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Accelerated partial breast irradiation: Past, present, and future

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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; Intracavitary brachytherapy; Accelerated partial breast irradiation; Interstitial brachytherapy

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 $\leqslant$ 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 $\leqslant$ 4 cm with negative inked margins and $\leqslant$ 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. One hundred thirty-three 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 Mammo Site® (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

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%
Polgár *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.

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 multi-catheter 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 Mammo Site® 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 h 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 phasee 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

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.

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 $\geqslant$ 48 years with DCIS or invasive non-lobular carcinoma $\leqslant$ 2 cm in maximum diameter and $\geqslant$ 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

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.

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 cu-

rrent 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.

REFERENCES

1 **Mustakallio S**. Treatment of breast cancer by tumour extirpation and roentgen therapy instead of radical operation. *J Fac Radiol* 1954; **6**: 23-26 [PMID: 24543730 DOI: 10.1016/S0368-2242(54)80037-6]

2 **Fisher B**, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, Jeong JH, Wolmark N. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002; **347**: 1233-1241 [PMID: 12393820 DOI: 10.1056/NEJMoa022152]

3 **van Dongen JA**, Voogd AC, Fentiman IS, Legrand C, Sylvester RJ, Tong D, van der Schueren E, Helle PA, van Zijl K, Bartelink H. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. *J Natl Cancer Inst* 2000; **92**: 1143-1150 [PMID: 10904087 DOI: 10.1093/jnci/92.14.1143]

4 **Veronesi U**, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, Aguilar M, Marubini E. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002; **347**: 1227-1232 [PMID: 12393819 DOI: 10.1056/NEJMoa020989]

5 **Litière S**, Werutsky G, Fentiman IS, Rutgers E, Christiaens MR, Van Limbergen E, Baaijens MH, Bogaerts J, Bartelink H. Breast conserving therapy versus mastectomy for stage I-II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. *Lancet Oncol* 2012; **13**: 412-419 [PMID: 22373563 DOI: 10.1016/S1470-2045(12)70042-6]

6 **Early Breast Cancer Trialists' Collaborative G**. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; **365**: 1687-1717 [PMID: 15894097 DOI: 10.1016/S0140-6736(05)66544-0]

7 **Fisher B**, Bryant J, Dignam JJ, Wickerham DL, Mamounas EP, Fisher ER, Margolese RG, Nesbitt L, Paik S, Pisansky TM, Wolmark N. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. *J Clin Oncol* 2002; **20**: 4141-4149 [PMID: 12377957 DOI: 10.1200/JCO.2002.11.101]

8 **Winzer KJ**, Sauerbrei W, Braun M, Liersch T, Dunst J, Guski H, Schumacher M. Radiation therapy and tamoxifen after breast-conserving surgery: updated results of a 2 x 2 randomised clinical trial in patients with low risk of recurrence. *Eur J Cancer* 2010; **46**: 95-101 [PMID: 19879131 DOI: 10.1016/j.ejca.2009.10.007]

9 **Cuzick J**, Sestak I, Baum M, Buzdar A, Howell A, Dowsett M, Forbes JF. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. *Lancet Oncol* 2010; **11**: 1135-1141 [PMID: 21087898 DOI: 10.1016/S1470-2045(10)70257-6]

10 **Whelan TJ**, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, Shelley W, Grimard L, Bowen J, Lukka H, Perera F, Fyles A, Schneider K, Gulavita S, Freeman C. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010; **362**: 513-520 [PMID: 20147717 DOI: 10.1056/NEJMoa0906260]

11 **Fowble B**, Solin LJ, Schultz DJ, Rubenstein J, Goodman RL. Breast recurrence following conservative surgery and radiation: patterns of failure, prognosis, and pathologic findings from mastectomy specimens with implications for treatment. *Int J Radiat Oncol Biol Phys* 1990; **19**: 833-842 [PMID: 2170305 DOI: 10.1016/0360-3016(90)90002-2]

12 **Gage I**, Recht A, Gelman R, Nixon AJ, Silver B, Bornstein BA, Harris JR. Long-term outcome following breast-conserving surgery and radiation therapy. *Int J Radiat Oncol Biol Phys* 1995; **33**: 245-251 [PMID: 7673011 DOI: 10.1016/0360-3016(95)02001-R]

13 **Huang E**, Buchholz TA, Meric F, Krishnamurthy S, Mirza NQ, Ames FC, Feig BW, Kuerer HM, Ross MI, Singletary SE, McNeese MD, Strom EA, Hunt KK. Classifying local disease recurrences after breast conservation therapy based on location and histology: new primary tumors have more favorable outcomes than true local disease recurrences. *Cancer* 2002; **95**: 2059-2067 [PMID: 12412158 DOI: 10.1002/cncr.10952]

14 **Smith TE**, Lee D, Turner BC, Carter D, Haffty BG. True recurrence vs. new primary ipsilateral breast tumor relapse: an analysis of clinical and pathologic differences and their implications in natural history, prognoses, and therapeutic management. *Int J Radiat Oncol Biol Phys* 2000; **48**: 1281-1289 [PMID: 11121624 DOI: 10.1016/S0360-3016(00)01378-X]

15 **Darby SC**, McGale P, Taylor CW, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. *Lancet Oncol* 2005; **6**: 557-565 [PMID: 16054566 DOI: 10.1016/S1470-2045(05)70251-5]

16 **Kahán Z**, Csenki M, Varga Z, Szil E, Cserháti A, Balogh A, Gyulai Z, Mándi Y, Boda K, Thurzó L. The risk of early and late lung sequelae after conformal radiotherapy in breast cancer patients. *Int J Radiat Oncol Biol Phys* 2007; **68**: 673-681 [PMID: 17350177 DOI: 10.1016/j.ijrobp.2006.12.016]

17 **Kirova YM**, Gambotti L, De Rycke Y, Vilcoq JR, Asselain B, Fourquet A. Risk of second malignancies after adjuvant radiotherapy for breast cancer: a large-scale, single-institution review. *Int J Radiat Oncol Biol Phys* 2007; **68**: 359-363 [PMID: 17379448 DOI: 10.1016/j.ijrobp.2006.12.011]

18 **Kwa SL**, Lebesque JV, Theuws JC, Marks LB, Munley MT, Bentel G, Oetzel D, Spahn U, Graham MV, Drzymala RE, Purdy JA, Lichter AS, Martel MK, Ten Haken RK. Radiation pneumonitis as a function of mean lung dose: an analysis of pooled data of 540 patients. *Int J Radiat Oncol Biol Phys* 1998; **42**: 1-9 [PMID: 9747813 DOI: 10.1016/S0360-3016(98)00196-5]

19 **Schaapveld M**, Visser O, Louwman MJ, de Vries EG, Willemse PH, Otter R, van der Graaf WT, Coebergh JW, van Leeuwen FE. Risk of new primary nonbreast cancers after breast cancer treatment: a Dutch population-based study. *J Clin Oncol* 2008; **26**: 1239-1246 [PMID: 18323547 DOI: 10.1200/JCO.2007.11.9081]

20 **Ribeiro GG**, Dunn G, Swindell R, Harris M, Banerjee SS. Conservation of the breast using two different radiotherapy techniques: interim report of a clinical trial. *Clin Oncol* (R Coll Radiol) 1990; **2**: 27-34 [PMID: 2261385 DOI: 10.1016/S0936-6555(05)80215-8]

21 **Magee B**, Swindell R, Harris M, Banerjee SS. Prognostic factors for breast recurrence after conservative breast surgery and radiotherapy: results from a randomised trial. *Radiother Oncol* 1996; **39**: 223-227 [PMID: 8783398 DOI: 10.1016/0167-8140(96)01747-1]

22 **Fentiman IS**, Poole C, Tong D, Winter PJ, Mayles HM, Turner P, Chaudary MA, Rubens RD. Iridium implant treatment without external radiotherapy for operable breast cancer: a pilot study. *Eur J*

Cancer 1991; **27**: 447-450 [PMID: 1827719 DOI: 10.1016/0277-5379(91)90383-O]

23 **Fentiman IS**, Poole C, Tong D, Winter PJ, Gregory WM, Mayles HM, Turner P, Chaudary MA, Rubens RD. Inadequacy of iridium implant as sole radiation treatment for operable breast cancer. *Eur J Cancer* 1996; **32A**: 608-611 [PMID: 8695261 DOI: 10.1016/0959-8049(95)00639-7]

24 **Fentiman IS**, Deshmane V, Tong D, Winter J, Mayles H, Chaudary MA. Caesium(137) implant as sole radiation therapy for operable breast cancer: a phase II trial. *Radiother Oncol* 2004; **71**: 281-285 [PMID: 15172143 DOI: 10.1016/j.radonc.2004.02.010]

25 **Veronesi U**, Banfi A, Del Vecchio M, Saccozzi R, Clemente C, Greco M, Luini A, Marubini E, Muscolino G, Rilke F. Comparison of Halsted mastectomy with quadrantectomy, axillary dissection, and radiotherapy in early breast cancer: long-term results. *Eur J Cancer Clin Oncol* 1986; **22**: 1085-1089 [PMID: 3536526 DOI: 10.1016/0277-5379(86)90011-8]

26 **Veronesi U**, Luini A, Galimberti V, Zurrida S. Conservation approaches for the management of stage I/II carcinoma of the breast: Milan Cancer Institute trials. *World J Surg* 1994; **18**: 70-75 [PMID: 8197779 DOI: 10.1007/BF00348194]

27 **King TA**, Bolton JS, Kuske RR, Fuhrman GM, Scroggins TG, Jiang XZ. Long-term results of wide-field brachytherapy as the sole method of radiation therapy after segmental mastectomy for T(is,1,2) breast cancer. *Am J Surg* 2000; **180**: 299-304 [PMID: 11113440 DOI: 10.1016/S0002-9610(00)00454-2]

28 **Vicini FA**, Kestin L, Chen P, Benitez P, Goldstein NS, Martinez A. Limited-field radiation therapy in the management of early-stage breast cancer. *J Natl Cancer Inst* 2003; **95**: 1205-1210 [PMID: 12928345 DOI: 10.1093/jnci/djg023]

29 **Vicini FA**, Chen PY, Fraile M, Gustafson GS, Edmundson GK, Jaffray DA, Benitez P, Pettinga J, Madrazo B, Ingold JA, Goldstein NS, Matter RC, Martinez AA. Low-dose-rate brachytherapy as the sole radiation modality in the management of patients with early-stage breast cancer treated with breast-conserving therapy: preliminary results of a pilot trial. *Int J Radiat Oncol Biol Phys* 1997; **38**: 301-310 [PMID: 9226316 DOI: 10.1016/S0360-3016(97)00035-7]

30 **Baglan KL**, Martinez AA, Frazier RC, Kini VR, Kestin LL, Chen PY, Edmundson G, Mele E, Jaffray D, Vicini FA. The use of high-dose-rate brachytherapy alone after lumpectomy in patients with early-stage breast cancer treated with breast-conserving therapy. *Int J Radiat Oncol Biol Phys* 2001; **50**: 1003-1011 [PMID: 11429228 DOI: 10.1016/S0360-3016(01)01547-4]

31 **Kuske RR**, Winter K, Arthur DW, Bolton J, Rabinovitch R, White J, Hanson W, Wilenzick RM. Phase II trial of brachytherapy alone after lumpectomy for select breast cancer: toxicity analysis of RTOG 95-17. *Int J Radiat Oncol Biol Phys* 2006; **65**: 45-51 [PMID: 16503383 DOI: 10.1016/j.ijrobp.2005.11.027]

32 **Arthur DW**, Winter K, Kuske RR, Bolton J, Rabinovitch R, White J, Hanson WF, Wilenzick RM, McCormick B. A Phase II trial of brachytherapy alone after lumpectomy for select breast cancer: tumor control and survival outcomes of RTOG 95-17. *Int J Radiat Oncol Biol Phys* 2008; **72**: 467-473 [PMID: 18294778 DOI: 10.1016/j.ijrobp.2007.12.056]

33 **Polgár C**, Fodor J, Major T, Németh G, Lövey K, Orosz Z, Sulyok Z, Takácsi-Nagy Z, Kásler M. Breast-conserving treatment with partial or whole breast irradiation for low-risk invasive breast carcinoma--5-year results of a randomized trial. *Int J Radiat Oncol Biol Phys* 2007; **69**: 694-702 [PMID: 17531400 DOI: 10.1016/j.ijrobp.2007.04.022]

34 **Polgár C**, Fodor J, Major T, Sulyok Z, Kásler M. Breast-conserving therapy with partial or whole breast irradiation: ten-year results of the Budapest randomized trial. *Radiother Oncol* 2013; **108**: 197-202 [PMID: 23742961 DOI: 10.1016/j.radonc.2013.05.008]

35 **Strnad V**, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, Lyczek J, Guinot JL, Dunst J, Gutierrez Miguelez C, Slampa P, Allgäuer M, Lössl K, Polat B, Kovács G, Fischedick AR, Wendt TG, Fietkau R, Hindemith M, Resch A, Kulik A, Arribas L, Niehoff P, Guedea F, Schlamann A, Pötter R, Gall C, Malzer M, Uter W, Polgár C. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. *Lancet* 2016; **387**: 229-238 [PMID: 26494415 DOI: 10.1016/S0140-6736(15)00471-7]

36 **Shah C**, Badiyan S, Ben Wilkinson J, Vicini F, Beitsch P, Keisch M, Arthur D, Lyden M. Treatment efficacy with accelerated partial breast irradiation (APBI): final analysis of the American Society of Breast Surgeons MammoSite(®) breast brachytherapy registry trial. *Ann Surg Oncol* 2013; **20**: 3279-3285 [PMID: 23975302 DOI: 10.1245/s10434-013-3158-4]

37 **Wallace M**, Martinez A, Mitchell C, Chen PY, Ghilezan M, Benitez P, Brown E, Vicini F. Phase I/II study evaluating early tolerance in breast cancer patients undergoing accelerated partial breast irradiation treated with the mammosite balloon breast brachytherapy catheter using a 2-day dose schedule. *Int J Radiat Oncol Biol Phys* 2010; **77**: 531-536 [PMID: 19775830 DOI: 10.1016/j.ijrobp.2009.05.043]

38 **Fisher B**, Daugherty L, Shaikh T, Reiff J, Perlingiero D, Alite F, Brady L, Komarnicky L. Tumor bed-to-skin distance using accelerated partial-breast irradiation with the strut-adjusted volume implant device. *Brachytherapy* 2012; **11**: 387-391 [PMID: 22104353 DOI: 10.1016/j.brachy.2011.09.009]

39 **Cuttino LW**, Arthur DW, Vicini F, Todor D, Julian T, Mukhopadhyay N. Long-term results from the Contura multilumen balloon breast brachytherapy catheter phase 4 registry trial. *Int J Radiat Oncol Biol Phys* 2014; **90**: 1025-1029 [PMID: 25442036 DOI: 10.1016/j.ijrobp.2014.08.341]

40 **Beitsch P**, Vicini F, Keisch M, Haffty B, Shaitelman S, Lyden M. Five-year outcome of patients classified in the "unsuitable" category using the American Society of Therapeutic Radiology and Oncology (ASTRO) Consensus Panel guidelines for the application of accelerated partial breast irradiation: an analysis of patients treated on the American Society of Breast Surgeons MammoSite® Registry trial. *Ann Surg Oncol* 2010; **17** Suppl 3: 219-225 [PMID: 20853036 DOI: 10.1245/s10434-010-1231-9]

41 **Olivotto IA**, Whelan TJ, Parpia S, Kim DH, Berrang T, Truong PT, Kong I, Cochrane B, Nichol A, Roy I, Germain I, Akra M, Reed M, Fyles A, Trotter T, Perera F, Beckham W, Levine MN, Julian JA. Interim cosmetic and toxicity results from RAPID: a randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. *J Clin Oncol* 2013; **31**: 4038-4045 [PMID: 23835717 DOI: 10.1200/JCO.2013.50.5511]

42 **Livi L**, Meattini I, Marrazzo L, Simontacchi G, Pallotta S, Saieva C, Paiar F, Scotti V, De Luca Cardillo C, Bastiani P, Orzalesi L, Casella D, Sanchez L, Nori J, Fambrini M, Bianchi S. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. *Eur J Cancer* 2015; **51**: 451-463 [PMID: 25605582 DOI: 10.1016/j.ejca.2014.12.013]

43 **Vaidya JS**, Tobias JS, Baum M, Keshtgar M, Joseph D, Wenz F, Houghton J, Saunders C, Corica T, D'Souza D, Sainsbury R, Massarut S, Taylor I, Hilaris B. Intraoperative radiotherapy for breast cancer. *Lancet Oncol* 2004; **5**: 165-173 [PMID: 15003199 DOI: 10.1016/S1470-2045(04)01412-3]

44 **Vaidya JS**, Tobias JS, Baum M, Wenz F, Kraus-Tiefenbacher U, D' souza D, Keshtgar M, Massarut S, Hilaris B, Saunders C, Joseph D. TARGeted Intraoperative radiotherapy (TARGIT): an innovative approach to partial-breast irradiation. *Semin Radiat Oncol* 2005; **15**: 84-91 [PMID: 15809933 DOI: 10.1016/j.semradonc.2004.10.007]

45 **Silverstein MJ**, Fastner G, Maluta S, Reitsamer R, Goer DA, Vicini F, Wazer D. Intraoperative radiation therapy: a critical analysis of the ELIOT and TARGIT trials. Part 2--TARGIT. *Ann Surg Oncol* 2014; **21**: 3793-3799 [PMID: 25138079 DOI: 10.1245/s10434-014-3999-5]

46 **Sawaki M**, Sato S, Noda S, Idota A, Uchida H, Tsunoda N, Kikumori T, Aoyama Y, Ishihara S, Itoh Y, Imai T. Phase I/II study of intraoperative radiotherapy for early breast cancer in Japan. *Breast Cancer* 2012; **19**: 353-359 [PMID: 21779813 DOI: 10.1007/s12282-011-0294-1]

47 **Silverstein MJ**, Fastner G, Maluta S, Reitsamer R, Goer DA, Vicini F, Wazer D. Intraoperative radiation therapy: a critical analysis of the ELIOT and TARGIT trials. Part 1--ELIOT. *Ann Surg Oncol* 2014; **21**:

3787-3792 [PMID: 25160734 DOI: 10.1245/s10434-014-3998-6]
48 **Bush DA**, Do S, Lum S, Garberoglio C, Mirshahidi H, Patyal B, Grove R, Slater JD. Partial breast radiation therapy with proton beam: 5-year results with cosmetic outcomes. *Int J Radiat Oncol Biol Phys* 2014; **90**: 501-505 [PMID: 25084608 DOI: 10.1016/j.ijrobp.2014.05.1308]
49 **Chang JH**, Lee NK, Kim JY, Kim YJ, Moon SH, Kim TH, Kim JY, Kim DY, Cho KH, Shin KH. Phase II trial of proton beam accelerated partial breast irradiation in breast cancer. *Radiother Oncol* 2013; **108**: 209-214 [PMID: 23891102 DOI: 10.1016/j.radonc.2013.06.008]
50 **Vermeulen S**, Cotrutz C, Morris A, Meier R, Buchanan C, Dawson P, Porter B. Accelerated Partial Breast Irradiation: Using the CyberKnife as the Radiation Delivery Platform in the Treatment of Early Breast Cancer. *Front Oncol* 2011; **1**: 43 [PMID: 22649764 DOI: 10.3389/fonc.2011.00043]
51 **Obayomi-Davies O**, Kole TP, Oppong B, Rudra S, Makariou EV, Campbell LD, Anjum HM, Collins SP, Unger K, Willey S, Tousimis E, Collins BT. Stereotactic Accelerated Partial Breast Irradiation for Early-Stage Breast Cancer: Rationale, Feasibility, and Early Experience Using the CyberKnife Radiosurgery Delivery Platform. *Front Oncol* 2016; **6**: 129 [PMID: 27242967 DOI: 10.3389/fonc.2016.00129]
52 **Smith BD**, Arthur DW, Buchholz TA, Haffty BG, Hahn CA, Hardenbergh PH, Julian TB, Marks LB, Todor DA, Vicini FA, Whelan TJ, White J, Wo JY, Harris JR. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *J Am Coll Surg* 2009; **209**: 269-277 [PMID: 19632605 DOI: 10.1016/j.jamcollsurg.2009.02.066]
53 **Bitter SM**, Heffron-Cartwright P, Wennerstrom C, Weatherford J, Einstein D, Keiler LC. WBRT vs. APBI: an interim report of patient satisfaction and outcomes. *J Contemp Brachytherapy* 2016; **8**: 17-22 [PMID: 26985193 DOI: 10.5114/jcb.2016.57816]
54 **Chafe S**, Moughan J, McCormick B, Wong J, Pass H, Rabinovitch R, Arthur DW, Petersen I, White J, Vicini FA. Late toxicity and patient self-assessment of breast appearance/satisfaction on RTOG 0319: a phase 2 trial of 3-dimensional conformal radiation therapy-accelerated partial breast irradiation following lumpectomy for stages I and II breast cancer. *Int J Radiat Oncol Biol Phys* 2013; **86**: 854-859 [PMID: 23726000 DOI: 10.1016/j.ijrobp.2013.04.005]
55 **Shah C**, Lanni TB, Saini H, Nanavati A, Wilkinson JB, Badiyan S, Vicini F. Cost-efficacy of acceleration partial-breast irradiation compared with whole-breast irradiation. *Breast Cancer Res Treat* 2013; **138**: 127-135 [PMID: 23329353 DOI: 10.1007/s10549-013-2412-6]
56 **Shaitelman SF**, Lin HY, Smith BD, Shen Y, Bedrosian I, Marsh GD, Bloom ES, Vicini FA, Buchholz TA, Babiera GV. Practical Implications of the Publication of Consensus Guidelines by the American Society for Radiation Oncology: Accelerated Partial Breast Irradiation and the National Cancer Data Base. *Int J Radiat Oncol Biol Phys* 2016; **94**: 338-348 [PMID: 26853342 DOI: 10.1016/j.ijrobp.2015.10.059]
57 **Strnad V**, Hildebrandt G, Pötter R, Hammer J, Hindemith M, Resch A, Spiegl K, Lotter M, Uter W, Bani M, Kortmann RD, Beckmann MW, Fietkau R, Ott OJ. Accelerated partial breast irradiation: 5-year results of the German-Austrian multicenter phase II trial using interstitial multicatheter brachytherapy alone after breast-conserving surgery. *Int J Radiat Oncol Biol Phys* 2011; **80**: 17-24 [PMID: 20605365 DOI: 10.1016/j.ijrobp.2010.01.020]
58 **Rabinovitch R**, Winter K, Kuske R, Bolton J, Arthur D, Scroggins T, Vicini F, McCormick B, White J. RTOG 95-17, a Phase II trial to evaluate brachytherapy as the sole method of radiation therapy for Stage I and II breast carcinoma--year-5 toxicity and cosmesis. *Brachytherapy* 2014; **13**: 17-22 [PMID: 24041956 DOI: 10.1016/j.brachy.2013.08.002]
59 **Antonucci JV**, Wallace M, Goldstein NS, Kestin L, Chen P, Benitez P, Dekhne N, Martinez A, Vicini F. Differences in patterns of failure in patients treated with accelerated partial breast irradiation versus whole-breast irradiation: a matched-pair analysis with 10-year follow-up. *Int J Radiat Oncol Biol Phys* 2009; **74**: 447-452 [PMID: 19058921 DOI: 10.1016/j.ijrobp.2008.08.025]
60 **Shah C**, Antonucci JV, Wilkinson JB, Wallace M, Ghilezan M, Chen P, Lewis K, Mitchell C, Vicini F. Twelve-year clinical outcomes and patterns of failure with accelerated partial breast irradiation versus whole-breast irradiation: results of a matched-pair analysis. *Radiother Oncol* 2011; **100**: 210-214 [PMID: 21497927 DOI: 10.1016/j.radonc.2011.03.011]
61 **Ott OJ**, Hildebrandt G, Pötter R, Hammer J, Hindemith M, Resch A, Spiegl K, Lotter M, Uter W, Kortmann RD, Schrauder M, Beckmann MW, Fietkau R, Strnad V. Accelerated partial breast irradiation with interstitial implants: risk factors associated with increased local recurrence. *Int J Radiat Oncol Biol Phys* 2011; **80**: 1458-1463 [PMID: 20675064 DOI: 10.1016/j.ijrobp.2010.04.032]
62 **Ott OJ**, Hildebrandt G, Pötter R, Hammer J, Lotter M, Resch A, Sauer R, Strnad V. Accelerated partial breast irradiation with multicatheter brachytherapy: Local control, side effects and cosmetic outcome for 274 patients. Results of the German-Austrian multicentre trial. *Radiother Oncol* 2007; **82**: 281-286 [PMID: 17126940 DOI: 10.1016/j.radonc.2006.08.028]
63 **Polgár C**, Major T, Fodor J, Sulyok Z, Somogyi A, Lövey K, Németh G, Kásler M. Accelerated partial-breast irradiation using high-dose-rate interstitial brachytherapy: 12-year update of a prospective clinical study. *Radiother Oncol* 2010; **94**: 274-279 [PMID: 20181401 DOI: 10.1016/j.radonc.2010.01.019]
64 **Shah C**, Vicini F, Wazer DE, Arthur D, Patel RR. The American Brachytherapy Society consensus statement for accelerated partial breast irradiation. *Brachytherapy* 2013; **12**: 267-277 [PMID: 23619524 DOI: 10.1016/j.brachy.2013.02.001]

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