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Review

Partial breast irradiation compared with whole breast irradiation: a systematic review and meta-analysis

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Abstract

Background: Early-stage breast cancer is among the most common cancer diagnoses. Adjuvant radiotherapy is an essential component of breast-conserving therapy, and several options exist for tailoring its extent and duration. This study assesses the comparative effectiveness of partial-breast irradiation (PBI) compared with whole-breast irradiation (WBI).

Methods: A systematic review was completed to identify relevant randomized clinical trials and comparative observational studies. Independent reviewers working in pairs selected studies and extracted data. Randomized trial results were pooled using a random effects model. Prespecified main outcomes were ipsilateral breast recurrence (IBR), cosmesis, and adverse events (AEs).

Results: Fourteen randomized clinical trials and 6 comparative observational studies with 17 234 patients evaluated the comparative effectiveness of PBI. PBI was not statistically significantly different from WBI for IBR at 5 years (RR = 1.34, 95% CI = 0.83 to 2.18; high strength of evidence [SOE]) and 10 years (RR = 1.29, 95% CI = 0.87 to 1.91; high SOE). Evidence for cosmetic outcomes was insufficient. Statistically significantly fewer acute AEs were reported with PBI compared with WBI, with no statistically significant difference in late AEs. Data from subgroups according to patient, tumor, and treatment characteristics were insufficient. Intraoperative radiotherapy was associated with higher IBR at 5, 10, and over than 10 years (high SOE) compared with WBI.

Conclusions: Ipsilateral breast recurrence was not statistically significantly different between PBI and WBI. Acute AEs were less frequent with PBI. This evidence supports the effectiveness of PBI among selected patients with early-stage, favorable-risk breast cancer who are similar to those represented in the included studies.

Breast cancer is the most commonly diagnosed malignancy worldwide (1), with the majority of cases detected at an early stage with widespread adoption of screening mammography (2). Among women with early-stage breast cancer who undergo lumpectomy, adjuvant breast radiotherapy reduces both recurrence and breast cancer mortality (3). Radiotherapy historically targeted the whole breast and was delivered daily over 3-5 weeks. For selected tumors with limited risk of recurrence outside of the lumpectomy cavity (4), the underlying hypothesis of partial - breast irradiation (PBI) is that a focused treatment volume around the lumpectomy cavity could provide similar disease control compared with whole-breast irradiation (WBI), improve convenience with an accelerated treatment course completed in approximately 1 week, and reduce adverse events (AEs) by limiting radiation exposure to adjacent normal tissues. Clinical trials involving more than 15 000 women have evaluated this hypothesis, more than threefold the number who participated in seminal clinical trials comparing mastectomy and breast conserving therapy.

Notwithstanding the abundance of high-quality data, difficulty remains in interpreting results with heterogeneous treatment techniques and variable patient selection. This systematic review and meta-analysis assesses the comparative effectiveness and harms of PBI compared with WBI for early-stage breast cancer and how those differences are influenced by patient, tumor, and treatment factors.

Methods

This manuscript was based on a systematic review and meta-analysis of partial breast irradiation for breast cancer funded by the Agency for Healthcare Research and Quality (AHRQ). A key informant panel and a 10-member technical expert panel were established at the beginning to guide the study. The study

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protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO #CRD42021284155) and is available on AHRQ's website (https://effectivehealthcare.ahrq.gov/products/accelerated-partial-breast-irradiation/protocol). The reporting of the manuscript is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statements.

Data sources and search strategy

We searched Embase, MEDLINE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Scopus, and other sources from study initiation through June 30, 2022. An experienced medical librarian developed and executed the literature search strategy, which was peer reviewed (Supplementary Table 1, available online). A Federal Register Notice was posted for this review (https://www.federalregister.gov/documents/2021/11/09/2021-24403/supplemental-evidence-and-data-request-on-partial-breast-irradiation-for-breast-cancer).

Study selection

Eligible studies 1) included adult women (18 years and older) with early-stage breast cancer, defined as a small tumor (≤3 cm) with minimal or no lymph node involvement (N0/1); 2) compared PBI modality (3-dimensional conformal external beam radiation therapy [3DCRT], intensity-modulated radiation therapy [IMRT], multi-catheter interstitial brachytherapy, single-entry catheter brachytherapy, proton radiation therapy, or intraoperative radiotherapy [IORT]) with WBI or another PBI technique; and 3) reported predefined outcomes of interest (cancer outcomes and AEs). Only RCTs and comparative observational studies published in English were included. We excluded studies describing patients with recurrent breast cancer and studies published before 2000 because older radiotherapy techniques are not relevant to current practice. We excluded conference abstracts, in vitro studies, and studies without original data. Independent reviewers, working in pairs, conducted abstract screening and then full-test screening. A third senior investigator resolved any conflicts between the reviewers.

Data extraction and quality evaluation

We developed a standardized form to guide data extraction. Independent reviewers extracted study-level data; a second reviewer audited and resolved conflicts.

For RCTs, the Cochrane Collaboration's Risk of Bias 2 tool was used to evaluate risk of bias (5). For comparative observational studies, we selected and modified items from the Newcastle-Ottawa Scale (6). Evaluation of risk of bias was conducted per outcome per study. One reviewer evaluated risk of bias for all eligible studies; a second reviewer audited and resolved conflicts.

Outcome measures

The prespecified main outcomes were ipsilateral breast recurrence (IBR), cancer-free survival, mastectomy-free survival, overall survival (OS), cosmesis, and AEs. Additional outcomes included quality of life, distant breast cancer recurrence, contralateral breast cancer recurrence, tumor bed IBR, and elsewhere IBR. Supplementary Table 2 (available online) lists the definition of outcomes. In this manuscript, we focus on findings related to IBR, cosmesis, and AEs. For detailed presentations of the other outcomes, please refer to the AHRQ report.

Data synthesis and analyses

All statistical analyses were analyzed based on participants' original allocation group at the beginning of the study. A priori, IORT was not meta-analyzed with other PBI modalities because of its distinctly different approach to treatment planning and delivery.

For binary outcomes, we calculated relative risk (RR) and corresponding 95% confidence intervals (CIs). Cosmesis scales were dichotomized to poor or fair vs good or excellent. For AEs, we calculated the incidence rate ratio (IRR). Meta-analyses were conducted based on length of follow-up: for health outcomes: ≥1 year to 5 years, >5 years to 10 years, over 10 years; for AEs: 3 months or less (acute AE), over 3 months (late AE). The DerSimonian-Laird random effects model with Hartung-Knapp-Sidik-Jonkman adjustment was used to pool effect sizes across studies (7,8). Statistical heterogeneity was evaluated using the I^2 indicator. We conducted prespecified subgroup analyses based on clinical, pathological, and treatment characteristics and risk of bias. We conducted sensitivity analysis by pooling hazard ratio (HR) reported by the studies. One study (9) was completed between 1986 and 1990 with antiquated radiation techniques that are no longer relevant to current practice but otherwise met our eligibility criteria. We included this study in the systematic review but not in the primary meta-analyses. As a sensitivity analysis, this study was combined with the other studies. Two-sided P value less than .05 was deemed statistically significant. Statistical analyses were conducted using Stata version 17.0 (StataCorp LLC, College Station, TX, USA).

Grading strength of evidence

We graded strength of evidence for IBR and cosmesis as "high," "moderate," "low," or "insufficient evidence" following the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews (10). Supplementary Table 3 (available online) describes the approaches.

Results

The literature search identified 6727 citations. Fourteen RCTs (9,11-48) and 6 comparative observational studies (49-57) involving 49 publications and 17 234 patients met the inclusion criteria (Figure 1). Details of the included trials are reported in Supplementary Table 4 (available online). Figures 2 and 4 and Supplementary Tables 5 and 6 (available online) summarize the results of meta-analyses on effectiveness. AEs are summarized in Figure 3. Comprehensive details regarding interventions of the included studies, AEs, secondary outcomes, subgroup analyses, and risk of bias summaries are available in the full-length report with the AHRQ. We found no statistically significant difference between studies with different risks of bias; additionally, sensitivity analyses showed no difference (Supplementary Table 7, available online).

PBI compared with WBI

Eleven RCTs (9,11,22-37,40-47) reported in 26 articles with a total of 10 520 patients (range = 102-4125) evaluated PBI vs WBI. PBI modalities included 3DCRT, IMRT, and multi-catheter interstitial brachytherapy. That average age was 58.54 years (range = 23-84 years), average tumor size was 1.31 cm; 76.46% had tumor grade 1-2; 6.36% had invasive lobular carcinoma; 93.43% had no involvement of lymph nodes; and 91.33% were estrogen receptor (ER) positive. Median follow-up ranged from 2.2 to 17 years.

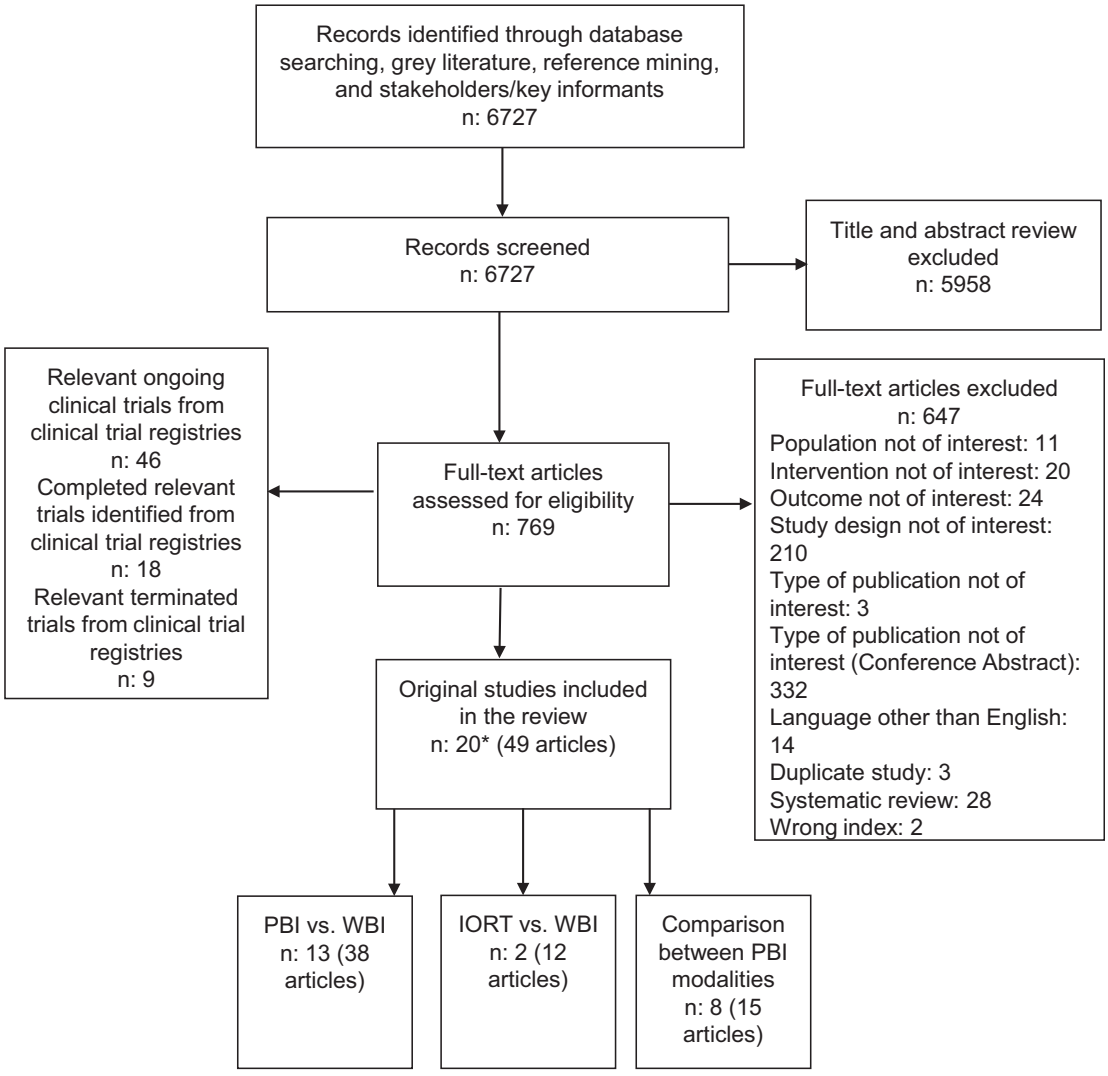

Figure 1. Selection of trials for inclusion in the review and meta-analysis. IORT = intraoperative radiotherapy; PBI = partial-breast irradiation; WBI = whole-breast irradiation.

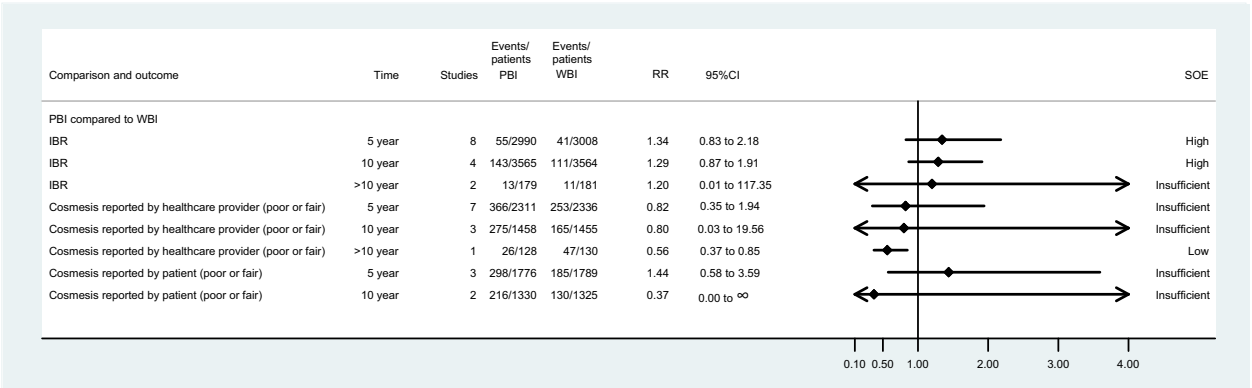

Figure 2. Findings of meta-analysis of PBI vs WBI for ipsilateral breast recurrence (IBR) and cosmetic outcome. PBI = partial-breast irradiation; RR = relative risk; SOE = strength of evidence; WBI = whole-breast irradiation; 95% CI = 95% confidence interval.

Cancer-specific outcomes

IBR was not statistically significantly different for PBI compared with WBI at 5 years (RR = 1.34, 95% CI = 0.83 to 2.18, I^2 = 0%; 8 RCTs; 5998 patients; high strength of evidence [SOE]) or at 10 years (RR = 1.29, 95% CI = 0.87 to 1.91, I^2 = 0%; 4 RCTs; 7129 patients; high SOE; Figure 2). Similar findings were observed at

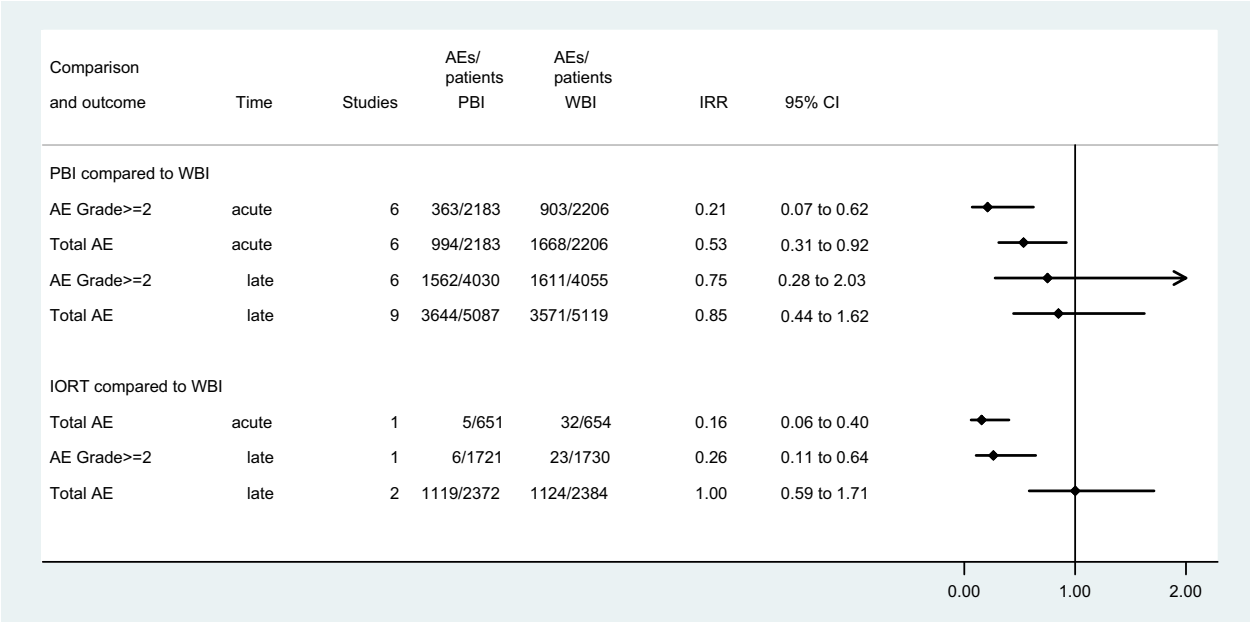

Figure 3. Findings of meta-analysis of adverse events (AEs) for partial-breast irradiation (PBI) and intraoperative radiotherapy (IORT) compared with whole-breast irradiation (WBI). IRR = incidence rate ratio; 95% CI = 95% confidence interval.

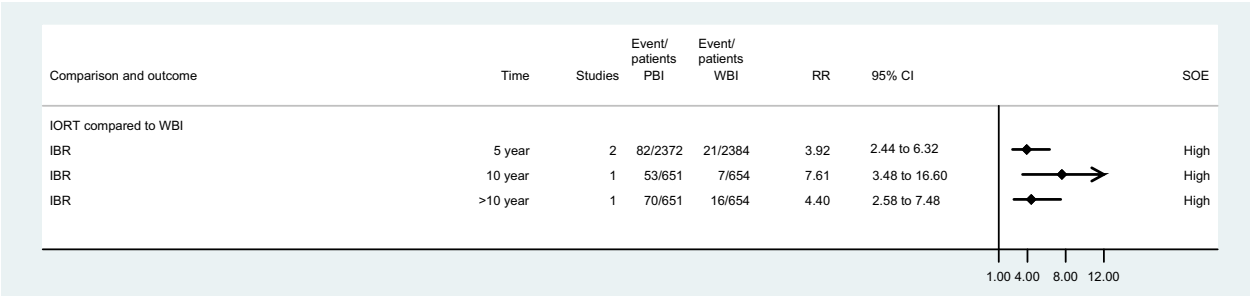

Figure 4. Findings of meta-analysis of IORT vs WBI for ipsilateral breast recurrence (IBR). IORT = intraoperative radiotherapy; RR = relative risk; SOE = strength of evidence; WBI = whole breast irradiation; pts = patients; 95% CI = 95% confidence interval.

over 10 years, but only 2 studies reported more than 10-year follow-up (insufficient SOE). Aggregate analysis of IBR regardless of length of follow-up showed similar findings (RR = 1.27 [95% CI = 0.97 to 1.65] for PBI compared with WBI; I^2 = 0%; 9 RCTs; 10 214 patients). PBI and WBI were not statistically different in the risk of tumor bed IBR, elsewhere IBR, or contralateral breast cancer recurrence at 5 years or 10 years; similar findings were observed at longer than 10 years with results from 1 RCT. There were no statistically significant differences in cancer-free survival, distant metastasis, or OS (Supplementary Table 5, available online).

When each PBI technique (multi-catheter interstitial brachytherapy, 3DCRT, and IMRT) was compared individually with WBI, there were no differences in IBR (Supplementary Table 5, available online), consistent with the comparison of all PBI techniques (in aggregate) vs WBI.

Cosmesis

There was no apparent difference in either patient- or provider-reported cosmetic outcomes at 5 and 10 years when comparing PBI and WBI; however, this conclusion is limited by insufficient SOE. A single randomized trial with over 10-year results observed better provider-rated cosmetic outcomes with PBI compared with WBI (RR = 0.56 for fair or poor cosmesis, 95% CI = 0.37 to 0.85, I^2 = N/A; 1 RCT; 258 patients; low SOE; Figure 2). When considering individual PBI modalities compared with WBI, 3DCRT PBI was associated with a statistically significantly higher rate of fair or poor cosmetic outcome reported by both providers (RR = 2.14, 95% CI = 1.74 to 2.61, I^2 = N/A; 1 RCT; 2135 patients; moderate SOE) and patients (RR = 2.32, 95% CI = 1.84 to 2.91, I^2 = N/A; 1 RCT; 2135 patients; moderate SOE) after 10 years. Compared with WBI, after 10 years, PBI with IMRT was associated with statistically significantly better patient-reported cosmesis (RR = 0.05, 95% CI = 0.01 to 0.22, I^2 = N/A; 1 RCT; 520 patients; low SOE). Provider-reported cosmesis with IMRT PBI was not statistically significantly different at 5 years and 10 years (insufficient SOE). In the comparison between multi-catheter interstitial brachytherapy and WBI, patient- and provider-reported cosmesis at 5 years was not statistically significantly different, however, with insufficient SOE.

Toxicity

Fewer acute AEs (IRR = 0.53, 95% CI = 0.31 to 0.92) and acute AEs grade 2 and over (IRR = 0.21, 95% CI = 0.07 to 0.62) were observed with PBI compared with WBI. The total number of late AEs and late AEs grade 2 and higher were not statistically different (Figure 3).

Subgroup analysis of PBI effectiveness

On subgroup analysis of patient, tumor, and treatment characteristics, there was no apparent difference in PBI effectiveness, although aggregate data for individual subgroup comparisons were limited. National Surgical Adjuvant Breast and Bowel (NSABP) B-39 (26) observed that PBI was associated with lower IBR at 10 years for patients with invasive tumor size equal to or smaller than 1 cm compared with a size greater than 1 cm ($P = .002$).

In subgroup comparison of PBI schedule, we observed fewer late AEs with PBI using once-daily fractionation compared with WBI in 1 clinical trial (IRR = 0.79, 95% CI = 0.70 to 0.89; Supplementary Table 8, available online) (27,28). PBI delivered with twice-daily treatment was associated with statistically significantly higher acute AEs, worse patient-reported cosmesis, and worse provider-reported cosmesis at 10 years compared with once-every-other-day fractionation (Supplementary Table 8, available online). There was lack of data for comparison of cosmesis with once-daily PBI regimens.

IORT compared with WBI

Two RCTs (12-21,38,39) reported in 12 articles with a total of 4756 patients (range = 1305-3451) compared IORT with WBI, with 9 to 12.4 years median follow-up. The rate of IBR with IORT was statistically significantly higher than WBI at 5 years (RR = 3.92, 95% CI = 2.44 to 6.32, $I^2 = 74.14\%$; 2 RCTs, 4756 patients, high SOE), 10 years (RR = 7.61, 95% CI = 3.48 to 16.60, I^2 = N/A; 1 RCT, 1305 patients, high SOE), and longer than 10 years (RR = 4.40, 95% CI = 2.58 to 7.48, I^2 = N/A, 1 RCT, 1305 patients high SOE; Figure 4). There was no statistically significant difference in cancer-free survival, mastectomy-free survival, or OS (Supplementary Table 6, available online). Compared with WBI, IORT was associated with statistically significantly fewer acute AEs as well as late AEs grade 2 and over.

Compared with WBI, IORT completed intraoperatively at the time of lumpectomy and delayed IORT as a second procedure were both associated with a statistically significantly higher rate of IBR at 5 years. In direct comparison of immediate and delayed IORT, there was no statistically significant difference.

Comparison between PBI modalities

Two RCTs (42-46,48), and 6 comparative retrospective and prospective cohort studies (49-57) with a total of 2086 patients (range = 98-656) evaluated direct comparisons between PBI techniques. There was insufficient evidence to estimate the comparative efficacy.

Discussion

In this systematic review and meta-analysis of 14 RCTs and 6 comparative observational studies, IBR at 5 and 10 years was not statistically significantly different for PBI compared with WBI, with high strength of evidence. PBI was associated with statistically significantly lower rate of acute AEs compared with WBI, with no difference in late AEs. These results support the adoption of PBI as a standard option for women with similarity to the population represented in the clinical trials.

Early experiences raised concern for the possibility of an adverse cosmetic outcome with APBI (23-25,58-60). In our analysis, there was insufficient evidence to draw comparative conclusions, primarily due to heterogeneity. Subgroup analysis of dose regimens for PBI with external beam radiotherapy are suggestive of suboptimal cosmetic outcome with external beam APBI with twice-daily fractionation compared with every other day for 5 fractions. However, results from several clinical trials evaluating twice-daily fractionation (26,61,62) have not yet reported mature cosmesis data and will be important to further inform this observation.

For cosmetic outcome and late toxicity, although there were no apparent differences between WBI and PBI in the aggregate analysis, the observation that several individual trials reported reduced late toxicity (11,22,27,30) and improved cosmetic outcome (27,33,43) with PBI suggests that certain PBI approaches may be better tolerated than others. We were unable to separately analyze the individual contributions of dose, fractionation schedule, volume of irradiated breast, and modality. The available data suggest that among women treated with APBI prescribed to 38.5 Gy in 10 fractions delivered twice daily, considered to be an intensive regimen (63), a larger proportion of ipsilateral breast receiving high-dose radiotherapy may be associated with adverse cosmesis (58-60,64). In contrast, for PBI delivered using a dose regimen that is also used for WBI, a larger PBI treatment volume is well tolerated, as observed in the IMPORT-LOW study (27). These observations highlight the need to define optimal PBI technique and dose, particularly for short accelerated regimens with once-daily treatment (65,66).

Patient selection for PBI is a key aspect of obtaining optimal oncologic outcomes. We attempted to evaluate outcomes for patients with moderate risk features who met eligibility criteria for trial enrollment but represent a small proportion of the study population. On subgroup analysis, 1 study observed more favorable IBR among women treated with PBI with tumor size 1 cm and smaller compared with larger tumors (26). There were no other apparent differences in IBR or other outcomes among subgroups defined by patient, tumor, and treatment features, although aggregate data were insufficient for individual subgroups. Most participants in clinical trials of PBI have had early-stage, node-negative, favorable-biology breast cancer and have been postmenopausal, suggesting the greatest applicability among similar patients.

The observation of reduced acute toxicity with PBI is a clinically meaningful finding. However, conventionally fractionated WBI with 5 weeks of daily treatment, described as the standard comparison arm for most included studies, has largely been replaced by hypofractionated WBI in a 3-week course that results in fewer AEs (67-69). The availability of "ultrahypofractionated" WBI provides an alternative to PBI that can be completed in 5 fractions. Patients considered as "cautionary" or "unsuitable" for PBI according to American Society for Therapeutic Radiology and Oncology (ASTRO) criteria (70) might consider accelerated WBI as an alternative to PBI. Notwithstanding ultrahypofractionated WBI as an option, minimizing radiation exposure of the breast and adjacent normal tissues represents a priority for many patients, and thus evaluating outcomes of PBI among moderate risk subgroups remains an important question. Additionally, ongoing trials may help define a biologically low-risk group of women who have less to gain from adjuvant radiotherapy (71).

The rate of IBR was statistically significantly higher for IORT compared with WBI, in contrast to findings for other PBI modalities. On the ELIOT trial, among patients considered "suitable" for PBI according to ASTRO guidelines (70), IORT resulted in a higher rate of IBR than WBI, suggesting consideration for more stringent selection criteria for IORT (38) and highlighting the importance of optimal IORT technique (72). With no apparent difference in survival and less acute and late toxicity than WBI, patients may

understandably favor the convenience of simultaneously completing radiotherapy during lumpectomy (73-75). However, the advantages of IORT are tempered by the observation of a statistically significantly higher risk of IBR.

The included studies used a variety of PBI techniques, including multicatheter interstitial brachytherapy, several methods of external beam radiation, and IORT. Treatment outcomes of individual radiation modalities were insufficiently reported, limiting comparisons between modalities. Outcomes from single-entry catheter brachytherapy and proton therapy were not amenable for meta-analysis due to the lack of comparative data evaluating these techniques. Evaluation of subgroup outcomes was similarly constrained by insufficient data. Because randomized assignment to PBI or WBI is not blinded, treatment assignment might have influenced patient or clinician perceptions of subjective measures such as cosmesis and AEs. There have been major advances in radiotherapy technology and treatment within the timeframe of the included clinical trials, which complicates comparisons that span 2 decades during a time of considerable changes.

Compared with WBI, PBI is not associated with an increased risk of IBR, and acute AEs are reduced with PBI. These findings support the use of PBI as a standard treatment option among women similar to those represented in randomized trials with early-stage, favorable-risk breast cancer. IORT had a statistically significantly higher risk of IBR than WBI, with lower acute and late toxicity. Further study is needed to inform the outcomes of PBI among patients with moderate-risk features who were eligible for enrollment in the available trials but represent a minority of those enrolled and to define optimal PBI dose and treatment techniques.

Data availability

The datasets were derived from sources in the public domain, and all data are incorporated into the article, its online supplementary material, and the full-length AHRQ report (https://effectivehealthcare.ahrq.gov/products/partial-breast-irradiation/research).

Author contributions

Dean A. Shumway, MD (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Validation; Visualization; Writing—original draft; Writing—review & editing), Kimberly S. Corbin, MD (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Validation; Visualization; Writing—original draft; Writing—review & editing), Magdoleen H. Farah, MBBS (Data curation; Writing—review & editing), Kelly E. Viola, MPS (Project administration; Writing—review & editing), Tarek Nayfeh, MD (Data curation; Writing—review & editing), Samer Saadi, MD (Data curation; Writing—review & editing), Vishal Shah, MD (Data curation; Writing—review & editing), Bashar Hasan, MD (Data curation; Writing—review & editing), Sahrish Shah, MBBS (Data curation; Writing—review & editing), Khaled Mohammed, MBBCh (Data curation; Writing—review & editing), Irbaz Bin Riaz, MBBS, MS (Data curation; Writing—review & editing), Larry J. Prokop, MLS (Data curation; Methodology; Writing—review & editing), M. Hassan Murad, MD, MPH (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing), Zhen Wang, PhD (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing).

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Conflicts of interest

The authors have no conflicts of interest to disclose.

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