



Topic Brief: Accelerated Partial Breast Irradiation for Breast Cancer

Date: 12/31/2020

Nomination Number: 0932

Purpose: This document summarizes the information addressing a nomination submitted on July 17, 2020 through the Effective Health Care Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

Issue: There is a high incidence of breast cancer diagnosis among women, and radiation therapy is an integral part of breast cancer treatment. Providing current evidence on radiation therapy for breast cancer is an important public health initiative. The current guidelines on accelerated partial breast irradiation (PBI) for breast cancer from the American Society for Radiation Oncology (ASTRO) were published in 2016. A new systematic review of current evidence would address uncertainties in the delivery and patient selection for different types of breast irradiation; and facilitate an update to the existing guideline to best inform practice.

Program Decision:

The EPC Program will develop a new systematic review based on this nomination. The scope of this topic will be further developed in the refinement phase. When key questions have been drafted, they will be posted on the AHRQ Web site and open for public comment. To sign up for notification when this and other Effective Health Care (EHC) Program topics are posted for public comment, please go to <https://effectivehealthcare.ahrq.gov/email-updates>.

Key Findings

- From a sample of 200 out of 878 studies published between 2017 and 2020, we found sufficient evidence for a new systematic review addressing all but one of five Key Questions (KQs).

Background

In 2017, female breast cancer was the form of cancer with the highest incidence of new cases and the second highest incidence of death in the United States.¹ The most common treatment for breast cancer is breast-conserving surgery with adjuvant radiation therapy.² The goal of radiation therapy in breast cancer treatment is to eradicate subclinical disease following the surgical removal of tumors.³

Radiation therapy administered in patients with early stage breast cancer reduces tumor recurrence and increases survival.⁴ According to ASTRO, the recommended dose-fractionation scheme for whole breast irradiation (WBI) is hypofractionated to 4000 cGy in 15 fractions or 4250 cGy in 16 fractions.⁵ Variations in technique from standard whole breast radiation therapy aim to reduce treatment time, facilitate convenience, and/or limit radiation exposure to normal tissue. Accelerated PBI is one such technique, and has been shown to accomplish some of these

aims.³ As part of PBI, radiation is delivered to tissue only immediately adjacent to the site of the removed tumor, and is convenient in that it can be completed in five treatment days.⁶ Methods of PBI include multicatheter brachytherapy, intracavitary balloon brachytherapy, intraoperative radiation therapy, and external beam conformal therapy.³

Contemporary studies of PBI continue to demonstrate significant variation in care. Clinicians face difficult patient presentations where numerous factors related to patient-specific values and expectations, and varied imaging and clinical features that must be considered.^{7,8} A new systematic review would serve to facilitate the development of an update to the current ASTRO 2016 guidelines that would include information that could provide indications for more tailored treatment based on patient characteristics and clinical features.

Scope

1. In adult women with early stage breast cancer, what is the comparative effectiveness of whole breast irradiation (WBI) compared to partial breast irradiation (PBI)? Which clinical-pathologic characteristics are associated with effectiveness for PBI compared to WBI?
2. In adult women with early stage breast cancer receiving PBI, what is the comparative effectiveness of PBI techniques (e.g., multicatheter interstitial brachytherapy, single-entry catheter brachytherapy [including devices such as MammoSite, Contura, and SAVI], 3-dimensional conformal external beam radiation therapy, intensity modulated radiation therapy, and proton radiation therapy, intra-operative radiotherapy) on ipsilateral breast cancer outcomes, harms, and quality of life?
3. In adult women with early stage breast cancer, what is the comparative effectiveness of different dose-fractionation schemes, target volumes, motion management, treatment techniques and optimal planning parameters for accelerated PBI compared to WBI on breast cancer outcomes, harms, and quality of life?
4. In adult women with early stage breast cancer, what is the comparative effectiveness of preoperative compared to postoperative imaging assessment for patients who meet clinical-pathologic criteria for treatment with PBI?
5. In adult women with early stage breast cancer, what is the comparative effectiveness in terms of cosmesis and treatment toxicities between PBI and WBI?

Table 1. Questions and PICO (population, intervention, comparator, outcome)

| Questions | 1. PBI vs. WBI | 2. PBI techniques | 3. Dose fractionation schemes, target volumes, etc. in PBI vs. WBI |
|-------------------|--|--|--|
| Population | Adult women with early stage breast cancer (invasive or non-invasive carcinoma less than or equal to 3 cm and NO/1). Consider patient characteristics such as age, breast cancer type, breast cancer stage, tumor size, tumor margin status, estrogen receptor status, etc. | Adult women with early stage breast cancer (invasive or non-invasive carcinoma less than or equal to 3 cm and NO/1) receiving PBI. | Adult women with early stage breast cancer (invasive or non-invasive carcinoma less than or equal to 3 cm and NO/1). |

| | | | |
|----------------------|--|--|---|
| Questions | 1. PBI vs. WBI | 2. PBI techniques | 3. Dose fractionation schemes, target volumes, etc. in PBI vs. WBI |
| Interventions | PBI | PBI techniques (e.g., multicatheter interstitial brachytherapy, single-entry catheter brachytherapy [including devices such as MammoSite, Contura, and SAVI], 3-dimensional conformal external beam radiation therapy, intensity modulated radiation therapy, and proton radiation therapy, IORT). | Dose-fractionation schemes, target volumes, motion management, treatment techniques, and optimal planning parameters (i.e., the diameter of the inflated balloon, the planning target volume, and the dose distribution) for PBI. |
| Comparators | WBI | PBI techniques. | WBI |
| Outcomes | breast cancer recurrence, survival, cancer-free survival | Breast cancer recurrence; short- and long-term harms(e.g., Radiation Therapy Oncology Group scores and Late Effects Normal Tissue Task Force-- Subjective, Objective, Management, Analytic scales), quality of life. | Breast cancer recurrence, short- and long-term harms (e.g., Radiation Therapy Oncology Group scores and Late Effects Normal Tissue Task Force-- Subjective, Objective, Management, Analytic scales), quality of life. |

| | | |
|----------------------|---|--|
| Questions | 4. Pre- vs. post- operative imaging assessment | 5. Cosmesis and treatment toxicity in PBI vs. WBI |
| Population | Adult women with early stage breast cancer (invasive or non-invasive carcinoma less than or equal to 3 cm and NO/1) who meet clinical-pathologic criteria for treatment with PBI. | Adult women with early stage breast cancer (invasive or non-invasive carcinoma less than or equal to 3 cm and NO/1) |
| Interventions | Post-operative imaging assessment for PBI | PBI |
| Comparators | Pre-operative imaging assessment for PBI | WBI |
| Outcomes | Cavity visualization score, harms | Cosmesis, treatment toxicities, other short- and long-term harms (e.g., Radiation Therapy Oncology Group scores and Late Effects Normal Tissue Task Force -- Subjective, Objective, Management, Analytic scales) |

Abbreviations: IORT=intra-operative radiotherapy PBI=partial breast irradiation; WBI=whole breast irradiation.

Assessment Methods

See Appendix A.

Summary of Literature Findings

To address clinical uncertainties and inform an update to the existing ASTRO 2016 guideline, we sampled (200 out of 878 studies) from studies published between 2017 and 2020. In that sample, we found studies relevant to all but KQ4.

For KQ1, we found three randomized control trials (RCTs)⁹⁻¹¹ and two observational studies^{12, 13} comparing PBI to WBI that measured the targeted outcomes, local tumor control and survival. Additionally, we found three RCTs comparing PBI and WBI that reported quality of life

outcomes.¹⁴⁻¹⁶ While quality of life was not an outcome included for KQ1, it might ultimately be of interest.

For KQ2, we found one observational study comparing interstitial brachytherapy, balloon-based brachytherapy, and 3-D conformal radiation therapy on tumor recurrence.¹⁷

For KQ3, we found two RCTs; one that compared two different PBI fractionation schemes using two different techniques to WBI,¹⁸ and one that compared PBI fractionation schemes, but without a comparison to WBI.¹⁹

We did not find any studies addressing KQ4.

For KQ5, we found four RCTs²⁰⁻²³ and one clinical trial²⁴ comparing PBI with WBI on cosmesis and/or toxicity. Though not directly applicable to the scope of this nomination we found 10 single arm studies measuring cosmesis and/or toxicity in PBI, but without a comparison to WBI.²⁵⁻³⁴

Table 2. Literature identified for each KQ

| Question | Systematic reviews (11/2017-11/2020) | Primary studies (11/2017-11/2020) |
|---|--------------------------------------|--|
| Question 1: PBI vs. WBI | Total: 0 | Total: 8 <ul style="list-style-type: none"> • RCT: 6 • Observational: 2 Clinicaltrials.gov: 0 |
| Question 2: PBI techniques | Total: 0 | Total: 1 <ul style="list-style-type: none"> • RCT: 0 • Observational: 1 Clinicaltrials.gov: 0 |
| Question 3: Dose fractionation schemes, target volumes, etc. in PBI vs. WBI | Total: 0 | Total: 2 <ul style="list-style-type: none"> • RCT: 2 • Observational: 0 Clinicaltrials.gov: 0 |
| Question 4: PBI imaging assessment | Total: 0 | Total: 0 |
| Question 5: cosmesis and toxicity in PBI vs. WBI | Total: 0 | Total: 4 <ul style="list-style-type: none"> • RCT: 4 • Observational: 0 Clinicaltrials.gov: 1 (recruiting; https://clinicaltrials.gov/ct2/show/NCT02681107) |

Abbreviations: KQ=key question; PBI=partial breast irradiation; RCT=randomized controlled trial; WBI=whole breast irradiation.

See Appendix B for detailed assessments of all EPC selection criteria.

Summary of Selection Criteria Assessment

This nomination meets all selection criteria. We found sufficient primary evidence for a new systematic review for all but one of five KQs. A new systematic review would inform clinical uncertainty in treatment and the update of the existing 2016 ASTRO guidelines on PBI.

Please see Appendix B for detailed assessments of individual EPC Program selection criteria.

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Appendix A: Methods

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Absence of Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years November 24, 2017 - November 24, 2020 on the questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
 - AHRQ Evidence Reports <https://www.ahrq.gov/research/findings/evidence-based-reports/index.html>
 - EHC Program <https://effectivehealthcare.ahrq.gov/>
 - US Preventive Services Task Force <https://www.uspreventiveservicestaskforce.org/>
 - AHRQ Technology Assessment Program <https://www.ahrq.gov/research/findings/ta/index.html>
- US Department of Veterans Affairs Products publications
 - Evidence Synthesis Program <https://www.hsrd.research.va.gov/publications/esp/>
 - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program <https://www.healthquality.va.gov/>
- Cochrane Systematic Reviews <https://www.cochranelibrary.com/>
- PROSPERO Database (international prospective register of systematic reviews and protocols) <http://www.crd.york.ac.uk/prospero/>
- PubMed <https://www.ncbi.nlm.nih.gov/pubmed/>

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a limited literature search in PubMed from the last three years since the current PBI guideline was published, November 24, 2017- November 24, 2020, on all key questions. Because a large number of articles were identified, we reviewed a random sample of 200 titles and abstracts for inclusion. We classified identified studies by question and study design, to assess the size and scope of a potential evidence review. We then calculated the projected total number of included studies based on the proportion of studies included from the random sample.

Search strategy

Ovid MEDLINE ALL 1946 to November 24, 2020

Date searched: November 25, 2020

1 breast neoplasms/ or breast carcinoma in situ/ or carcinoma, ductal, breast/ or carcinoma, lobular/ or "hereditary breast and ovarian cancer syndrome"/ or inflammatory breast neoplasms/ or triple negative breast neoplasms/ or unilateral breast neoplasms/ (295124)

2 (breast adj5 (cancer* or carcinoma* or invasive or malignan* or noninvasive or metast* or oncolog* or tumor* or tumour*)).ti,ab,kf,hw. (350229)

3 or/1-2 (408689)

4 ((early or "stage 0" or "stage 1" or "stage 1a" or "stage 1b" or "stage 2" or "stage 2a" or "stage 2b" or "stage I" or "stage Ia" or "stage Ib" or "stage II" or "stage IIa" or "stage IIb" or "stage zero" or "stage one" or "stage two") adj2 breast).ti,ab,kf. (16806)

5 Radiotherapy/ or Brachytherapy/ or Heavy Ion Radiotherapy/ or Proton Therapy/ or Hemibody Irradiation/ or Radiotherapy Dosage/ or Dose Fractionation, Radiation/ or Radiation Dose Hypofractionation/ or Radiotherapy, Adjuvant/ or Radiotherapy, Computer-Assisted/ or Radiotherapy, Conformal/ or Radiotherapy, Intensity-Modulated/ or Radiotherapy, High-Energy/ or exp Neutron Capture Therapy/ or Radiotherapy, Image-Guided/ or Re-Irradiation/ (146172)

6 ("Accelerated Partial Breast " or APBI or VAPBI or brachytherap* or irradiation or radiotherap* or radiation or re-irradiation or HWBI or IORT or WBI).ti,ab,kf,hw. (775118)

7 or/5-6 (776049)

8 and/3-4,7 (4162)

9 8 not (exp Animals/ not Humans/) (4156)

10 9 not ((Women/ not Men/) or (male or males or men).ti.) (4142)

11 limit 10 to english language (3892)

12 ("randomized controlled trial" or "controlled clinical trial" or "clinical trial").pt. or (controlled or placebo* or random* or trial*).ti. or ((control or controlled or group* or placebo* or random*) adj10 trial*).ab. (1312141)

13 and/11-12 (958)

14 limit 13 to yr="2015 -Current" (284)

15 14 not ((meta-analysis or review or "systematic review").pt. or Cochrane database of systematic reviews.jn. or (metaanaly* or meta-analy* or ((evidence or systematic or umbrella) adj3 (review or synthesis))).ti,ab,kf.) (222) TRIAL RESULTS

16 (meta-analysis or "systematic review").pt. or Cochrane database of systematic reviews.jn. or (metaanaly* or meta-analy* or ((evidence or systematic or umbrella) adj3 (review or synthesis))).ti,ab,kf. (348030)

17 and/11,16 (152)

18 limit 17 to yr="2017 -Current" (29) SYSTEMATIC REVIEW/META-ANALSES RESULTS

19 exp cohort studies/ or exp epidemiologic studies/ or (cohort or cross-sectional or ((clinical or comparative or evaluation or follow-up or multicenter or observational or retrospective) adj3 study)).ti. or (clinical study or evaluation study or multicenter study or observational study).pt. (3066894)

20 and/11,19 (1559)

21 limit 20 to yr="2015 -Current" (422)

22 21 not (15 or 18) (315) OBSERVATIONAL STUDIES RESULTS

Ovid EBM Reviews - Cochrane Central Register of Controlled Trials October 2020

Date searched: November 25, 2020

1 (breast adj5 (cancer* or carcinoma* or invasive or malignan* or noninvasive or metast* or oncolog* or tumor* or tumour*)).ti,ab. (37760)

2 ((early or "stage 0" or "stage 1" or "stage 1a" or "stage 1b" or "stage 2" or "stage 2a" or "stage 2b" or "stage I" or "stage Ia" or "stage Ib" or "stage II" or "stage IIa" or "stage IIb" or "stage zero" or "stage one" or "stage two") adj2 breast).ti,ab. (5747)

3 ("Accelerated Partial Breast " or APBI or VAPBI or brachytherap* or irradiation or radiotherap* or radiation or re-irradiation or HWBI or IORT or WBI).ti. (22505)

4 and/1-3 (768)

5 limit 4 to yr="2015 -Current" (307) TRIAL RESULTS

ClinicalTrials.gov [expert search mode]

Date searched: November 25, 2020

(early OR EXPAND[Concept] "stage 0" OR EXPAND[Concept] "stage 1" OR EXPAND[Concept] "stage 1a" OR EXPAND[Concept] "stage 1b" OR EXPAND[Concept] "stage 2" OR EXPAND[Concept] "stage 2a" OR EXPAND[Concept] "stage 2b" OR EXPAND[Concept] "stage I" OR EXPAND[Concept] "stage Ia" OR EXPAND[Concept] "stage Ib" OR EXPAND[Concept] "stage II" OR EXPAND[Concept] "stage IIa" OR EXPAND[Concept] "stage IIb" OR EXPAND[Concept] "stage zero" OR EXPAND[Concept] "stage one" OR EXPAND[Concept] "stage two" OR EXPAND[Concept] "Accelerated Partial Breast" OR APBI OR VAPBI OR brachytherapy OR irradiation OR radiotherapy OR radiation OR re-irradiation OR HWBI OR IORT OR WBI) AND (AREA[ConditionSearch] (breast AND (cancer OR carcinoma)) OR AREA[TitleSearch] (breast AND cancer or carcinoma)) AND AREA[OverallStatus] EXPAND[Term] COVER[FullMatch] ("Active, not recruiting" OR "Completed") AND AREA[InterventionSearch] (EXPAND[Concept] "Accelerated Partial Breast" OR APBI OR VAPBI OR brachytherapy OR irradiation OR radiotherapy OR radiation OR re-irradiation OR HWBI OR IORT OR WBI) AND AREA[Gender] EXPAND[Term] COVER[FullMatch] NOT "Male" AND AREA[StdAge] EXPAND[Term] COVER[FullMatch] ("Adult" OR "Older Adult") AND AREA[StudyFirstPostDate] EXPAND[Term] RANGE[01/01/2017, 11/25/2020]

(72) TRIAL RESULTS

clinicaltrials.gov link

Value

We assessed the nomination for value. We considered whether or not the clinical, consumer, or policymaking context had the potential to respond with evidence-based change; and if a partner organization would use this evidence review to influence practice.

Appendix B. Selection Criteria Assessment

| Selection Criteria | Assessment |
|---|---|
| 1. Appropriateness | |
| 1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the United States? | Yes |
| 1b. Is the nomination a request for an evidence report? | Yes |
| 1c. Is the focus on effectiveness or comparative effectiveness? | Yes |
| 1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic? | Yes |
| 2. Importance | |
| 2a. Represents a significant disease burden; large proportion of the population | As measured in 2017, female breast cancer was the cancer type with the highest incidence of new cases (125 in 100,000 people; 250,000 new cases) and with the second highest incidence of death in the U.S. (19.9 per 100,000 women; 42,000 deaths). ¹ |
| 2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the United States population or for a vulnerable population | Yes. As measured in 2017, female breast cancer was the cancer type with the highest incidence of new cases (125 in 100,000 people; 250,000 new cases) and with the second highest incidence of death in the U.S. (19.9 per 100,000 women; 42,000 deaths). ¹ |
| 2c. Incorporates issues around both clinical benefits and potential clinical harms | Yes |
| 2d. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers | Yes. As measured in 2016, costs in the year after diagnosis for all stages of breast cancer ranged from \$60,637 to \$134,682, and, in the 24 months after diagnosis, \$71,909-\$182,655. ³⁵ |
| 3. Desirability of a New Evidence Review/Absence of Duplication | |
| 3. A recent high-quality systematic review or other evidence review is not available on this topic | Yes. We did not find any existing systematic reviews that would be appropriate for the time period since the current guideline was published. |
| 4. Impact of a New Evidence Review | |
| 4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)? | Yes. Clinicians face difficult patient presentations where numerous factors related to patient-specific values and expectations, and varied imaging and clinical features that must be considered. In the 2017 ASTRO consensus guideline, their recommendations around patient selection based on age, tumor margins, and pathology were rated as “weak.” While there was consensus around the recommendations, new evidence may better inform and strengthen guidance. |
| 4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)? | Contemporary studies continue to demonstrate significant variation in care. |

| Selection Criteria | Assessment |
|--|---|
| 5. Primary Research | |
| 5. Effectively utilizes existing research and knowledge by considering: <ul style="list-style-type: none"> - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies) | We found a total of 15 primary studies addressing four of five KQs. We did not find any studies addressing KQ4. We took a sample (200 studies) from a total of 878 studies published between 2017 and 2020. We estimate that a new systematic review would be medium in size (66 studies). |
| 6. Value | |
| 6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change | Yes, ASTRO plans to use a new systematic review to update the existing guidelines. |
| 6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation) | Yes, ASTRO, the nominator, plans to use a new systematic review to update their existing guidelines. |

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; ASTRO=American Society of Radiation Oncology; KQ=key question.