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CLINICAL TRIALS (JE LANG, SECTION EDITOR)

Partial-Breast Irradiation: Review of Modern Trials

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Abstract

Purpose of Review Following partial mastectomy, whole-breast irradiation (WBI), delivered over 3 to 6 weeks, has been the standard adjuvant radiation approach for early-stage breast cancer. A growing body of literature over the past decade has suggested that irradiation of the partial breast, including the tumor bed plus a margin, may be a suitable alternative for appropriately selected patients. The use of partial breast irradiation (PBI) has been studied in multiple prospective randomized trials, now with up to 10 years of follow-up, establishing similar safety and efficacy compared with WBI. Advantages of PBI include (1) reduced treatment duration, (2) potential reductions in treatment-related toxicity, (3) improved cosmetic outcomes, and (4) reduced costs. The purpose of this article is to review appropriate patient selection criteria, clinical and toxicity outcomes data, clinical consensus practice guidelines, and the various PBI techniques.

Recent Findings The National Surgical Adjuvant Breast and Bowel Project (NSABP) B39/Radiation Therapy Oncology Group (RTOG) 0413 study (NRG Oncology) is the most recently published (abstract form only) prospective randomized trial comparing PBI using 3D conformal external beam radiation therapy (3D-CRT, 38.5 Gy/10 fractions, twice daily) or brachytherapy (interstitial catheters or applicator based, 34 Gy/10 fractions, twice daily), vs. WBI (50 Gy ± tumor a bed boost). With a median follow-up of 10.2 years, the 10-year ipsilateral breast tumor recurrence-free interval was 95.2% vs. 95.9% for PBI and WBI, although it did not meet the statistical significance for equivalence. Similarly, the randomized trial of accelerated partial breast irradiation using 3-dimensional conformal radiotherapy (RAPID) trial is a prospective randomized trial comparing primarily 3D-CRT (38.5 Gy/10 fractions, twice daily) with WBI, (42.5 Gy/16 daily fractions or 50 Gy/25 daily fractions ± tumor bed boost). Rates of ipsilateral breast tumor recurrence (IBTR) at 8 years were not statistically significantly different (PBI vs WBI, 3% vs. 2.8%; HR = 1.27; 90% VI, 0.84–1.91).

Summary There is a growing body of literature supporting the use of PBI in appropriately selected patients and its use should continue to increase.

Keywords Breast cancer · Radiation therapy · APBI · Partial-breast irradiation · Whole-breast irradiation

Introduction

Breast conservation therapy (BCT) consisting of partial mastectomy followed by adjuvant whole-breast irradiation (WBI) represents a standard of care for early-stage breast cancer [1, 2]. Omission of adjuvant radiation therapy after partial mastectomy has consistently demonstrated higher rates of local recurrence and meta-analyses have demonstrated higher breast cancer mortality without its use [1, 2]. Historically, WBI has been delivered over 6–7 weeks including a tumor bed boost. Protracted radiotherapy schedules may be one reason why patients choose mastectomy or why up to 20% of patients who undergo partial mastectomy forgo adjuvant radiation therapy [3–5]. More recently, there has been increased utilization of hypofractionated whole-breast irradiation

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(HWBI) delivered over 3–4 weeks. HWBI has been shown to have equivalent outcomes compared to standard WBI with 10 years of follow-up [6, 7, 8•]. HWBI is now recommended as a standard approach for most women undergoing breast conservation for those patients with ductal carcinoma in situ (DCIS)/early-stage cancers. However, data on patterns of failure in patients treated with either conventional WBI or HWBI have demonstrated that the majority of breast recurrences are observed in close proximity to the index lesion, suggesting that irradiation of the entire breast may not be necessary in all patients [9].

The use of partial-breast irradiation (PBI) is supported by a growing body of prospective data and expert consensus panel guidelines. Partial-breast irradiation, which involves irradiation of the tumor bed plus a variable margin of adjacent uninvolved adjacent breast tissue (depending on the PBI technique), offers the potential for shortened treatment duration and decreased toxicity, with similar efficacy outcomes in appropriately selected patients [10••, 11••, 12•]. Multiple treatment delivery techniques for PBI have been developed including interstitial catheter-based brachytherapy, applicator-based brachytherapy, and external beam radiation therapy using 3D conformal external beam radiation therapy (3D-CRT) or intensity-modulated radiation therapy (IMRT) delivered over 1 to 3 weeks [12•]. The purpose of this review is to summarize appropriate patient selection criteria, prospective randomized data, the various PBI techniques, and potential future directions for PBI.

Patient Selection

Based upon expert consensus opinion and eligibility criteria as well as results from prospective randomized trials, recommendations for appropriate patient selection criteria have been provided by several organizations including (1) the American Society for Radiation Oncology (ASTRO), (2) the American Brachytherapy Society (ABS), (3) the American Society for Breast Surgeons (ASBrS), and (4) the Groupe Europeen de Curietherapie-European Society for Radiotherapy and Oncology (GEC-ESTRO) [12•, 13•, 14, 15•]. Criteria for eligibility for PBI by expert consensus guidelines are summarized in Table 1. There is variability among the clinical guidelines with respect to patient age, nodal status, histology, and margins.

The updated ASTRO consensus panel guidelines identify patients who are aged ≥ 50 with invasive ductal or invasive lobular carcinoma, tumor size ≤ 3 cm, ≥ 2-mm margins, any estrogen receptor status, and with up to limited/focal lymphovascular space invasion (LVSI) as suitable candidates for the application of PBI off protocol [15•]. Furthermore, patients aged 40–49 with invasive ductal carcinoma, tumor size ≤ 3 cm, with ≥ 2-mm negative margins, no LVSI, estrogen positive, and unifocal tumor are also suitable for PBI. Finally, patients with low-risk ductal carcinoma in situ (DCIS) as defined by the eligibility criteria for the RTOG 9804 phase III trial, including screen-detected, low or intermediate nuclear grade, ≤ 2.5 cm, and with ≥ 3-mm negative margins are

Table 1 Suitable or low-risk candidates for PBI by expert consensus guideline

Criteria	ASTRO	ABS	ASBrS	GEC-ESTRO
Age	- ≥ 50 years - 40–49 years without - Tumor size 2.1–3.0 cm - Limited/focal LVSI - ER (−) - Invasive lobular	≥ 45 years	≥ 45 years	≥ 50 years
Margins	≥ 2 mm	No tumor on ink	No tumor on ink	≥ 2 mm
Tumor size	≤ 3 cm	≤ 3 cm	≤ 3 cm	≤ 3 cm
Histology	Any	Any	Any	Invasive ductal only
Estrogen receptor	(+) or (−)	(+) or (−)	(+) or (−)	(+) or (−)
Nodal status	Negative	Negative	Negative	1–3 positive lymph nodes
LVSI	Limited	No	Focal	No
Other factors	Extensive intraductal component ≤ 3 cm	Unifocal tumor	Multifocal ≤ 3 cm	Unifocal tumor No extensive intraductal component
DCIS	Screen detected ≥ 3-mm margins ≤ 2.5-cm tumor size Grade 1 or 2	≥ 2-mm margins ≤ 3-cm tumor size	≥ 2-mm margins ≤ 3-cm tumor size	No

ASTRO, American Society for Radiation Oncology; *ABS*, American Brachytherapy Society; *ASBrS*, American Society of Breast Surgeons; *GEC-ESTRO*, Groupe Europeen de Curietherapie-European Society for Radiotherapy and Oncology; *ER*, estrogen receptor; *LVSI*, lymphovascular space invasion

considered suitable candidates for PBI per the ASTRO consensus guidelines.

The updated ABS consensus guidelines identify acceptable criteria for PBI as patients who are ≥ 45 years old, tumor size ≤ 3 cm, invasive ductal or lobular histology or pure DCIS, negative surgical margins (for invasive cancer), and ≥ 2-mm negative margins (for DCIS), any estrogen receptor status, negative LVSI, and negative lymph nodes [12•]. Note that the age cutoff per the ABS guidelines is slightly lower than the ASTRO recommendations. The original Hungarian randomized trial noted increased rates of local recurrence in younger patients undergoing PBI and later amended their criteria to include women aged ≥ 50 years [16]. However, the GEC-ESTRO trial had 15% of patients age 40–50 years old and did not observe a significantly higher rate of ipsilateral breast tumor recurrence (IBTR) [17••]. Similarly, the University of Florence randomized trial also included patients aged ≥ 40 years and also did not observe higher rates of IBTR in younger patients [10••]. Given the results of these studies, the ABS has recommended patients aged ≥ 45 years as acceptable for PBI, but further mature data from clinical trials will help to identify optimal age cutoffs [12•]. Similar to the WBI and mastectomy literature, estrogen receptor–negative tumors have also demonstrated higher rates of local recurrence in PBI clinical trials; however, there is no data to suggest that rates of local recurrence are higher with PBI compared with WBI for estrogen receptor–negative tumors [18–20]. Therefore, the inclusion of estrogen receptor–negative tumors for PBI remains for both the ASTRO (if 50 years or older) and ABS guidelines [12•, 15•].

PBI Techniques

The majority of available prospective data compare PBI vs. WBI, whereas there is limited prospective data directly comparing different PBI techniques. However, recent consensus guidelines do provide some recommendations regarding PBI techniques. For example, the updated ASTRO consensus guidelines recommend the use of low-energy intraoperative radiation therapy (IORT) only on clinical trial due to the higher rates of local recurrence observed on the TARGIT-A trial [15•, 21]. The updated ABS guidelines recommend multicatheter interstitial brachytherapy (MIB) and IMRT as the techniques with the strongest supporting evidence, in addition to moderate recommendations for 3D-CRT and applicator-based brachytherapy (AB), and weak recommendations for IORT, protons, and electronic brachytherapy [12•]. The NSABP B-39/RTOG 0413 (NRG Oncology) trial allowed for the use of 3D-CRT, MIB, and AB as PBI techniques. Although preliminary results are now available, the study was not powered to detect differences between the techniques [11••]. Table 2 summarizes inclusion criteria for prospective randomized trials utilizing PBI.

Interstitial Brachytherapy

Multicatheter interstitial brachytherapy is a PBI technique in which catheters are implanted within and around the lumpectomy cavity. Typically, high-dose rate (HDR) radiation therapy is utilized but low-dose rate (LDR) and pulsed-dose rate (PDR) can be used as well [22, 23]. There are now three prospective randomized trials that included MIB as the PBI technique compared with WBI [11••, 17••, 24]. The first randomized trial is from the National Institute of Oncology in Hungary in which women were randomized to 50 Gy WBI or PBI after breast-conserving surgery [24]. PBI techniques included 36.4 Gy HDR MIB (69% of patients) or 50 Gy electron beam irradiation (31% of patients). With a median follow-up of 10.2 years, the 10-year local recurrence rate was 5.1% vs. 5.9% ($p = 0.77$) for WBI and PBI, respectively. There was no statistically significant difference between WBI and PBI in 10-year overall survival (OS) (82% vs. 80%), cancer-specific survival (CSS) (94% vs. 92%), and disease-free survival (DFS) (84% vs. 85%), respectively. Patient reported excellent and good cosmesis was significantly higher with PBI (81% vs. 63%; $p < 0.01$).

Similarly, the GEC-ESTRO trial, which was a randomized prospective non-inferiority study that included patients with low-risk invasive ductal carcinoma or DCIS and randomized them to adjuvant WBI or PBI using MIB [17••]. With a median follow-up of 5 years, the 5-year cumulative incidence of local recurrence was 0.9% vs. 1.4%, $p = 0.42$ for WBI and PBI, respectively. 5-year OS and DFS were also not significantly different. There was no significant difference in Grade 2–3 skin toxicity, subcutaneous tissue toxicity, or severe (Grade 3) fibrosis between the two techniques [25]. An analysis of quality of life at 5 years demonstrated no significant difference in quality of life with PBI and significantly worse breast symptom scores after WBI compared with PBI at 3 months [26].

Finally, the recent results of the NSAPB B-39/RTOG 0413 trial, which have been presented in abstract form, also support the use of MIB [11••]. This trial allowed the use of MIB (34 Gy in 3.4 Gy/fx twice daily) as one of the PBI techniques, as well as AB and 3D-CRT external beam radiation therapy (71% of PBI patients). Eligibility criteria for the trial included patients with 1–3 positive lymph nodes (representing 10% of the patient population). The study found that the 10-year IBTR-free interval was 95.9% with WBI vs. 95.2% with APBI, although it did not meet the statistical significance for equivalence as the trial required the 90% confidence interval to lie between 0.667 and 1.5 and it was 0.94–1.58. The intention-to-treat and as-treated analyses could not refute the

Table 2 Eligibility criteria for prospective randomized trials evaluating PBI

Trial	Eligibility criteria	PBI technique
National Institute of Oncology (Hungary) Polgar et al. Number of patients 258	• ≤ 2-cm tumor size • pN0–1mic • Grade 1–2 • Invasive ductal carcinoma • No tumor on ink margins • No extensive intraductal component • ER (+) or (−)	MIB
GEC-ESTRO Strnad et al. Number of patients 1184	• Age ≥ 40 years • ≤ 3-cm tumor size • pN0–1mic • ≥ 2-mm margins (≥ 5 mm for ILC or DCIS) • Negative LVSI • ER (+) or (−)	MIB
NSABP B-39 Vicini et al. Number of patients 4216	• ≤ 2-cm tumor size • pN0–1 • No tumor on ink margins • ER (+) or (−)	MIB, AB, 3D-CRT
RAPID Trial Whelan et al. Number of patients 2135	• Age ≥ 40 years • ≤ 3-cm tumor size • Invasive ductal or DCIS • No tumor on ink • ER (+) or (−)	3D-CRT
IMPORT LOW Coles et al. Number of Patients: 2,018	• Age ≥ 50 years • pN0–1 • Invasive ductal carcinoma • ≥ 2-mm margins • ER (+) or (−)	3D-CRT
Florence Trial Livi et al. Number of Patients: 520	• Age ≥ 40 years • ≤ 2.5-cm tumor size • pN0–1 • ≥ 5-mm margins • ER (+) or (−)	IMRT
TARGIT-A Vaidya et al. Number of Patients: 3,451	• Age ≥ 45 years • Invasive ductal carcinoma •	IORT with 50 kV X-rays
ELIOT Veronesi et al. Number of patients 1305	• Age 48–75 • ≤ 2.5-cm tumor size	IORT with electrons

PBI, partial-breast irradiation; *ER*, estrogen receptor; *MIB*, multicatheter interstitial brachytherapy; *GEC-ESTRO*, Groupe Europeen de Curietherapie-European Society for Radiotherapy and Oncology; *ILC*, invasive lobular carcinoma; *DCIS*, ductal carcinoma in situ; *LVSI*, lymphovascular space invasion; *NSABP*, National Surgical Adjuvant Breast and Bowel Project; *3D-CRT*, 3-dimensional conformal radiotherapy; RAPID, randomized trial of accelerated partial-breast irradiation using 3-dimensional conformal radiotherapy; *IMPORT LOW*, intensity-modulated partial organ radiation therapy LOW trial; *IMRT*, intensity-modulated radiation therapy; *TARGIT*, targeted intraoperative radiotherapy; *ELIOT*, electron intraoperative radiotherapy; *AB*, applicator brachytherapy

hypothesis that PBI was inferior and could not declare that WBI and PBI were equivalent in controlling local in-breast tumor recurrence. However, the absolute difference in the 10-year cumulative incidence of IBTR was only 0.7%. A statistically significant difference in recurrence-free interval (RFI) was noted favoring WBI (93.4% WBI vs. 91.9% APBI, $p = 0.02$). However, there were no statistically significant differences in distant disease-free interval (DDFI) ($p = 0.15$), OS ($p = 0.35$), or DFS ($p = 0.11$). Grade 3 toxicity (9.6% vs. 7.1%) and Grade 4–5 toxicity (0.5% vs. 0.3%) were modestly higher with PBI. In other trials, toxicity was found to be lower with the increased use of MIB or AB and alternatively, the use of IMRT, which will be discussed further below. Given the results of these three prospective randomized trials, suggesting similar efficacy and significantly improved cosmesis on the Hungarian trial and reduced late toxicity in the GEC-ESTRO trial, the ABS has given MIB a strong recommendation as an ideal technique for PBI [12•].

Applicator-Based Brachytherapy

Applicator-based brachytherapy includes placement of single lumen, multilumen, strut, or alternative applicators within and/or surrounding the lumpectomy cavity, with a common dose/fractionation of 34 Gy in 10 fractions delivered twice daily separated by 6 h (HDR brachytherapy) [12•]. The majority of data for this technique comes from prospective registries or retrospective series. The use of the MammoSite® balloon catheter is supported by data from the ASBrS MammoSite® registry trial, which demonstrated a low rate of local recurrence at 5 years (3.8%) [27•]. The toxicity profile was good, with the rate of good or excellent cosmesis at 7 years being 90.6%, fat necrosis at 2 years 2.5%, and infection at 2 years 9.6% [28]. While previous population-based analyses have suggested potentially higher toxicities with brachytherapy, prospectively collected data such as the ASBrS MammoSite® Registry trial have not confirmed these findings [29, 30]. A matched pair analysis of 3009 patients treated with WBI or PBI (interstitial catheter or the MammoSite® balloon) matched by age, stage, and estrogen receptor status demonstrated no significant difference in 10-year IBTR (4% vs. 4%; $p = 0.11$), regional recurrence (1% vs. 1%; $p = 0.20$), DFS (93% vs. 91%; $p = 0.10$), and OS (83% vs. 75%; $p = 0.34$) for WBI and PBI, respectively [31]. These results were confirmed with a second matched pair analysis [32]. Clinical outcomes with multilumen and strut applicators also suggest excellent clinical outcomes with decreased dose to the skin and chest wall [33–35]. With the results of the NSABP B-39/RTOG 0413 trial, which included patients receiving AB, there is now prospective randomized evidence to support its use as well, although as previously mentioned the NSABP B-39/RTOG 0413 trial was not designed to compare outcome based upon individual PBI techniques [11••].

External Beam PBI

External beam PBI offers the benefit of not requiring an additional invasive procedure as with the use of MIB or AB brachytherapy. The initial modern external beam technique (the NIH Hungary trial used a limited electron field) employed 3D-CRT delivered with multiple non-coplanar fields [11••, 24]. However, some prospective studies have suggested that PBI delivered in this fashion may have higher rates of toxicity and inferior cosmetic outcomes [11••, 36, 37]. RTOG 0319 was a Phase I/II clinical trial which included patients with Stage I or II invasive ductal or lobular carcinoma with tumor size ≤ 3 cm, ≤ 3 positive lymph nodes, and negative margins treated with 3D-CRT PBI, 38.5 Gy in 3.85 Gy/fx twice daily [36]. Initial cosmetic outcomes were favorable, but with further follow-up, good or excellent cosmesis dropped from 82% at 1 year to 64% at 8 years. Similarly, on the RAPID study, women were randomized to 3D-CRT (38.5 Gy in 3.85 Gy/fx twice daily) or WBI (42.5 Gy in 2.67 Gy/fx daily or 50 Gy in 2 Gy/fx daily ± tumor bed boost) [37]. The rate of IBTR at 8 years was 3.0% and 2.8% for PBI and WBI, respectively. Acute toxicity (within 3 months of treatment start) was significantly less with PBI compared with WBI (≥ Grade 2, 28% vs 45%, $p < 0.001$). The initial publication reported rates of late adverse cosmesis at 3 years graded by trained nurses (29% vs. 17%; $p < 0.001$), by patients (26% vs. 18%; $p = 0.002$), and by physicians (35% vs. 17%; $p < 0.001$) were significantly worse with PBI compared with WBI, respectively. On updated results, late toxicity, including breast induration and telangiectasia (≥ Grade 2, 32% vs 13%, $p < 0.001$ and Grade 3, 4.5% vs 1.0%, $p < 0.001$) and adverse cosmesis at 5 years (32% vs 16%, $p < 0.001$) was significantly higher with PBI compared with WBI [38••]. However, on NSABP B-39/RTOG 0413, which utilized 3D-CRT in patients who underwent external beam PBI, no significant increase in Grade 3–5 toxicity was noted compared with WBI [11••]; however, the study was not designed to look at differences in toxicity based on APBI technique. Recently, data from 950 patients from NSABP B-39/RTOG 0413 who completed the patient reported outcomes (PRO) portion of the study and had follow-up data were reported on [39]. PBI was associated with reduced fatigue ($p = 0.011$) and did not meet criteria for cosmesis equivalence; cosmesis was equivalent in patients receiving chemotherapy but not for those patients that did not receive chemotherapy. The higher rates of toxicity and worse cosmetic outcomes with 3D-CRT observed in some other trials may be attributed to the use of twice daily fractionation and the addition of larger margins, which may be

mitigated by the use of once daily fractionation and IMRT with image guidance to reduce treatment margins.

3D-CRT PBI does have the advantage of being a cost-effective PBI technique compared with other PBI and WBI techniques [40]. However, utilization of a 5 fx IMRT course was shown to be cost effective compared with WBI delivered with 3D-CRT in 15 fx [41]. Therefore, while 3D-CRT PBI has good evidence for similar clinical efficacy, the role of 3D-CRT PBI will need to be further elucidated in light of data supporting IMRT with respect to similar clinical outcomes and reduced toxicity/improved cosmesis as compared with WBI.

There is strong level I evidence supporting IMRT external beam PBI, with similar clinical outcomes and significantly improved cosmesis compared with WBI. The University of Florence trial included 520 women, aged > 40 years with invasive ductal or lobular carcinoma, with tumor size ≥ 2.5 mm, and randomized them to WBI (50 Gy in 2 Gy/fx daily ± tumor bed boost) or PBI (30 Gy in 6 Gy/fx every other day) with IMRT [10••]. The PBI arm utilized a 1-cm clinical target volume and 1-cm planning target volume margin with no daily image guidance. With a median follow-up of 5 years, IBTR (1.5% vs. 1.5%; $p = 0.86$) and OS (96.6% vs. 99.4%; $p = 0.06$) were not significantly different between WBI and PBI, respectively. Patients treated with PBI experienced significantly improved acute toxicity ($p = 0.0001$), late toxicity ($p = 0.004$), and cosmesis ($p = 0.045$). A recent study from the Cleveland Clinic demonstrated the feasibility of further reducing toxicity with this approach using image guidance with cone beam CT as well as breath hold to limit breast motion, reducing target volumes [41]. Similarly, results of the intensity-modulated partial organ radiotherapy (IMPORT) LOW trial support PBI with IMRT compared with hypofractionated WBI [42]. This prospective, randomized, non-inferiority study included women aged ≥ 50 years with invasive ductal carcinoma, tumor size ≤ 3 cm, with 0–3 positive lymph nodes, and negative margins ≥ 2 mm. Patients were randomized to 40 Gy in 2.67 Gy/fx daily WBI, 36 Gy WBI with boost to 40 Gy in 2.67 Gy/fx to the partial breast (reduced-dose group), or 40 Gy in 2.67 Gy/fx daily PBI. PBI was delivered using field-infield IMRT with standard tangential beams or "mini-tangents." Clinical outcomes were non-inferior with the reduced-dose and PBI groups. Adverse events were similar between the three groups, but change in breast appearance ($p = 0.007$) and breast harder or firmer ($p < 0.0001$) were significantly better with PBI compared with WBI.

Intraoperative Radiation Therapy

Intraoperative radiation therapy (IORT) involves delivery of radiation therapy to the lumpectomy cavity using a single fraction of radiation. The most well-studied IORT techniques in breast cancer include low-energy X-rays (50 kV) or electrons (3–12 MeV) [43]. With the use of low-energy X-rays and electrons, concerns regarding delivery of dose beyond the surface of the cavity arise [43]. Dosimetric studies demonstrate that about 5–7 Gy of dose is delivered at 1-cm depth with low-energy X-rays, which may be inadequate given that the area of highest concern is within 1 cm of the lumpectomy cavity [43–45]. With the properties of lower energy X-rays or electrons, attempts to deliver dose to a deeper depth would result in unacceptably high surface doses and also the potential for toxicities such as fat necrosis [43, 44]. Finally, without the use of image guidance, it is unknown whether a deep lumpectomy cavity may be abutting the chest wall, leading to higher than expected doses to the chest wall or the left ventricle of the heart for a left-sided breast cancer (unless shielding is utilized) [43–45].

There are two randomized trials comparing IORT and WBI. The first, TARGIT-A, is a prospective, randomized, non-inferiority study including women aged ≥ 45 years, with early-stage invasive ductal carcinoma treated with WBI (50 Gy in 2 Gy/fx daily) or 50 kV X-ray IORT, 20 Gy in 1 fx [21]. There was a significantly increased rate of local recurrences at 5 years with IORT compared with WBI (3.3% vs. 1.3%; $p = 0.04$), although it was within the non-inferiority threshold. Patients with margins ≤ 1 mm, extensive in situ component, or incidental invasive lobular carcinoma on final pathology were specified to undergo additional adjuvant WBI in addition to IORT, and some centers specified close margins (1–10 mm), several positive lymph nodes, and extensive LVSI as criteria to add adjuvant WBI. In the entire cohort, 15.2% of patients underwent adjuvant WBI after IORT due to adverse pathology (21.6% pre-pathology (IORT given at time of lumpectomy), 3.6% post-pathology (IORT as a second procedure after lumpectomy)). In the pre-pathology cohort, the difference in local recurrence with IORT was not found to be statistically lower, but this was not a primary pre-specified endpoint, but a secondary analysis. The majority of patients on the trial had a median follow-up of 2 years; however 5-year local recurrence outcomes are reported and have not been updated since.

The ELIOT trial included women age 48–75 with early-stage breast cancer, tumor size ≤ 2.5 cm, and randomized them to WBI (50 Gy in 2 Gy/fx daily) or IORT with 3–12 MeV electrons (21 Gy in 1 fx) [46•]. The 5-year rate of IBTR was significantly higher with IORT compared with WBI (4.4% vs. 0.4%; $p < 0.0001$), with no significant difference in OS and significantly fewer skin side effects with IORT ($p = 0.0002$). However, an analysis of electron IORT demonstrated a 1.5% rate of local recurrence at 5 years for suitable PBI patients [47].

IORT provides advantages including not requiring additional procedures, completion of adjuvant therapy at the time of surgery, and the potential to be a cost-effective PBI

technique [43, 48]. However, when accounting for the costs associated with management of the increased local recurrences after IORT, the cost of the modality increases and was shown to be potentially higher than other PBI techniques [49]. Unlike IORT, all other randomized trials using PBI have demonstrated no significant difference in local recurrence compared with WBI [12]. Also, at this time, there is no randomized trial available comparing IORT and endocrine therapy alone in patients who meet criteria for omission of adjuvant WBI [50, 51]. IORT has been shown to be safe and efficacious as a tumor bed boost followed by WBI, particularly in the setting of oncoplastic reduction, when postoperative delineation of the surgical cavity for external beam tumor bed boost after WBI is very challenging [52]. Further studies with IORT monotherapy are necessary before it can be considered a standard of care option for patients who do not meet criteria for omission of adjuvant radiation therapy.

Future Directions

Multiple prospective randomized trials, some with over 10-year follow-up, now support the use of PBI in appropriately selected patients [12•]. Increased utilization of techniques such as deep inspiratory breath hold, active breathing control, and image-guided radiation therapy with cone beam CT may allow for further reduction of treatment volumes and therefore a potential reduction in toxicities. Some clinical trials are evaluating condensed WBI into 5 fractions (fx), such as the UK FAST trial (28.5 Gy or 30 Gy in in 5 fx once weekly) and the FAST-FORWARD trial (26 Gy or 27 Gy in 5 fx daily in 1 week) compared with standard WBI fractionations, with good long-term results [53–55]. Comparison of these 5 fx WBI regimens with PBI regimens may be worthwhile. Further, condensed schedules of PBI are also being investigated as well, including a single-fraction preoperative PBI Phase I trial utilizing IMRT with a 1.5-cm margin on the tumor, which demonstrated no dose limiting toxicity or local recurrence at median follow-up of 23 months [56]. A phase II trial utilizing PBI with AB for 2–3 fx has also been published with initial outcomes [57]. Mature data is necessary to support these approaches and future study should focus on identifying appropriate candidates for such techniques.

Conclusion

With thousands of patients included in PBI randomized trials (a greater number than those included in studies comparing standard WBI and HWBI), a robust collection of randomized data now exists to support PBI as an optional approach for appropriately selected women with early-stage breast cancer. Clinical decision-making regarding the use of PBI should be consistent with randomized trial eligibility criteria, expert consensus guidelines, institutional expertise, and patient preference. Techniques with the strongest level I evidence include MIB and IMRT, with moderate recommendation for AB brachytherapy in the absence of robust randomized data. The use of IORT requires further study and based on current data and guidelines should not be recommended outside prospective studies.

Compliance with Ethics Standards

Conflict of Interest Chirag Shah reports grants, personal fees, and others from Varian Medical Systems; grants from VisionRT; and personal fees from Impedimed outside the submitted work. Bindu Manyam, Thomas Julian, and Frank Vicini declare no conflicts of interest relevant to this manuscript.

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- • Of importance
- •• Of major importance

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