trial evaluating APBI given in 3 fractions of 7.3 Gy using EBRT or 7 Gy using catheter-based brachytherapy (NCT02453737).

**Additional APBI Techniques**

***Intraoperative radiation therapy***

**Intrabeam:** Intraoperative radiation therapy (IORT) refers to radiation treatment of the tumor bed in a single treatment delivered in the operating room after resection and prior to closure. The rationale for IORT is that a single fraction delivered at the time of surgery, makes post-operative radiotherapy unnecessary. In the past, the popularity of IORT was limited because of the expense and impracticality of the specialized radiation delivery devices, but more recently advances in technology have made IORT devices more mobile and available[43]. The first widely available IORT device, Intrabeam®, was first used introduced 1998. Since then, at least two mobile IORT-capable linear accelerators, the Mobetron and Novac-7 systems have become available. While Intrabeam® is a kilovoltage photon system, Mobetron and Novac-7 generate megavoltage electrons.

Intrabeam® (Oberkochen, Germany) uses spherical applicators to deliver kilovoltage photons once inserted into the surgical cavity for uniform dose deposition. The estimated time required to deliver APBI using this device is 20 to 35 min in a single application (this is comparable to the treatment times for each of the 10 fractions delivered for EBRT) making this type of treatment more convenient in some setting. In addition it has been hypothesized that single fraction IORT has a better therapeutic index[44].

The TARGIT-A trial randomized 3451 patients to either EBRT or TARGIT-A (20 Gy IORT with 50 kV photons). Patient eligibility criteria included: Age ≥ 45 years, tumor size ≤ 3.5 cm, N0-1, M0, and unifocal invasive ductal carcinoma[45]. TARGIT-A patients with adverse risk factors identified on final pathology were given an additional 50 Gy equivalent of EBRT. At 29 mo of median follow-up, the 5-year recurrence rates for patients treated with TARGIT-A and WBI were 3.3% and 1.3%, respectively (*P* = 0.042). Wound complication rates between the 2 groups were similar; however, grade 3 or 4 skin complications were lower with TARGIT-A *vs* EBRT (*P* = 0.029). Twenty-one percent of prepathology TARGIT-A patients received 5 wk of EBRT. Patients who received only TARGIT-A had 3 times the recurrence rate of those who received TARGIT-A plus EBRT (2.7 *vs* 0.9%). Breast cancer mortality was similar between two groups; however, the number of non-breast cancer deaths was lower in the TARGIT-A group (1.4% *vs* 3.5%, *P* = 0.0086). The study concluded that longer follow-up is needed, but the results are promising, given the good survival rate and low recurrence rate. Importantly, some of the patients included in the trial might not be suitable for APBI according to current guidelines.

**Mobetron:** The Mobetron consists of a mobile robotic arm linear accelerator with multiple electron energies. The Mobetron device is inserted into the surgical cavity for the delivery of electron radiation. An acrylic resin-copper disk may be placed between the breast tissue and the underlying muscle to protect the thoracic wall. A phase I/II single arm dose-escalation study treated patients with 19 to 21 Gy at the 90% isodose line[46]. Selection criteria for the study included age > 50 years, tumors < 2.5 cm, surgical margins > 1 cm, no extensive intraductal component, no prior chest irradiation, and free surgical margins by intraoperative pathology. The target volume is lumpectomy cavity with 2 cm margin. 6-12 MeV electrons were used for treatment. With only 9 patients and an average follow-up of 11.3 mo, conclusions are limited; however, the largest dose of 21 Gy seemed to be well-tolerated. The authors used Common Terminology Criteria for Adverse Events v3.0 for reporting toxicities and reported grade 1 hematoma in 1 of 3 patients, grade 1 soft tissue infection in 1 of 3 patients, and grade 2 soft tissue necrosis in 2 of 3 patients[46].

**Novac7:** Novac7 (Hitesys, Latina, Italy) is also a mobile linear accelerator with electrons of multiple energies delivered *via* a cylindrical perspex applicator with a diameter of 4 to 10 cm. The unit is mounted on a robotic arm for positioning. The phase III Electron IntraOperative Therapy (ELIOT) trial randomized 1305 patients, who were ≥ 48 years with tumors ≤ 2.5 cm, to either a single intraoperative dose of 21 Gy or to EBRT of 50 Gy WBI with a 10 Gy boost all delivered over 6 wk[47]. The trial employed the Novac7, as well as a similar device, the Liac. At 5.8 years of median follow-up, the 5-year recurrence rates for ELIOT and EBRT were 4.4% and 0.4% respectively (*P* = 0.0001). A low risk ELIOT group had a 5-year recurrence rate of 1.5%. The ELIOT group had significantly less skin toxicity (erythema, dryness, hyperpigmentation, or itching), but a higher incidence of fat necrosis.

***Proton therapy***

Bush *et al*[48] reported the 5-year results of a phase II trial using proton beam radiation to deliver APBI in patients with invasive nonlobular carcinoma with a maximal dimension of 3 cm, negative axillary lymph nodes on sampling, and negative surgical margins. Proton therapy was given to the surgical bed with 40 Gy in 10 fractions, once daily over 2 wk, using skin-sparing techniques. The study enrolled 100 patients. At median follow-up of 60 mo, the 5-year actuarial rates of IBTR-free survival, DFS, and OS were 97%, 94% and 95%, respectively. There were no grade 3 or higher acute skin reactions, and patient- and physician-reported cosmesis was good to excellent in 90%[48]. In addition, Chang *et al*[49] reported results of prospective study of 30 patients treated with 30 cobalt gray equivalent in 6 fractions delivered daily over 5 consecutive days. At 59 mo of median follow-up, no patients had local or metastatic recurrence, and all patients were alive at the last follow-up. Qualitative physician cosmetic assessments of good to excellent were 69% at 3 years[49].

***CyberKnife stereotactic APBI***

With technological advances in stereotactic radiotherapy, CyberKnife has been investigated as a method to deliver APBI. CyberKnife provides for real-time tracking, respiratory motion management, and submillimeter accuracy and allows for treatment intensification while reducing dose to surrounding normal structures[50]. Georgetown University Hospital treated 10 patients, who were ≥ 48 years with DCIS or invasive non-lobular carcinoma ≤ 2 cm in maximum diameter and ≥ 2 mm of negative margin, using CyberKnife[51]. The planning target volume was delineated on CT scans with 5 mm expansion, and 30 Gy was delivered in daily fractions for 5 consecutive days to the planning target volume. All 10 patients experienced good to excellent cosmetic outcomes with no breast events recorded at median follow-up of 1.3 years. The authors concluded that CyberKnife was reliable in delivering APBI that was well-tolerated; however, the study was limited by its small sample size and brief follow-up.

**Current Patient Selection Guidelines**

The initial APBI trials have demonstrated the importance of patient selection. With more strict criteria, APBI has been shown to have comparable local recurrence rates in addition to better cosmetic outcome. The most recent American Society for Radiation Oncology (ASTRO) consensus guidelines were published in 2009[52]. Patients were classified into three groups: Suitable, cautionary, and unsuitable. The specific criteria are listed in Table 2. In addition, Table 3 compared the guidelines from different task groups.

**Other Considerations**

***Patient reported quality of life***

Quality of life is a vital consideration when patients are choosing their breast cancer treatments. Bitter *et al*[53] analyzed self-reported cosmetic outcomes for the treated breast and quality of life for patients treated with WBI or APBI *via* single and multilumen HDR brachytherapy. Two hundred and forty-two patients between 2004 and 2014 with early breast cancer treated with APBI were compared to 59 matched patients treated with WBI from 2012 to 2014. They were evaluated with modified Functional Assessment of Chronic Illness Therapy breast quality of life questions which measured pain, lymphedema, energy level, self-consciousness, and breast cosmesis. Compared to APBI eligible patients treated with WBI, the APBI cohort experienced significantly better lymphedema (*P* = 0.0002), self-consciousness (*P* = 0.0004), and energy level (*P* = 0.009) scores during the first year after treatment. The APBI group reported significantly better breast cosmesis during the second year after treatment. There were no significant differences in the recurrence rates (*P* > 0.05)[53]. Moreover, analyses of late toxicities and cosmesis of patients treated with APBI on RTOG 0319 demonstrated good to excellent cosmesis in 82% and 64% of patients at 1 year and 3 years, respectively. When questioned at 3 years, 31 patients were satisfied with their treatment, 5 were not satisfied but would choose 3D-CRT again, and no patients would elect standard radiation therapy[54].

***Economics of treatment***

In addition to identifying the group of patients with the appropriate breast cancer biology, it is important to consider other factors, such as socioeconomic issues. Shah *et al*[55] reported results of cost-efficacy of multiple APBI techniques compared with WBI. Their analyses included cost minimization, incremental cost-effectiveness ratio (ICER), and cost per quality adjusted life year (QALY) analyses. For 1000 patients treated, the cost savings would be $6.0 million (APBI 3D-CRT), $2.0 million (APBI IMRT), and $0.7 million (APBI interstitial) with the utilization of APBI compared to WBI 3D-CRT. The cost per QALY was $54698 and $49009 for APBI multilumen and APBI 3D-CRT, respectively, when incorporating the cost of recurrences and non-medical costs[55].

**Conclusion**

APBI has gained acceptance for appropriately selected cases of early stage breast cancer, as outlined by current guidelines. Shaitelman *et al*[56] showed increased utilization of APBI from 3.8% of breast cancer radiation in 2004 to 10.6% in 2011 (*P* < 0.0001), with most of the APBI given *via* brachytherapy. The proliferation of APBI demonstrates its acceptance by patients in the modern era owing in part to its increased convenience and potential for reduced toxicities. As the use of APBI expands, the need for patient selection guidelines and consensus statements becomes even more important. There are many ongoing phase III trials that are testing the non-inferiority and equivalence of various forms of APBI compared to WBI (Table 4). Some of these ongoing studies have reported results of interim analyses. As the data matures, we will be able to more appropriately select the specific patients benefiting most from APBI. Furthermore, as patient reported outcome measures, such as quality of life, gain traction in parallel to outcome studies, this data should be incorporated into shared decision making with patients.

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**Table 1 Additional selected, non-randomized clinical experience with interstitial brachytherapy with more than 5 years follow-up**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **No. of patients** | **Follow-up interval (yr)** | **Modality** | **Scheme** | **Total dose (Gy)** | **5-yr LR (%)** | **Good/ excellent cosmesis** |
| **Strnad *et al*[57]** | 274 | 5.25 | PDR/ HDR | PDR = 0.6 Gy/h HDR = 4 Gy × 8 | PDR = 50 Gy HDR = 32 Gy | 2.9% | 90% |
| **Rabinovitch *et al*[32,58]** | 98 | 11.3 | LDR/ HDR | LDR = 3.5-5 d HDR = 3.4 Gy × 10 | LDR = 45 Gy  HDR = 34 Gy | 4% | 68% |
| **Shah *et al*[59,60]** | 199 | 12.0 | LDR/ HDR | LDR 0.52 Gy/h × 96 h HDR = 4 Gy × 8 HDR = 3.4 Gy × 10 | LDR = 50 Gy HDR = 32 Gy HDR = 34 Gy | 5% (12-yr 5%) | 99% |
| **King *et al*[27]** | 51 | 6.25 | LDR/ HDR | LDR = 4 d HDR = 4 Gy × 8 | LDR = 45 Gy  HDR = 32 Gy | 3.9% | 75% |
| **Ott *et al*[61,62]** | 274 | 5.33 | PDR/ HDR | PDR = 0.6 Gy/h HDR = 4 Gy × 8 | PDR = 49.8 Gy HDR = 32 Gy | 2.3% | 92% |
| **Polgar *et al*[63]** | 45 | 11.1 | HDR | 4.33 Gy × 7 5.2 Gy × 7 | 30.3 Gy 36.4 Gy | 4.4% (12-yr 9.3%) | 78% |

HDR: High-dose rate; LDR: Low dose rate; LR: Local recurrence; PDR: Pulsed-dose rate.

**Table 2 Accelerated partial breast irradiation patient selection criteria according to American Society for Radiation Oncology consensus statement[52]**

|  |  |  |  |
| --- | --- | --- | --- |
| **Factors** | **Suitable** | **Cautionary** | **Unsuitable** |
| **Age (yr)** | > 60 | 50-59 | < 50 |
| **BRCA1/2 mutation** | Not present | NS | Present |
| **Tumor size** | < 2 cm | 2.1-3.0 cm | > 3 cm |
| **T stage** | T1 | T0 or T2 | T3-4 |
| **Margins** | Negative (> 2 mm) | Close (< 2 mm) | Positive |
| **Grade** | Any | NS | NS |
| **LVSI** | No | Limited/focal | Extensive |
| **ER status** | Positive | Negative | NS |
| **Multicentricity** | Unicentric only | NS | Present |
| **Multifocality** | Clinically unifocal with total size < 2 cm | Clinically unifocal with total size 2.1-3.0 cm | Microscopically multifocal > 3 cm in total size or if clinically multifocal |
| **Histology** | Invasive ductal or other favorable subtypes | Invasive lobular | NS |
| **Pure DCIS** | Not allowed | < 3 cm | > 3 cm |
| **EIC** | Not allowed | < 3 cm | > 3 cm |
| **Associated LCIS** | Allowed | NS | NS |
| **LN status** | pN0 (i-, i+) | NS | pN1, pN2, pN3, or if not evaluated |
| **Neoadjuvant therapy** | Not allowed | NS | If used |

DCIS: Ductal carcinoma *in situ*; EIC: Extensive intraductal component; ER: Estrogen receptor; LCIS: Lobular carcinoma *in situ*; LVSI: Lymphovascular space invasion; LN: Lymph node; NS: Not specified.

**Table 3 Accelerated partial breast irradiation patient selection criteria from selected organizations**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Organization** | **Age** | **Tumor size** | **Margin** | **Histology** | **LN status** |
| **American Brachytherapy Society[64]** | > 50 | < 3 cm | Negative (at inked margin) | Invasive ductal carcinoma | pN0; by SLN or axillary dissection |
| **American Society of Breast Surgeons[36]** | > 45 | < 2 cm | Negative (> 2 mm) | Invasive ductal carcinoma or DCIS | pN0; by SLN or axillary dissection |
| **ASTRO[52]** | > 60 | < 2 cm | Negative (> 2 mm) | Invasive ductal or other favorable subtypes (mucinous, tubular, and colloid) | pN0; by SLN or axillary dissection |

ASTRO: American Society for Radiation Oncology; DCIS: Ductal carcinoma *in situ*; SLN: Sentinel lymph node.

**Table 4 Phase III prospective randomized trials evaluating the equivalence or non-inferiority of accelerated partial breast irradiation with whole-breast irradiation**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Trial** | **No. of patients** | **Follow up interval (yr)** | **Inclusion criteria** | **APBI technique** | **5-yr LR APBI *vs* WBI (%)** |
| **TARGIT-A[45]** | 3451 | 2.4 | Age ≥ 45 yr; T1, small T2, N0, N1; ductal; non-lobular and no EIC | 20 Gy in 1 fraction, IORT low energy X-rays (50 kV) | 3.3 *vs* 1.3 |
| **ELIOT[47]** | 1305 | 5.8 | Age ≥ 48 yr; T ≤ 2.5 cm, N0; invasive carcinoma; quadrantectomy | 21 Gy in 1 fraction, IORT, electrons up to 9 MeV | 4.4 *vs* 0.4 |
| **RAPID (OCOG)[41]** | 2135 | Pending | Age > 40 yr; T ≤ 3 cm, N0; DCIS or invasive carcinoma; negative margins | 38.5 Gy in 10 fractions (5-8 d) using 3D-CRT | Pending |
| **GEC-ESTRO[35]** | 1184 | 5.0 | Age ≥ 40 yr; T ≤ 3 cm, pN0-Nmi; stage 0, I, II; DCIS, ductal or lobular carcinoma; margin ≥ 2 mm | 32 Gy in 8 fractions or 30.3 Gy in 7 fractions MIB HDR or 50 Gy MIB PDR (1 pulse/h, 24 h/d; 0.6-0.8 Gy/h) | 1.4 *vs* 0.9 |
| **Florence (NCT02104895)[42]** | 520 | 5.0 | Age > 40 yr; T < 2.5 cm; clear margins > 5 mm | IMRT 30 Gy in 5 daily fractions | 1.5 *vs* 1.5 |
| **IMPORT-LOW** | 2018 | Pending | Age ≥ 50 yr; T ≤ 3 cm, node negative; invasive adenocarcinoma; margin ≥ 2 mm | IMRT; Arm 1: 40 Gy in 15 fractions to primary tumor region + 36 Gy in 15 fractions to low-risk region (EBRT) Arm 2: 40 Gy in 15 fractions to primary tumor region (EBRT) | Pending |
| **IRMA (NCT01803958)** | 3302  (Currently Enrolling) | Pending | Age ≥ 49 yr; T < 3 cm, N0; invasive carcinoma; margins ≥ 2 mm | 38.5 Gy in 10 fractions using 3D-CRT, BID | Pending |
| **SHARE (NCT01247233)** | 1006 | Pending | Age ≥ 50 yr; invasive carcinoma; T ≤ 2 cm; margin ≥ 2 mm; pN0 (i+/-) | 3D-CRT 40 Gy in 10 fractions, BID | Pending |
| **NSABP B-39/RTOG 0413** | 4300 | Pending | Age ≥ 18 yr; DCIS or invasive adenocarcinoma; stage 0, I, II (T < 3 cm); lumpectomy; margins free of tumor; ≤ 3 positive nodes | 34 Gy in 10 fractions using MIB or MammoSite®/MammoSite® ML/SAVI® or 38.5 Gy over 10 fractions using 3D-CRT | Pending |

3D-CRT: 3D conformal external-beam radiation; BID: Twice daily; DCIS: Ductal carcinoma *in situ*; EBRT: External beam radiation therapy; EIC: Extensive intraductal component; HDR: High-dose rate; MIB: Multicatheter interstitial brachytherapy; ML: Multilumen; IMRT: Intensity modulated radiotherapy; IORT: Intraoperative radiotherapy; PDR: Pulsed-dose rate; WBI: Whole-breast irradiation.