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Accelerated Partial Breast Irradiation: A New Strategy for Early-Stage Breast Cancer

Mahdi Aghili^{*a}, Marzieh Lashkari^a, Mohammad Babaei^a, Sepideh Mansouri^{a,b}^a Radiation Oncology Research Center, Tehran University of Medical Sciences, Tehran, Iran^b Recombinant Proteins Department, Breast Cancer Research Center, Motamed Cancer Center, ACECR, Tehran, Iran

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ABSTRACT

Background: Accelerated partial breast irradiation (APBI) is defined as applying high doses of radiation with a shorter interval to the lumpectomy cavity in the setting of breast-conserving therapy for early-stage breast cancer. This treatment strategy is attractive to patients, and its utilization has increased during recent years because of the shorter treatment schedule, better cosmetic outcomes, and acceptable local control rates in selected patients undergoing breast-conserving therapy. Here we provide an overview of various APBI techniques in terms of clinical and cosmetic outcomes, quality of life, and cost of treatment. We also review the current guidelines for selecting suitable breast cancer patients for APBI strategy.

Methods: A comprehensive literature search of PubMed between 1996 -2019 that was made was made for case series and randomized studies with at least 2 years of follow-up in term of clinical and cosmetic outcomes, quality of life, and treatment costs.

Results: Technological advances have made various APBI modalities, including intracavitary and interstitial brachytherapy, intraoperative radiation therapy, and external-beam radiation therapy, more accessible in the community. Mature data from several randomized and prospective nonrandomized trials have contributed to the development of consensus guidelines for selecting the most appropriate candidates ABPI.

Conclusion: APBI represent an attractive treatment option for appropriately selected patients with early breast cancer. Irrespective to various techniques used for APBI it is very important to select the most appropriate patient population according to reliable guidelines for this treatment strategy that could be non-inferiority to whole breast irradiation especially in high-volume radiation centers with long waiting lists and for patients who live far away from the radiotherapy centers.

Introduction

Breast cancer is the most prevalent female malignancy worldwide. Nowadays, more patients present with early-stage breast cancer because of breast screening and mass education programs, and

the majority of them undergo breast-conserving surgery (BCS). In addition to tumor control and survival, the breast conservation approach is important in terms of cosmetic outcomes, which is associated with improvement in emotional adjustment of the patient with early-stage breast cancer. Whole-breast irradiation (WBI) is almost always recommend as an adjuvant treatment in patients undergoing BCS.¹ Whole-breast irradiation following BCS can reduce the risk of local recurrence to very low levels comparable to those achieved with mastectomy.

* Address for correspondence:

Mahdi Aghili, MD
 Address: Radiation Oncology Research Center, Imam Khomeini Hospital, Keshavarz Blv., Tehran, Iran
 Tel: +98 21 6694 8672
 Email: aghili@tums.ac.ir



In spite of the many benefits of WBI, the treatment is also associated with some disadvantages. For one thing, it is relatively complex and expensive and needs physical and human resources. Another major disadvantage of WBI is that the treatment is highly inconvenient as it usually includes 6 to 7 weeks of daily high-dose radiation treatments to the whole breast, which, aside from radiation-related discomforts, may require patients to miss work or undergo other significant lifestyle alterations (such as temporary lodging expenses or separating from their family, friends, and other supporters). In fact, a negative relationship has been observed between the distance from a patient's home to the nearest radiation facility and the tendency to use breast conservation therapy, and some patients have refused BCS simply because of difficulties in accessing to radiation therapy facilities.^{2,3}

WBI has some late complications such as fibrosis, lymphedema, cardiac toxicity, radiation to the contralateral breast, and secondary malignancy.^{4,6} However, newer EBRT technologies such as three-dimensional radiotherapy, intensity-modulated radiotherapy, deep inspiration breath hold, and prone position techniques, have significantly contributed to decreased complications because of better dose conformity and delivery to the target volume and normal tissue sparing.⁷ Yet, there are still some complications remaining. Here we provide the rationale for using accelerated partial breast irradiation (APBI) and an overview of various APBI techniques in term of clinical and cosmetic outcomes, quality of life, and the cost of treatment. We also review the current guidelines for selecting suitable breast cancer patients for APBI.

Methods

We conducted a comprehensive search of PubMed from 1996 to 2019 for case series or randomized studies that had used various APBI techniques and followed up the patients for at least 2 years in terms of the clinical and cosmetic outcomes, quality of life, and costs of treatment.

Results and Discussion

The rationale for Using APBI

It has been argued that since ipsilateral breast tumor recurrences (IBTR) develop in and around the tumor bed in 44%-86% of cases⁸, focusing the radiation to the areas with high potential of recurrence may be a better approach compared with WBI. Thus, much of the surrounding tissues, including the uninvolved ipsilateral breast, contralateral breast, heart, lungs, and skin, could be spared. This could result in better cosmetic outcomes as well as reduced toxicity.^{9,10}

The early experiences in APBI came from the UK in the 1990s. The first randomized trial was conducted in Christie Hospital from 1982 to 1987.

The study enrolled 708 patients, 355 of whom were treated with WBI and 353 with APBI.¹¹ Inclusion criteria were being younger than 70 years, having a tumor size of ≤ 4 cm, and having undergone lumpectomy with negative margins. The WBI group received 40 Gy in 15 fractions to the whole breast and the axillary, infraclavicular, and supraclavicular regions. The APBI group received 40-42 Gy in 8 fractions delivered by electron beam over 10 days to the tumor bed only. After a median follow-up of 8 years, both groups had the same survival rate (72%); however, the local recurrence rate was significantly greater in the APBI group than in the WBI group (25% vs 13%). The conclusion was that APBI was possible but would need more rigorous patient selection criteria.¹²

In another trial, conducted by Guy's Hospital in the late 1980s, 27 patients underwent BCS and axillary dissection followed by low dose rate (LDR) brachytherapy, where iridium 192 needles were used to deliver constant focal radiation of 55 Gy over 5 days to a 2-cm margin around the tumor bed. At 6-year follow-up, 37% of patients treated with limited irradiation versus 16% of patients treated with WBI had developed local recurrences.¹³ The authors speculated that the inclusion of subjects with known risk factors, such as positive margins and node-positive disease, might have underlain the high rate of local relapse in partial irradiation.

Other APBI trials were conducted at Careggi Hospital (Florence, Italy), the Royal Devon and Exeter Hospital (Exeter, England), and Guy's Hospital (London, United Kingdom) around the same period, all reporting high rates of local recurrence compared with WBI.¹⁴⁻¹⁶

Once the feasibility of APBI was demonstrated, studies were designed to establish the factors and conditions associated with a higher risk of recurrence in patients treated with APBI. Among these factors were younger age, positive margin status, larger tumors, high nuclear grade, extensive ductal carcinoma in situ, invasive lobular carcinoma, involved nodes, and lymphovascular invasion. Table 1 demonstrates selected nonrandomized phase 1/2 clinical trials of APBI.

APBI Techniques

APBI is administered in 3 modalities including brachytherapy (BT), intraoperative radiotherapy (IORT), and external-beam radiotherapy (EBRT).

Brachytherapy

Most of the basic experiences of APBI come from BT. As noted earlier, most preliminary studies on APBI had used BT modality. There are two methods for BT: multicatheter interstitial BT (MIB) and intraluminal (balloon) BT. According to GEC-ESTRO Breast Cancer Working Group, published in 2009 (Table 2), patient selection criteria for APBI are



Table 1. Selected nonrandomized phase 1/2 clinical trials with interstitial brachytherapy with longer follow-up

Reference	APBI Technique	Patient Number/ Median Follow-up	Patient Characteristics	Radiotherapy Dose	Cosmetic Results and Locoregional Failure Rate
Ochsner Medical Institution ¹⁷	MIB	50/75 mo	T ≤ 4 cm; negative inked margin; LN+ ≤ 3	LDR = 45 Gy/4 d HDR = 32 Gy/8 fr	GECR = 75% in both arms LFR = 4 (8%)
William Beaumont Hospital ¹⁸	MIB	199/60 mo	T ≤ 3 cm; age ≥ 40; no extensive DCIS or ILC; negative margin ≥ 2 mm	LDR = 50 Gy/5 d (125 seeds) HDR = 32 Gy/8 fr or 34 Gy/10 fr	GECR = 90% LFR = 1.2%.
Strnad <i>et al.</i> ¹⁹	MIB	274/64 mo	T < 3 cm; age > 35 y; negative margin ≥ 2 mm; HR+; G1-2	PDR = 50 Gy/3.5 d HDR = 32 Gy/8 fr	GECR = 90% LFR = 1.2% and 2.9%
Rabinovitch <i>et al.</i> ²⁰	MIB	98/135 mo	T < 3 cm, LN+ = 0-3	LDR = 45 Gy/3.5-5 d HDR = 34 Gy/10 fr	GECR = 68% LFR = 4%
Shah <i>et al.</i> ²¹	MIB	199/144 mo	T1-T2; HR+; LN+ = 1-3; margin negative	LDR = 50 Gy/8 d HDR = 32 Gy/8 fr HDR = 34 Gy/10 fr	GECR = 99% LFR = 5%
Ott <i>et al.</i> ²²	MIB	274/64 mo	T < 3 cm; age > 35 y; negative margin ≥ 2 mm; HR+; G1-2	PDR = 50 Gy/3.5 d HDR = 32 Gy/8 fr	GECR = 92% LFR = 2.3%
Polgár <i>et al.</i> ²³	MIB	5/132 mo	T1N0-N1mi; no extensive DCIS or ILC; negative margin ≥ 2 mm	HDR = 30.3 Gy/7 fr HDR = 36.4 Gy/7 fr	GECR = 78% LFR = 2.3% (at 12 y = 9.3%)
MammoSite Breast BT Registry Trial ²⁴	Single lumen Catheter	1449/63 mo	T ≤ 3 cm; age ≥ 40; no extensive DCIS or ILC; negative margin ≥ 2 mm	HDR = 34 Gy/10 fr	GECR = 90.6% (at 84 mo) LFR = 3.8%
Sawaki <i>et al.</i> ²⁵	IORT (Electron beam)	26/26 mo	T < 2.5 cm; age > 50 y; surgical margin > 1 cm; LN-	19-21 Gy at the 90% isodose line	fibrosis (G1 = 88%, G2 = 7%), hematoma = 34, infection = 15% necrosis = 11% LFR = 0
Kraus-Tiefenbache <i>et al.</i> ²⁶	IORT (KV x-ray beam)	24/12 mo	stage I or II; previous RT to breast (7 second primary and 1 with local recurrence)	20 Gy to the applicator surface	No severe acute side effects or complication LFR = 4%

MIB, multicatheter interstitial brachytherapy; DCIS, ductal carcinoma in situ; ILC, invasive lobular carcinoma; HR, hormone receptor; LDR, low dose rate; PDR, pulse dose rate; HDR, high dose rate; GEGR, good or excellent cosmetic result; LFR, local failure rate.

Table 2. Patient selection criteria for accelerated partial breast irradiation from selected organizations

	Age	Tumor size	Margin	ER/PR status	LN status	Histology	Other Factors
GEC-ESTRO ²⁷	> 50 y 45-50 y (cautionary)	≤ 3 cm	Negative (> 2 mm)	any	pN0 by SNB or AND	DCIS, IDC ILC (cautionary)	No LVSI, no multifocality, no ECI
American Breast surgeon ²⁸	> 45 y	≤ 3 cm	Ink margin negative, ≥ 2 mm for DCIS	any	p by SNB or AND N0	DCIS or IDC	Multifocal ok if T ≤ 3 cm Focal LVSI, no genetic mutations
ABS ²⁹	> 60 y (suitable) > 50 y (cautionary)	< 2 cm (suitable) 2-3 cm (cautionary)	> 2 mm (suitable) < 2 mm (cautionary)	Positive (suitable) Negative (cautionary)	pN0 (I-, by SNB or AND I+)	IDC non ILC (suitable) ILC and no pure DCIS (cautionary)	No LVSI, no multifocality, no genetic mutations
ASTRO ³⁰	> 50 y (suitable) 45-50 y (cautionary)	≤ 2.5 cm	Negative (> 2 mm) > 3mm for DCIS	any	pN0 by SNB or AND	IDC and low/intermediate DCIS ILC (cautionary)	ECI ≤ 3cm No or focal LVSI

SNB, sentinel node biopsy; AND, axillary node dissection; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LVSI, lymphovascular space invasion; ECI, extensive component invasion

as follows: being older than 50 years with unicentric, unifocal nonlobular carcinoma ≤ 3 cm in dimension, pN0, with no lymphovascular invasion (LVI) or an extensive intraductal component (EIC), and having a negative surgical margin of ≥ 2 mm. In addition, GEC-ESTRO suggested APBI for high-risk patients in the context of clinical trials.²⁷ The GEC-ESTRO consensus is based on at least 19 studies investigating oncologic outcomes, which revealed that there was no difference in local recurrence

between APBI and WBI, and also 17 studies surveying cosmetic outcomes, which all showed acceptable cosmetic outcomes except for one study that showed higher adverse effects with MIB administration. Furthermore, the consensus was made based upon different BT techniques including low dose rate (LDR)-BT, pulse dose rate BT, high dose rate (HDR)-BT, and MammoSite BT. The results of studies showed that, during a follow-up period of more than 4 years, the local failure rate of



APBI was similar to that of WBI, with the annual failure rate of APBI being less than 1%.

In addition, the American Brachytherapy Society (ABS) released a consensus statement on APBI using MIB in 2017 based on two large randomized clinical trials, e.g., the GEC-ESTRO trial (which recruited 1118 patients)³¹ and a study by the National Institute of Oncology of Hungary (enrolling 258 patients)³², and 19 nonrandomized trials. The ABS's findings were similar to GEC-ESTRO's statement in terms of patient selection criteria, oncologic outcomes, and cosmetic adverse effect of APBI.³³

A guideline issued by ESTRO-ACROP in 2018 addressed MIB treatment planning, different methods of catcher insertion, and dose constraints and also answered the questions about using APBI as boost or salvage.³⁴ Selecting patients who could receive boost was based on trials such as the EORTC "boost vs no boost" phase 3 trial (1989-1996)^{35, 36} and a systematic review by board members of the GEC-ESTRO Breast Working Group, which characterized suitable high-risk patients.²⁷ The ESTRO-ACROP guideline suggested HDR-BT schedules such as 7 × 4.3 Gy and 8 × 4 Gy, twice a day for 4-5 days according to the GEC-ESTRO trial, a European multicenter, randomized, phase 3 trial which recruited stage 0-IIA breast cancer patients aged 40 years and older.³⁷ The aim of this trial was to compare WBI with MIB APBI in terms of both oncologic and cosmetic outcomes. It revealed that not only late subcutaneous toxicities in two treatment modalities

were not different, but also cumulative grade 2-3 late toxicity rate after 5 years was around 4% lower in APBI. Late toxicities such as telangiectasia, fibrosis, fat necrosis, pain, and arm lymphedema were similar in the two treatment modalities. However, skin hyperpigmentation was lower in MIB compared to WBI. Furthermore, the rate of excellent-to-good cosmetic outcome for both treatment modalities was the same 92%.²³ In another study, the cumulative incidence of local recurrence was around 1.4% with APBI and 0.92% with WBI at 5-year follow-up; however, the difference was not statistically significant.³⁸ According to GEC-ESTRO Breast Cancer Working Group (II) guidelines on APBI using MIB, the total size of safety margin should be 20 mm, with clinical target volume being limited to the chest wall and 5 mm below the skin.³⁷

Table 3 summarizes recently published randomized studies using brachytherapy APBI techniques.

Accelerated Partial Breast Irradiation Using EBRT

EBRT could be done with three-dimensional conformal external-beam irradiation (3D-CRT) using photons, mixed photons and electrons, or protons. Unlike BT and IORT, EBRT can be delivered at local facilities. Although the method requires irradiation of larger areas of the breast compared with the other two methods, the irradiated volume can be reduced by using intensity-modulated radiation therapy (IMRT).

Table 3. Summary of recently published randomized studies using different APBI techniques

Trial	Number of Patients / Median Follow-up	Inclusion Criteria	Radiotherapy Dose
GEC-ESTRO ²³ (MIB)	1328/10 y	Age ≥ 40 y; T ≤ 3 cm; pN0-N1mi; stage 0, I, II; DCIS, ductal, or lobular carcinoma; margin ≥ 2 mm	HDR: 32 Gy/8 fr HDR: 30.3 Gy/7 fr or PDR: 50 Gy/2.6-3 d vs WBI: 50 Gy with a boost of 10 Gy
National Institute of Oncology (Hungary) ³² (MIB)	258/10.2 y	pT1 pN0-1mi M0; G1-2; nonlobular; without the presence of extensive DCIS and negative margins	HDR: 36.4 Gy/7 fr WBI: 50 Gy
TARGIT-A ³⁹ (IORT-photon x)	3451/5 y	Age ≥ 45 y; T1, small T2, N0, N1; ductal; nonlobular; no EIC	20 Gy in 1 fraction, IORT low-energy X-rays (50 kV) vs WBI: 50 Gy with a boost of 10 Gy
ELIOT ⁴⁰ (IORT-Electron)	1305/5.8 y	Age ≥ 48 y; T ≤ 2.5 cm; N0; invasive carcinoma	21 Gy in 1 fraction, IORT, electrons up to 9 MeV vs WBI: 50 Gy with a boost of 10 Gy
Florence study ⁴¹ (EBRT-IMRT)	520/5 y	Age > 40 y with early BC suitable (T < 2.5 cm)	IMRT: 30 Gy/10 fr vs WBI: 50 Gy with a boost of 10 Gy
RAPID Trial ⁴² (EBRT-3DCRT)	2135/3 y	Age > 40 y, T ≤ 3 cm; IDC and DCIS breast cancer	3D-CRT: 38.5 Gy/10 fr (twice daily) vs WBI: 42.5 Gy/16 fr or 50 Gy ± boost
UK IMPORT LOW trial (EBRT-3DCRT) ⁴³	2018 (674 WBI, 673 RD-WBI, 669 PBI)/6 y	Age ≥ 50 y; T1, small T2, N0, N1; ductal	3D-CRT: 40 Gy/15 fr or 36 Gy/15 fr vs WBI: 40 Gy/15 or 36 Gy ± boost
NSABP B-39/RT0G 0413 (NRG Oncology) ⁴⁴ (MIB)	4216/10.2 y	Age > 40 y, stage 0, I, or II	HDR: 34-38.5 Gy /10 fr (twice daily) vs WBI: 42.5 Gy/16 fr or 50 Gy ± boost

MIB, multicatheter interstitial brachytherapy; IORT, intraoperative radiotherapy; EBRT, external-beam radiotherapy; IMRT, intensity-modulated radiotherapy; 3D-CRT, 3-dimensional conformal radiotherapy; DCIS, ductal carcinoma in situ; ILC, invasive lobular carcinoma; HR, hormone receptor; LDR, low dose rate; PDR, pulse dose rate; HDR, high dose rate; GECC, good or excellent cosmetic result; LFR, local failure rate; RD-WBI, reduced-dose whole-breast irradiation; IDC, invasive ductal carcinoma



In 2006, a review of data from several preliminary clinical studies using three-dimensional conformal EBRT pointed to technical feasibility, satisfactory cosmetic results, and acceptable recurrence rates of the method.⁴⁵ However, several single-arm studies have reported poor cosmetic outcomes in approximately 20% of patients treated with EBRT-based APBI.⁴⁶ These conflicting results may be attributed to variations in planning techniques or prescribed radiation doses.

Anbumani and colleagues assessed the feasibility of EBRT-APBI using dosimetric parameters comparable to those used in HDR-BT planning.⁴⁷ Analysis of pulmonary and cardiac dosimetry data showed that EBRT was associated with lower percentages of lung and cardiac tissue volume receiving doses of 20 Gy and 5 Gy, as well as more homogenous dose distribution. Their data suggested that EBRT planning for APBI was technically feasible.⁴⁷

Another study was done by Mózsa and colleagues, who reported the 5-year results of EBRT-APBI after BCS in 44 low-risk breast cancer patients between 2006 and 2011. The patients received 3D-CRT using 3-5 noncoplanar fields with a total dose of 36.9 Gy in 9 fractions. After a median follow-up of 58.2 months, only 1 (2.3%) local recurrence occurred (the 5-year actuarial rate was 3.7%), and there was no regional or distant failure. Cancer-specific and overall survival rates were 100% and 95.1%, respectively. Acute side effects, late side effects, and cosmetic outcomes were also evaluated in the study, which was comparable to other APBI modalities.⁴⁸

In another trial, 142 patients ≥ 40 years of age with stage 0-II breast tumors measuring ≤ 2.5 cm without lymph node involvement received 38.5 Gy in 10 fractions over 5 consecutive days using 3D-CRT. The median cavity, clinical target volume, and breast volume were 16.9 cm³ (range 1.6-203 cm³), 75.1 cm³ (range 4.1-443 cm³), and 744 cm³ (range 150-3551 cm³), respectively. The margin around the lumpectomy cavity was 10-15 mm. The median cavity to breast ratio was 2.6 (range 0.16-14). Twenty-six patients showed no signs of toxicity; tenderness was observed in 70 patients, hyperpigmentation in 62, and induration in 45. The results suggested that acceptable toxicity could be achieved in 3D-CRT APBI by decreasing the volume of irradiated normal breast tissue.⁴⁹

Kumar et al. compared APBI using EBRT with hypofractionated WBI in early-stage breast cancer patients in a prospective cohort study. They assessed 390 patients aged 40 years or older with T1N0, ER-positive breast cancer who received lumpectomy followed by radiation treatment. Of them, 96 patients received EBRT-APBI with 38.5 Gy in 10 fractions, twice daily, while 294 patients received hypofractionated WBI with 42.56 Gy in 16 fractions

with or without a 1-3 fraction boost. Patients were adjusted for age, histology, and margin status in treatment groups. At a median follow-up of 4.2 years, no difference was observed in the rate of local recurrence between the two treatment modalities.⁵⁰

Ott and colleagues conducted a prospective phase 2 trial for APBI over a 6-year period. They enrolled 72 patients aged ≥ 50 years with histologically confirmed breast cancer or pure ductal carcinoma in situ (DCIS). Inclusion criteria were having a tumor size ≤ 3 cm, clear resection margins ≥ 2 mm, and no axillary lymph node involvement. Patients whose mammograms showed a multicentric invasive growth pattern or had residual diffuse microcalcifications postoperatively, an extensive intraductal component, or vascular invasion were excluded. They underwent 3D-CRT APBI at a dose of 38 Gy in 10 fractions for 1-2 weeks and were followed up for a median of 25.5 months. Three-year local recurrence rate was 2.1%. Early toxicity (grade 1 dermatitis) was reported in 25 (34.7%) patients, and no late side effect of grade 3 or higher was observed. Excellent-to-good cosmetic results were seen in 96.7% of patients. They concluded that APBI by means of EBRT radiotherapy is a good option with low toxicity for a selected subgroup of patients.⁵¹

Olivetto et al compared cosmetic and toxicity results of APBI using 3D-CRT with those of WBI in a multicenter randomized trial between 2006 and 2011. They enrolled 2135 breast cancer (tumor size ≤ 3 cm) patients aged > 40 years who had undergone BCS and assigned them to either 3D-CRT (38.5 Gy in 10 fractions twice daily) or WBI (42.5 Gy in 16 fractions or 50 Gy in 25 daily fractions \pm boost irradiation) treatment group. At 3-year follow-up, patients treated with 3D-CRT showed significantly greater adverse cosmetic side effects and grade 1/2 toxicities compared with those treated using WBI.⁴² Other randomized trials using EBRT for APBI are summarized in Table 3.

Newer Techniques of EBRT in APBI

With recent technological advances in radiation therapy, newer methods have been developed to be used in APBI for better normal tissue sparing and dose delivery. One of these methods is proton therapy. The use of proton beams has some physical advantages over photon beams, as it is associated with minimal entry, exit, or scattered radiation dose, deposition of radiation dose over a more limited range of depth, and, consequently, reduced side effects. Wang and colleagues evaluated the use of multiple proton beams in EBRT by comparing a proton therapy planning with 3D-CRT photon APBI. The absolute reduction of dose constraints in target volume was the same in both methods, but proton therapy was associated with a significantly lower exit dose to the normal breast, lung, and heart



tissues.⁵²

Bush and colleagues reported the 5-year results of a phase 2 trial of APBI by means of proton beam radiation in 100 patients with invasive nonlobular carcinoma, with a dimension of ≤ 3 cm, who had undergone BCS with negative margins and no lymph node involvement. The surgical bed was irradiated at a dose of 40 cobalt Gy equivalents in 10 fractions, once daily, over 2 weeks. IBTR-free survival, disease-free survival, and overall survival rates were 97%, 94%, and 95%, respectively. There were only 7 cases of grade 1 telangiectasia at 5-year follow-up, and the cosmetic outcome was evaluated as good to excellent in 90% of the patients.⁵³ In another study, 30 patients undergoing proton therapy (30 cobalt Gy equivalents in 6 fractions over 5 consecutive days) after BCS were followed up for a median of 59 months. All of the patients were alive at the last follow-up, with no cases of IBTR or local or distant metastasis, although the percentage of patients with a good-to-excellent cosmetic outcome decreased from 83% at the end of treatment to 69% at 3-year follow-up.⁵⁴

Another method of delivering APBI is stereotactic radiotherapy (SRT) (e.g., CyberKnife™). SRT has some advantages over 3D-CRT as it is characterized by pinpoint accuracy, offers real-time tracking and respiratory motion management, and is able to deliver higher doses of radiation with significantly lower radiation scattering to surrounding tissue. In one trial conducted at Georgetown University Hospital, 10 patients (aged ≥ 48 years) with DCIS or invasive nonlobular carcinoma with a maximum diameter of 2 cm underwent partial mastectomy with ≥ 2 -mm negative margins, followed by EBRT using CyberKnife. The patients received a total dose of 30 Gy in 5 fractions for 5 consecutive days. The cosmetic results were rated as good or excellent in all 10 patients at a median follow-up of 1.3 years. Although it was concluded that CyberKnife could be used as a tolerable and reliable device to deliver APBI, the small sample size and short follow-up period were among the study limitations.⁵⁵

Intensity-modulated radiation therapy (IMRT) is another technique in APBI that is proposed to decrease late toxicity by improving radiation homogeneity. A phase 3 trial was conducted at the University of Florence to compare treatment outcomes of WBI and APBI using IMRT. Patients received either WBI (n = 260; 50 Gy in 25 fractions plus 10 Gy boost to the tumor bed) or APBI using IMRT (n = 260; 30 Gy in 5 nonconsecutive fractions). At a median follow-up of 5 years (interquartile range: 3.4-7 years) there was no difference between the groups in IBTR or survival rate, although the IBTR group had significantly better toxicity and cosmetic outcomes.⁵⁶ A second analysis of the data from the same trial was published recently, with focus on the patients with DCIS who

had undergone APBI using IMRT (n = 22). At a median of 9.2 years of follow-up, the incidence rate for contralateral invasive cancer/DCIS, distant metastasis, and late toxicities, breast cancer-related death, and 5- and 10-year IBTR was zero. The 10-year overall survival rate was 90.9%, and cosmetic results were rated good to excellent in 21 of the 22 patients.⁴¹

In conclusion, APBI has been studied in phase 1-3 trials with different EBRT techniques and protocols in more than 1000 patients during the past decades, yielding comparable, or even better, outcomes to those of WBI.

Intraoperative Radiation Therapy in APBI

Intraoperative radiation therapy (IORT) is a type of APBI given in a single fraction after lumpectomy during the surgery. IORT has many advantages over WBI, including patient convenience, decreased irradiation of normal tissues, patient compliance^{57, 58}, and higher breast-related quality of life.^{39, 59}

There are two IORT techniques for APBI: electron beam therapy and kilovoltage X-ray beam radiation therapy. The first widely available IORT device, Intrabeam®, was introduced in 1998. Since then, several mobile linear accelerators for IORT have been developed. While Intrabeam® and Xofig® are kilovoltage photon systems, Mobetron®, Novac-7®, and LIAC® generate megavoltage electron beams. (Table 1 demonstrates some phase 1-2 IORT trials.)

Intrabeam® (Oberkochen, Germany) and Xofig® Axxent Electronic Brachytherapy System use spherical applicators, or balloons, that allows for delivering uniform doses of radiation directly to the surgical bed. Delivering APBI using these systems is normally achieved in 20 to 35 minutes in a single application, which is significantly time-effective when compared with the conventional EBRT.

The Mobetron, Novac, and LIAC systems are mobile linear accelerators that produce high-energy electron beams. 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.

IORT enjoys several advantages over other methods of APBI. The target tissue is directly visible in this method, which guarantees that the high-risk tissue gets complete treatment while avoiding the risk of marginal miss. Also, it provides the chance of getting a BCS for those women who otherwise would choose a mastectomy because of having no access to radiotherapy facilities or being unable to undergo a several-week radiotherapy regimen. Besides, it is associated with a favorable toxicity profile and may offer overall survival benefits owing to a reduced dose deposition in cardiopulmonary.⁶⁰

A major downside to IORT is that there is no final



pathologic data on the tumor size, histology, margins, and nodal status available, which may necessitate an additional course of WBI later, thereby offsetting the low-toxicity benefits of IORT. However, studies show that IORT as a tumor bed boost is safe and is associated with acceptable toxicity.⁶⁰

IORT has been compared with WBI in two large prospective randomized trials.^{61, 62} The first one, TARGIT-A, enrolled 3451 patients (aged ≥ 45) with unifocal invasive ductal carcinoma (≤ 3.5 cm in diameter). The patients in the WBI arm received 50 Gy over 3-5 weeks with or without a lumpectomy bed boost, while the IORT arm received 20 Gy via a 1.5-5-cm balloon applicator delivering 50 kV-energy X-rays to the tumor bed.⁶¹ The 5-year IBRT rate was higher in the IORT group compared with the WBI arm (3.3% vs 1.3%). However, the rate of non-breast cancer mortality was significantly lower for the IORT group (1.4% vs 3.5%) Also, IORT was associated with a significantly lower rate of severe skin complications (0.2% vs 0.8%).⁶¹ Another paper reporting the late toxicity results from the same trial found no significant difference in fibrosis, breast edema, retraction, lymphedema, or pain between the two treatment arms.⁴⁰ Telangiectasia was reported at a similar rate (17%) for patients who received IORT plus WBI or WBI but was not reported after IORT alone. Also, IORT alone has less considerable breast and arm symptoms.⁴⁰

In the second trial, known as the ELIOT trial, 1305 patients, aged 48 to 75, with a tumor size of ≤ 2.5 cm were enrolled and treated with either WBI (50 Gy + 10 Gy boost) or IORT (21 Gy).⁶² In this study, IORT was performed using a mobile linear accelerator that produced high-energy electrons beams through an applicator inserted in the lumpectomy cavity. The researchers observed a significantly higher 5-year IBTR rate for the IORT arm compared with the WBI arm (4.4% vs 0.4%). There were 14 new ipsilateral breast carcinomas in the IORT arm versus 0 in the WBI arm. On the other hand, 5-year IBTR rate in lower-risk women (tumor size ≤ 2 cm, grade 1 or 2, estrogen receptor positive, ≤ 3 positive nodes) was 1.7%. These patients are considered most suitable for receiving IORT.⁶²

In the IORT group, toxicity was lower. Skin adverse reactions were notably lower compared to WBI. A subgroup of patients voluntarily underwent a follow-up spiral computed tomography. At this subgroup, the pulmonary fibrosis was more prevalent in patients who had received WBI. Fat necrosis, conversely, occurred at a higher rate in the IOERT group (15% vs 7%).

Patient-Reported Quality of Life and Cost of Treatment

Quality of life is an important consideration for patients when they are choosing their breast cancer

treatments. Bitter and colleagues⁶³ and Schäfe *et al.*⁶⁴ analyzed self-reported cosmetic outcomes for the treated breast and quality of life for patients treated with WBI or APBI and found better cosmetic satisfaction and quality of life among patients who had undergone APBI.

APBI, in comparison with WBI, has socioeconomically different results. APBI methods are generally considered more cost-effective. Shah *et al.* estimated that treatment with 3D-CRT APBI, IMRT APBI, and MIB APBI was associated with, respectively, \$6.0 million, \$2.0 million, and \$0.7 million cost saving per 1000 patients compared with treatment using WBI. Comparing the costs of different APBI modalities, they found that, after allowing for nonmedical costs and costs due to recurrences, MIB APBI and 3D-CRT APBI would cost \$54698 and \$49009, respectively, per quality of life year.⁶⁵ A study by Grobmyer and colleagues also estimated that treatment costs associated with IORT were significantly lower compared with WBI (\$1857 vs \$9653).⁶⁶ Alvarado *et al.*, too, reported that IORT would bring about greater cost efficiency and quality of life outcomes compared with WBI if used for appropriate patients.⁶⁷

However, the cost-effectiveness advantage of IORT might fade away when compared with 3D-CRT APBI. A cost-per-QALY analysis from the TARGIT-A and ELIOT trials found that, after incorporating additional medical costs, nonmedical costs, and cost of recurrences, 3D-CRT APBI had a lower overall cost compared with IORT.⁶⁸

In conclusion, APBI represents an attractive treatment option for appropriately selected patients with early-stage breast cancer, especially in high-volume radiation centers with long waiting lists and for patients who live far away from the radiotherapy centers. Irrespective of the technique used for APBI, it is very important to select the most appropriate patient population for this treatment strategy. According to the guidelines, the most suitable patients to treat with APBI are those with a low-grade tumor less than 3 cm negative node status, and negative margins. Table 2 demonstrates patient selection criteria developed by various authoritative organizations.

There are many ongoing phases 3 trials that are testing the noninferiority and equivalence of various forms of APBI against WBI. Among various APBI methods, interstitial brachytherapy and IMRT seem to have the strongest data supporting their utilization, as they offer the most acceptable local control and cosmetic results.²⁹ However, patient selection remains one of the most important considerations, and this should be performed in a high-volume referral center and by experienced and trained hands.

Conflict of Interest

None.



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