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Partial breast irradiation: An updated consensus statement from the American brachytherapy society

Bethany Anderson[1,*], Douglas Arthur[2], Jean-Michel Hannoun-Levi[3], Mitchell Kamrava[4], Atif Khan[5], Robert Kuske[6], Daniel Scanderbeg[7], Chirag Shah[8], Simona Shaitelman[9], Timothy Showalter[10], Frank Vicini[11], David Wazer[12], Catheryn Yashar[7]

[1] *Department of Human Oncology, University of Wisconsin School of Medicine and Public Health, Madison, WI*
[2] *Department of Radiation Oncology, Virginia Commonwealth University, Richmond, VA*
[3] *Department of Radiation Oncology, University of Cote d'Azur, Nice, France*
[4] *Department of Radiation Oncology, Ceders Sinai, Los Angeles, CA*
[5] *Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY*
[6] *Arizona Breast Cancer Specialists, Scottsdale, AZ*
[7] *Department of Radiation Medicine and Applied Sciences, University of California San Diego, San Diego, CA*
[8] *Department of Radiation Oncology, Taussig Cancer Institute, Cleveland, OH*
[9] *Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*
[10] *Department of Radiation Oncology, University of Virginia School of Medicine, Charlottesville, VA*
[11] *Genesis Care, Farmington Hills, MI*
[12] *Department of Radiation Oncology, Tufts Medical Center, Boston, MA*

ABSTRACT

PURPOSE: In recent years, results with mature follow-up have been reported for several Phase III trials randomizing women to receive whole breast irradiation (WBI) versus varying modalities of partial breast irradiation (PBI). It is important to recognize that these methods vary in terms of volume of breast tissue treated, dose per fraction, and duration of therapy. As such, clinical and technical guidelines may vary among the various PBI techniques.

METHODS: Members of the American Brachytherapy Society with expertise in PBI performed an extensive literature review focusing on the highest quality data available for the numerous PBI options offered in the modern era. Data were evaluated for strength of evidence and published outcomes were assessed.

RESULTS: The majority of women enrolled on randomized trials of WBI versus PBI have been age >45 years with tumor size <3 cm, negative margins, and negative lymph nodes. The panel also concluded that PBI can be offered to selected women with estrogen receptor negative and/or Her2 amplified breast cancer, as well as ductal carcinoma in situ, and should generally be avoided in women with extensive lymphovascular space invasion.

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* Corresponding author. University of Wisconsin, 600 Highland Ave K4/B100, Madison WI 53792. Tel.: 608-263-8500; fax 608-263-1967.
E-mail address: anderson@humonc.wisc.edu (B. Anderson).

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CONCLUSIONS: This updated guideline summarizes published clinical trials of PBI methods. The panel also highlights the role of PBI for women facing special circumstances, such as history of cosmetic breast augmentation or prior breast irradiation, and discusses promising novel modalities that are currently under study, such as ultrashort and preoperative PBI. Updated consensus guidelines are also provided to inform patient selection for PBI and to characterize the strength of evidence to support varying PBI modalities.

Keywords: Breast cancer; Ductal carcinoma in situ; Partial breast irradiation; Brachytherapy; Intensity modulated radiation therapy; 3D conformal radiation therapy; Intraoperative radiotherapy

Introduction

In recent years, results with mature follow-up have been reported for several Phase III trials randomizing women to receive whole breast irradiation (WBI) versus varying modalities of partial breast irradiation (PBI). This represents a phenomenal research endeavor, with over 10,000 women participating in randomized trials of WBI versus PBI given as external beam or brachytherapy, and an additional 5000 women in studies of WBI versus intraoperative radiotherapy (IORT). It is important to recognize that these methods vary in terms of volume of breast tissue treated, dose per fraction, and duration of therapy. As such, clinical and technical guidelines may vary among the various PBI techniques. Here we present an updated summary of published clinical trials of PBI methods with the outcomes achieved, including cancer control, toxicity, and quality of life. We also highlight the role of PBI for women facing special circumstances, such as history of cosmetic breast augmentation or prior breast irradiation, and we discuss promising novel modalities that are currently under study, such as ultrashort and preoperative PBI. Updated consensus guidelines are also provided to inform patient selection for PBI and to characterize the strength of evidence to support varying PBI modalities.

Efficacy outcomes from randomized trials

Multiple randomized trials have been performed comparing PBI to WBI. These trials have evaluated several different PBI modalities, including multicatheter interstitial brachytherapy (MIBT) (1,2), single-entry applicator brachytherapy (SEABT) (3), and external beam techniques such as 3D conformal radiotherapy (3D-CRT) (3–6) and intensity modulated radiotherapy (IMRT) (7). Although techniques and dosimetry vary considerably among these PBI methods, there are some universal themes that are important to consider when evaluating the clinical utility of PBI.

First, the majority of PBI approaches do shorten the overall duration of therapy and/or decrease the number of fractions relative to WBI, a concept referred to as accelerated partial breast irradiation (APBI). The IMPORT LOW trial, by contrast, studied a PBI regimen consisting of 40 Gy in 15 fractions over 3 weeks, which is shorter than conventionally fractionated WBI (CF-WBI) but equivalent in duration to modern hypofractionated WBI (5).

The volume of breast tissue treated also varies by PBI technique. Most randomized trials have targeted the tumor bed with approximately 2 cm total margin. Outliers include the IMPORT LOW trial, which treated a larger volume of breast tissue by utilizing medial and lateral tangent beams of reduced length, but not width (5). The NSABP B39 trial, on the other hand, allowed women to receive APBI using SEABT with a 1 cm total planning target volume (PTV) margin (3). Margins utilized for varying forms of PBI have been shaped by the specific technique utilized for treatment. For example, with brachytherapy there is a direct expansion from the lumpectomy cavity to a PTV that excludes the muscle and first 5 mm of tissue underneath the skin; no additional margin is necessary for setup error and/or respiratory motion. With SEABT, dose is prescribed to a depth of 1 cm to limit hot spots close to the applicator, while with MIBT the PTV margin can be increased by adding additional catheters. With external beam PBI techniques, a clinical target volume (CTV) is typically created first, then expanded to a PTV margin determined by the anticipated reproducibility of the patient's position for treatment. Most randomized trials of external beam PBI have utilized a 1 cm CTV margin followed by a 1 cm PTV margin. Exceptions are IMPORT LOW, which used a 1.5 cm CTV + 1 cm PTV, and the Barcelona trial which treated the quadrant of the primary tumor site (Table 1). The amount of breast tissue beyond the PTV which receives prescription dose also varies between modalities and among patients; for example, with the IMPORT LOW technique all medial and lateral breast tissue within the mini-tangent beams targeting the PTV will receive close to the prescription dose, whereas with IMRT techniques the high-dose region can drop off more quickly in the breast tissue, at the potential cost of increased low-dose exposure to underlying organs at risk. A 2004 pathologic analysis of early breast cancer patients suggested that 1 cm was an appropriate CTV margin for early-stage breast cancer receiving PBI (8), and subsequent randomized trials have not provided additional clarification regarding the ideal total volume of breast tissue to irradiate.

Table 1
Randomized partial breast irradiation trials: Treatment methods and eligibility criteria.

	Hungary (1)	GEC-ESTRO (2)	RAPID (3)	NSABP B-39 (4)	University of Florence (5)	IMPORT LOW (6)	Barcelona (7)
Treatment Methods							
Whole breast dose/fractionation	50 Gy/25 Fx[a]	50–50.4 Gy/25–28 Fx + electron boost (10 Gy/5 Fx)	50 Gy/25 Fx or 42.5 Gy/16 Fx, boost optional	50 Gy/25 Fx, boost optional	50 Gy/25 Fx + electron boost (10 Gy/5 Fx)	40 Gy/15 Fx[b]	48 Gy/24 Fx, optional boost
Partial breast technique and dose/fractionation	MIBT HDR: 36.4 Gy/7 Fx, PTV 1–2 cm Electron: 50 Gy/25 Fx, PTV 1.5–2 cm	MIBT HDR: 32 Gy/8 Fx or 30.1 Gy/7 Fx MIBT PDR: 50 Gy PTV per GEC-ESTRO method[c]	3D-CRT[d]: 38.5 Gy/10 fx BID, 1 cm CTV + 1 cm PTV	3D-CRT: 38.5 Gy/10 fx BID, 1.5 cm CTV + 1 cm PTV MIBT: 34 Gy/10Fx BID, 1.5 cm PTV Applicator: 34 Gy/10 Fx bid, 1 cm PTV	Step and shoot IMRT: 30 Gy/5 fx (QOD), 1 cm CTV + 1 cm PTV	Field-in-field medial and lateral tangents: 40 Gy/15 Fx, 1.5 cm CTV + 1 cm PTV	3D-CRT: 37.5 Gy/10 Fx BID to quadrant of primary tumor site
EQD2 ($\alpha/\beta = 3.5$)	57.6	43.6 (8 Fx) 42.7 (7 Fx)	51.4	51.4 (3DCRT) 42.7 (brachytherapy)	51.8	44.9	49.4
Partial breast duration of therapy	MIBT HDR: 4 days Electron: 5 weeks	MIBT HDR: 4 days MIBT PDR: 3–4 days	5 days	5 days	1.5–2 weeks	3 weeks	5 days
Eligibility Criteria							
Age	≥40 years (after 2001)	≥40 years	≥40 years	>18 years	>40 years	≥50 years	≥60 years
Tumor Size	≤2 cm	≤3 cm	≤3 cm	≤3 cm	≤2.5 cm	≤3 cm	≤3 cm
Nodal Stage	N0–1mi (single micrometastasis permitted)	N0–1mi	N0–1mi	N0–1a (≤3 positive axillary nodes permitted)	N0–1	N0–1 (≤3 positive axillary nodes permitted)	N0
Margins	No tumor on ink	≥2 mm; ≥5 mm for ILC or DCIS	No tumor on ink	No tumor on ink	≥5 mm	≥2 mm	>3mm
ILC	No	Yes	No	Yes	Yes	No	No
DCIS	No	Yes (VNPI <8)	Yes	Yes	Yes	No	No
Multifocal	No	No	–	Yes	No	No	–
EIC	No	No	–	Yes	No	–	No
LVSI	Yes	No	Yes	Yes	Yes	Yes	–
Additional factors	Grade 1–2			Life expectancy ≥10 years	Clips mandated	Neoadjuvant endocrine therapy permitted	Grade 1–2 Hematoma >2 cm excluded

Gy = gray; Fx = fractions; MIBT = multicatheter interstitial brachytherapy; HDR = high dose rate; PDR = pulsed dose rate; IMRT = intensity modulated radiation therapy; ILC = invasive lobular carcinoma; DCIS = ductal carcinoma in situ; VNPI = Van Nuys prognostic index; EIC = extensive intraductal component; LVSI = lymphovascular space invasion.

[a] 2D treatment planning for all patients.

[b] 3rd reduced-dose group included 36 Gy/15 Fx to whole breast with 40 Gy/15 Fx to tumor bed.

[c] GEC-ESTRO method determines brachytherapy PTV individually in each direction, calculated such that the sum of the width of the clear pathologic surgical margin plus the brachytherapy margin equals 20 mm.

[d] IMRT permitted.

Future studies in this area would be valuable. In the meantime, physicians prescribing PBI should recognize the heterogeneity in PBI trials and techniques to avoid incorrectly extrapolating the outcomes achieved with one technique to another.

The absolute dose prescribed for PBI in randomized trials also varies based upon technique, with the general principle of aiming for a radiobiological equivalent of 45–50 Gy at 1.8–2 Gy/F. For example, the NSABP B39 protocol estimated that 3.85 Gy x 10 (3DCRT) would provide a biologically equivalent dose of 45 Gy in 1.8 Gy fractions, assuming an α/β ratio of 10. Much has been learned over the past two decades regarding the radiobiology of breast cancer, and we now know that the α/β for tumor control in

breast cancer is closer to 3.5 (9,10). Dose homogeneity and differences in duration of therapy further complicate simplistic radiobiological comparisons among PBI techniques; for example, EBRT doses are generally set slightly higher than brachytherapy doses to account for the heterogeneity found within brachytherapy treatment plans. A basic linear quadratic estimate of EQD2 among PBI techniques studied in randomized trials is provided in Table 1.

Eligibility criteria for randomized trials comparing WBI with PBI have been fairly similar, focusing on women with early-stage breast cancer with low-risk features; some have included ductal carcinoma in situ (DCIS). The NSABP B39 study is unique in that it allowed a slightly broader demographic of patients to enroll (i.e., age >18, any histological subtype permitted) and it closed recruitment to the lowest risk patient groups approximately 20 months after the study opened due to rapid accrual. Table 1 provides a summary of randomized trials comparing WBI with various forms of PBI, including details regarding the target volumes and duration of each PBI method, as well as the eligibility criteria of each clinical trial.

The first randomized study to be conducted was the Hungarian National Institute of Oncology trial, which included 258 women with early-stage breast cancer who received WBI or PBI (69% MIBT, 31% electrons). A total of 20 year outcomes have been published, demonstrating no difference in rates of ipsilateral breast tumor recurrence (IBTR) (9.6% APBI vs. 7.9% WBI) or overall survival (OS) (1). This study led to the GEC-ESTRO randomized trial, which included 1184 women who received WBI or MIBT; 5 year outcomes demonstrated no difference in rates of local recurrence (1.4% APBI vs. 0.9% WBI) or OS (97% APBI vs. 95% WBI) (2). These two studies represent the largest single study evaluating brachytherapy as a PBI technique; no randomized trials have evaluated SEABT exclusively. The NSABP B-39 trial allowed for APBI to be delivered with MIBT, SEABT, or 3D-CRT, and most patients in that study treated with APBI received 3D-CRT (73%). At 10 years, the rate of IBTR was 4.6% with APBI and 3.9% with WBI, failing to meet criteria for equivalence despite the difference being <1% (3). However, the RAPID trial enrolled more than 2100 women and compared 3D-CRT APBI with WBI; at 8 years no difference in rates of IBTR was noted (3.0% APBI vs. 2.8% WBI) (4). The IMPORT LOW trial compared WBI to APBI using the same schedule of 40 Gy in 15 fractions, and also included a third arm of reduced dose WBI. Five year outcomes demonstrated no difference in rates of local recurrence (5). Taken together, these three large randomized trials have shown consistently comparable local recurrence rates with 3D-APBI versus WBI, and similar findings have been seen in another small study (6). IMRT techniques have also been applied to APBI. Most notably, the University of Florence randomized trial compared IMRT APBI (30 Gy in 5 fractions) to WBI and with 10 year follow-up, no difference in rates of local recurrence was found (3.7% APBI vs. 2.5% WBI). (7) Table 2 summarizes the patient demographics and cancer control outcomes of these trials.

Quality of life, toxicity, and cosmetic outcome

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Randomized trials conducted by the Hungarian National Institute of Oncology (NIO) and GEC-ESTRO have analyzed the toxicity, quality of life, and cosmetic outcomes achieved with MIBT versus conventionally fractionated whole breast irradiation (CF-WBI). The GEC-ESTRO study found that CF-WBI resulted in higher rates of acute Grade 3 radiation dermatitis (7% vs. 0.2%, $p < 0.0001$) and Grade 1–2 skin toxicity (86% vs. 21%, $p < 0.0001$). MIBT had higher rates of Grade 1–2 hematoma (20% vs. 2%, $p < 0.0001$) and Grade 1–2 breast infection (5% vs. 2%, $p = 0.01$). No difference in acute Grade 1–2 breast pain was noted (11). Quality of life (QOL) analysis found that MIBT did not result in clinically significant deterioration of overall QOL, and that all domains of QOL after APBI were not inferior to CF-WBI (12). Breast and arm symptom scale scores were more favorable with MIBT that with CF-WBI. Emotional functioning, fatigue, and financial difficulty scores were slightly better with MIBT on the last day of radiation and 3 months post-treatment. Similar QOL findings were found by another prospective nonrandomized trial (13).

Late toxicity analysis of the GEC-ESTRO trial revealed 5 year Grade 2–3 skin toxicity was worse with CF-WBI (10.7% vs. 6.9%, $p = 0.02$). Equal outcomes were seen for Grade 2–3 subcutaneous tissue side effects, Grade 2–3 breast pain, and cosmesis. (14) A total of 20 year follow-up of the NIO study found good-excellent cosmetic outcome in 79.2% of PBI patients versus 59.5% of CF-WBI patients ($p < 0.0007$) (1). Of note, a subset of PBI patients on this study ($n = 40$) received electron beam irradiation and had lower rates of good-excellent cosmesis that did not reach statistical significance (72.5% vs. 82.4% with MIBT, $p = 0.9315$). Table 3 summarizes the cosmetic outcomes achieved with MIBT and other PBI modalities.

NSABP B39 is the only randomized trial to date which has included patients treated with SEABT. On this study, PBI technique was at the discretion of the treating physicians, and 73% of PBI patients were planned to receive 3D-CRT ($n = 1536$), with a smaller proportion of patients receiving SEABT (21%, $n = 451$) and MIBT (6%, $n = 120$) (3). There is a significant amount of nonrandomized data regarding outcomes with SEABT. The first FDA-approved applicator had a single dwell position at the center of the device and produced a spherically symmetric dose distribution. With a single dwell location, it lacked the capability to alter the dose distribution with respect to the skin and chest wall. Distance between the applicator and skin surface of <6 mm was associated with increased late toxicity

Table 2
Randomized partial breast irradiation trials: Patient characteristics and outcomes.

	Hungary (1)	GEC-ESTRO (2)	RAPID (3)	NSABP B-39 (4)	University of Florence (5)	IMPORT LOW (6)	Barcelona (7)
Number of Patients	258	1184	2135	4216	520	2018	102
Age	Mean 59 years 2.3% age ≤40	Median 62 years 14% age ≤50	Median 61 years	Median 54 years 38% age <50	15.8% age <50	Median 62 years	Mean 67.1 years
Tumor size	Median 1.3 cm 63.3% 1.1–2cm	Median 1.2 cm 49% 1.1–2 cm 11% >2 cm	29% 1.5–3 cm	30% 1.1–2 cm 9% >2cm	37.3% 1.1–2 cm 5.4% >2cm	Median 1.2cm	Median 1.0 cm 39.2% 1.1–2 cm 7.8% >2 cm
Nodal stage	2.3% N1mi	1% N1mi	<1% N1	10% N1	7.3% N1	2% N1	No N1
Margins	0% <2 mm 58.6% 2-<10 mm 37.5% ≥10mm	Median 8mm	–	–	–	–	–
Histology	No ILC No DCIS No Grade 3	13% ILC 6% DCIS 9% Grade 3	No ILC 18% DCIS 15% Grade 3	5% ILC 25% DCIS 26% Grade 3	8.1% ILC 8.8% DCIS 10% Grade 3	No ILC No DCIS	No ILC No DCIS
LVSI	2.3%	No LVSI	7%	–	7.3%	7%	–
Receptor Status	7.8% ER- 17.2% PR-	5% ER-/PR-	9% ER- 6% Her2+	19% ER-/PR-	4.6% ER- 10.8% PR- 2.5% Her2+	5% ER- 20% PR- 6% Her2+	3.9% ER- 15.7% PR- 1.9% Her2+
Endocrine therapy	69%	87%	61%	85% (ER+)	64%	91%	98%
Chemotherapy	2%	10%	12%	29%	1.5%	7%	2%
Follow-Up (years)	17	6.6	8.6	10.2	10.7	6.0	5.0
Local Recurrence	7.9% WBI vs. 9.6% APBI	0.9% WBI vs. 1.4% APBI	2.8% WBI vs. 3.0% APBI	3.9% WBI vs. 4.6% APBI	2.5% WBI vs. 3.7% APBI	1.1% WBI vs. 0.2% SIB vs. 0.5% APBI	0% both arms
Survival	60% WBI vs. 60% APBI	96% WBI vs. 97% APBI	97% WBI vs. 97% APBI	91% WBI vs. 91% APBI	92% WBI vs. 92% APBI	94% all arms	No difference

Patient characteristics for entire patient population were used when available. When only patient characteristics for each arm were reported, APBI patient characteristics were used in the event of a difference between the two arms.

after SEABT (15,16), leading to a preferred distance of ≥7 mm or limitation of the skin dose to <120% (17) or even 100% (18) of the prescription dose. Contemporary single-entry applicators have increased ability to modulate radiation dose with multiple dwell positions, and the corresponding reduction in skin and chest wall radiation has resulted in low toxicity rates in modern studies. For example, one modern registry trial reported outcomes of 342 women treated with HDR brachytherapy (34 Gy in 10 bid fractions) from 2008 to 2011 (19). After a median follow-up time of 36 months, 88% had good-excellent cosmesis. Treatment-related toxicities evolved over time; at any time-point, 8.5% of patients had a breast infection, 6.8% fat necrosis (2.1% symptomatic), 20.5% seroma (4.4% symptomatic), 8.2% breast pain (any grade), 7.6% telangiectasia (Grade 1), and 9.7% hyperpigmentation (Grade 1–3). No Grade 2 or higher fibrosis was observed. Another registry trial reported outcomes of 250 women treated with HDR brachytherapy (34 Gy in 10 bid fractions) from 2007 to 2010 (20). With a median follow-up time of 59.5 months, 85.9% had good-excellent cosmesis. Infection occurred in 3.7% of patients. Other Grade ≥2 toxicities at any time included symptomatic fat necrosis (1.3%), symptomatic seroma (4.8%), induration (3%), breast pain (3.9%), telangiectasia (3.0%), and hyperpigmentation (0.4%).

In summary, much has been learned over the last several decades about how to optimize cosmetic and quality of life outcomes with breast brachytherapy. Guidelines for catheter insertion, 3D treatment planning, dosimetry and quality assurance for MIBT have been published by the GEC-ESTRO Breast Cancer Working Group in 2018 (21). The ABS has also recently published updated dosimetric guidelines for both MIBT and SEABT (22). A detailed practical description of the typical side effects of both MIBT and SEABT, as well as their management, has also been published in 2020 (23).

Table 3
Cosmetic outcome at 5 years or greater achieved with various forms of partial breast irradiation.

	Modality	Number of PBI patients	Timepoint	Good-excellent cosmesis with APBI(%, assessed by)	Good-excellent cosmesis with WBI(%, assessed by)
GEC-ESTRO (8	MIBT vs. CF-WBI	633	5 years	92% patient 93% physician	91% patient 90% physician
Hungary (1)	MIBT or EB-PBI vs. CF-WBI	125	20 years	79.2% physician	59.5% physician[a]
SAVI registry (9)	SEABT	250	5 years	85.9% physician	N/A
MammoSite registry (10)	SEABT	331[b]	7 years	90.6% physician	N/A
RAPID (3)	3D-APBI	690[c]	7 years	64% nurse 69% patient	81% nurse[a] 85% patient[a]
University of Florence (5)	IMRT-APBI vs. CF-WBI	260	10 years	99.2% patient 100% physician	85.4% patient[a] 98.1% physician[a]
PAPBI (11)	Preoperative 3D-APBI	133	5 years	92% physician	N/A
TARGIT-A (12)	IORT	90[d]	5 years	90% patient	68.4% patient[a]

Studies reporting percentages of patients with excellent, good, fair, and poor cosmetic outcomes are included. Nonrandomized studies included when randomized data is unavailable.

MIBT = multicatheter interstitial brachytherapy; CF-WBI = conventionally fractionated whole breast irradiation; EB-PBI = electron beam partial breast irradiation; SEABT = single-entry applicator brachytherapy; NIBB = noninvasive breast brachytherapy; PSI = permanent seed implantation; 3D-APBI = 3D conformal external beam accelerated partial breast irradiation; IMRT-APBI = intensity modulated radiation therapy accelerated partial breast irradiation; IORT = intraoperative radiotherapy; EB = electron beam; PAPBI = preoperative accelerated partial breast irradiation.

[a] Statistically significant difference.

[b] 1440 total patients treated.

[c] 1070 total patients assigned to receive PBI, of which 1034 had cosmetic data available at earlier timepoint(s).

[d] 1721 total patients assigned to receive IORT.

External beam radiation therapy

Similar to the experience with brachytherapy, there has been a learning curve with external beam PBI as this technique has developed. Suboptimal cosmetic outcomes were reported in some early studies (24–26). most notably the RAPID trial which randomly assigned 2135 women to receive CF-WBI or hypofractionated WBI (H-WBI) versus external beam APBI using a 3D-conformal technique (3D-APBI) at 38.5 Gy in 10 bid fractions. Interim toxicity and cosmetic analyses were published after a median follow-up time of 36 months, when fair and/or poor cosmesis was noted to be significantly increased in women treated with 3D-APBI as assessed by trained nurses (29% vs. 17%; $p < 0.001$), patients (26% vs. 18%; $p < 0.0022$), and physicians (35% vs. 17%; $p < 0.001$) (25). Updated analysis revealed a tendency for cosmetic outcomes to worsen over time, with 7 year fair and/or poor cosmesis rates of 36% versus 19%, as assessed by nurses (4). Acute radiation toxicity was less with 3D-APBI, with Grade $\geq$2 toxicities (particularly radiation dermatitis and breast swelling) noted in 28% vs. 45% ($p < 0.0001$) for WBI. Late toxicity, however, was more common with 3D-APBI, with Grade $\geq$2 toxicities (particularly induration and telangiectasia) noted in 32% vs. 13% ($p < 0.001$). A small analysis of 60 patients treated with this technique found that risk for fair and/or poor cosmetic outcome was correlated with the ratio of the planning tumor volume to the whole breast volume, as well as the ratio of the volume of breast tissue receiving 5% and 20% of the prescription dose to the whole breast volume (26). The RAPID trial, however, did not identify treatment-related factors such as high-dose volume that correlated with fair and/or poor cosmetic outcome; instead, it was tumor location, seroma volume, smoking, and age that negatively impacted cosmesis (27).

Further information regarding the toxicity and QOL outcomes achieved with this regimen (3D-CRT, 38.5 Gy in 10 bid fractions) will be gleaned from the IRMA trial, which has been presented in abstract form showing similar concerns for late fibrosis and cosmetic outcome (28), as well as the 73% of PBI patients treated with 3D-APBI on NSABP B39. Initial outcomes demonstrated low rates of toxicity in NSABP B39's 3D-APBI cohort (29), similar to the long-term results of RTOG 0319 (30). Another abstract reporting cosmetic outcome in all patients treated on NSABP B39 found that cosmesis was equal with APBI and WBI as rated by patients, but worse for APBI as rated by physicians (31).

The increased toxicity seen with 3D-APBI may reflect fractionation as well as treatment technique. For example, one study randomly assigned 113 patients to receive 38.5 Gy in 10 fractions via 3D-CRT in once daily versus twice daily fractions, and significantly lower rates of Grade 3 late skin toxicity, Grade 3 subcutaneous fibrosis, and poor cosmetic outcome were seen with the once daily schedule (32). Another small randomized trial has found that a reduced dose of 34 Gy in 10 bid fractions resulted in better cosmetic outcome and fewer late toxicities than HF-WBI $\pm$ boost (20). Another Phase II trial is studying a reduced-

dose 3D-APBI regimen (35 Gy in 10 fractions), delivered once daily (NCT03077841).

The IMPORT LOW study compared HF-WBI (40 Gy in 15 fractions, no boost) with PBI (40 Gy in 15 fractions) using mini-tangents (MT-PBI) with a field-in-field planning technique referred to as forward-planned IMRT; on a third reduced-dose arm, women received 36 Gy in 15 fractions to the whole breast and 40 Gy in 15 fractions to the lumpectomy site (5). The 5 year cumulative incidence of change in breast appearance was lower with MT-APBI versus HF-WBI (35.1% vs. 47.7%, $p < 0.0001$) and breast firmness was similarly less (15.3% vs. 35.3%, $p = 0.024$). No difference was noted in arm or shoulder symptoms. Five year patient-reported outcomes showed the average number of adverse events per person was lower in partial breast arm (33). While this option does not offer the benefits inherent with a shorter treatment time or fewer fractions, it may be preferred for selected patients; for example those in whom the lumpectomy cavity size is prohibitively large for more accelerated techniques. In 2021, the Royal College of Radiologists published an updated consensus statement on postoperative hypofractionated radiotherapy for breast cancer in which they recommended extrapolating the results of Fast-Forward to the PBI context, and "very strongly supported" offering 26 Gy in five fractions over 1 week for PBI (34).

At the University of Florence, 520 patients were randomly assigned to receive CF-WBI + boost versus IMRT-APBI to 30 Gy in five fractions, delivered on non-consecutive days. The IMRT-APBI group had no acute Grade 3 toxicity and significantly less acute Grade 1–2 toxicity than WBI (35). Skin erythema was the most common acute toxicity for both groups, occurring in 19.9% of patients with IMRT-APBI and 66.5% for CF-WBI (any grade). The most common late toxicity was skin fibrosis, occurring in 4.5% of IMRT-APBI patients and 11.2% of CF-WBI patients (any grade). Updated results with median follow-up time of 10.7 years confirmed fewer acute and late toxicities and better cosmesis in the IMRT-APBI group (7). This is particularly reassuring in light of the abovementioned concerns regarding deteriorating cosmetic outcome with time after 3D-CRT ABPI. QOL data was collected on 205 of 520 total patients showing no difference between the two groups at baseline (36). At the end of radiotherapy, the IMRT-APBI group had significantly better physical, role, emotional and social functioning, better body image and future perspective, and better symptom-related QOL (fatigue, pain, dyspnea, insomnia, appetite loss). At 2 years post-treatment, global health status and multiple symptom and functional scores favored the IMRT-APBI arm, including breast and arm symptoms. This study's results are quite promising, and its technique emerged as preferred treatment option at some centers during the COVID-19 pandemic (37). It is worth noting, however, that it was conducted at a single center, so there may be more to learn about nuances to this technique as it is utilized and modified on a more widespread basis. Future analyses of the results achieved at centers utilizing 30 Gy in five fractions delivered on consecutive days (38), or in patient populations with a high percentage of women with large breast size, may clarify if unexpected toxicities are seen in these or other contexts.

An alternative external beam approach has been the development of stereotactic body radiation therapy (SBRT); this technique allows for higher doses to be delivered to potentially smaller target volumes with high dose gradients, thereby allowing for even shorter regimens. For example, a Phase I dose escalation trial has was conducted in which 75 women received breast SBRT starting at 30 Gy in five fractions, increasing by 2.5 Gy per cohort to a maximum prescription of 40 Gy in five fractions, which was calculated to be the equivalent of 60 Gy in 30 fractions (39). With a median follow-up time of 61 months, a total of 11 patients developed fat necrosis (five of which were painful) at a median timepoint of 12.7 months. On multivariate analysis, larger ipsilateral breast volume (1063 cm^3) was associated with development of any fat necrosis, while V45 Gy and two consecutive daily fractions were associated with painful fat necrosis. Long-term cosmetic outcomes demonstrated that 90% of patients had excellent and/or good cosmesis at 3 years with no difference between dose cohorts (40). Recently outcomes from the same group were published evaluating single fraction SBRT; a total of 30 patients were accrued to a dose escalation study (22.5 Gy, 26.5 Gy, 30 Gy) (41). No acute Grade 3 or higher toxicities were noted with 2 late Grade 3 toxicities and 14% ($n = 4$) developing fat necrosis. Similarly, a prospective study from Washington University enrolled 50 patients in a study delivering 20 Gy in a single fraction to the lumpectomy cavity (42). With short follow-up, low rates of toxicity were noted with subsequent studies evaluating MRI linear accelerator delivery of SBRT (43). At this time, initial outcomes with SBRT are promising. However, further study with long term follow-up is needed with concerns existing around the rates of fat necrosis seen in initial studies. Additionally, given the low rates of recurrence seen without dose escalation (3–4% at 10 years), there remains a question of the role of dose escalation; future studies may evaluate if subsets of patients with sub-optimal local control (e.g., triple negative breast cancer) may be better suited for SBRT.

Special circumstances

Ultrashort brachytherapy

Recent scientific efforts have aimed to further reduce the inconvenience of breast radiotherapy while maintaining high tumor control rates with low toxicity and excellent cosmetic outcomes. Ultrashort APBI (uAPBI) is typically delivered in 1 to 4 fractions over 1 to 3 days. Radiobiology

calculations of tumor control probability and late normal tissue effects are important because larger doses per fraction can lead to fibrosis, fat necrosis, telangiectasia, rib fractures, or cosmetic failure. The formulae do have some uncertainty, however, in doses per fraction above 8 Gy. In comparison to whole breast irradiation, APBI and uAPBI expose only a fraction of the volume of normal tissue irradiated, thereby reducing the risk of late complications. Applying the alpha and/or beta for the breast of 4 Gy, 16 Gy in one fraction is calculated as radiobiologically equivalent to 53 Gy in conventional fractionation (44). By comparison, the post-operative irradiation of 34 Gy in 10 fractions over 5 days has a 72.5 Gy EQD2 for an alpha and/or beta of 3 Gy (45).

One of the earliest uAPBI studies was conducted at William Beaumont Hospital, where the single-lumen MammoSite balloon brachytherapy applicator was used to deliver 28 Gy in four fractions over 2 days (7 Gy per fraction), prescribed to 1.0 cm beyond the surgical cavity and delivered using one or three dwell positions. This dose schedule was estimated to be radiobiologically equivalent to WBI plus lumpectomy cavity boost (60 Gy). (46) A total of 45 patients were enrolled and treated. Toxicities reported at 6.2 years median follow-up include one Grade 3 telangiectasia, five chronic asymptomatic fat necrosis, six asymptomatic seromas, and two rib fractures. Locoregional recurrence was zero, cosmesis was good-excellent in 91% and fair in 9%.

More recently, the TRI-fraction Radiotherapy Utilized to Minimize Patient Hospital Trips (TRIUMPH-T) trial was launched in August 2015 to study the toxicity, cosmesis, and actuarial local control rates of a three fraction brachytherapy treatment delivered over 2 to 3 days (47). This multi-institution Phase II trial enrolled 200 patients age ≥45 years with invasive ductal carcinoma (79%), DCIS (14%), and invasive lobular carcinomas (7%) measuring ≤3 cm with positive ER, negative surgical margins, and negative lymph nodes. The dose of 22.50 Gy in three fractions of 7.50 Gy was delivered to a planning treatment volume of 1 to 2 cm beyond the edge of the surgical cavity, depending on the brachytherapy modality utilized (1 cm for SEABT, up to 2 cm for MIBT). HDR brachytherapy was delivered twice daily, separated by 6–8 h, over two sequential treatment days. Radiobiology calculations showed a BED approximated the usual whole breast irradiation dose of 50 Gy in 25 fractions.A total of 63% had SEABT, and 37% had MIBT. At 12 months median follow-up, 90 Grade 1, 23 Grade 2, and three Grade 3 toxicities were reported, experienced by 39% of the patients. Most common were dermatitis, breast pain, and deep-tissue fibrosis. Two patients had infections requiring antibiotics and 2 patients had Grade 3 nonhealing wounds requiring surgical intervention. The incidence and type of complications were similar to other reports after brachytherapy APBI. In the NSABP B-39/RTOG 0413 randomized trial, the 5 day APBI arm experienced 9.6% Grade 3 and 0.5% Grade 4–5 toxicity, and the WBI arm had 7.1% Grade 3 and 0.3% Grade 4–5 toxicity (3).

Updated results of the TRIUMPH-T trial, with 3.6 years median follow-up, were presented at the 2021 American Society of Therapeutic Radiology and Oncology (ASTRO) meeting (48). There were no Grade 4 toxicities observed, with rates of 1.7% for Grade 3 fibrosis and 32% for Grade 1–2 fibrosis at the treatment site. Other reported toxicities included 7.4% Grade 1 hyperpigmentation, 2% Grade 2 telangiectasias, 1.7% symptomatic seromas, 1.7% abscess, and 1.1% symptomatic fat necrosis. There was one rib fracture. IBTR occurred in 2 patients (1.1%) and nodal recurrence in 2 (1.1%). One patient had a contralateral breast cancer and another 2 patients developed separate lung malignancies (48).

The Mayo Clinic has conducted a prospective trial of a similar regimen, 7 Gy per fraction over 3 days to a total dose of 21 Gy using the SAVI applicator for most patients (49). One novel objective of this study was to deliver the radiation very quickly after BCS, so the applicator was placed intraoperatively after confirming negative surgical margins and lymph nodes using frozen section pathologic assessment. Seventy-three women enrolled on this trial, and preliminary outcomes are favorable for toxicity and patient-reported cosmetic and quality-of-life outcomes with a median follow-up time of 14 months.

Multiple studies of uAPBI have also been conducted in Europe. The GEC-ESTRO Breast Working Group performed the Very Accelerated Partial Breast Irradiation (VAPBI) multicenter Phase I-II trial, which included 81 patients treated from August, 2017 to July, 2019 for pT1–2 pN0 invasive carcinomas with clear margins ≥2 mm (50). Thirty-three women received 6.25 Gy for four fractions over 2–3 days, and 48 women received 7.45 Gy for three fractions over 2 days. Thirty-six patients were implanted intraoperatively and 45 post-operatively. The observed acute effects, which were all Grades 1–2, included: 11% dermatitis, 18.5% hematoma, 3.7% infection, 16% pockmarks, and 14.8% pain. At a median follow-up of 20 months, Grade 1–2 induration was 18.5% and Grade 1–2 fibrosis was 2.5%, and telangiectasia was not observed. Cosmetic outcome was good-excellent in 97.5% and fair in 2.5%.

Outcomes from single-fraction MIBT to 16 Gy has also been reported by French investigators (51,52). A retrospective cohort study included 48 women age ≥65 years who received MIBT to 16 Gy in one fraction. (51) With a median follow-up time of 64 months, no IBTR was seen, but 1 patient had an axillary nodal relapse (2.1%). Fourteen patients had Grade 1 toxicity (mostly late fibrosis) but there were no Grade 3 toxicities. Excellent cosmetic outcome was noted in 76% of patients. The prospective Phase II SiFEBI trial enrolled 26 patients to treatment with MIBT to 16 Gy in one fraction prescribed to 2.0 cm beyond surgical clips minus the surgical margin (52). With a median follow-up of 63 months, late toxicity was observed in 5

patients (19.2%), Grade 1 in 3 and Grade 2 in 2 patients (pain and fibrosis). Cosmetic evaluation was excellent in 21 patients (81%) and good for 2 patients (19%) (52). The SiFEBI trial findings suggest minimal impact of treatment on QoL among a cohort of elderly patients (mean age of 77 years) (53). Furthermore, comparison of toxicity, cosmetic outcomes, and recurrence rates for the retrospective cohort who received a single fraction (16 Gy) of APBI to a comparison cohort of patients who received a 10-fraction course of APBI (34 Gy in 10 fractions) revealed no significant differences between the treatment groups (54). The French experience with single-fraction APBI therefore suggests that ultrashort courses of breast brachytherapy may offer an attractive option for treatment de-escalation for breast cancer patient who wish to minimize treatment burden while also reducing the risk of local recurrence.

The University of Virginia (UVA) is also studying a novel single-fraction breast brachytherapy regimen, wherein 12.5 Gy is delivered intra-operatively at a depth of 1 cm using a multi-lumen balloon applicator, which is then removed prior to the patient being awakened from anesthesia (55). The initial Phase I trial at UVA enrolled 28 patients and demonstrated that the treatment was feasible, with average treatment time of 67.2 min, and safe, with no Grade 3+ toxicities and a 21% rate of Grade 2 acute toxicity events (56). One unique advantage to this approach is the opportunity to perform rigorous quality assurance via intraoperative CT imaging, which allows for correction of issues such as nonconformity of the lumpectomy cavity to the applicator surface prior to treatment. A review of the utility of CT imaging in the first 103 patients treated on Phase I and Phase II trials at UVA found that imaging identified need for clinical action like applicator adjustment in 26.2% of patients (57). Outcomes from the first 204 patients enrolled on the Phase II clinical trial with 12 months of follow-up have been reported. Inclusion criteria were age $\geq$45 years, size $\leq$3 cm, and node negative. Adverse events were observed at any grade for 48.0% of patients, including 32.4% Grade 1, 13.2% Grade 2, and 3.4% Grade toxicities among patients. There were no Grade 4–5 toxicities. Most patients (95%) had good or excellent cosmetic outcomes at 12 months (55). These findings suggest favorable outcomes with single-fraction APBI, with additional evidence expected after the Phase II trial is complete and reported.

In summary, there are now several nonrandomized studies demonstrating the efficacy of an ultrashort treatment approach with brachytherapy delivered in courses as short as a single fraction. In addition to the brachytherapy studies described above, small studies that have been conducted to evaluate uAPBI regimens using external beam radiation therapy have contributed additional evidence to support ultrashort treatment approaches (42). uAPBI remains a focus of ongoing research and may represent the next generation breast irradiation modality of choice (58). As promising as a 1 to 3 day option is, future research remains to define the boundaries of how far we can push hypofractionation without sacrificing safety and effectiveness. It is not yet clear what the optimal APBI regimen is for a given clinical scenario, and decision-making must also consider the various treatment delivery alternatives (brachytherapy vs. 3D-CRT vs. IMRT) as well as timing (pre vs. post-lumpectomy; see Preoperative Accelerated Partial Breast Irradiation below).

Noninvasive breast brachytherapy

An alternative delivery mechanism for delivering APBI with Ir-192 utilizes non-invasive breast brachytherapy (NIBB) applicators (59). For each fraction, the breast is compressed in immobilization plates, x-rays are obtained to visualize the tumor bed and surgical clips, simulation is performed and finally treatment is delivered using externally applied round, D-shaped, or conical applicators ranging from 4.5 to 8 cm in diameter. The process is then repeated for the orthogonal axis (i.e., cranial-caudal and medial-lateral). When delivering 3.4 Gy/F, each fraction requires an average of 43 min (range 30–63 min) to deliver, including an average of 14 min of radiation treatment time (range 5–20 min) per axis. A Phase II trial of 40 patients treated with 34 Gy in 10 fractions once daily ($n=29$) or twice daily ($n=11$) found that Grade 1 dermatitis occurred in 53% of patients, Grade 2 dermatitis in 28%, and no patient had acute Grade $\geq$3 toxicity of any type (59). At a median follow-up time of 69 months, the actuarial 5 year freedom from IBTR rate was 93.3 $\pm$ 4.8% (60). Cosmetic outcome at last follow-up was good-excellent in 95% of patients. Grade 1 and 2 telangiectasia developed in 27.5% and 5% of patients, respectively, and was seen more commonly in women with breast compression separation of $>$7 cm during treatment delivery.

A second Phase II trial has also been conducted, in which 40 women received NIBB to a total dose of 28.5 Gy in five once daily fractions (61). Acutely, skin reaction was reported to be Grade 0–1 in 70%, Grade 2 in 27.5% and Grade 3 in 2.5% of patients. Larger breast separation with compression and larger applicator size were associated with increased risk for acute skin toxicity. With a median follow-up time of 14 months, cosmetic outcome remains good-excellent in all patients, one patient developed Grade 2 fibrosis, and no Grade $\geq$3 toxicities were observed. A registry study has also been published examining the outcomes of 252 women treated with NIBB at eight institutions, including both Phase II trials described above (62). Acutely, radiation dermatitis was reported as Grade 0–1 in 77%, Grade 2 in 19%, and Grade 3 in 4% of the whole cohort, with Grade $\geq$2 dermatitis occurring more commonly in women treated with twice daily schedules and/or $\geq$7 cm separation. Late outcomes were evaluable in 191 patients with a median follow-up time of 18 months, and the actuarial freedom from IBTR rate was found to be 98.3% at 2 years, 90.9% at 5 years. Two Grade 3 late toxicities developed, both pain from fat necrosis. Grade 2

toxicity was seen in 8.8% of patients, including telangiectasia ($n=7$), hyperpigmentation ($n=6$), fibrosis ($n=5$), breast pain and/or fat necrosis ($n=4$), volume loss ($n=2$), and seroma ($n=1$). Factors correlating with development of late Grade 2–3 toxicity included twice daily fractionation, first-generation applicators, and breast separation ≥ 7 cm with compression. Cosmetic outcome at last follow-up was good-excellent in 98% of patients.

Permanent seed implantation

Selected centers have also developed expertise in permanently implanting ^{103}Pd seeds into the lumpectomy cavity, utilizing a technique that incorporates some of the brachytherapy fundamentals utilized for permanent prostate seed implantation (63). Permanent seed implantation (PSI) is appealing in that it requires only a one-time procedure to complete all adjuvant breast radiation. Limitations to this technique include the need to follow radiation precautions (i.e., wear a xenoprene breast shield inside the bra for 3 weeks after the procedure if there will be close contact with pregnant women, babies or small children) and geometric requirements of the lumpectomy cavity. Recently, investigators pooled the results of three prospective studies treating a total of 134 women with PSI. With a median follow-up time of 63 months, the 5 year local recurrence-free survival rate was 98.8 ± 1.2% (64). Treatment was well-tolerated, with the most common acute side effect being skin erythema just above the implant, occurring in 42% of patients and affecting daily activities in 6%. Acute moist desquamation at the site occurred in 16% of women. There were relatively few late effects noted, with asymptomatic skin induration seen in 23% of women after 2 years and 39% after 5 years of follow-up. At 2 years and beyond, Grade 1 telangiectasia developed in 19% of women, and Grade 2 telangiectasia in 3%. NSABP/RTOG quality of life questionnaires administered at least 6 months after the procedure revealed that 94% of respondents were "very satisfied" or "totally satisfied" with the treatment (63).

Intraoperative radiotherapy

IORT has been evaluated in two large Phase III trials. The ELIOT trial randomized 1305 women to CF-WBI versus IORT, given as 21 Gy to the 90% isodose line, using 6–9 MeV electrons (65). Patients with 4 or more positive axillary nodes received regional nodal irradiation in addition to WBI, starting 8–12 weeks post-op in the IORT group. This occurred in only 31 IORT patients (5%), and WBI was not administered for other indications. At 5 years, IORT was associated with increased rates of local recurrence (4.4% vs. 0.4%). Long-term results from the study with a median follow up of 12 years confirmed these results, finding IORT to be associated with increased rates of local recurrence (11% vs. 2%, $p < 0.0001$), with no difference seen in overall survival (66). A very low-risk subgroup was identified, consisting of women with Grade 1 tumors <1 cm in size with luminal A molecular subtype and Ki-67 <14. Women with all of these characteristics had 15 year IBTR rates of 8.1% with IORT versus 3.1% with WBI ($p=0.45$). Tumor size >2 cm, Grade 3 histology, Ki-67 >20%, four or more positive axillary lymph nodes, and triple negative or luminal B subtype were associated with increased risk for local recurrence with IORT. Toxicity data was available for 876 women on the ELIOT trial and revealed lower rates of skin toxicity with IORT; specifically, less erythema, dryness, hyperpigmentation, and pruritus (65). There was no difference in fibrosis, retraction, pain or burning. A higher incidence of radiological fat necrosis was seen with IORT.

Another trial, TARGIT-A, randomized 3451 women to receive WBI versus IORT given as low energy x-rays (50 kV maximum) to a dose of 20 Gy at the surface of the lumpectomy cavity, which yields a dose of 5–7 Gy at 1 cm depth (67). Patients could receive IORT at the time of initial surgery (pre-pathology cohort; 21.6% received WBI) or as a second procedure (post-pathology cohort; 3.6% received WBI). Initial outcomes from the study presented 5 year recurrence rates with 29 months of follow up time, finding that IORT was associated with an increase in local recurrence (3.3% IORT vs. 1.3% WBI), though this was within the 2.5% non-inferiority margin of the study (68). Recently, the trial has been updated with longer follow-up; however, the study was not presented in its entirety but rather as two manuscripts that each presented one of the cohorts. The update of the post-pathology cohort found increased rates of local recurrence exceeding the non-inferiority criteria (3.96% vs. 1.05%) (69). For the pre-pathology cohort, local recurrence was seen in 2.11% of women treated with IORT (24/1140) and 0.95% of women treated with WBI (11/1158), which was within the non-inferiority margin (70). With >20% of the pre-pathology IORT patients receiving WBI, it is important for clinicians to understand rates of local recurrence after IORT with and without WBI, which were not presented. The TARGIT-R (retrospective) North American registry study found that the 5 year IBTR rate was 6.6% for all patients ($n=667$), 8% for women receiving IORT alone at the time of lumpectomy ($n=477$), and 1.7% for the "unintended-boost" cohort ($n=116$) which received WBI post-operatively due to unexpected high-risk pathologic features (71). Only 20 women on the TARGIT-R study received delayed IORT and 54 women received IORT as an intended boost with planned WBI; no ipsilateral breast tumor recurrences were seen in these groups.

Regarding treatment-related toxicity, the TARGIT-A trial found similar outcomes in patients randomized to receive 50 kV IORT ± CF-WBI versus CF-WBI (67). No patient had Grade 4 toxicity. The rate of any RTOG Grade 3 toxicity was slightly lower in the IORT group (0.5%

vs. 2.1%, $p=0.002$) and the rate of needing three or more seroma aspirations was higher in the IORT group (2.1% vs. 0.8%, $p=0.012$). There was no difference in the number of patients who had hematoma evacuation, IV antibiotics or surgical intervention for infection, or problems with delayed wound healing or skin breakdown. Detailed patient-reported cosmetic and QOL outcomes were collected for 126 of the 1153 patients on the post-pathology arm of the TARGIT-A trial, excluding any IORT patients who also received WBI. (72) Breast-related QOL was generally more favorable with IORT alone, as were arm concerns at the 1 year timepoint. Global QOL was more favorable patients who received IORT alone at baseline and every subsequent timepoint. On multivariate analysis, patient-reported cosmesis was equal for both groups at all time points (baseline through 5 years). Univariate analysis showed a higher rate of good-excellent cosmesis with IORT alone at the 5 year timepoint (90% vs. 68.4%, $p=0.042$). Additionally, 342 patients treated on the post-pathology arm at two centers consented to have frontal photographs taken at baseline and annually for up to 5 years for a cosmesis sub-study (73). These were assessed for asymmetry, color change and scar visibility using software-based analysis (BCCT. core), which showed better overall cosmesis with IORT at 1 and 2 years post-treatment.

In conclusion, two randomized trials have been conducted comparing different forms of IORT with WBI: one (ELIOT) showed higher local recurrence rates with IORT, and another (TARGIT-A) has not yet been published showing long-term outcomes of all enrolled patients. This raises concern regarding the methodology of the study, as it has previously been noted that "the protocol clearly states that the primary analysis population includes all randomized patients." (74) While the 5 year results of the pre-pathology cohort appear promising, it must be remembered that >20% received WBI, and the 5 year results of the post-pathology cohort appear similar to the rates of local recurrence seen with no radiation in the PRIME II study at 5 years (75). Additionally, the investigators did not provide long-term local recurrence rates but rather local recurrence free survival, which raises concerns regarding composite endpoints (76,77).

Electronic brachytherapy

Electronic brachytherapy (EB) is a technique that uses electrically generated x-rays, typically 50–70 kVp energy, to deliver radiation therapy with multiple commercial devices available (78). Similar to low-energy IORT, limited dose is delivered beyond the first few millimeters, given increasing surface doses at the applicator. For example, at 1 cm from the applicator, the dose with EB is 28%, as compared to 100% with HDR which is often prescribed to 1 cm (79). This raises concerns regarding whether the entire clinical target volume is covered with appropriate dose (8).

EB has been used to deliver PBI in a single fraction intra-operatively, similar to low-energy IORT. Initial reports have demonstrated promising outcomes. A series of approximately 1000 patients treated with EB found a four-year LR of 3.9%, (80,81) which is higher than seen with other PBI techniques including brachytherapy and EBRT. However, it is consistent with the higher rates of LR seen with low-energy IORT in the TARGIT-A trial. Studies of toxicity with the technique demonstrated 5% of patients having significant complications, with an acute toxicity rate of 21% and a chronic rate of 13% (82). These outcomes have been confirmed in additional series (83–85), though no randomized trials have been published to date. EB can also be used to deliver fractionated PBI using applicators similar to SEABT. However, given differences in dose at depth, outcomes from SEABT using Iridium-192 should not be extrapolated to fractionated EB.

Proton therapy

Proton therapy offers the potential to deliver PBI while limiting dose to organs at risk including the heart and lungs. Initial studies found appropriate rates of local control, though concerns regarding increased acute toxicity exist, with data from Massachusetts General Hospital demonstrating severe moist desquamation in 22% of patients at 6–8 weeks (86). Longer-term outcomes have been published, demonstrating the safety and efficacy of proton PBI, though these studies are limited by small numbers of patients with lack of follow-up beyond 5 years, and randomized trials are not available for this modality (87–90). Additionally, one study found increased toxicity and worse cosmetic outcomes with proton therapy in comparison to alternative external beam PBI techniques (87). At this time, novel proton PBI approaches are being evaluating including the use of new field arrangements and intensity modulated proton therapy (IMPT), which may reduce toxicity profiles (91). Finally, it should be noted that ultra-short proton therapy regimens are currently being studied; for example, a three-fraction regimen was evaluated with promising short-term outcomes (92).

Preoperative accelerated partial breast irradiation

Several investigators have explored the option of delivering APBI prior to BCS. It has been hypothesized that preoperative APBI (PAPBI) may confer multiple benefits, including decreasing interobserver variability in target contouring, reducing the volume of tissue irradiated, facilitating the use of APBI in patients undergoing oncoplastic resection, reducing rates of fibrosis due to subsequent surgical resection of irradiated tissue, and introducing the opportunity to assess radiation response by imaging & pathologic criteria (93,94).

For example, a multi-institution Phase II study of PAPBI has been conducted in Europe and published with

a median follow-up time of 5 years (95). A total of 133 women age >60 with unifocal cT1–2 cancer by mammogram and MRI underwent upfront SLNB to confirm pN0 status prior to receiving PAPBI using 3DCRT or IMRT to deliver 4 Gy x 10 fractions bid over one week or 6 Gy x 5 fractions over 1 week. Treatment was well-tolerated, with 65% of patients showing no acute radiation dermatitis, 34% Grade 1 and only 1 patient Grade 2 toxicities. 14% of patients had a post-operative complication such as a hematoma, seroma, or infection. At 5 years, 92% of patients had a good-excellent cosmetic outcome as assessed by the physician, and 82% of patients reported being satisfied or very satisfied with their cosmetic outcome. The proportion of patients with any grade of fibrosis peaked at 1 year (79%), declining to 43% at 5 years. Approximately 90% of patients had either no fibrosis or mild fibrosis from 2 years onward. A total of 5 patients had recurrence of invasive carcinoma or DCIS in the same breast, of which three were invasive deposits along the biopsy tract. The protocol was therefore modified to include excision of the biopsy tract. This study has led to the development of a randomized Phase III trial comparing PAPBI with postoperative APBI, utilizing IMRT to 28.5 Gy in five fractions over 1 week (NCT02913729), and for which consideration is being given to allow treatment with 26 Gy in five fractions over 1 week.

There have been multiple efforts to deliver ablative dose radiotherapy using PAPBI. A Phase I dose escalation study at Duke University which delivered 15, 18, or 21 Gy 10 days prior to lumpectomy yielded no dose-limiting toxicity and good-excellent cosmesis in all patients who did not require adjuvant RT (96). Investigators at the University Medical Center Utrecht delivered 20 Gy x 1 preoperatively and waited 6–8 months before lumpectomy (97). All tumors were estrogen receptor positive and HER2 non-amplified, and 17% of the 36 patients received neoadjuvant endocrine therapy. The rate of pathologic complete response was 33% (5 of 15 patients) who underwent surgery 6 months after PAPBI and 48% (10 of 21 patients) in those who waited 8 months. Studies such as these provide a platform for evaluating radioresponsiveness and interrogation of biological parameters that are modulated by radiotherapy to an intact breast tumor.

Another novel concept is under investigation is utilizing PAPBI for higher risk breast cancers in order to improve pathologic complete response rates and increase the rate of breast conservation. One example is the Phase II randomized NeoAPBI 01 study, which is currently accruing patients with triple negative and luminal B breast cancers for whom breast conserving surgery with good cosmetic outcome is not felt to be feasible (NCT02806258). Patients receive at least six cycles of neoadjuvant anthracycline and/or taxane-based chemotherapy, and those on the experimental arm also receive PAPBI using 3D conformal technique.

Special patient circumstances

Cosmetic breast augmentation

Breast radiotherapy in the context of cosmetic breast augmentation is a topic worthy of special consideration. After BCS, the historically reported rate of capsular contracture with WBI was >50% (98), resulting in many mastectomies for early-stage disease. It is postulated that circumferential exposure of the entire surface area of the implant to radiotherapy results in a migration of fibroblasts that surround the implant and deposit collagen, creating an "encompassing fibrosis." As the collagen builds and contracts it squeezes the implant, making it feel harder, and can displace the implant superiorly towards the clavicle. It should be noted that radiation techniques have improved significantly in recent years, with one modern series showing only 25% of women developing new or worsening capsular contracture after WBI (99).

PBI, however, has the advantage of non-circumferential exposure to a minimal percentage of the surface of the implant, which should reduce the risk of capsular contracture to lower rates than are seen with even modern WBI techniques. The largest reported experience using any form of radiation after BCS in women with cosmetic breast augmentation is a series of 320 augmented women treated at two high-volume brachytherapy centers (100). MIBT was utilized in 263 (84%) and SEABT in 52 patients (16%), with the most common prescription being 34 Gy in 10 bid fractions. With a median follow-up time of over 6 years, the good-excellent cosmesis rate was quite favorable at 97.5%, and only 12 patients (4%) experienced IBTR.

There are challenges to be overcome in utilizing brachytherapy to treat women with breast cancer in the presence of augmentation:

1) Unless the breast cancer is located in the tail of the breast or far periphery away from the implant, the space between the skin surface and the implant is usually just 1 to 2 cm or less. This makes SEABT challenging, as the space is often too narrow for proper placement of applicator brachytherapy devices.
2) MIBT catheters are feasible, but a reproducible insertion method is required to avoid rupturing the implant by the local anesthetic or brachytherapy needles.
3) Therapeutic radiation coverage of the planning treatment volume from the surface of the implant to the dermis with a defined margin of 1 to 2 cm beyond the cavity edge must be reliable.
4) It can be difficult to achieve desired treatment plan parameters, such as dose homogeneity index, skin dose, and at least 90% coverage by the 90% isodose curve.

These MIBT obstacles can be overcome by CT-guided catheter insertion with implant displacement using a template with pre-drilled holes. Brachytherapy treatment planning software displays the pathway for each intended

Table 4
Outcomes achieved with breast conserving surgery followed by radiation in women with cosmetic breast augmentation.

	Method	No. Patients	Years treated	Follow-up (median)	Good/Excellent cosmesis	Capsular contracture	Other late events
Partial Breast Irradiation							
Akhtari et al. (13)	SEABT; 34 Gy in 10 bid fractions	7	2009–2013	32 months	86% (6/7)	None reported	Grade 2 erythema/edema ($n=1$), implant rupture ($n=1$), implant exchange due to age related leakage ($n=1$)
Lei et al. (14)	EB-APBI; 38.5 Gy in 10 bid fractions	16	2008–2012	24 months	81.2% (13/16) patient-reported 93.8% (15/16) physician-reported	0%	Grade 2 fibrosis ($n=1$), painful seroma ($n=1$)
Blitzer et al. (15)	MIBT (82%) SEABT (17%); median 34 Gy in 10 bid fractions	320	2001–2021	74 months	97.5%	9%	Grade 2 fibrosis ($n=2$), Grade 1 telangiectasia ($n=1$), excision of fat necrosis ($n=4$), implant replacement ($n=21$)
Whole Breast Irradiation							
Handel et al. (16)	WBI	26	1981–1994	–	–	Increased Baker Grade in 73% on treated breast vs. 31% nontreated breast ($p<0.05$).	Revision surgery for capsular contracture ($n=8$)
Mark et al. (17)	WBI	21	1989–1994	22 months	43% (9/21)	57% (12/21)	Revision surgery for capsular contracture ($n=7$)
Karanas et al. (18)	WBI	19	1991–2001	–	–	16% (3/19)	Implant-related complications in 58% (11/19), surgical intervention in 16% (3/19)
Gray et al. (19)	WBI	17	1994–2002	36 months	64.7% (11/17) prior to revision surgery	29.4% (5/17)	Implant exchange or removal for severe capsular contracture ($n=3$)
Tadros et al. (20)	WBI	71	2006–2017	16 months	87.4% (62/71)	25% (18/71)	12.7% (9/71) referred for revision surgery. No implant loss.

Some series include women treated with multiple techniques, including mastectomy; only outcomes for those treated with breast conserving surgery followed by radiotherapy are included.

SEABT = single-entry applicator brachytherapy; MIBT = multicatheter interstitial brachytherapy; EB-APBI = external beam accelerated partial breast irradiation; WBI = whole breast irradiation.

catheter site, ensuring that needles do not puncture the breast implant.

Table 4 summarizes published literature concerning the outcomes achieved with various forms of radiation after BCS in women with history of breast augmentation. It can be challenging to interpret data regarding capsular contracture and the need for additional surgeries after BCS in this patient population because age-related implant replacement is an expected procedure following cosmetic breast augmentation, and the techniques and methods of reporting complications vary widely. In summary, however, it is apparent that brachytherapy is a strong alternative to WBI in the presence of breast augmentation, minimizing the risk of capsular contracture. Although there are no large published series of external beam APBI in women with cosmetic breast augmentation, many of the panelists also use IMRT-APBI in this patient population.

Prior breast radiation

The most common management of an in-breast tumor recurrence after prior lumpectomy and whole breast radiation is mastectomy (101). There is, however, emerging data that a second lumpectomy followed by partial breast re-irradiation is safe and effective. Re-irradiation using interstitial brachytherapy currently has the most published data in this setting. The largest experience was reported by Hannoun-Levi et al. (102). The GEC-ESTRO breast cancer working group database was used to create a propensity-score matched cohort analysis with patients who received mastectomy for a second breast cancer event. 377 mastectomy patients were matched to 377 patients treated with lumpectomy and re-irradiation with MIBT. Five-year outcomes for conservative treatment versus mastectomy for overall survival (87% vs. 88%) and incidence of third breast event (3% vs. 2%) were similar between groups.

Other oncologic outcomes including 5 year regional relapse, distant metastasis, disease-free survival, and cancer specific survival were also similar between the two groups. Grade 1–2, 3, and 4 toxicities were seen in 90%, 9%, and 1%, respectively. Additional data was recently complied in a systematic review on second conservative treatment for an in-breast tumor recurrence that summarized outcomes on 13 papers that used brachytherapy (103). The average rate of third in-breast event free survival was about 88% with a range of 63–97%. The average rate of Grade 3 or higher toxicities was 6%. The most common late side effects were skin fibrosis, telangiectasia, hyperpigmentation, and breast pain. In one study, a cumulative radiation dose (initial radiation plus re-irradiation) of greater than 100 Gy on univariate analysis was associated with a higher rate of Grade $\geq$2 complications (104).

The majority of re-irradiation studies, to date, have utilized MIBT with fewer published studies utilizing SEABT, IORT, or external beam radiation (103,105). One notable external beam re-irradiation study was NRG Oncology/RTOG 1014, the only published prospective study conducted in this space (106). Eligibility criteria included an in-breast tumor recurrence of 3 cm or less occurring 1 year or more after initial breast conserving therapy, unicentric by MRI imaging, and without evidence of skin involvement. Recurrent invasive and non-invasive histologic subtypes were included. 3D-CRT was used with 1.5 Gy given twice daily for 30 treatments after second lumpectomy. The 5 year cumulative incidence of breast cancer recurrence and ipsilateral mastectomy was 5% and 10%, respectively. Grade 3 toxicities were seen in 7% and no Grade 4 toxicities were noted. Whether the outcomes are similar or not between various techniques is an area in need of further investigation. Re-irradiation studies have typically used similar margins and dose regimens as one would use for initial therapy. There is currently no data using ultra-hypofractionated regimens in the re-irradiation setting.

Ideal patient selection for conservative management in the setting of an in-breast tumor recurrence is also evolving. A retrospective study on a group of 159 patients, with a median follow-up of 71 months, treated with lumpectomy followed by re-irradiation with brachytherapy showed significantly different third in-breast tumor recurrence risks when stratifying patients by GEC-ESTRO APBI classification risk groups of low, intermediate, or high (107). Six year third in-breast tumor recurrence free rates for low, intermediate, or high-risk groups patients were 100%, 96%, and 93%, respectively. There were no differences by risk groups for relapse free survival or metastasis free survival. Additional studies are needed to assist in ideal patient selection, but the eligibility criteria for RTOG 1014 and GEC-ESTRO APBI risk classifications (Table 5) can provide some guidance.

While there is no Level 1 evidence comparing conservative management after an in-breast tumor recurrence versus mastectomy there is evidence supporting consideration for conservative management of appropriately selected patients after multi-disciplinary discussion and appropriate patient consent.

Consensus recommendations: Patient selection and modality

Updated guidelines regarding patient selection for brachytherapy and external beam PBI are summarized in Table 6. The strongest randomized evidence is in women with ER positive breast cancer (Table 2). However, NSABP B39 included 771 women with ER/PR negative breast cancer, and exploratory post-hoc analysis did not show increased local recurrence with PBI. The 10 year cumulative incidence of IBTR was 7.2% with WBI and 6.5% with APBI (3). Her2 status was not included in this analysis, so the percentage of Her2 amplified women in this ER/PR negative subgroup was not reported.

Nonrandomized studies of PBI for women with triple negative and Her2 amplified breast cancers have shown mixed results, and without a WBI comparison group it is impossible to know if outcomes in higher-risk subtypes would have been different with WBI versus PBI. For example, one multi-institution retrospective review of 582 patients treated with BCS followed by MAPBI used grade, ER/PR, and Her2 status to approximate molecular subtypes and found the 5 year actuarial IBTR rate to be 3.5% for luminal A, 4.1% for luminal B, 5.2% for luminal Her2, 13.3% for Her2, and 11.3% for triple-negative breast cancer (108). Surprisingly, the 5 year RNR rate was 0.3% for luminal A, 4.6% for luminal B, 2.6% for luminal Her2, 34.5% for Her2, and 2.3% for triple-negative breast cancer. Small patient numbers in the luminal Her2 ($n=47$), Her2 ($n=15$), and triple negative ($n=48$) groups are a limiting factor in this analysis, and the majority of Her2 positive women did not receive Her2 directed therapy due the time period in which they were treated. A single-institution analysis of 1486 women treated with BCS followed by SEABT found 5 year IBTR rates were 2.1 for luminal A, 1.5% for luminal B, 4.9% for Her2, and 5.4% for TNBC (109). When outcomes were compared for women with luminal A or luminal B cancers versus those with Her2 positive or triple negative breast cancers, a statistically significant difference was noted in the 5 year IBTR rate (2.1% for luminal A or B vs. 5.1% for triple negative or Her2 positive). These recurrence rates were all quite low. In this patient cohort, 57.7% of Her2 positive patients (71/123) and 55.1% of triple negative patients (65/118) received chemotherapy, and 64.2% of Her2 positive patients received trastuzumab. Other nonrandomized series have similarly shown favorable local control outcomes with PBI in ER negative and Her2 positive breast cancer (110–113).

Systemic therapy has long been known to reduce risk for local as well as distant recurrence, and in the modern era this is particularly relevant for Her2 positive breast

Table 5
Eligibility criteria for RTOG 1014 and GEC-ESTRO APBI risk classifications.

Study	Patient Characteristics	Outcome
RTOG 101,4 (21)	Eligibility criteria: >1 year after initial BCT, tumor ≤3 cm, unicentric by MRI, no skin involvement, negative margins, 0–3 positive axillary nodes without ECE	5 year IBTE 5%
Montagne et al. (22)	GEC-ESTRO low risk: age >50, nonlobular invasive, tumor ≤3 cm, margins ≥2 mm, unicentric and unifocal, no EIC, no LVSI, pN0	6 year IBTE-free survival 100%
	GEC-ESTRO intermediate risk: age >40–50, any histology including ILC and DCIS, tumor ≤3 cm, negative margins <2 mm, unicentric, multifocal within 2 cm, no EIC, no LVSI, pN1mi-pN1a	6 year IBTE-free survival 95.8%
	GEC-ESTRO high risk: age ≤40, tumor >3 cm, positive margins, multicentric, multifocal >2 cm from index lesion, EIC, LVSI, 4 or more positive nodes	6 year IBTE-free survival 92.9%

Patients with at least one intermediate or high-risk factor fall into the corresponding GEC-ESTRO category.

BCT = breast conserving therapy; MRI = magnetic resonance imaging; ECE = extracapsular extension; EIC = extensive intraductal component; LVSI = lymphovascular space invasion; IBTE = in breast tumor event.

Table 6
American brachytherapy society patient selection criteria for partial breast irradiation.

Age	≥45 years[a]
Size	≤3 cm
Histology	All invasive subtypes and ductal carcinoma in situ
Estrogen Receptor	Any
Her2 Receptor	Negative[b]
Surgical Margins	No tumor on ink for invasive, ≥2 mm for ductal carcinoma in situ[c]
Extensive lymphovascular space invasion	Not present
Nodal status	Negative

Due to the rarity of male breast cancer, men are frequently excluded from randomized trials and greatly underrepresented on nonrandomized series reporting breast cancer outcomes. The panel recommends offering PBI to men who have undergone breast conserving surgery and have clinical and pathologic features otherwise appropriate for treatment with PBI.

[a] PBI is permissible for patients age <45, provided that they have luminal A features (ER or PR positive, Her2 nonamplified, and Grade 1–2) and/or low-risk genomic recurrence score results.

[b] PBI is permissible for patients with Her2 positive breast cancers, provided that they receive Her2 directed therapy as recommended by NCCN guidelines.

[c] PBI is permissible for selected patients with DCIS who have negative margins <2 mm, in the context of appropriate multidisciplinary and shared decision-making discussions.

cancer. The NSABP B31 trial compared four cycles of doxorubicin and cyclophosphamide followed by paclitaxel with the same chemotherapy regimen with the addition of 52 weeks of trastuzumab, and found that local or regional recurrence as a first event occurred in 35 of 872 women on the control arm, versus 15 of 864 women who received trastuzumab (114). A prospective multi-institutional study of 406 women with early stage Her2 amplified breast cancer, most of whom receive mastectomy or WBI, found that local recurrence rates were very low in the context of Her2 directed therapy (115).

In summary, regarding molecular subtype, the panel acknowledges that the majority of women treated in randomized controlled trials of PBI versus WBI had ER positive, Her2 negative breast cancer. The rate of ER negativity was approximately 5–10% for most trials, and the combination of ER and PR negativity was reported to be 5% on the GEC-ESTRO trial and 19% on the NSABP B39 trial (Table 2). Since NSABP B39 did not show more favorable outcomes in ER/PR- women with WBI versus APBI, ER positivity is no longer a patient selection criterion for PBI in this revised consensus statement. When PBI is utilized for TNBC, there should be a shared decision-making process that carefully considers the entire clinical picture, including the potential benefits of PBI to the specific patient as well as her other risk factors like younger age, larger tumor size, and LVSI. Her2 status was not reported for some trials, including NSABP B39, and ranged from approximately 2–6% on other trials (Table 2). As such, Her2 negative status is still preferred for treatment with PBI. However, considering the positive impact of Her2 directed therapy on locoregional recurrence rates and the favorable outcomes reported by several small nonrandomized series, the panel does support PBI in selected women with Her2 positive breast cancers provided that they are receiving Her2 directed therapy when appropriate based upon current National Comprehensive Cancer Network guidelines.

Appropriately identifying a minimum age cutoff for PBI is challenging. As summarized in Table 1, most randomized trials of PBI versus WBI have required that women be at least 40 years old to participate, except for the NSABP B39 trial, which allowed women age >18 to participate, and two trials that set a higher minimum age: IMPORT LOW (age ≥50) and Barcelona (age ≥60). Women under age 50, therefore, are underrepresented on most randomized trials, except for NSABP B39 (38% age <50). Additionally, the University of Florence and GEC-ESTRO trials each had approximately 15% of patients age ≤50, and the Hungarian trial reported that 2.3% of patients were age ≤40 (Table 2). None of these trials have identified an age below which IBTR rates are increased with PBI versus WBI, and exploratory analysis of NSABP B39 specifically showed no difference in outcome for PBI versus WBI based upon menopausal status (3). Interestingly, the ELIOT trial (see Intraoperative Radiation Therapy section below) did have enough IBTR events to identify a subgroup of women in whom IBTR rates were <10% at 15 years, but this did not include a minimum age; all risk factors were related to tumor size and biology (66). Young age has long been recognized as a risk factor for breast cancer recurrence, although through means such as ER/PR/Her2 and genomic testing we have learned that, to a certain extent, young age is simply a surrogate for high-risk cancer biology, with more aggressive tumor types occurring more often in younger age groups. Currently available biomarkers and genomic assays may not completely capture all increased recurrence risk associated with young age, however. For example, analysis of locoregional recurrence risk on the NSABP B14 and B20 studies has revealed that OncotypeDx score and age <50 are independent predictors for LRR in women with ER positive, node negative breast cancers (116). Nonetheless, there is sufficient data supporting de-escalation of locoregional therapy in this context to justify several ongoing studies such as LUMINA (NCT01791829), IDEA (NCT02400190), PRECISION (NCT0265375), EXPERT (NCT02889874), PRIME-TIME, and DEBRA (NCT04852887), which are investigating omitting radiation after BCS for younger women (age ≥50–55) with favorable tumor biology as determined by ICH or genomic testing. For this revised consensus guideline, the panel has opted not to invoke a minimum age requirement for treatment with PBI, provided that women age <45 have luminal A features (ER or PR positive, Her2 nonamplified, and Grade 1–2) and/or low-risk genomic recurrence score results.

We adhere to the margin recommendations for invasive cancer (117) and ductal carcinoma in situ (DCIS) (118) put forth by the Society of Surgical Oncology-American Society for Radiation Oncology, without mandating more widely negative margins to offer PBI. The surgical margin requirements for randomized trials of WBI versus APBI have been variable, ranging from no tumor on ink to ≥5 mm, with no apparent difference in IBTR rate on the basis of margin width. (119) Similarly, the CALGB 9343 trial required only no tumor on ink for omission of radiation, (120) although PRIME II did require margins to be negative by ≥1 mm (75). The RTOG 9804 and ECOG-ACRIN E5194 trials both required margins to be negative by ≥3 mm for omission of RT in women with DCIS (121,122); however, margins greater than 2 mm have not been shown to translate into lower IBTR rates. Of note, the American Society of Breast Surgeons 2018 consensus guideline does not recommend routinely re-excising to achieve >2 mm margins for DCIS (123). As such, the panel agrees that it is reasonable to have an informed discussion about PBI with women with DCIS who have a focally close margin, if re-excision is not being recommended.

Regarding lymph node status, the panel recommends limiting APBI to women with negative lymph nodes. Positive lymph nodes were allowed on some randomized trials, but relatively few women with pN1mic and pN1 breast cancer were enrolled (Table 2). Additionally, since the publication of ACOSOG Z11, most women with 1–2 positive sentinel lymph nodes do not undergo axillary lymph node dissection, as WBI with or without elective nodal irradiation is utilized to treat this region. Regarding micrometastases specifically, it should be noted that the IBCSG 23–01 trial randomizing women with pN1mic breast cancer to no further surgery versus axillary lymph node dissection did permit IORT, which was utilized in 19% of patients (124). The authors do not report the outcomes of this group separately, however. A multi-institutional retrospective review compared the outcomes of 835 node-negative patients with 72 pN1mic-pN1a patients who were all treated with BCS followed by MAPBI and found no difference in 5 year actuarial local control (96.3% vs. 95.8%), regional control (98.5% vs. 96.7%), or overall survival (95.4% vs. 89.4%, $p=0.07$) (125). Five year cause-specific survival was significantly higher for node-negative patients (98.7% vs. 91.3%, $p=0.0001$), though without a WBI comparison group the impact of radiation modality is unknown.

Lymphovascular space invasion (LVSI) is a known poor prognostic feature in breast cancer. Studies have shown mixed impact of LVSI on IBTR (126–129), and it is unclear if LVSI is an independent risk factor for IBTR or simply found often in combination with other high risk features (127). LVSI was permitted on most randomized trials of WBI versus PBI (Table 1), though the majority of patients who participated did not have LVSI (Table 2). The low event rates of most of these trials have not yielded patient subgroups with higher IBTR risk with PBI versus APBI, except for the ELOIT trial (66), and LVSI was not one of the risk factors considered in their analysis. In light of the data available at this time, the panel recommends considering the presence of LVSI when deciding upon PBI versus WBI, but has modified prior ABS patient selection criteria (130) to state that PBI can be appropriate in some patients who have LVSI that is not known to be extensive. It should be recognized that there is not a standardized

Table 7
Partial breast irradiation techniques and strength of recommendation.

	Pros	Cons	Recommendation
Multicatheter interstitial brachytherapy	20-year data from RCT Low cost QOL favorable vs. WBI	Training requirements	Strong: appropriate for use on and off protocol
External beam: IMRT	8–10-year outcomes from RCT Noninvasive Value vs. WBI (23,24) Reduced toxicities vs. WBI	Randomized data limited to one single institutional study	Strong: appropriate for use on and off protocol
External beam: 3DCRT	8–10 year data from RCTs Noninvasive Low cost	Worse cosmesis and increased subcutaneous fibrosis in some studies with twice daily fractionation	Strong: appropriate for use and on off protocol, once daily fractionation preferred
Single entry applicator brachytherapy	5-year nonrandomized data Ease of use	Cost	Moderate: appropriate for use on and off protocol
Intraoperative radiotherapy	Single treatment	Higher rates of local recurrence from RCTs and prospective data (ELIOT, TARGIT-A, TARGIT-R) Up to 20% require whole breast irradiation (TARGIT-A) Small margin treated with low-energy 50 kV beams Lack of imaging limits opportunities for quality verification	Weak: appropriate for use on protocol
Electronic brachytherapy	Single treatment	Lack of long-term data from RCT or prospective studies	Weak: appropriate for use on-protocol
Permanent seed implantation	Single treatment	Training and radiation shielding requirements Lack of long-term data from RCT	Weak: appropriate for use on-protocol
Noninvasive breast brachytherapy	Noninvasive	Compression required for treatment delivery Lack of long-term data from RCT	Weak: appropriate for use on-protocol
Stereotactic body radiation	Reduced duration of therapy Noninvasive Potential for dose escalation in patient subsets with suboptimal local control	Potential for increased toxicities Lack of long-term data from RCT or prospective studies	Weak: appropriate for use on-protocol
Proton beam	5 year nonrandomized data Noninvasive	Small number of patients treated High rates of acute toxicity in initial studies Lack of long-term data from RCT	Weak: appropriate for use on protocol

definition for reporting extent of LVSI, however. One definition that has been utilized characterizes LVSI as absent, focal (one focus of LVSI in one tumor block), moderate (more than one focus of LVSI in one tumor block) and extensive (one or more foci of LVSI in more than one tumor block) (131).

Additional selection criteria have not changed relative to previously published ABS guidelines (130), including tumor size and histology. Tumor size <3 cm was a selection criterion for the original clinical trials of PBI, so data for PBI outcomes in women with larger tumors is lacking.

Table 6 outlines parameters beyond which PBI is not recommended off-trial. Panel members recommend considering the entire clinical picture of each patient when deciding on WBI versus PBI, and engaging patients in the decision-making process, particularly when an individual patient has features that have been underrepresented in randomized clinical trials.

Table 7 summarizes the strength of recommendation for each PBI modality. Significant effort and creativity have contributed to the development of multiple techniques for delivering PBI, all sharing a common goal of reducing the extent of life disruption and side effects experienced by women requiring radiation for early stage breast cancer. As described above, these PBI methods do have meaningful differences in terms of factors such as treatment logistics and volume of breast tissue treated. There is also significant variation regarding the extent of clinical studies conducted among PBI options and the results of those trials, both in terms of side effects and local control rates. Prior to treatment with modalities demonstrated to have a higher recurrence rate in randomized trials, such as IORT, an informed discussion with the patient balancing the risks and benefits of treatment should be performed. In 2019, the ABS published guidelines focusing specifically on IORT, which did not recommend this modality outside of prospective trials (132). The panel has concluded that there has not been enough additional data published since that time to justify changing this recommendation. Similarly, for novel PBI methods with published but nonrandomized data, consideration should be given to treating on trial and an informed discussion should be held with the patient regarding the currently available data while balancing the risks and benefits specific to that patient.

Conclusion

Options and indications for APBI have expanded significantly over the past several decades. With ongoing research exploring options such as ultrashort and preoperative APBI, the role of this technique will likely continue to grow. It is important for radiation oncologists to understand how to select patients who are best treated with APBI, the pros and cons of various APBI methods, and the techniques required to execute their chosen method appropriately in order to provide patients with the best outcomes.

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