Comparative Effectiveness Review
Number 259

Partial Breast Irradiation for Breast Cancer

Executive Summary

Main Points

- There was no significant difference between partial breast irradiation (PBI) and whole breast irradiation (WBI) in terms of ipsilateral breast recurrence (IBR), overall survival, and cancer-free survival at 5 and 10 years (high strength of evidence [SOE]). Evidence for cosmetic outcome was insufficient.
- Individual assessments of various PBI approaches—3-dimensional conformal external beam radiation therapy (3DCRT), intensity-modulated radiation therapy (IMRT), and multi-catheter interstitial brachytherapy—compared with WBI yielded results consistent with comparing combined PBI approaches with WBI.
- Acute adverse events (AEs) were significantly fewer with PBI compared with WBI, with no apparent difference in late AEs (moderate SOE).
- Compared with WBI, intraoperative radiotherapy (IORT) was associated with a higher IBR rate at 5, 10, and over 10 years (high SOE), with no difference in overall survival (low to high SOE), cancer-free survival (high SOE), or mastectomy-free survival (low to high SOE). There were significantly fewer acute AEs and late AEs Grade ≥2 with IORT.
- Data were insufficient to draw conclusions regarding differences in IBR or other outcomes according to individual patient, tumor, and treatment characteristics.
- Head-to-head comparisons between the different PBI modalities showed insufficient evidence to estimate an effect on main outcomes.
- Compared with conventionally fractionated WBI over several weeks, accelerated PBI was associated with lower transportation costs and days away from work. PBI was also associated with less subjective financial difficulties at various time points after radiotherapy.

Agency for Healthcare Research and Quality

Background and Purpose

With an estimated 2.3 million new cases in 2020, breast cancer is the leading cause of global cancer incidence and remains a leading cause of cancer mortality worldwide.[1] Breast conserving therapy has been widely adopted as standard treatment for early-stage breast cancer. Radiotherapy as a component of breast conserving therapy has traditionally included the whole breast volume as a target, now standardly delivered using hypofractionation, with 15-20 treatments delivered over three to four weeks.[2, 3] Although WBI successfully reduces the risk of recurrence after lumpectomy,[4] the protracted course of daily radiotherapy over several weeks represents a significant barrier for many women.[5, 6] Analysis of patterns of recurrence and pathology findings have supported that the area at highest risk for tumor recurrence is adjacent to the lumpectomy cavity.[7, 8] Therefore, PBI has been developed with the hypothesis that limiting the treatment volume may provide similar disease control, enable an accelerated treatment course, and potentially reduce radiation exposure to adjacent normal tissues.[9-12] This hypothesis has been evaluated in clinical trials involving over 15,000 women. However, significant variation in patient selection, treatment technique, and reported clinical outcomes makes interpretation of the data challenging when selecting the preferred treatment for an individual patient.

This systematic review assesses the comparative effectiveness and harms of PBI compared with WBI for early-stage breast cancer, defined as a small tumor less than or equal to 3 cm that has minimal or no lymph node involvement (N0/1), and how differences in effectiveness and harms are influenced by patient, tumor, and treatment factors, including treatment modality, target volume, dose, and fractionation. We also evaluated the relative financial toxicity of PBI versus WBI.

Methods

We followed the established methodologies of systematic reviews as outlined in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[13] The reporting complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.[14] The study protocol was published on the AHRQ website (https://effectivehealthcare.ahrq.gov/products/accelerated-partial-breast-irradiation/protocol) and was registered to the International Prospective Register of Systematic Reviews (PROSPERO #: CRD42021284155). The literature search spanned from each database inception to June 30, 2022.

Results

Twenty-three original studies with 17,510 patients evaluated the comparative effectiveness of PBI, including 14 randomized clinical trials (RCTs), six comparative observational studies, and three single-arm observational studies (Appendix Figure B-1).

Eight studies (3 RCTs, 3 comparative observational studies, 1 single-arm observational study, and 1 cost evaluation study) addressed concepts closely related to financial toxicity.

Comparative Effectiveness and Harms of PBI Versus WBI

Thirteen RCTs reported in 38 articles with a total of 15,276 patients were included in the assessment of the comparative effectiveness and harms of PBI versus WBI. The results were generally consistent when PBI approaches were compared with WBI, whether compared individually or combined. These PBI approaches include 3DCRT, IMRT, and multi-catheter interstitial brachytherapy. As a priori, we did not combine IORT with the other PBI modalities and presented the findings separately.

There was no significant difference between PBI and WBI in terms of IBR, overall survival, and cancer-free survival at 5 and 10 years (high SOE). Evidence for the outcome of cosmesis comparing PBI to WBI was insufficient.

3DCRT compared with WBI showed no difference in IBR, overall survival, or cancer-free survival at 5 and 10 years (moderate to high SOE). IMRT compared with WBI showed no difference in IBR and overall survival at 5 and 10 years (low SOE) and better patient-rated cosmesis at 10 years (low SOE). IORT compared with WBI showed a higher IBR rate with IORT at 5, 10, and over 10 years, in contrast to the similar IBR rate observed with other PBI modalities. IORT showed no difference in overall survival, cancer-free survival, or mastectomy-free survival (low to high SOE). There were significantly fewer acute AEs with IORT. Multi-catheter interstitial brachytherapy compared with WBI showed no difference in IBR, overall survival, cancer-free survival at 5 years (low SOE). The rates of acute AEs were significantly less with PBI compared with WBI, with no apparent difference in late AEs (moderate SOE).

Compared with PBI in once-daily fractionation, twice-daily fractionation (3DCRT PBI) was associated with significantly higher rate of patient- and provider-rated adverse cosmetic outcomes and acute AEs. There were no significant differences in IBR or other outcomes according to patient, tumor, and treatment characteristics; however, data for subgroups were insufficient to draw conclusions.

Comparative Effectiveness and Harms of PBI Modalities

Two RCTs, six comparative observational studies, and three single-arm observational studies with 2,362 patients were included in the assessment of comparative effectiveness and harms of PBI modalities. Head-to-head comparisons between the different PBI modalities showed insufficient SOE to estimate an effect on main outcomes. These comparisons included IMRT versus 3DCRT, multi-catheter interstitial brachytherapy versus 3DCRT, proton versus 3DCRT, single-entry catheter brachytherapy versus

3DCRT, and single-entry catheter brachytherapy versus multi-catheter interstitial brachytherapy.

Financial Toxicity Related to PBI

No studies explicitly addressed the construct of financial toxicity, defined as subjective or objective financial distress and hardship experienced by patients due to cancer-related (or anticipated) treatment; however, eight studies (3 RCTs, 3 comparative observational studies, 1 single-arm observational study, and 1 cost evaluation study) addressed concepts closely related to financial toxicity.

Compared with standard fractionation WBI, accelerated PBI was associated with lower transportation costs and days away from work. PBI was also associated with less subjective financial difficulties at various time points after radiotherapy.

Limitations

The clinical trials included in our aggregate analysis represent a variety of treatment techniques, including several methods of external beam radiotherapy (3DCRT, IMRT, proton therapy), brachytherapy (multi-catheter interstitial brachytherapy, single lumen applicator brachytherapy, multi-lumen applicator brachytherapy), and IORT (low-energy x-ray, electrons). Treatment outcomes of each individual radiation modality were insufficiently reported, which limited the ability to make comparisons across modalities.

Evaluation of outcomes according to patient, tumor, and treatment subgroups was similarly limited by the available data. Many of the included clinical trials did not report subgroup analyses, and often, the subgroups were not able to be combined for aggregate analysis. As a result, we were unable to assess many of the prespecified subgroups. Additionally, the results of subgroup analysis are limited by sample size and the risk of false-positive or false-negative findings. Our results from subgroup analysis may inform future areas of investigation but cannot definitively determine the magnitudes of risk associated with each characteristic. This highlights the need to investigate outcomes of PBI among patients with adverse risk factors.

Radiotherapy technology has developed and dramatically changed over the past two to three decades, with a transition from 2D radiotherapy to routine use of 3D radiotherapy, IMRT, and other advanced planning technologies. These advancements result in improved dose homogeneity that may lower the risk for adverse events. In addition, localization with image guidance improves treatment accuracy, which limits the interpretation of studies that span a wide time interval of significant changes in radiotherapy technology and treatment. Although the volume of the treatment target relative to the breast, dose/fractionation schedule, and planning parameters are recognized as critically important to understand the risks related to treatment, these data were very limited or unavailable for many studies. Defining an optimal radiation dose, fractionation, and target size using contemporary techniques for treatment planning and image guidance, and characterizing the outcomes of that approach, represent key areas for future study.

Implications and Conclusions

Among patients similar to those enrolled in clinical trials of PBI, there was no significant difference in the risk of IBR compared with WBI. PBI is associated with fewer acute adverse effects, but the risk of IBR among patients treated with PBI who have adverse clinical or pathologic features is unclear. IORT was found to have a significantly higher rate of IBR than was WBI. Further investigation is needed to evaluate outcomes of PBI in moderate risk subgroups with less favorable clinicopathologic features and to define the optimal radiation treatment technique and dose for PBI.

Appropriate patient selection is a critically important aspect of the success of PBI. There is broad consensus in multiple treatment guidelines and systematic reviews that PBI is an acceptable treatment option for patients with clinical and tumor characteristics similar to those represented in clinical trials, for example, postmenopausal age range, estrogen receptor (ER) positive status, grade 1-2, no lymph node involvement, and tumor size $\leq$ 2 cm. The results presented in this report represent data from 15,276 patients who participated in RCTs of PBI versus WBI, more than three-fold the number of patients who participated in clinical trials that led to the adoption of breast-conserving surgery and WBI as a standard treatment approach.[15] In aggregate, the results of our meta-analysis and systematic review showed no difference between PBI and WBI for selected patients. The finding of reduced acute toxicity with PBI represents a significant finding that will meaningfully inform patient and physician decision making.

Uncertainty remains regarding the magnitude of increased risk associated with features that are perceived as less favorable that were included within the eligibility criteria but represent a minority of patients who participated, for example age <50 years, invasive lobular carcinoma, tumor size 2.1-3 cm, grade 3, ER negative status, Human Epidermal Growth Factor Receptor 2 (HER2) positive status, positive for lymphovascular invasion, or elevated Ki-67. Our analysis revealed the lack of data on the outcomes in these subgroups and highlight the importance of future investigation to develop more robust evidence to inform treatment recommendations.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-49. doi: 10.3322/caac.21660. PMID: 33538338.

2. Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol. 2013 Oct;14(11):1086-94. doi: 10.1016/s1470-2045(13)70386-3. PMID: 24055415.

3. Whelan TJ, Pignol J-P, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med. 2010 Feb 11;362(6):513-20. doi: https://dx.doi.org/10.1056/NEJMoa0906260. PMID: 20147717.

4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet. 2011 Nov 12;378(9804):1707-16. doi: 10.1016/s0140-6736(11)61629-2. PMID: 22019144.

5. Nattinger AB, Kneusel RT, Hoffmann RG, et al. Relationship of distance from a radiotherapy facility and initial breast cancer treatment. J Natl Cancer Inst. 2001 Sep 5;93(17):1344-6. doi: 10.1093/jnci/93.17.1344. PMID: 11535710.

6. Lam J, Cook T, Foster S, et al. Examining Determinants of Radiotherapy Access: Do Cost and Radiotherapy Inconvenience Affect Uptake of Breast-conserving Treatment for Early Breast Cancer? Clin Oncol (R Coll Radiol). 2015 Aug;27(8):465-71. doi: 10.1016/j.clon.2015.04.034. PMID: 26009548.

7. Wallner P, Arthur D, Bartelink H, et al. Workshop on partial breast irradiation: state of the art and the science, Bethesda, MD, December 8-10, 2002. J Natl Cancer Inst. 2004 Feb 04;96(3):175-84. PMID: 14759984.

8. Veronesi U, Marubini E, Mariani L, et al. Radiotherapy after breast-conserving surgery in small breast carcinoma: long-term results of a randomized trial. Ann Oncol. 2001 Jul;12(7):997-1003. doi: 10.1023/a:1011136326943. PMID: 11521809.

9. Fisher ER, Anderson S, Redmond C, et al. Ipsilateral breast tumor recurrence and survival following lumpectomy and irradiation: pathological findings from NSABP protocol B-06. Semin Surg Oncol. 1992 May-Jun;8(3):161-6. PMID: 1496227.

10. Smith TE, Lee D, Turner BC, et al. True recurrence vs. new primary ipsilateral breast tumor relapse: an analysis of clinical and pathologic differences and their implications in natural history, prognoses, and therapeutic management. Int J Radiat Oncol Biol Phys. 2000 Dec 1;48(5):1281-9. doi: 10.1016/s0360-3016(00)01378-x. PMID: 11121624.

11. Huang E, Buchholz TA, Meric F, et al. Classifying local disease recurrences after breast conservation therapy based on location and histology: new primary tumors have more favorable outcomes than true local disease recurrences. Cancer. 2002 Nov 15;95(10):2059-67. doi: 10.1002/cncr.10952. PMID: 12412158.

12. Fowble B, Solin LJ, Schultz DJ, et al. Breast recurrence following conservative surgery and radiation: patterns of failure, prognosis, and pathologic findings from mastectomy specimens with implications for treatment. Int J Radiat Oncol Biol Phys. 1990 Oct;19(4):833-42. doi: 10.1016/0360-3016(90)90002-2. PMID: 2170305.

13. Agency for Healthcare Research and Quality. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Agency for Healthcare Research and Quality; 2014.

14. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009 Jul 21;6(7):e1000097. doi: 10.1371/journal.pmed.1000097. PMID: 19621072.

15. Hepel JT, Wazer DE. Partial Breast Irradiation Is the Preferred Standard of Care for a Majority of Women With Early-Stage Breast Cancer. J Clin Oncol. 2020 Jul 10;38(20):2268-72. doi: 10.1200/jco.19.02594. PMID: 32442074.

Full Report

Shumway DA, Corbin KS, Farah MH, Viola KE, Nayfeh T, Saadi S, Shah V, Hasan B, Shah S, Mohammed K, Riaz IB, Prokop LJ, Wang Z, Murad MH. Partial Breast Irradiation for Breast Cancer. Comparative Effectiveness Review No. 259. (Prepared by the Mayo Clinic Evidence-based Practice Center under Contract No. 75Q80120D00005.) AHRQ Publication No. 23-EHC001. Rockville, MD: Agency for Healthcare Research and Quality; January 2023. DOI: https://doi.org/10.23970/AHRQEPCCER259. Posted final reports are located on the Effective Health Care Program search page.