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RADIATION ONCOLOGY (W WOODWARD, SECTION EDITOR)

Accelerated Partial Breast Irradiation (APBI): Where Are We Now?

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Abstract

Purpose of Review Accelerated partial breast irradiation (APBI) is an alternative approach to breast conserving therapy (BCT) where radiation (RT) is delivered over a shorter period of time compared with whole breast irradiation (WBI), resulting in improved patient convenience and cost savings. APBI can be delivered using brachytherapy, intraoperative RT, or conformal external beam radiation therapy (EBRT) techniques. In this review, the authors appraise the latest modern randomized controlled trials (RCTs) of APBI and discuss the application of the data to clinical practice.

Recent Findings The OCOG-RAPID and NSABP B-39/RTOG 0413 trials recently reported long-term outcomes of APBI. The OCOG-RAPID trial delivered 38.5 Gy/10 fractions twice daily (at least 6 h apart using EBRT) or WBI and demonstrated non-inferiority of APBI compared with WBI (8-year cumulative rate of ipsilateral breast tumor recurrence (IBTR) was 3% after APBI or 2.8% after WBI, HR 1.27, 90%CI: 0.84–1.91). While acute toxicity was reduced, late toxicity and breast cosmesis were worse with APBI. The NSABP B-39 trial included higher risk patients and was unable to demonstrate equivalence between APBI (38.5 Gy/10 fractions delivered twice daily using EBRT or brachytherapy techniques) and WBI. However, 10-year IBTR rates were low: 4.6% vs. 3.9%, respectively, HR 1.22, 90%CI: 0.94–1.58. The University of Florence demonstrated low rates of local recurrence at 10 years and overall excellent breast cosmetic outcomes when APBI was delivered using EBRT to a dose of 30 Gy/5 fractions delivered on non-consecutive days.

Summary Recent RCTs of APBI have shed light on important factors for the integration of APBI into clinical practice, including patient selection and treatment delivery. APBI should be limited to patients with low-risk ductal carcinoma in situ or early stage (T1) invasive ductal cancer with clear margins of excision, estrogen receptor positivity, and node negative disease. Ongoing research should focus on the optimal dose/fractionation for delivery of EBRT-based APBI.

Keywords Breast cancer · Accelerated partial breast irradiation · External beam radiation therapy · Brachytherapy · Intraoperative radiation therapy · Breast conserving therapy

Introduction

In the 1970s, the local treatment of breast cancer shifted from radical surgical approaches including the modified radical or simple mastectomy, towards conserving a woman's breast. Both the National Surgical Adjuvant Breast and Bowel Project (NSABP) and Veronesi et al. from Milan initiated two large randomized trials of mastectomy versus breast conserving therapy (BCT) (lumpectomy with whole breast irradiation (WBI)). In these trials, WBI was delivered with conventional fractionation of 50 Gy in 25 daily fractions of 2 Gy over 5 weeks. Publications with now 20-year follow-up data have provided robust evidence of acceptable local control and equivalent survival after BCT compared with mastectomy [1, 2], supporting its use as a continued standard of care. Subsequent trials established that hypofractionated WBI (40–42.5 Gy/15–16 fractions over 3 weeks) compared with conventional fractionation of 50 Gy in 25 fractions over 5 weeks after breast conserving surgery (BCS) resulted in similar local recurrence and toxicity [3, 4].

Currently, with the advent of screening mammography, a vast majority of breast cancers are diagnosed at early stages and most women are eligible for BCT. Overall excellent breast cancer outcomes have permitted the opportunity to explore treatment approaches to improve patient satisfaction and convenience, such as shortening the overall duration of therapy.

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Studies of BCT suggest that the majority of local breast cancer recurrences occur at the site of the primary tumor [5, 6]. Pathologic studies have also shown that residual microscopic disease normally lies within 1.5 cm of the initial tumor in > 90% of cases [7]. In conjunction with advanced CT planning and modern radiotherapy techniques, researchers hypothesized that targeting only the primary tumor site with a margin of 1–2 cm would result in similar local control to WBI. Accelerated partial breast irradiation (APBI) delivers therapeutic irradiation to the tumor bed with a margin using a higher (than 2 Gy) dose per fraction. This allows for treatment delivery over a shorter period of time (1 week or less) compared with the 3–5-week time frame seen with WBI, resulting in cost savings and reduced resource utilization for treating centers. Shorter treatment durations are also more convenient for patients, results in less time off work and less travel costs. APBI may have potentially fewer acute side effects [8] and it has been suggested that tumor control may be improved with the shorter overall treatment time. Early adopters have also postulated improved breast cosmesis and sparing of the lung and heart when only the partial breast is irradiated.

Three major approaches for APBI have been developed including brachytherapy, intraoperative radiotherapy, and conformal external beam techniques. Modern trials of APBI first utilized brachytherapy and demonstrated promising local control and breast cosmetic outcomes [9–11]. Since then, other modalities have been explored including intraoperative radiotherapy where a radiation applicator or source is placed in the surgical cavity to treat the tumor bed at the time of surgery [12, 13]. Brachytherapy and intraoperative techniques require specialized equipment, physician training and resources, and are not easily accessible to most patients. Recent interest has focused on external beam radiation therapy (EBRT) techniques to deliver APBI [14••, 15••, 16••, 17••, 18••]. EBRT utilizes conformal linear accelerator-based technology such as 3D conformal RT (3D-CRT) or intensity-modulated RT (IMRT) readily available at radiation facilities making it the most accessible and cost-effective modality.

Despite ongoing interest related to APBI, many physicians have been hesitant to offer it to patients outside of a clinical trial. Until recently, cancer control outcomes were limited to primarily 5 years of follow-up and early trial results demonstrated conflicting outcomes related to local tumor control and toxicity [16, 18, 19]. Two long awaited randomized clinical trials (RCTs) of APBI versus WBI just published 10-year results [14, 15]. Publication of these trials has re-invigorated discussions around use of APBI as a standard of care for appropriately selected patients. Moreover, the ongoing COVID-19 pandemic has encouraged institutions and clinicians to preserve limited resources and minimize exposure risk for patients. Reducing the duration of radiation treatments has been important in pandemic planning. This review will appraise modern RCTs of APBI with a focus on the larger trials with long-term follow-up. We will highlight new studies and discuss the implications of these new findings for current breast cancer care and future research directions.

Modern RCTs of Partial Breast Irradiation

The largest RCT of brachytherapy was led by the Group European de Curietherapie of the European Society for Radiotherapy and Oncology (GEC-ESTRO). They randomized 1184 women with tumors 3 cm or smaller to receive either APBI using high-dose rate (HDR) or pulsed-dose rate (PDR) multi-catheter brachytherapy (30.3–32 Gy in 7–8 fractions given twice a day for HDR) or WBI (50 Gy/25–28 fractions plus a tumor bed boost of 10Gy/5 fractions) after BCS with negative surgical margins. The study was a non-inferiority design, and the primary endpoint was local recurrence in the breast. At 5 years, the cumulative incidence of local recurrence in the breast was 1.44% (95% confidence interval (CI): 0.51–2.38) after APBI and 0.92% (0.12–1.73) after WBI, meeting the pre-specified criteria for non-inferiority [9]. No differences in other breast cancer outcomes were seen between groups including regional recurrence, distant metastases, breast cancer mortality, or overall survival. Patient and physician reported breast cosmetic outcomes were very good and did not differ between groups [20•].

There have been two RCTs of intraoperative APBI. In the ELIOT trial, 1305 women with tumors up to 2.5 cm were randomized to receive intraoperative APBI using electrons (21 Gy in a single fraction prescribed to the tumor bed) or 50 Gy/25 fractions with a 10 Gy/5 fraction boost. In this study, the primary outcome was ipsilateral breast tumor recurrence (IBTR). The 5-year event rate for IBTR was 4.4% (95%CI: 2.7–6.1) after intraoperative APBI and 0.4% (0.0–1.0) after WBI [13]. While the event rate after APBI did lie within the pre-specified non-inferiority margin (7.5%), it was significantly higher than that seen after APBI, hazard ratio (HR) for IBTR 9.3 (95%CI: 3.3–26.3). Regional nodal recurrence was also higher after intraoperative APBI compared with WBI at 5 years, 1% versus 0.3%, respectively, $p = 0.03$. Overall survival and breast cancer death were similar. Skin toxicity was less after intraoperative APBI, though the rate of fat necrosis was increased [13]. The TARGIT-A trial was a non-inferiority trial of 3451 women suitable for lumpectomy on clinical exam and preoperative imaging. Patients were randomized to receive APBI with intraoperative kilovoltage energy of 20 Gy in a single fraction to the surface of the applicator inserted in the surgical cavity, or WBI (conventional dosing, varied by treating center). In this trial, a risk-adaptive approach was taken whereby WBI was given after intraoperative APBI for high-risk features identified on final pathology. Some patients were randomized after their initial lumpectomy and intraoperative APBI was delivered during a

second surgical procedure. Five-year IBTR was 3.3% after APBI versus 1.3% after WBI, $p = 0.042$ [12]. Overall survival and breast cancer death were similar. No significant differences in surgical complications were reported. Radiation-related skin complications were uncommon but less with the intraoperative approach compared with WBI alone (0.2% vs 0.8%, respectively, $p = 0.03$) [12].

The UK IMPORT LOW Trialists evaluated non-accelerated partial breast irradiation (PBI) using an external beam IMRT technique. In a three arm non-inferiority trial, 2018 women with tumors 3 cm or smaller and 0–3 involved nodes were randomized to receive PBI of 40 Gy in 15 fractions, a combination of WBI of 36 Gy with 40 Gy to the partial breast, or WBI only of 40 Gy in 15 fractions, all given over 3 weeks [18••]. Estimates for 5-year IBTR were 0.5% (95%CI: 0.2–1.4) after PBI, 0.2% (0.02–1.2) after WBI 36 Gy/40 Gy partial breast, and 1.1% (0.5–2.3) after WBI (40 Gy). Regional recurrence, distant relapse, and overall survival were similar between groups. Reporting on late adverse effects such as breast shrinkage, induration, or telangiectasia, no significant differences between arms were observed. At 5 years, patient-reported change in breast appearance was reduced after PBI compared with WBI alone (15% vs 27%, respectively, $p < 0.001$). On photographic assessment, no difference in change in breast appearance from baseline was observed between treatment arms at 5 years (18% vs 23%, respectively, $p = 0.17$).

The OCOG-RAPID non-inferiority clinical trial randomized 2135 women with node negative tumors ≤ 3 cm to APBI using 3D-CRT (90%) or IMRT (10%) to a dose of 38.5 Gy/10 fractions delivered twice daily (at least 6 h apart) or WBI (42.56 Gy/16 fractions or 50 Gy/25 fractions, ± boost of 10 Gy/4–5 fractions). The 8-year cumulative rate of IBTR was 3.0% (95%CI: 1.9–4.0) after APBI or 2.8% (1.8–3.9) after WBI (HR = 1.27 (90%CI: 0.84–1.91)), with the upper bound of the 90%CI not exceeding the pre-defined non-inferiority margin [14•]. Although the rates of IBTR were relatively similar between treatment arms, their distribution was not. In patients treated with WBI, more local recurrences were true/marginal occurring at or near the tumor bed. In patients treated with APBI, more IBTRs occurred elsewhere in the breast. Disease-free survival, overall survival, or breast cancer mortality did not differ between treatment groups. Acute toxicity (primarily related to radiation dermatitis and breast edema) was less with APBI compared with WBI (grade ≥ 2: 28% vs 45%, $p < 0.0001$). Late toxicity (primarily related to breast induration) was more with APBI (grade ≥ 2: 32% vs 13%, $p < 0.0001$). Fair or poor cosmetic outcomes at 7 years were also worse with APBI compared with WBI as assessed by nurses (36% vs 19%, respectively) or patient self-assessment (31% vs 15%, respectively). This was primarily due to an increase in fair cosmesis, and poor cosmesis was uncommon.

The NSABP B-39/RTOG 0413 trial randomized 4216 women in an equivalence design to APBI using 3D-CRT (73%) (38.5 Gy/10 fractions delivered twice daily) or brachytherapy (34 Gy/10 fractions delivered twice daily) using multi-catheter (6%) or single lumen (21%) techniques versus WBI (50 Gy/25 fractions, ± 10–16 Gy boost). Eligible women were 18 years or older with tumors ≤ 3 cm and 0–3 involved axillary nodes. The 10-year cumulative incidence of IBTR (primary endpoint) was 4.6% (95%CI: 3.7–5.7) after APBI and 3.9% (3.1–5.0) after WBI with a HR 1.22 (90%CI: 0.94–1.58) that did not meet the pre-specified criteria for equivalence [15••]. Recurrence-free interval was less with APBI compared with WBI (91.8% vs 93.4%, respectively, HR 1.33 (95%CI: 1.04–1.69), $p = 0.02$). Overall survival and breast cancer mortality did not differ between treatment arms. Acute and late toxicities were not reported separately. Overall toxicity profiles appeared similar with grades ≥ 3 slightly more common with APBI (10% vs. 7%). Cosmetic outcome as assessed by patients, treating physician, and photographic review was reported for a subset of patients treated with and without chemotherapy. Results were varied. Equivalence between arms was shown for patient and photographic assessments. Cosmesis at 36 months was worse for APBI compared with WBI on physician assessment [21•].

A smaller trial from the University of Florence was recently updated with 10-year results. In this study, 520 women were randomized to APBI (30 Gy/5 fractions delivered on non-consecutive days over 2 weeks) using IMRT or WBI (50 Gy/25 fractions plus 10 Gy/5 fractions to the tumor bed). At 10 years, IBTR occurred in 3.9% of patients after APBI and 2.6% after WBI, HR 1.57 (95%CI: 0.56–4.41), $p = 0.39$ [22]. No differences in breast cancer survival or overall survival were seen. The incidence of late skin toxicity was very uncommon in both treatment arms. Similarly, adverse cosmesis (fair or poor) as assessed by patients was infrequent and was less in those treated with APBI compared with WBI (1% vs 15%, $p < 0.001$).

Based on the available randomized evidence, APBI delivered with multi-catheter brachytherapy results in non-inferior local control compared with WBI, with similar toxicity and breast cosmetic outcomes. Intraoperative RT using electrons or kilovoltage x-rays results in higher local recurrence events compared with WBI. This may be related to the tight conformality of RT dose to the tumor bed and/or the inability to adequately select appropriate patients based on clinical and radiographic findings preoperatively. EBRT-based approaches appear to result in acceptable local control, with similar overall survival and breast cancer mortality in low-risk patients, but the optimal dosing and fractionation to minimize toxicity and adverse cosmetic

Table 1 Select randomized controlled trials of accelerated partial breast irradiation (APBI) after breast conserving surgery (BCS)

	GEC-ESTRO	ELIOT	TARGIT-A	IMPORT LOW	OCOG-RAPID	NSABP-B39/RTOG 0413	University of Florence
Number of patients randomized	$n = 1184$	$n = 1305$	$n = 3451$	$n = 2018$	$n = 2135$	$n = 4216$	$n = 520$
Primary endpoint/ trial design	Local recurrence/non-inferiority trial	IBTR/non-inferiority trial	IBTR/non-inferiority trial	IBTR/non-inferiority trial	IBTR/non-inferiority trial	IBTR/equivalence trial	IBTR/equivalence trial
Median follow-up	6.6 years	5.8 years	2.4 years	6 years	8.6 years	10.2 years	10 years
Study eligibility/ exclusion criteria	≥ 40 years	48–75 years	≥ 45 years	≥ 50 years	≥ 40 years	> 18 years	> 40 years IDC/lobular carcinoma
	Negative surgical margins (≥ 2 mm for IDC, ≥ 5 mm for ILC)	All histologies and grades eligible	IDC	IDC (ILC excluded)	IDC (ILC excluded)	All histologies and grades eligible	Negative surgical margins (≥ 5 mm)
	≤ 3 cm, pN0/pN1mi	Suitable for BCS	Suitable for BCS	Negative surgical margins (≥ 2 mm)	Negative surgical margins ≤ 3 cm (invasive and in situ combined), pN0-N1mi or N0i+	Negative surgical margins ≤ 3 cm, pN0–1	≤ 2.5 cm, pN0-N1
	Unifocal	≤ 2.5 cm	Unifocal on conventional imaging	≤ 3 cm, pN0–1 grade I-III		DCIS allowed	Pure DCIS
	Pure DCIS allowed if Van Nuys Prognostic index score < 8			LVI allowed	Pure DCIS allowed	Unifocal/multifocal only (multicentric excluded)	Grade I-III
	Grade I-III			Unifocal	Grade I-III		LVI allowed
	LVI & EIC excluded				LVI allowed		Unifocal only
	Paget's or skin involvement excluded				Multicentric excluded		EIC excluded

IBTR ipsilateral breast tumor recurrence, *EIC* extensive intraductal component, *LVI* lymphovascular invasion, *DCIS* ductal carcinoma in situ, *LCIS* lobular carcinoma in situ, *mi* micrometastases, *i+* isolated tumor cells, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *BCS* breast conserving surgery

outcomes remains in question. The details of these trials of APBI are summarized in Tables 1 and 2.

Integration of Accelerated Partial Breast Irradiation in Clinical Practice

Patient Selection

Patient eligibility in the published randomized trials of APBI is summarized in Table 1.

In the main trials, eligibility characteristics were designed to identify low-risk patients: > 40–50 years of age; invasive cancers ≤ 2.5–3 cm with clear margins of excision, and node negative or pN1mic. Few trials included patients with DCIS alone. Looking at actual characteristics of patients entered in the trials, the majority were very low risk: median age 60–65 years, T1 tumors, clear margins of excision post-breast conserving surgery, grades 1–2, ER receptor positive cancers treated with endocrine therapy. Although N1mic and N1 tumors were permitted in some trials, few of these patients were well represented except for the two intraoperative trials and the NSABP B-39 trial.

The American Society for Radiation Oncology (ASTRO) developed a consensus statement in 2009 which was updated in 2017 to assist radiation oncologists in selecting appropriate patients for APBI. Patients were characterized into groups: "suitable", "cautionary", and "unsuitable" for APBI (Table 3) [23]. These recommendations were based on available evidence at that time including the GEC-ESTRO trial [9] and the two intraoperative radiotherapy trials [12, 13]. Current data supports the use of APBI for postmenopausal women with invasive ductal histology, stage T1 breast cancers with clear margins of excision, estrogen receptor positivity, and node negative disease. In all the major trials, the majority of patients were treated with endocrine therapy. This seems like a reasonable approach given the observation in the RAPID trial of a higher proportion IBTRs occurring elsewhere in the breast in patients treated with APBI. Invasive lobular histology should probably remain a 'cautionary' feature given findings of higher local recurrences after partial breast RT compared with whole breast seen (34% versus 8%) in an early trial [24] and underrepresentation in modern studies. Trials were not adequately powered to look at the impact of baseline characteristics in treatment effectiveness, but given the higher risk of local recurrence in patients treated with APBI observed in the NSABP B-39 and intraoperative trials, it seems appropriate to avoid APBI in pN1 patients.

DCIS alone was not well represented in most of the APBI trials except for RAPID (18% of patients) and the NSABP B-39 (25% of patients). In the RAPID trial, there was a non-significant increase in local recurrence rates after APBI compared with WBI (6.8% vs 3.7%, HR 1.81 (90% CI: 0.84 to 3.91)) [14••], but no

Table 2 Planning target volumes, dose, and constraints in randomized controlled trials of accelerated partial breast irradiation (APBI)

	GEC-ESTRO	ELIOT	TARGIT-A	IMPORT LOW	OCOG-RAPID	NSABP-B39/RTOG 0413	University of Florence
Study dose/fractionation	PBI: 32 Gy/8# BID or 30.3 Gy/7# BID (HDR multi-catheter BT) OR 50 Gy, 0.6–0.8 Gy/h PDR multi-catheter BT WBI: 50–50.4 Gy/25–28# + 10 Gy/5# tumor bed boost	PBI: 21 Gy/1# WBI: 50 Gy/25# + 10 Gy/5# tumor bed boost	PBI: 20 Gy/1# WBI: varied	PBI: 40 Gy/15# daily or 36 Gy/15# to whole breast and 40 Gy/15# to partial breast or WBI: 40 Gy/15#	PBI: 38.5 Gy/10# BID WBI: 42.5 Gy/16# or 50 Gy/25# ± 10 Gy/4–5# tumor bed boost	PBI: 34 Gy/10# BID (BT) or 38.5 Gy/10# BID (3D-CRT) WBI: 50–50.4 Gy/25–28# ± 10–16 Gy tumor bed boost	PBI: 30 Gy/5# non-consecutive days (over 2 weeks) WBI: 50Gy/25# + 10 Gy/5# tumor bed boost
Partial breast irradiation modality	HDR multi-catheter BT or PDR	Intraoperative (electrons)	*Intrabeam* intraoperative device (kV X-rays)	Forward planned field-in-field IMRT	3D-CRT (87%) IMRT (10%)	3D-CRT (73%) or HDR multi-catheter (6%) or single entry (e.g., *Mammosite* or SAVI) (21%) BT	IMRT
Partial breast planning volume	Tumor bed + at least 2 cm margin (defined individually for each patient based on width of pathologically clear surgical margin and radiation safety margin)	CTV based on tumor size and site	Tumor bed	Visualized surgical cavity + 1.5 cm (CTV) + 1 cm (PTV) *CTV edited to 5 mm from skin surface and pectoralis fascia posteriorly *PTV edited to 5 mm from skin surface	Visualized surgical cavity + 1 cm (CTV) + 1 cm (PTV) *CTV excludes 5 mm from skin, chest wall and pectoralis muscle *PTV edited from skin and chest wall to create a PTVeval	3DCRT: Visualized surgical cavity + 1.5 cm (CTV) + 1 cm (PTV) *CTV excludes 5 mm from skin, chest wall and pectoralis muscle *PTV edited from skin and chest wall to create a PTVeval Multicatheter BT/Mammosite: excision cavity/balloon + 1.5/1 cm = CTV=PTV = PTVeval * edited from skin and chest wall to create a PTVeval	Visualized surgical cavity + 1 cm (CTV) + 1 cm (PTV) *CTV excludes 3 mm from skin surface *PTV extends only 4 mm into lung, and excludes 3 mm from skin
Target dose constraints	100% prescribed dose to ≥ 90% target volume	Dose prescribed to 90% isodose line	20 Gy to tumor bed surface, attenuating to 5–7 Gy at 1 cm depth	≥ 95% CTV should be covered by 95% isodose line	95–107% prescription dose to PTVeval	3DCRT: ≥ 90% PTVeval be covered by 90% isodose Multicatheter BT/Mammosite: ≥ 90% PTVeval be covered by ≥ 90% isodose	100% PTV covered by 95% prescribed dose;
Homogeneity constraints	V100%/V150% < 0.35	-	-	Dose to 2 cc < 105–107%	Maximum dose to PTV ≤ 107%	3DCRT: Maximum dose to PTV ≤ 120% Multicatheter BT: V150% ≤ 70 cc, V200% ≤ 20 cc, 1-V150/V100 ≥ 0.75 Mammosite: V150% ≤ 50 cc, V200% ≤ 10 cc	Maximum dose to PTV < 105%; minimum dose to PTV = 93%;
Ipsilateral breast volume constraints	Maximum skin dose < 70% of prescription dose	-	-	-	< 25% (35% acceptable) to be covered by > 95% isodose; < 50% (up to 60% acceptable) to be covered by 50% isodose; 0% to receive > 107%	3DCRT: < 35% to be covered by 100% isodose; < 60% to be covered by ≥ 50% isodose Multicatheter BT: skin dose ≤ prescription dose, < 60% to be covered by ≥ 50% isodose Mammosite: maximum skin dose ≤ 145% prescription dose, < 60% to be covered by ≥ 50% isodose	≤ 50% uninvolved breast to receive > 50% of prescribed dose

BT brachytherapy, *HDR* high-dose rate, *PDR* pulsed-dose rate, *IMRT* intensity-modulated radiation therapy, *3D-CRT* 3D conformal radiation therapy, *kV* kilovoltage, *PBI* partial breast irradiation, # = fractions, *WBI* whole breast irradiation, *CTV* clinical target volume, *PTV* planning target volume, *PTVeval* planning target volume for dose volume evaluation

Table 3 Patient groups by suitability according to the ASTRO Consensus Statement

Risk factors	Suitable	Cautionary	Unsuitable
Age	≥ 50 years	40–49 years if otherwise meets criteria for "suitable" OR ≥ 50 years with at least 1 poor pathologic criteria of: - T2 (up to 3 cm) - Margin < 2mm - Limited LVI - Estrogen receptor negative - Microscopically multifocal given total size including intervening unaffected breast parenchyma is 2.1-3 cm (provided lesion is clinically unifocal on physical exam and imaging) - Invasive lobular histology - Pure DCIS ≤3 cm - EIC ≤3 cm	< 40 years OR 40–49 years with poor pathologic features
Margins	≥ 2 mm	< 2 mm	Positive
T stage	Tis or T1		
N stage	pN0 (axillary staging required)		pN1-N3
Pure DCIS	If screen detected, ngrI-II, ≤ 2.5 cm size, margins ≥ 3 mm	≤ 3 cm and not otherwise 'suitable'	> 3 cm

Tis in situ disease, *T1* tumors up to 2 cm in size, *pN0* pathologically node negative, *ngr* nuclear grade, *LVI* lymph vascular invasion, *DCIS* ductal carcinoma in situ, *EIC* extensive intraductal component, *pN1-N3* pathologically node positive disease

differences were observed in NSABP B-39 (7% vs 6.2%, respectively, HR 1.07 (95% CI: 0.66 to 1.73)) [15••]. Although APBI was initially not recommended for pure DCIS in the original ASTRO guidelines [25], the updated consensus recommendations for APBI categorize patients with DCIS as "suitable" if they fall into the low-risk subgroup defined as widely clear resection margins (≥ 3 mm), size ≤ 2.5 cm, low or intermediate nuclear grade, and screen-detected [23, 26, 27]. Favorable DCIS outcomes after APBI seen the NSABP B-39 trial lend support for inclusion of these patients in the 'suitable' category and suggest that APBI may be a reasonable approach especially when treated with endocrine therapy.

Interventions

In terms of techniques, three approaches are currently available. Data from the GEC-ESTRO trial supports the use of HDR or PDR interstitial brachytherapy as administered in the trial. Single lumen brachytherapy, e.g., *Mammosite*, has been widely used in the past [11], but there has been little data from randomized trials. It was incorporated in NSABP B-39 in a smaller proportion of patients but early result data suggest a higher risk of recurrence compared with WBI which may be related to the highly conformal nature of this approach [28].

Intraoperative therapy is also an option for patients. Electron therapy is not widely available, and results of the ELIOT trial are not supportive for its use. Kilovoltage treatment using *Intrabeam* is now widely available in North America. While overall results from the TARGIT trial were not positive, but the risk adaptive approach where intraoperative treatment is administered during the time of initial surgery followed by WBI if necessary, for higher-risk patients, remains an option. Some of the challenges of using this approach include indefinite criteria regarding the need for additional WBI and lack of data about long-term toxicity when both treatment modalities are administered.

Perhaps the largest amount of data in support of APBI is for conformal external beam techniques: 3D-CRT and IMRT. General guidelines for application in these trials were very similar. After CT simulation planning, the tumor bed or seroma (also referred to as the gross tumor volume, GTV) should be contoured based on visible architectural distortion, surgical clips, and the operative report. Surgical clip placement at the tumor bed, fiducial markers, use of preoperative imaging, and ultrasound will aid in delineation of the operative bed [29–33]. An additional margin of 1–1.5 cm beyond the seroma is added for microscopic disease spread (clinical target volume, CTV). Subsequently, an additional 0.5–1 cm for between fraction movement and setup inconsistencies (planning target volume, PTV) is added. The partial breast PTV is targeted using 3D-conformal or intensity-modulated approaches with 2 or more angled beams.

The intended irradiated breast volume and constraints to remaining ipsilateral breast were similar across the randomized trials of EBRT-based APBI with the recognition that an additional PTV for between fraction movement was not required for brachytherapy or intraoperative techniques (Table 2). While volume of irradiated breast tissue for brachytherapy and external beam APBI has been shown to correlate with worse late effects on univariate analysis in smaller series [34–36], a multivariate analysis of the RAPID trial was unable

to demonstrate an independent correlation between high-dose volume and adverse cosmesis at 3 years [37].

The appropriate dose fractionation for EBRT continues to be somewhat uncertain. A total of 38.5 Gy in 10 fractions BID was the most commonly used schedule, but it was associated with worse toxicity and cosmesis in the RAPID trial. The schedule of 40 Gy in 15 fractions as performed in IMPORT LOW may also be used, but this is non-accelerated, and treatment is given over 3 weeks. The dose fractionation schedule in the Florence trial 30 Gy in five fractions on alternate days has demonstrated limited toxicity and has been increasingly used. A number of new schedules of five daily fractions over 1 week are also being studied (see details below) [38–40].

Future Directions

APBI is an appropriate treatment for patients with low-risk breast cancer to reduce the risk of IBTR following BCS. Recent large trials have established the efficacy and tolerability of APBI. Trials to date suggest that multi-catheter brachytherapy or conformal EBRT appear to be the most effective. Treatment is often given twice daily for 4–5 days although some studies suggest increase toxicity when EBRT is given in this manner. Reducing treatment volume using more conformal EBRT approaches may reduce toxicity and on-going trials are evaluating this approach [41]. Alternatively, investigators are also evaluating the delivery of RT once daily. The suboptimal breast cosmetic outcome seen in the RAPID trial may be related to twice daily fractionation. The half-life of tissue repair for late fibrosis which correlates strongly with adverse breast cosmesis is estimated to be 4.4 h [42]. The interfraction interval of 6 h used in these trials may not be sufficient for complete normal tissue repair leading to increase toxicity. As a result, a number of investigators are evaluating schedules of 27 Gy to 30 Gy in 5.4–6 Gy fractions once a day over 1 week using conformal EBRT techniques. Preliminary results suggest limited toxicity with these approaches [39]. Another approach that is being evaluated is the use of preoperative EBRT. This allows for a smaller volume to be radiated and studies are ongoing [43–47]. Other potential long-term benefits of APBI including a reduction in second cancers or cardiac disease have yet to be reported in many of the trials.

A newer approach to de-escalation of RT is very short hypofractionated WBI given over 1 week. The FAST Forward trial compared 26 Gy or 27 Gy in 5 fractions over 1 week to 40 Gy in 15 fractions over 3 weeks. At 5 years, the two experimental regimens were shown to be non-inferior to 40 Gy with respect to local recurrence in the breast; 27 Gy had increased toxicity but 26 Gy did not [48••]. Some limitations to the approach are patients with DCIS were not included; the treatment technique required considerable homogeneity of breast dose which may not be achievable in women with large breast size; and some concerns remain about the impact of large fraction size on the whole breast with respect to long-term toxicity and cosmetic outcome [49, 50].

Another important treatment de-escalation approach being studied for low-risk breast cancers is the use of adjuvant endocrine therapy alone with the avoidance of breast irradiation altogether. This method has already been advocated for women with T1 tumors over the age of 70 [51] and is currently being evaluated in women > 50 in a number of cohort studies and randomized trials [52–57].

Conclusions

APBI represents an important de-escalation of treatment option for low-risk patients. In the future, women with low-risk breast cancer following BCS may have a number of treatment options to choose from including APBI, 5 fractions WBI, or endocrine therapy alone. Decision making will be based on patient preference and relevant comorbidities as they relate to either radiation or endocrine therapy. Determinants of APBI versus 5 fractions WBI may relate to the patient breast size and the ability to spare heart and lung. Women with larger breasts, pulmonary or cardiac morbidity, or reduced access to cardiac sparing technology such as deep inspiration breath hold may be better suited for APBI.

Compliance with Ethical Standards

Conflict of Interest Mira Goldberg and Timothy Whelan have no conflicts of interest to declare.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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