



Evidence-based Practice Center Systematic Review Protocol

Project Title: *Partial Breast Irradiation for Breast Cancer*

I. Background and Objectives for the Systematic Review

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 Two major developments within the last four decades have resulted in a significant shift in the treatment paradigm for breast cancer. First, screening mammography has resulted in increased detection of smaller tumors, and in countries with widespread adoption of mammography screening, the majority of breast cancer is detected at an early stage.² Second, clinical trials have suggested that breast conserving therapy, consisting of breast conserving surgery (i.e., lumpectomy, partial mastectomy) and radiotherapy, offers equivalent survival to total mastectomy and low rates of recurrence, with the added benefit of breast preservation^{3, 4} and other quality-of-life advantages.⁵ Hence, 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.^{6, 7} Although whole breast irradiation (WBI) successfully reduces the risk of recurrence after lumpectomy⁸, the protracted course of daily radiotherapy over several weeks represents a significant barrier for many women.^{9, 10} 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. Therefore, partial breast irradiation (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.¹¹⁻¹⁴ This hypothesis has been evaluated in clinical trials involving over 10,000 women, which is more than twice the number of women who participated in the clinical trials that resulted in adoption of breast conserving therapy as a standard treatment several decades ago.¹⁵ The data have shown that in select populations, PBI often enables more convenient, efficient therapy with similar oncologic outcomes. Yet, 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.

Patient selection is critical to achieve optimal oncologic outcomes for PBI. Notwithstanding the high-quality data from randomized trials of PBI, there is considerable controversy regarding the applicability of PBI for patients who were considered eligible for trial participation but represent a minority of those enrolled. Most women who enrolled in randomized trials of PBI have been postmenopausal, with the median age ranging from 54 to 63 years among the five largest trials of PBI.¹⁶⁻²⁰ Despite the majority of enrollees being older, subgroup analyses from these trials provide support for the effectiveness of PBI in women aged 40-50 years; however conflicting data from earlier studies resulted in guidelines from both American Society for Radiation Oncology (ASTRO)²¹ and European Society for Radiotherapy and Oncology

(ESTRO)²² defining age ≥ 50 years as an appropriate selection criterion for PBI. For women age 40-50 years who are keen to receive PBI, these incongruent observations result in confusion regarding choices for radiotherapy.

Similar observations could be made for a number of tumor features that were included in clinical trials of PBI, such as larger tumor size (2-3 cm), high tumor grade, close margins, human epidermal growth factor receptor 2 (HER2) status, and invasive lobular carcinoma. In the trials, the number of participants with these tumor features was insufficient to draw conclusions regarding the suitability of PBI. Even the most elemental selection criteria of estrogen receptor status remain controversial. While estrogen receptor expression is well established for systemic therapy decision-making, its role as a selection criterion for PBI remains a topic of discussion. There is discrepancy between ESTRO guidelines, which include estrogen receptor negative tumors as suitable for PBI²², and ASTRO guidelines, which do not.²¹ There has not yet been a systematic review to ascertain the role of these factors in determining the suitability for partial breast irradiation.

The optimal treatment volume, dose, and fractional scheme for PBI remain areas of clinical uncertainty as well. There is considerable heterogeneity in the treatment regimens within reported PBI trials, ranging from 21 Gy in a single fraction to the surface of the lumpectomy cavity for kV based intraoperative radiation therapy (IORT), to 38.5 Gy in 10 fractions given twice daily to a 2 to 2.5 cm expansion on the lumpectomy cavity for external beam PBI. This heterogeneity creates a challenge for clinicians in determining the optimal treatment approach, as the total dose, fraction size, and treatment delivery schedule may impact clinical outcomes, including tumor control, cosmesis, toxicity, and quality of life. It is also unclear whether financial toxicity, which is defined as financial distress and hardship related to the cost of treatment and is common among individuals with cancer, is reduced with PBI.²³

Purpose of the Review

This systematic review will assess 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). We will also assess how differences in effectiveness and harms are influenced by patient, tumor, and treatment factors, including treatment modality, target volume, dose, and fractionation. The review will also provide rates of adverse events of the various PBI modalities necessary for shared decision-making.

II. The Key Questions (KQs)

The key questions were posted for public comment between April 14, 2021 and May 14, 2021. The public comments emphasized the importance of evaluating outcomes by timing of occurrence and adding specific outcomes (e.g., mastectomy-free survival, overall survival, cancer-free survival). The public comments also questioned the assessment of preoperative versus postoperative imaging as this issue is irrelevant in clinical practice. The public comments were discussed with Key Informants. In response, we have revised the key questions to add specific outcomes (i.e., mastectomy-free survival and breast conservation) and will analyze outcomes at the following intervals (comparative effectiveness and cosmesis outcomes: ≥ 1 year to 5 years; >5 years to 10 years; and >10 years; adverse events: <3 months; and ≥ 3 months). We also removed the question about the assessment between preoperative and postoperative imaging.

KQ 1. In adult women with early stage breast cancer, what are the comparative effectiveness, adverse events, and cosmetic outcomes of partial breast irradiation compared to whole breast irradiation?

KQ1a. How does effectiveness of partial breast irradiation vary by clinical-pathologic characteristics?

KQ1b. How do the effectiveness, adverse events, and cosmetic outcomes of partial breast irradiation vary by target volumes, dose-fractionation schemes, motion management, and planning parameters?

KQ 2. In adult women with early stage breast cancer, what are the comparative effectiveness, adverse events, and cosmetic outcomes of different partial breast irradiation modalities (including multicatheter interstitial brachytherapy, single-entry catheter brachytherapy, 3-dimensional conformal external beam radiation therapy, intensity modulated radiation therapy, proton radiation therapy, and intraoperative radiotherapy)?

KQ 2a. When there are no eligible comparative studies to address KQ2 for a particular PBI modality, what are the rates of adverse events in noncomparative series of such modality?

KQ 2b. When there are no eligible comparative studies to address KQ2 for a particular PBI modality, what are the rates of long-term (> 5 years) effectiveness outcomes and cosmesis in noncomparative series of such modality?

Contextual Question

CQ 1. In adult women with early stage breast cancer, to what extent does financial toxicity differ between partial and whole breast irradiation?

Table 1. PICOTS (Populations, Interventions, Comparators, Outcomes, Timing, and Settings)

| PICOTS Elements | Inclusion Criteria | Exclusion Criteria |
|----------------------|--|--|
| Population | <ul style="list-style-type: none"> Adult women (i.e., 18 years and older) with early stage breast cancer (i.e., a small tumor less than or equal to 3 cm that has minimal or no lymph node involvement (N0/1)) | <ul style="list-style-type: none"> Animals Children (i.e., age <18 years) Men Recurrent breast cancer |
| Interventions | For all KQs and CQ1, PBI includes the following modalities: <ul style="list-style-type: none"> Multicatheter interstitial brachytherapy Single-entry catheter brachytherapy 3-dimensional conformal external beam radiation therapy Intensity modulated radiation therapy Proton radiation therapy Intraoperative radiotherapy | <ul style="list-style-type: none"> Combination of PBI and WBI |

| PICOTS Elements | Inclusion Criteria | Exclusion Criteria |
|--------------------|---|--------------------|
| Comparators | KQ 1, CQ 1: WBI KQ 2: A different PBI modality <ul style="list-style-type: none"> • Multicatheter interstitial brachytherapy • Single-entry catheter brachytherapy • 3-dimensional conformal external beam radiation therapy • Intensity modulated radiation therapy • Proton radiation therapy • Intraoperative radiotherapy KQ 2a and 2b: No comparator | None |
| Outcomes | KQ 1 and 2: <ul style="list-style-type: none"> • Ipsilateral breast cancer recurrence (i.e., tumor bed ipsilateral breast cancer recurrence, elsew here ipsilateral breast cancer recurrence) • Mastectomy-free survival • Overall survival • Cancer-free survival • Contralateral breast cancer recurrence • Distant breast cancer recurrence • Regional breast cancer recurrence • Any breast cancer recurrence • Breast conservation • Quality of life (e.g., BCTOS, FACT-B, SF-36, Breast Q scale) • Patient-reported and physician-assessed cosmesis (e.g., including Harvard Breast Cosmesis Scale, Global Cosmesis Scale, or the EORTC breast cancer cosmetic rating system) • Sexual health • Adverse events, including scales measuring radiation toxicity: <ul style="list-style-type: none"> ○ RTOG/EORTC scores ○ LENT-SOMA scales ○ CTCAE scores CQ 1: Contextual information about the construct of financial toxicity (i.e., financial distress and hardship) | None |
| Timing | At the following intervals: For effectiveness and cosmetic outcomes <ul style="list-style-type: none"> • >=1 year to 5 years • >5 years to 10 years • >10 years For adverse events <ul style="list-style-type: none"> • <3 months • >=3 months | None |
| Settings | Any | None |

| PICOTS Elements | Inclusion Criteria | Exclusion Criteria |
|-----------------|--|---|
| Study design | KQ1: <ul style="list-style-type: none"> • RCTs KQ 2: <ul style="list-style-type: none"> • RCTs • Comparative observational studies KQ 2a: <ul style="list-style-type: none"> • Single-arm observational studies (≥ 50 patients) KQ 2b: <ul style="list-style-type: none"> • Single-arm observational studies (≥ 50 patients and ≥ 5 year follow up) CQ 1: <ul style="list-style-type: none"> • RCTs • Comparative observational studies • Qualitative studies • Cost-benefit analyses • Surveys All KQs and CQ 1: <ul style="list-style-type: none"> • Relevant systematic reviews or meta-analyses (used for identifying additional studies) | <ul style="list-style-type: none"> • In vitro studies • Nonoriginal studies (e.g. narrative reviews, editorials, letters, or erratum), • Cross-sectional (i.e., nonlongitudinal) studies |

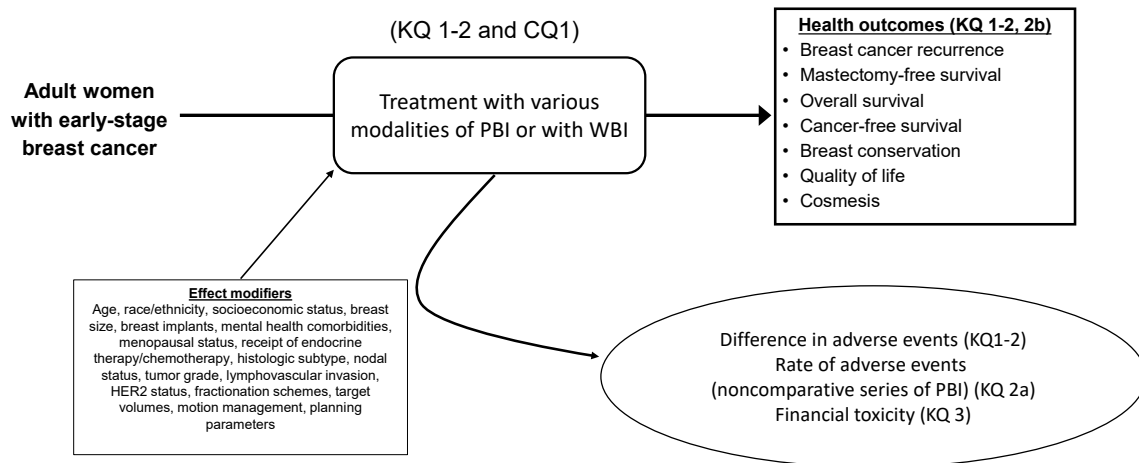
| PICOTS Elements | Inclusion Criteria | Exclusion Criteria |
|-------------------|---|--------------------|
| Subgroup analysis | <p>KQ 1 and 2:</p> <ul style="list-style-type: none"> • Age • Treatment schedule (i.e., accelerated, nonaccelerated) • Race/ethnicity • Socioeconomic status • Area Deprivation Index • DCIS vs. invasive disease • Breast size • BMI • Cup size • Breast implants • Mental health comorbidities • Menopausal status • Receipt of systemic therapy (i.e., none, endocrine therapy, and/or chemotherapy, both) • Histologic subtype (e.g., invasive ductal carcinoma, invasive lobular carcinoma, DCIS, other) • Nodal status (i.e., N0, N1, NX, number of positive nodes) • Nodal assessment (i.e., sentinel lymph node biopsy, axillary lymph node dissection, none) • Tumor grade • Tumor size (i.e., <1 cm, 1-2 cm, 2-3 cm, >3 cm) • Focality (unifocal vs multifocal) • Margin status (i.e., positive, <2 mm, 2-3 mm, >3 mm) • Extensive intraductal component • Ki-67 (<20% vs. ≥ 20%) • ASTRO or ESTRO risk category (i.e., suitable, cautionary, unsuitable; low, intermediate, high) • Germline genetic mutation (e.g., <i>BRCA1</i>, <i>BRCA2</i>, <i>CHEK2</i>, <i>PALB2</i>, <i>ATM</i>, etc.) • Cancer-predisposing syndrome • Estrogen receptor status • Progesterone receptor status • Hormone receptor status • Lymphovascular invasion • HER2 status • Prior chemotherapy • Monoelectron therapy • Dermatologic Rheumatologic conditions (i.e., lupus, scleroderma, rheumatoid arthritis) • Dose-fractionation schemes (i.e., accelerated, nonaccelerated, daily vs every other day vs twice daily, total dose, EQD2) • Target volumes (i.e., size of expansion on cavity, diameter of the inflated balloon, size of the planning target volume) • Motion management • Planning parameters (i.e., the diameter of the inflated balloon, the planning target volume, and the dose distribution organ-at-risk constraints and dose received [such as ipsilateral breast V50 and V100], number of beams, PTV coverage goals and constraints) • Number of treatment fields • Image guidance (i.e., MV imaging, kV imaging, cone beam CT, use of clips for localization) • Risk of bias (i.e., low, moderate, high) | None |

| PICOTS Elements | Inclusion Criteria | Exclusion Criteria |
|-----------------|--|--|
| Publications | <ul style="list-style-type: none"> Studies published in English as peer reviewed full text Published after Year 2000 | <ul style="list-style-type: none"> Foreign language studies Conference abstracts |

Abbreviations: ASTRO = American Society for Radiation Oncology; *ATM* = ataxia telangiectasia mutated; BCTOS = Breast Cancer Treatment Outcomes Scale; BMI = body mass index; *BRCA1* = breast cancer 1; *BRCA2* = breast cancer 2; *CHEK2* = checkpoint kinase 2; cm = centimeter; CQ = contextual question; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; DCIS = ductal carcinoma in situ; EORTC = European Organisation for Research and Treatment of Cancer; ESTRO = European Society for Radiotherapy and Oncology; FACT-B = Functional Assessment of Cancer Therapy-Breast; EQD2 = Equivalent Dose in 2 Gy fractions; HER2 = human epidermal growth factor receptor 2; KQ = key question; kV = kilovoltage; LENT-SOMA = Late Effects Normal Tissue Task Force- Subjective, Objective, Management, Analytic; mm = millimeter; MV = megavoltage; N0 = no involved lymph nodes; N1 = 1-3 involved lymph nodes; NX = lymph nodes not assessed; *PALB2* = partner and localizer Of *BRCA2*; PBI = partial breast irradiation; PICOTS = populations, interventions, comparators, outcomes, timing, and settings; PTV = planning target volume; RCT = randomized controlled trial; RTOG = Radiation Therapy Oncology Group; SF-36 = Short Form (36) Health Survey; V50 = volume (%) receiving $\geq 50\%$ of the prescription dose; V100 = volume (%) receiving $\geq 100\%$ of the prescription dose; WBI = whole breast irradiation

III. Analytic Framework

Figure 1. Draft analytic framework



Abbreviations: CQ = contextual question; HER2 = human epidermal growth factor receptor 2; KQ = key question; PBI = partial breast irradiation; WBI = whole breast irradiation

IV. Methods

Criteria for Inclusion/Exclusion of Studies in the Review

We will apply the following inclusion and exclusion criteria for the studies identified in the literature search (Table 1). We will limit the literature search to studies published after 2000 as older studies do not reflect contemporary clinical practice. For KQ2a, single-arm studies with less than 50 patients will be excluded. For KQ2b, single-arm studies with fewer than 50 patients or fewer than 5-year followup will be excluded. Both of these restrictions were made in order to improve generalizability and to reduce number of low methodological quality case series.

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

We plan to conduct a comprehensive database search, including Embase®, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE® Daily, MEDLINE®, Cochrane Central Registrar of Controlled Trials, Ovid® Cochrane Database of Systematic Reviews, and Scopus® from database inception to the present. We have developed a preliminary database search strategy (Appendix A) and found that these databases can adequately identify the relevant literature. We will use relevant systematic reviews and meta-analysis to identify additional existing and new literature. We will also search FDA, ClinicalTrials.gov, Health Canada, Medicines and Healthcare Products Regulatory Agency (MHRA), the Agency for Healthcare Research and Quality's (AHRQ's) Horizon Scanning System, conference proceedings, patient advocate group websites, and medical society websites. Reference mining of relevant publications will be conducted. The search strategy will be peer-reviewed by an independent information specialist. An experienced librarian will conduct the search. All citations identified through the process will be imported to a reference management system (EndNote® Version X9; Thomson Reuters, Philadelphia, PA). In addition, a Supplemental Evidence and Data for Systematic Reviews (SEADS) portal will be available to collect additional study-specific information from industry stakeholders, professional societies, and researchers. A Federal Register Notice will be posted for this review.

Independent reviewers, working in pairs, will screen the titles and abstracts of all citations using prespecified inclusion and exclusion criteria. Studies included by either reviewer will be retrieved for full-text screening. Independent reviewers, again working in pairs, will screen the full-text version of eligible references. Discrepancies between the reviewers will be resolved through discussions and consensus. If consensus cannot be reached, a third reviewer will resolve the difference. We will use a web-based systematic review software, DistillerSR® (Evidence Partners Incorporated, Ottawa, Canada), to facilitate study selection process.

Data Abstraction and Data Management

At the beginning of data abstraction, we will develop a standardized data extraction form to extract study characteristics (author, year, study design, inclusion and exclusion criteria, patient characteristics, intervention, comparisons, outcomes, and related items for assessing study quality and applicability). The standardized form will be pilot tested by all study team members using 10 studies. We will iteratively continue testing the form until no additional items or unresolved questions exist. After we finalize the form, reviewers will work independently to extract study details. An additional reviewer will review data extraction and resolve conflicts. If the included studies do not report all necessary information (e.g., methods and results), we will contact authors directly. DistillerSR® will also be used to create data extraction forms and facilitate data extraction.

Assessment of the Risk of Bias of Individual Studies

We will evaluate the risk of bias of the included RCTs using the Cochrane Collaboration's Risk of Bias 2 tool²⁴ to assess bias from the randomization process, intended interventions, missing outcome data, outcome measurement, selective reporting, and other sources. For observational studies, we will select appropriate items from the Newcastle-Ottawa Scale.²⁵ For noncomparative series, we will use the methodological quality assessment tool designed for noncomparative case series developed by Murad, *et al.*²⁶

Data Synthesis

We will qualitatively summarize key features/characteristics (e.g. study populations, design, intervention, outcomes, and conclusions) of the included studies and present the findings in evidence tables for each KQ.

We will determine whether meta-analysis is appropriate (i.e., more than two studies address the same PICOTS and provide point estimates and dispersion measures) to quantitatively summarize study findings based on the similarities of PICOTS presented by the studies. If meta-analysis is deemed appropriate, we plan to use the DerSimonian and Laird random-effects method with Hartung-Knapp-Sidik-Jonkman variance correction to combine direct comparisons between treatments if the number of studies included in the analysis is larger than three.²⁷ The fixed effect method based on the Mantel and Haenszel method will be adopted when the number of studies is three or fewer. We will evaluate heterogeneity between studies using I^2 indicator. To further explore heterogeneity, we plan to conduct preplanned subgroup analyses (listed in Table 1).

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

We will grade the strength of the body of evidence (SOE) for KQs 1 and 2 per the Evidence-based Practice Center (EPC) Methods Guide for Comparative Effectiveness Reviews on assessing SOE.²⁸ We will grade SOE for the most critical health outcomes, which are ipsilateral breast cancer recurrence, mastectomy-free survival, cancer-free survival, overall survival, and cosmesis. These outcomes are chosen because they are either clinically important from a patient's perspective or highly relevant for stakeholders' decision-making.

RCTs start with a provisional high SOE grade, while observational studies start with a provisional low SOE grade.²⁸ The domains to be used for determining final SOE grade will be: the methodological limitations of the studies (i.e., risk of bias); precision (based on the size of the body of evidence, number of events, and confidence intervals); directness of the evidence to the KQs (focusing on whether the outcomes were important to patients vs surrogates); consistency of results (based on qualitative and statistical approaches to evaluate for heterogeneity); and the likelihood of reporting and publication bias.

We will lower SOE grading when sensitivity analyses 1. show substantial difference in estimates derived from high or unclear risk of bias studies versus estimates derived from studies at low risk of bias; or 2. when all the available studies (in a particular comparison) have high or unclear risk of bias. SOE grading will be also lowered when important heterogeneity is identified.

Based on this assessment and the initial study design, we will assign SOE rating as high, moderate, low, or 'insufficient evidence' to estimate an effect.

High - We are very confident that the estimate of effect lies close to the true effect (the body of evidence has few or no deficiencies and is judged to be stable).

Moderate - We are moderately confident that the estimate of effect lies close to the true effect (the body of evidence has some deficiencies and is judged to be likely stable).

Low - We have limited confidence that the estimate of effect lies close to the true effect (the body of evidence has major or numerous deficiencies and is likely unstable).

Insufficient - We are unable to estimate an effect or have no confidence in the estimate of effect.

We will produce summary of evidence tables that will provide for each comparison and for each outcome: data source, effect size, SOE rating, and rationale for judgments made on each domain of evidence rating.

Assessing Applicability

We will follow the procedures outlined in the EPC Methods Guide for Comparative Effectiveness Reviews to assess the applicability of the findings within and across studies.²⁸ Applicability for each outcome will be summarized and presented qualitatively using the PICOTS framework and not a specific checklist or scale. We will summarize the available data to present the range of PICOTS characteristics that was studied in the available literature, thus facilitating future decision making based on this body of literature. The following factors that may affect applicability include patient factors (e.g., demographic characteristics [age, race, ethnicity, socioeconomic status]), patient medical comorbidities (e.g., mental health comorbidities, menopausal status), and intervention factors (e.g., dose-fractionation, target volume, treatment duration). We will use this information to evaluate applicability of the evidence to real-world clinical practice in typical U.S. settings. We will report any limitations in applicability of individual studies in evidence tables and limitations of applicability of the whole body of evidence in the summary of evidence tables.

V. References

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27. Rover C, Knapp G, Friede T. Hartung-Knapp-Sidik-Jonkman approach and its modification for random-effects meta-analysis with few studies. *BMC Med Res Methodol.* 2015 Nov 14;15:99. doi: 10.1186/s12874-015-0091-1. PMID: 26573817.
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VI. Definition of Terms

| Term | Definition |
|-----------|--|
| AHRQ | Agency for Healthcare Research and Quality |
| ASTRO | American Society for Radiation Oncology |
| BCTOS | Breast Cancer Treatment Outcomes Scale |
| CTCAE | Common Terminology Criteria for Adverse Events |
| EORTC | European Organisation for Research and Treatment of Cancer |
| ESTRO | European Society for Radiotherapy and Oncology |
| EPC | Evidence-based Practice Center |
| FACT-B | Functional Assessment of Cancer Therapy-Breast |
| HER2 | Human Epidermal Growth Factor Receptor 2 |
| IORT | Intraoperative Radiation Therapy |
| KQ | Key Question |
| LENT-SOMA | Late Effects Normal Tissue Task Force- Subjective, Objective, Management, Analytic |
| PBI | Partial Breast Irradiation |
| PICOTS | Populations, Interventions, Comparators, Outcomes, Timing, and Settings |
| RCT | Randomized Controlled Trial |
| RTOG | Radiation Therapy Oncology Group |
| SEADS | Supplemental Evidence and Data for Systematic Reviews |
| SF-36 | Short Form (36) Health Survey |
| SOE | Strength of Evidence |
| TEP | Technical Expert Panel |
| TOO | Task Order Officer |
| WBI | Whole Breast Irradiation |

VII. Summary of Protocol Amendments

If the EPC needs to amend the protocol, we will give the date of each amendment, describe the change, and give the rationale in this section. Changes will not be incorporated into the protocol.

VIII. Review of Key Questions

The Agency for Healthcare Research and Quality (AHRQ) posted the Key Questions on the AHRQ Effective Health Care Website for public comment from April 14 to May 14, 2021. The Evidence-based Practice Center (EPC) refined and finalized them after reviewing of the public comments and seeking input from Key Informants. This input is intended to ensure that the Key Questions are specific and relevant.

IX. Key Informants

Key Informants are the end-users of research; they can include patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into the decisional dilemmas and help keep the focus on Key Questions that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for the systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The AHRQ Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. The Technical Expert Panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that fosters a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind; neither do they contribute to the writing of the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Members of the TEP must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer Reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparing the final report. Peer Reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers.

The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers with any financial conflict of interest greater than \$5,000 will be disqualified from Peer Review. Peer Reviewers who disclose potential business or professional conflicts of interest can submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Direct financial conflicts of interest that cumulatively total more than \$1,000 will usually disqualify an EPC core team investigator.

XIII. Role of the Funder

This project was funded under Contract No. 75Q80120D00005 from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ Task Order Officer reviewed the EPC response to contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by either the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XIV. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

Appendix A. Search Strategies

Search Strategies KQ 1-2

Ovid

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials May 2021, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to June 23, 2021, Embase 1974 to 2021 June 29, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to June 29, 2021

Search Strategy:

- | # | Searches |
|----|--|
| 1 | exp Breast Neoplasms/rt [Radiotherapy] |
| 2 | exp Radiotherapy/ |
| 3 | exp Radiation/ |
| 4 | exp irradiation/ (APBI or brachytherap* or Contura or IMRT or IORT or irradiat* or linac or MammoSite or |
| 5 | PBI or proton or radiation* or "radio therap*" or "radio treatment*" or radiotherap* or radiotreatment* or SAVI or "Single-entry catheter*" or WBI or "x ray*").ti,ab,hw,kw. |
| 6 | or/1-5 |
| 7 | ((APBI or PBI or WBI) and breast) or "partial breast" or "whole breast").ti,ab,hw,kw. |
| 8 | 6 and 7 |
| 9 | ("consensus development" or guideline* or "position statement*").ti,pt. |
| 10 | exp meta analysis/ |
| 11 | exp Meta-Analysis as Topic/ |
| 12 | exp "systematic review"/ |
| 13 | ((meta adj analys*) or (systematic* adj3 review*)).mp,pt. |
| 14 | 10 or 11 or 12 or 13 |
| 15 | exp controlled study/ |
| 16 | exp Randomized Controlled Trial/ |
| 17 | exp triple blind procedure/ |
| 18 | exp Double-Blind Method/ |
| 19 | exp Single-Blind Method/ |
| 20 | exp latin square design/ |
| 21 | randomised controlled trials.sd. (control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or "pragmatic clinical trial" or |
| 22 | (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square" or random*).mp,pt. |
| 23 | or/15-22 |
| 24 | exp comparative study/ |
| 25 | exp intervention studies/ |

- 26 exp Cross-Sectional Studies/
- 27 exp Cross-Over Studies/
- 28 exp Cohort Studies/
- 29 exp longitudinal study/
- 30 exp prospective study/
- 31 exp population research/
- 32 exp observational study/
- 33 exp clinical trial/
- 34 clinical study/
- 35 exp Evaluation Studies/
- 36 exp Evaluation Studies as Topic/
- 37 exp quantitative study/
- 38 exp validation studies/
- 39 exp experimental study/
- 40 exp quasi experimental study/
- 41 exp field study/
- 42 in vivo study/
- 43 exp panel study/
- 44 exp Pilot Projects/
- 45 exp pilot study/
- 46 exp prevention study/
- 47 exp replication study/
- 48 exp theoretical study/
- 49 exp Feasibility Studies/
- 50 exp trend study/
- 51 exp correlational study/
- 52 exp case-control studies/
- 53 exp confidence interval/
- 54 exp regression analysis/
- 55 exp proportional hazards model/
- 56 exp multivariate analysis/
- 57 exp qualitative study/
 - (multivariate or "comparative study" or "comparative survey" or "comparative analysis" or (intervention* adj2 study) or (intervention* adj2 trial) or "cross-sectional study" or "cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or "prevalence analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or "disease frequency survey" or crossover or "cross-over" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or "prospective study" or "prospective survey" or

"prospective analysis" or prospectiv* or (population adj3 (stud* or survey* or analys* or research)) or "concurrent study" or "concurrent survey" or "concurrent analysis" or "incidence study" or "incidence survey" or "incidence analysis" or (("follow-up" or followup) adj (stud* or survey or analysis)) or ((observation or observational) adj (study or survey or analysis)) or "case study" or "case series" or "clinical series" or "case studies" or "clinical study" or "clinical trial" or (("phase 0" or "phase 1" or "phase I" or "phase 2" or "phase II" or "phase 3" or "phase III" or "phase 4" or "phase IV") adj5 (trial or study)) or "evaluation study" or "evaluation survey" or "evaluation analysis" or "quantitative study" or "quantitative analys*" or "numerical study" or "validation study" or "validation survey" or "validation analysis" or "experimental study" or "experimental analysis" or "quasi experimental study" or "quasi experimental analysis" or "quasiexperimental study" or "quasiexperimental analysis" or "field study" or "field survey" or "field analysis" or "in vivo study" or "in vivo analysis" or "panel study" or "panel survey" or "panel analysis" or "pilot study" or "pilot survey" or "pilot analysis" or "pilot project" or ((prevention or preventive) adj3 (trial or study or analysis or survey)) or "replication study" or "replication analysis " or "replication trial" or "theoretical study" or "theoretical analysis " or "feasibility study" or "feasibility analysis" or "trend study" or "trend survey" or "trend analysis" or ((correlation* adj2 study) or (correlation* adj2 analys*)) or "case control study" or "case base study" or "case referrent study" or "case referent study" or "case referent study" or "case compeer study" or "case comparison study" or "matched case control" or "multicenter study" or "multi-center study" or study or trial or pilot or "odds ratio" or "confidence interval" or "regression analysis" or "least square" or "least squares" or (hazard* adj (model* or analys* or regression or ratio or ratios)) or "Cox model" or "Cox multivariate analyses" or "Cox multivariate analysis" or "Cox regression" or "Cox survival analyses" or "Cox survival analysis" or "Cox survival model" or "change analysis" or ((study or trial or random* or control*) and compar*) or qualitative or ((retrospective or "ex post facto") not "single arm")).mp.pt.

59 or/24-58

60 or/9-59

61 8 and 60

62 limit 61 to yr="2000 -Current"

limit 62 to (editorial or erratum or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient

63 education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in CCTR,CDSR,Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) PubMed not MEDLINE,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]

64 from 63 keep 1

65 (62 not 63) or 64

66 limit 65 to yr="2015 -Current"

67 remove duplicates from 66

68 65 not 66

69 remove duplicates from 68

70 67 or 69

ClinicalTrials.Gov

Condition or disease:

Breast Cancer

Other Terms:

"partial breast" OR "whole breast" or APBI or PBI or WBI

Intervention/treatment

APBI OR brachytherapy OR Contura OR IMRT OR IORT OR irradiation OR linac OR
MammoSite OR PBI OR proton OR radiation OR "radio therapy" OR "radio treatment" OR
radiotherapy OR radiotreatment OR SAVI OR "Single-entry catheter" OR WBI OR "x ray"

First Posted

01/01/2000 to 06/30/2021

Scopus

- 1 TITLE-ABS-KEY(APBI or brachytherap* or Contura or IMRT or IORT or irradiat* or linac or MammoSite or PBI or proton or radiation* or "radio therap*" or "radio treatment*" or radiotherap* or radiotreatment* or SAVI or "Single-entry catheter*" or WBI or "x ray*")
- 2 TITLE-ABS-KEY(((APBI or PBI or WBI) and breast) or "partial breast" or "whole breast")
- 3 TITLE-ABS-KEY("consensus development" or guideline* or "position statement*")
- 4 TITLE-ABS-KEY((meta W/1 analys*) or (systematic* W/3 review*))
- 5 TITLE-ABS-KEY((control* W/3 study) or (control* W/3 trial) or (randomized W/3 study) or (randomized W/3 trial) or (randomised W/3 study) or (randomised W/3 trial) or "pragmatic clinical trial" or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or "latin square" or random*)
- 6 TITLE-ABS-KEY(multivariate or "comparative study" or "comparative survey" or "comparative analysis" or (intervention* W/2 study) or (intervention* W/2 trial) or "cross-sectional study" or "cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or "prevalence analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or "disease frequency survey" or crossover or "cross-over" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or (population W/3 (stud* or survey* or analys* or research)) or "concurrent study" or "concurrent survey" or "concurrent analysis" or "incidence study" or "incidence survey" or "incidence analysis" or (("follow-up" or followup) W/1 (stud* or survey or analysis)) or ((observation or observational) W/1 (study or survey or analysis)) or "case study" or "case series" or "clinical series" or "case studies" or "clinical study" or "clinical trial" or (("phase 0" or "phase 1" or "phase I" or "phase 2" or "phase II" or "phase 3" or "phase III" or "phase 4" or "phase IV") W/5 (trial or study)) or "evaluation study" or "evaluation survey" or "evaluation analysis" or "quantitative study" or "quantitative analys*" or "numerical study" or "validation study" or "validation survey" or "validation analysis" or "experimental study" or "experimental analysis" or "quasi experimental study" or "quasi experimental analysis" or "quasiexperimental study" or "quasiexperimental analysis" or "field study" or "field survey" or "field analysis" or "in vivo study" or "in vivo analysis" or "panel study" or "panel survey" or "panel analysis" or "pilot study" or "pilot survey" or "pilot analysis" or "pilot project" or ((prevention or preventive) W/3 (trial or study or analysis or survey)) or "replication study" or "replication analysis" or "replication trial" or "theoretical study" or "theoretical analysis" or "feasibility study" or "feasibility analysis" or "trend study" or "trend survey" or "trend analysis" or ((correlation* W/2 study) or (correlation* W/2 analys*)) or "case control study" or "case base study" or "case referent study" or "case referent study" or "case referent study" or "case compeer study" or "case comparison study" or "matched case control" or "multicenter study" or "multi-center study" or study or trial or pilot or "odds ratio" or "confidence interval" or "regression analysis" or "least square" or "least squares" or (hazard* W/1 (model* or analys* or regression or ratio or ratios)) or "Cox model" or "Cox multivariate analyses" or "Cox multivariate analysis" or "Cox regression" or "Cox survival analyses" or "Cox

- survival analysis" or "Cox survival model" or "change analysis" or ((study or trial or random* or control*) and compar*) or qualitative or ((retrospective or "ex post facto") not "single arm"))
- 7 PUBYEAR AFT 1999
 - 8 1 and 2 and (3 or 4 or 5 or 6) and 7
 - 9 DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
 - 10 8 and not 9
 - 11 INDEX(embase) OR INDEX(medline) OR PMID(0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)
 - 12 10 and not 11

Search Strategies CQ 1

Ovid

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials July 2021, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to August 4, 2021, Embase 1974 to 2021 August 06 , Ovid MEDLINE® and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to August 06, 2021

Search Strategy:

- | # | Searches |
|----|--|
| 1 | exp Breast Neoplasms/rt [Radiotherapy] |
| 2 | exp Radiotherapy/ |
| 3 | exp Radiation/ |
| 4 | exp irradiation/ (APBI or brachytherap* or Contura or IMRT or IORT or irradiat* or linac or MammoSite or |
| 5 | PBI or proton or radiation* or “radio therap*” or “radio treatment*” or radiotherap* or radiotreatment* or SAVI or “Single-entry catheter*” or WBI or “x ray*”).ti,ab,hw,kw. |
| 6 | or/1-5 |
| 7 | ((APBI or PBI or WBI) and breast) or “partial breast” or “whole breast”).ti,ab,hw,kw. |
| 8 | 6 and 7 |
| 9 | ((patient* and (cost or costs or economic* or expense* or financ* or expenditure*) and (stress* or anxiet* or impact* or burden*)) or “financial toxicity”).ti,ab,hw,kw. |
| 10 | 8 and 9 |
| 11 | exp meta analysis/ |
| 12 | exp Meta-Analysis as Topic/ |
| 13 | exp “systematic review”/ |
| 14 | ((meta adj analys*) or (systematic* adj3 review*)).mp,pt. |
| 15 | 11 or 12 or 13 or 14 |
| 16 | exp controlled study/ |
| 17 | exp Randomized Controlled Trial/ |
| 18 | exp triple blind procedure/ |
| 19 | exp Double-Blind Method/ |
| 20 | exp Single-Blind Method/ |
| 21 | exp latin square design/ |
| 22 | randomised controlled trials.sd. ((control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or “pragmatic clinical trial” or |
| 23 | (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or “latin square” or random*).mp,pt. |
| 24 | or/16-23 |

- 25 exp comparative study/
- 26 exp intervention studies/
- 27 exp Cross-Sectional Studies/
- 28 exp Cross-Over Studies/
- 29 exp Cohort Studies/
- 30 exp longitudinal study/
- 31 exp prospective study/
- 32 exp population research/
- 33 exp observational study/
- 34 exp clinical trial/
- 35 clinical study/
- 36 exp Evaluation Studies/
- 37 exp Evaluation Studies as Topic/
- 38 exp quantitative study/
- 39 exp validation studies/
- 40 exp experimental study/
- 41 exp quasi experimental study/
- 42 exp field study/
- 43 in vivo study/
- 44 exp panel study/
- 45 exp Pilot Projects/
- 46 exp pilot study/
- 47 exp prevention study/
- 48 exp replication study/
- 49 exp theoretical study/
- 50 exp Feasibility Studies/
- 51 exp trend study/
- 52 exp correlational study/
- 53 exp case-control studies/
- 54 exp confidence interval/
- 55 exp regression analysis/
- 56 exp proportional hazards model/
- 57 exp multivariate analysis/
- 58 exp qualitative study/
- 59 exp "Surveys and Questionnaires"/
- 60 (multivariate or "comparative study" or "comparative survey" or "comparative analysis" or (intervention* adj2 study) or (intervention* adj2 trial) or "cross-sectional study" or "cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or "prevalence analysis" or "prevalence survey" or "disease frequency study" or

“disease frequency analysis” or “disease frequency survey” or crossover or “cross-over” or cohort* or “longitudinal study” or “longitudinal survey” or “longitudinal analysis” or “longitudinal evaluation” or longitudinal* or “prospective study” or “prospective survey” or “prospective analysis” or prospectiv* or (population adj3 (stud* or survey* or analys* or research)) or “concurrent study” or “concurrent survey” or “concurrent analysis” or “incidence study” or “incidence survey” or “incidence analysis” or (“follow-up” or followup) adj (stud* or survey or analysis)) or ((observation or observational) adj (study or survey or analysis)) or “case study” or “case series” or “clinical series” or “case studies” or “clinical study” or “clinical trial” or (“phase 0” or “phase 1” or “phase I” or “phase 2” or “phase II” or “phase 3” or “phase III” or “phase 4” or “phase IV”) adj5 (trial or study)) or “evaluation study” or “evaluation survey” or “evaluation analysis” or “quantitative study” or “quantitative analys*” or “numerical study” or “validation study” or “validation survey” or “validation analysis” or “experimental study” or “experimental analysis” or “quasi experimental study” or “quasi experimental analysis” or “quasiexperimental study” or “quasiexperimental analysis” or “field study” or “field survey” or “field analysis” or “in vivo study” or “in vivo analysis” or “panel study” or “panel survey” or “panel analysis” or “pilot study” or “pilot survey” or “pilot analysis” or “pilot project” or ((prevention or preventive) adj3 (trial or study or analysis or survey)) or “replication study” or “replication analysis “ or “replication trial” or “theoretical study” or “theoretical analysis “ or “feasibility study” or “feasibility analysis” or “trend study” or “trend survey” or “trend analysis” or ((correlation* adj2 study) or (correlation* adj2 analys*)) or “case control study” or “case base study” or “case referent study” or “case referent study” or “case referent study” or “case compeer study” or “case comparison study” or “matched case control” or “multicenter study” or “multi-center study” or study or trial or pilot or “odds ratio” or “confidence interval” or “regression analysis” or “least square” or “least squares” or (hazard* adj (model* or analys* or regression or ratio or ratios)) or “Cox model” or “Cox multivariate analyses” or “Cox multivariate analysis” or “Cox regression” or “Cox survival analyses” or “Cox survival analysis” or “Cox survival model” or “change analysis” or ((study or trial or random* or control*) and compar*) or qualitative or ((retrospective or “ex post facto”) not “single arm”) or “case study” or “case series” or “clinical series” or “case studies” or survey* or questionnaire*).mp.pt.

61 or/11-60

62 10 and 61

63 limit 62 to yr="2000 -Current"

limit 63 to (editorial or erratum or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient

64 education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in CCTR,CDSR,Embase,Ovid MEDLINE®,Ovid MEDLINE® Daily Update,Ovid MEDLINE® PubMed not MEDLINE,Ovid MEDLINE® In-Process,Ovid MEDLINE® Publisher; records were retained]

65 63 not 64

66 remove duplicates from 65

ClinicalTrials.Gov

Condition or disease:

Breast Cancer

Other Terms:

“partial breast” OR “whole breast” or APBI or PBI or WBI

Intervention/treatment:

APBI OR brachytherapy OR Contura OR IMRT OR IORT OR irradiation OR linac OR MammoSite OR PBI OR proton OR radiation OR “radio therapy” OR “radio treatment” OR radiotherapy OR radiotreatment OR SAVI OR “Single-entry catheter” OR WBI OR “x ray”

Outcome measure:

Financial toxicity

(patient and (cost or costs or economic or expense or financial or expenditure) and (stress or anxiety or impact or burden))

(patient and (economics or expenses or finance or finances or expenditures) and (stress or anxiety or impact or burden))

First Posted

01/01/2000 to 08/09/2021

Scopus

- 1 TITLE-ABS-KEY(APBI or brachytherap* or Contura or IMRT or IORT or irradiat* or linac or MammoSite or PBI or proton or radiation* or "radio therap*" or "radio treatment*" or radiotherap* or radiotreatment* or SAVI or "Single-entry catheter*" or WBI or "x ray*")
- 2 TITLE-ABS-KEY(((APBI or PBI or WBI) and breast) or "partial breast" or "whole breast")
- 3 TITLE-ABS-KEY((patient* and (cost or costs or economic* or expense* or financ* or expenditure*) and (stress* or anxiet* or impact* or burden*)) OR "financial toxicity")
- 4 TITLE-ABS-KEY((meta W/1 analys*) or (systematic* W/3 review*))
- 5 TITLE-ABS-KEY((control* W/3 study) or (control* W/3 trial) or (randomized W/3 study) or (randomized W/3 trial) or (randomised W/3 study) or (randomised W/3 trial) or "pragmatic clinical trial" or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or "latin square" or random*)
- 6 TITLE-ABS-KEY(multivariate or "comparative study" or "comparative survey" or "comparative analysis" or (intervention* W/2 study) or (intervention* W/2 trial) or "cross-sectional study" or "cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or "prevalence analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or "disease frequency survey" or crossover or "cross-over" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or (population W/3 (stud* or survey* or analys* or research)) or "concurrent study" or "concurrent survey" or "concurrent analysis" or "incidence study" or "incidence survey" or "incidence analysis" or (("follow-up" or followup) W/1 (stud* or survey or analysis)) or ((observation or observational) W/1 (study or survey or analysis)) or "case study" or "case series" or "clinical series" or "case studies" or "clinical study" or "clinical trial" or (("phase 0" or "phase 1" or "phase I" or "phase 2" or "phase II" or "phase 3" or "phase III" or "phase 4" or "phase IV") W/5 (trial or study)) or "evaluation study" or "evaluation survey" or "evaluation analysis" or "quantitative study" or "quantitative analys*" or "numerical study" or "validation study" or "validation survey" or "validation analysis" or "experimental study" or "experimental analysis" or "quasi experimental study" or "quasi experimental analysis" or "quasiexperimental study" or "quasiexperimental analysis" or "field study" or "field survey" or "field analysis" or "in vivo study" or "in vivo analysis" or "panel study" or "panel survey" or "panel analysis" or "pilot study" or "pilot survey" or "pilot analysis" or "pilot project" or ((prevention or preventive) W/3 (trial or study or analysis or survey)) or "replication study" or "replication analysis " or "replication trial" or "theoretical study" or "theoretical analysis " or "feasibility study" or "feasibility analysis" or "trend study" or "trend survey" or "trend analysis" or ((correlation* W/2 study) or (correlation* W/2 analys*)) or "case control study" or "case base study" or "case referent study" or "case referent study" or "case referent study" or "case compeer study" or "case comparison study" or "matched case control" or "multicenter study" or "multi-center study" or study or trial or pilot or "odds ratio" or "confidence interval" or "regression analysis" or "least square" or "least squares" or (hazard* W/1 (model* or analys* or regression or ratio or ratios)) or "Cox model" or "Cox multivariate analyses"

- or "Cox multivariate analysis" or "Cox regression" or "Cox survival analyses" or "Cox survival analysis" or "Cox survival model" or "change analysis" or ((study or trial or random* or control*) and compar*) or qualitative or ((retrospective or "ex post facto") not "single arm") or "case study" OR "case series" OR "clinical series" OR "case studies" or survey* or questionnaire*)
- 7 PUBYEAR AFT 1999 AND LANGUAGE(english)
- 8 1 and 2 and 3 and (4 or 5 or 6) and 7
- 9 DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
- 10 8 and not 9
- 11 INDEX(embase) OR INDEX(medline) OR PMID(0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)
- 12 10 and not 11