



## Evidence-based Practice Center Systematic Review Protocol

### Project Title: *Radiation Therapy for Bone Metastases*

Initial publication date if applicable: July 1, 2022

Amendment Date(s) if applicable: August 10, 2022

(Amendments Details—see Section VII)

## I. Background and Objectives for the Systematic Review

### *Nature and Burden of Bone Metastases*

Spine and non-spine bone metastases are common in advanced cancers, representing the third most common type of metastasis.<sup>1</sup> A 2020 population-based study<sup>2</sup> based on the Surveillance, Epidemiology, and End Results (SEER) database revealed that among patients with metastatic disease, particularly high incidence of metastatic bone disease (MBD) was seen from solid primary tumors originating from the prostate (89%), breast (54%), kidneys (39%) and lung (18% to 37%, depending on histology) with median survival of 25, 27, 6 months and 3 to 7 months, respectively, for these cancers when MBD is present. Severe pain and complications that compromise quality of life are the primary symptoms of MBD. Debilitating skeletal-related events (SREs) such as pathological fractures, metastatic spinal cord compression, myelosuppression, and hypercalcemia may contribute to increased pain and impaired function and are common.<sup>3,4</sup> The prognosis for patients with MBD is generally poor. Once cancer involves the bone, it can rarely be cured, therefore, palliation is the focus. Pain relief, improved quality of life, reduction in analgesic requirements, and stabilization or enhancement of skeletal function are primary palliative treatment goals. Treatment may also prevent SREs and enhance local tumor control and survival.<sup>3</sup>

### *Radiotherapy and Management of Bone Metastases*

External beam radiotherapy (EBRT) has been an integral component of palliative care for symptomatic MBD for decades as it provides substantial pain relief. While curative EBRT is delivered over frequent small radiation doses (fractions) to reduce long term permanent side effects in normal tissues, for palliative treatment, shorter courses of larger fraction size (hypofractionation) are delivered. Short-term side effects may include nausea, vomiting, emotional and physical fatigue, and skin irritation at the radiation site and are usually managed conservatively. Other longer term side effects may be mild to life-threatening, depending on the irradiated site and the sensitivity of surrounding tissues and organs, and may include radiation-induced fractures. Late term effects are less common with palliative radiation due to lower total radiation doses and shorter survival;<sup>5,6</sup> however, as patient survival lengthens, later term effects become more relevant. The evidence on this continues to evolve. Historically, conventional, two-

dimensional external beam radiotherapy (cEBRT) has been used for treatment of bone metastasis. Advances in three-dimensional imaging, computerization and use of linear accelerators or cyclotrons have improved the precision and consistency of radiation delivery techniques, potentially decreasing the radiation impact on healthy or sensitive tissue around the lesions. Newer techniques include three-dimensional conformal radiation therapy (3DCRT), which has largely replaced cEBRT for most applications and is generally considered the current standard, as well as intensity modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT). These advances may allow delivery of higher radiation doses, influencing frequency (fractionation) of treatment for initial palliative radiotherapy<sup>7</sup> and for re-radiation<sup>8</sup> of MBD, particularly for spinal lesions. There is also emerging evidence for use of these newer techniques in nonspine MBD.<sup>9</sup>

MBD is a heterogeneous disease. Planning for initial MBD radiotherapy (dose, fractionation) is complex. It involves consideration of primary tumor histology, patient prognosis and life expectancy, existing or predicted bone pathology, lesion characteristics (number, location, whether they are osteolytic, osteoblastic, or mixed), the mechanical stability of the affected bones, patient characteristics (e.g., sex, age, health and functional status, comorbidities), and the use of additional therapies.<sup>10,11</sup> These may include bone-modifying agents (e.g., bisphosphonates), bone-targeting radionuclides,<sup>3</sup> surgery including minimally invasive surgery, or minimally invasive procedures such as ablation, kyphoplasty, vertebroplasty or sacroplasty.<sup>12,13</sup> Commonly, such therapies are planned for use in concert with radiotherapy and are in addition to systemic anticancer therapies (cytotoxic agents, molecular therapies, and immunotherapies). As cancer treatment advances have enhanced patient survival, recurrence and the need for re-treatment of previously irradiated areas have become more common.<sup>10,14</sup> Additional considerations related to re-irradiation planning include the acuity and urgency, prediction of tissue recovery based on prior radiation dose fractionation, time since prior radiation and volume treated to evaluate re-radiation related toxicity and dose tolerance.<sup>14</sup> Side effects may be greater in patients undergoing re-radiation. Patients with recurrent pain after initial prior response, ongoing pain following a partial response, or no pain response may be considered for re-radiation.<sup>14</sup> Decision making in all scenarios involves multidisciplinary input, consideration of patient prognosis and preferences, and weighing benefits and harms. Treatment is tailored to individual patient circumstances.

The complexities associated with palliative radiotherapy planning noted above present numerous decisional dilemmas. While the general evidence on benefits and harms of palliative radiotherapy is widely understood, there is lack of clarity regarding subsets of patients who are most likely to benefit from specific palliative radiotherapy regimen (e.g., based on age, sex, primary tumor histology). In addition, evidence has also emerged related to use of additional therapies (e.g., minimally invasive surgical procedures, radionuclide therapy, interventional radiology procedures) in combination with radiotherapy; however, the impact on patient outcomes compared with radiotherapy alone is unclear.

Planning for either primary radiotherapy or retreatment must lead to decisions regarding overall radiation dose, dose fractions per treatment, frequency of treatment, and techniques for their delivery. There is substantial variation in how palliative radiotherapy is delivered to patients with MBD<sup>15-20</sup> and lack of consensus on indications for use of 3DCRT versus other advanced techniques or on optimal dose-fractionation schemes for techniques such as SBRT. A 2017 American Society for Radiation Oncology (ASTRO) guideline update<sup>21</sup> addressed use of palliative radiotherapy for initial primary treatment of symptomatic MBD to relieve pain and/or prevent morbidity as well as retreatment of lesions causing recurrent pain. It states that single 8 Gy fraction (SFRT) or higher doses (20 to 30 Gy) delivered over multiple fractions (5 to 10) for unirradiated painful MBD confer equivalent pain relief and indicates that re-treatment should be considered for recurrent or persistent pain. The guideline also states that high quality evidence supporting routine use of advanced techniques (e.g., SBRT) was limited leading to a recommendation that data were insufficient to routinely support use of advanced techniques for primary treatment or re-treatment of MBD. Subsequent to publication of the 2017 guideline, additional evidence has been published related to use of advanced techniques for initial radiotherapy<sup>9,22-25</sup> and reirradiation<sup>8</sup> (particularly SBRT), some of which also compare dose and fractionation schemes for primary palliative radiation. Therefore, for both initial radiation or re-radiation for palliation of MBD, synthesis of more recent evidence is needed to help resolve the above decisional dilemmas and facilitate update of clinical recommendations related to dose-fractionation schemes, use of advanced radiotherapy techniques and related harms. The 2017 guideline did not explicitly address the benefits and harms of therapies used in addition to EBRT compared with EBRT alone. Harms associated with the combination of therapies is of particular concern. Updated evidence synthesis will help inform shared decision-making between clinicians and patients related to palliative EBRT.

Evidence-based clinical guideline recommendations are intended to promote and improve healthcare quality by reducing variations in care and promoting effective therapy while discouraging ineffective and potentially hazardous interventions.<sup>26,27</sup> However, in order to impact clinical decision making, clinical practice, cost-conscious utilization, and patient outcomes, information on strategies, barriers and facilitators for guideline promotion and implementation are important to consider. Clarity regarding patient financial distress and hardship related to the clinical options for palliative radiotherapy for MBD would also be of value.

### **Rationale for Evidence Review**

To facilitate resolution of the decisional dilemmas identified above and provide updated evidence for clinical recommendations and shared decision-making, this systematic review will compare the effectiveness and harms of EBRT for palliative treatment of MBD in conjunction with additional therapies compared with EBRT alone. We will compare dose-fractionation schemes and techniques of delivery for both initial palliative radiation therapy and reradiation. We will also assess how effectiveness and harms may be modified by patient and clinical characteristics (e.g., age, sex, tumor histology) in an effort to identify subsets of patients who may most benefit from specific palliative

radiotherapy regimens and advanced techniques. Intended audiences for this review are those seeking to update clinical recommendations or guidelines as well as other stakeholders including clinicians, policy makers, patients, their caregivers and researchers. The American Society for Radiation Oncology (ASTRO) is the non-sponsoring partner for this review.

## **II. The Key Questions**

Provisional Key Questions, description of patients, interventions, comparators, outcomes, timing, settings, and study design (PICOTS), and an analytic framework for this topic were posted on the Agency for Healthcare Research and Quality (AHRQ) Website from January 25, 2022, until February 10, 2022. One public comment was received which focused on the use of SBRT and its potential for extending life expectancy. An additional key question was suggested. It focused on consideration of patient disease characteristics (e.g., tumor location, disease burden) as well as technical requirements and impact of the technology, treatment intent, timing of radiation therapy relative to other treatments, use and deferral of systemic treatments, and survival-specific outcomes. Factors such as patient and disease characteristics are already part of the key questions and PICOTS. Aspects of the suggested question related to technological advances, technology impact, and timing of treatments were considered beyond the scope and resources for this review.

The key questions, analytic framework and PICOTS table below incorporate input from Key Informants and a multidisciplinary Technical Expert Panel.

**Key Questions:** The Key Questions (KQs) for this review are as follows:

**KQ 1:** What is the effectiveness and what are the harms of EBRT in the palliative treatment of bone metastases in symptomatic adults when combined with additional therapies (e.g., , surgery, radionuclide therapy, bisphosphonate therapy, ablation kyphoplasty/vertebroplasty) compared with EBRT alone?

**KQ 2:** For symptomatic adults with bone metastases who will receive initial radiation for palliation, what is the comparative effectiveness and what are the comparative harms of dose-fractionation schemes and techniques for delivery (e.g., three-dimensional conformal radiation therapy, stereotactic body radiation)?

**KQ 3:** For symptomatic adults with bone metastases who will receive re-irradiation for palliation, what is the comparative effectiveness and what are the comparative harms of dose-fractionation schemes and techniques for delivery (e.g., three-dimensional conformal radiation therapy, stereotactic body radiation)?

For all key questions, we will look at whether treatment effects and harms are modified by factors related to patient and clinical characteristics (e.g., age, sex, social determinants of health, primary tumor histology, site of metastases).

**Contextual Questions:** Following the methods of the U.S. Preventive Services Task Force (USPSTF)<sup>28</sup> contextual questions represent issues in a review for which a valid, but not necessarily systematic, summary of current research is needed in order to provide context on specific issues. See the Methods section below for more details.

**CQ 1:** What are common barriers and facilitators to implementing guidance in radiation oncology, specifically related to palliative radiation for MBD?

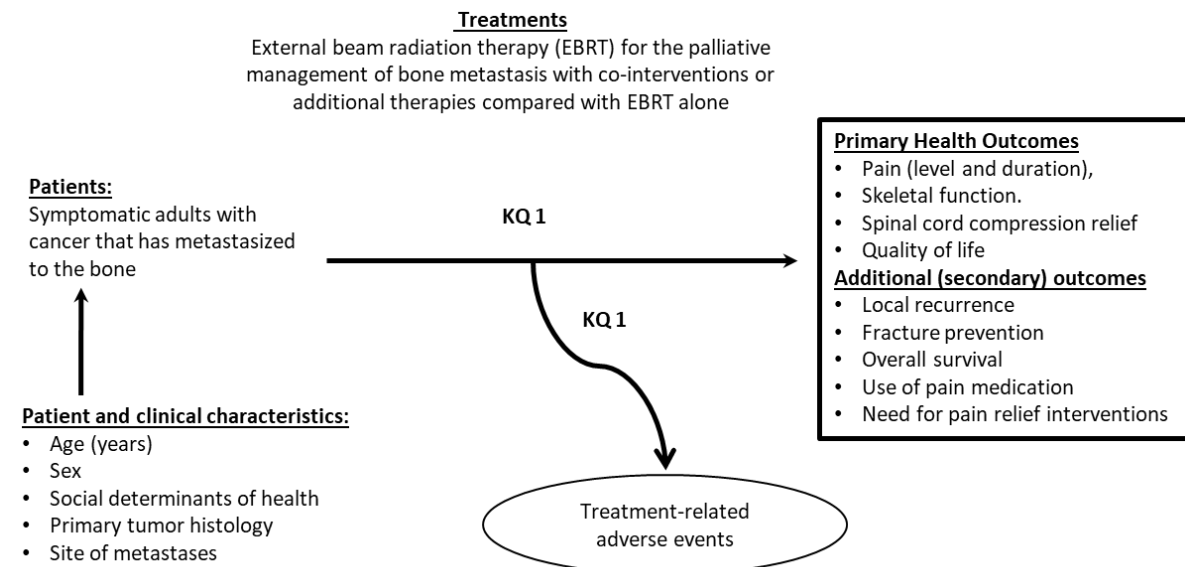
**CQ 2:** What strategies could be used to promote the use and implementation of guidance in radiation oncology, specifically related to palliative radiation for MBD?

**CQ 3:** In symptomatic patients considered for palliative radiation therapy for MBD, to what extent does patient financial distress/hardship differ between EBRT dose/fraction schemes or technique?

For purposes of this report, palliative radiation therapy is defined as EBRT delivered with the intent of reducing patient symptoms related to MBD, promoting skeletal stability, and facilitating local control as an objective versus extending life or treating patient disease beyond the MBD.

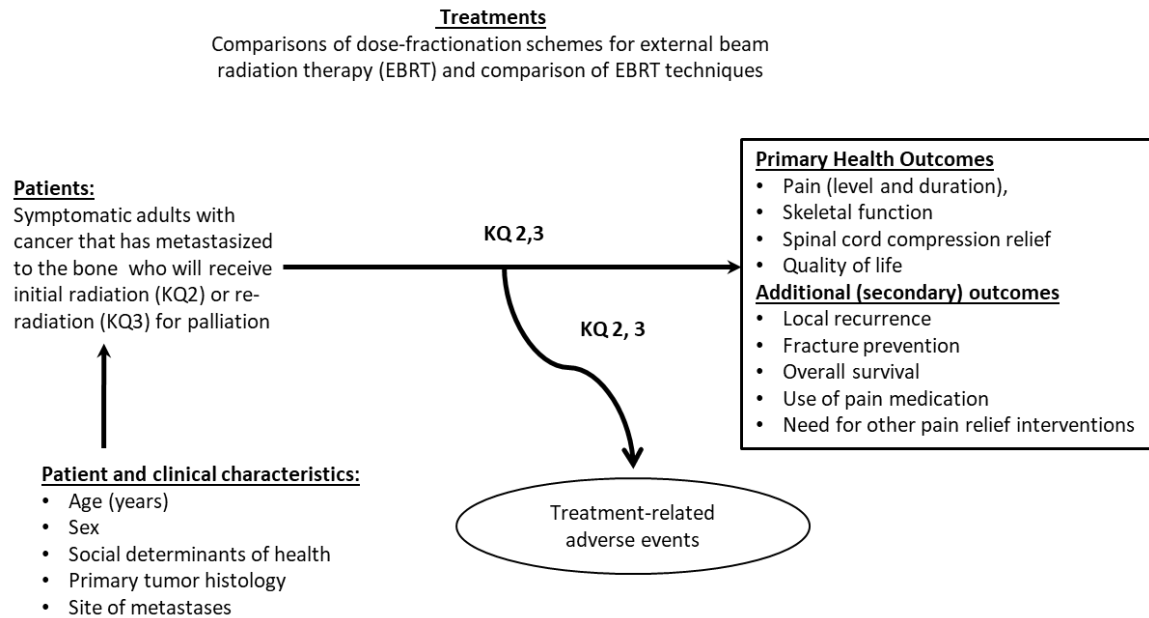
### III. Analytic Framework

**Figure 1. Draft analytic framework for Key Question 1**



KQ=Key Question; EBRT=external beam radiation therapy

**Figure 2. Draft analytic framework for Key Questions 2 and 3**



KQ=Key Question; EBRT=external beam radiation therapy.

## IV. Methods

### Criteria for Inclusion/Exclusion of Studies in the Review

The criteria for inclusion and exclusion of studies for the systematic review will be based on the Key Questions and the specific criteria listed below in Table 1.

**Table 1. PICOTS: Inclusion and exclusion criteria**

	Inclusion	Exclusion
<b>Population</b>	<p><b>KQ 1:</b> Symptomatic adults with cancer that has metastasized to the bone.</p> <p><b>KQ 2:</b> Symptomatic adults with bone metastases who will receive initial palliative radiation</p> <p><b>KQ 3:</b> Symptomatic adults with bone metastases who will receive re-radiation for palliation</p> <p><b>For all KQ:</b> Consider patient and clinical characteristics (e.g., age, sex, social determinants of health, primary tumor histology, site of metastases)</p>	<ul style="list-style-type: none"> <li>• Patients &lt;18 years old</li> <li>• Asymptomatic patients</li> <li>• Patients with primary bone tumors</li> </ul>
<b>Interventions</b>	<p><b>KQ 1:</b> External beam radiation therapy for the palliative management of bone metastasis <i>with co-interventions</i>, additional therapies (e.g., , surgery,</p>	<p><b>KQ 1, 2, 3:</b> Proton beam therapy</p> <p>KQ1 Brachytherapy</p>

	radionuclide therapy, bisphosphonate therapy, ablation, kyphoplasty/vertebroplasty)  <b>KQ 2 and KQ 3:</b> Comparisons of dose-fractionation schemes for EBRT, comparisons of EBRT techniques (e.g., conventional RT vs. SBRT, SBRT vs. IMRT)	
<b>Comparators</b>	<b>KQ 1:</b> No cointervention (i.e., EBRT alone)  <b>KQ 2 and KQ 3:</b> Comparisons of dose-fractionation schemes, comparisons of EBRT modalities/techniques	
<b>Outcomes</b>	<b>Effectiveness:</b> Primary outcomes <ul style="list-style-type: none"> <li>• Pain (level and duration)</li> <li>• Skeletal function</li> <li>• Relief of spinal cord compression</li> <li>• Quality of life</li> </ul> Additional (secondary) outcomes <ul style="list-style-type: none"> <li>• Local recurrence</li> <li>• Fracture prevention</li> <li>• Overall survival</li> <li>• Need for re-radiation</li> <li>• Use of pain medication, need for other interventions for pain relief</li> </ul> <b>Harms and adverse events</b> Harms (e.g., rate of radiation/treatment toxicity, radiation-induced fracture rates, reduced mobility, reduced independence), adverse events (pain flare, radiation recall, fatigue, skin changes, etc.)	<ul style="list-style-type: none"> <li>• Non-validated measurement instruments for clinician or patient rated outcomes (e.g., pain, function, HRQOL)</li> </ul>
<b>Timing</b>	Any (timing may depend on treatments provided and outcomes assessed)	None
<b>Setting</b>	Any	None
<b>Study design and publication dates</b>	<b>All KQ:</b> Focus will be on the best evidence available that permits direct comparisons to answer key questions  RCTs will be initially sought; in the absence of RCTs, prospective comparative studies that control for confounding will be considered; if no comparative prospective studies are available, retrospective comparative studies that control for confounding will be considered.  In the absence of comparative studies, single arm (e.g., case series, pre-post studies) may be considered  For evaluation of harms, comparative cohort and case-control studies will be included; we will focus on studies specifically designed to evaluate harms.  Studies of at least 10 patients per treatment arm	<b>GENERAL</b> <ul style="list-style-type: none"> <li>• Dosimetry modeling studies</li> <li>• Non-human studies</li> <li>• NRSI for effectiveness if RCTs are available</li> <li>• Studies with &lt;10 patients per arm</li> <li>• Single arm studies (unless no comparative studies); if used, exclude studies of &lt;10 patients</li> <li>• Case reports</li> </ul> <b>Publication dates:</b> Prior to 1985  <b>Publication types:</b> Conference abstracts or proceedings, editorials, letters, white papers, citations that have not been peer-reviewed, single site reports of multi-site studies

EBRT = external beam radiation therapy; HRQOL = health-related quality of life; IMRT = intensity modulated radiation therapy; KQ = key question; NRSI = nonrandomized studies of intervention; RCT = randomized controlled trial; RT = radiation therapy; SBRT = stereotactic radiation therapy.

**Study Designs:** We will use a best evidence approach<sup>29</sup> and randomized controlled trials (RCTs) will be sought initially. Given that there will likely be a paucity of RCTs available to answer some key questions, prospective comparative studies that control for confounding will be considered; if none are identified, retrospective comparative studies that control for confounding will be considered. In the absence of comparative studies, single arm (e.g., case series, pre-post studies) with at least 10 patients may be considered. For evaluation of harms, we will include comparative cohort and case-control studies with a focus on those specifically designed to evaluate harms.

**Non-English Language Studies:** We will restrict to English-language articles but will review English language abstracts of non-English language articles to identify studies that would otherwise meet inclusion criteria, to assess the likelihood of language bias.

### **Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions**

**Publication Date Range:** Searches will be conducted for relevant studies published after January 1, 1985 for all key questions. Electronic literature searches will be updated while the draft report is posted for public comment and peer review to capture any new publications. Literature identified during the updated search will be assessed using the same process of dual review as all other studies considered for inclusion in the report. If any pertinent new literature is identified for inclusion in the report, it will be incorporated before the submission of the final report.

**Literature Databases:** MEDLINE® (PubMed), EMBASE, the Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews will be searched. Appendix A contains our sample MEDLINE® search strategy which will be adapted to search the other databases

**Supplemental Evidence and Data for Systematic review (SEADS):** Manufacturers and other stakeholders of included interventions will be informed about submitting information relevant to this review using a Federal Register notification. A portal about the opportunity to submit information will be made available on the EHC website.

**Hand Searching:** Reference lists of included articles will also be reviewed for includable literature.

**Contacting Authors:** If information regarding methods or results appears to be omitted from the published results of a study, or if we are aware of unpublished data, we will query the authors to obtain this information.

### **Process for Selecting Studies**

In accordance with the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*,<sup>30</sup> we will use the pre-established criteria above to screen citations (titles and



abstracts) identified through our searches or SEADS submissions to determine eligibility for full-text review. We will use DistillerSR® to improve efficiency in screening articles and risk of bias assessment. Given the likely paucity of RCTs for portions of this review, we will include NSRI. We will follow a “best-evidence” approach<sup>29</sup> and to the extent possible, focus on comparative NRSI which control for confounding in the absence of RCTs. We will focus on primary studies and review systematic review (SR) references for relevant studies as it is unlikely that SRs will fully answer the key questions. If all studies in a systematic review meet inclusion criteria and report on outcomes of interest to this review, consideration will be given to updating the SR analyses with new evidence and the totality of the evidence will be evaluated. All excluded abstracts will be dual reviewed to assure accuracy for inclusion. All citations deemed appropriate for inclusion by at least one reviewer will be retrieved. Each full-text article will be independently reviewed for eligibility by two team members, including any articles suggested by Technical Expert Panel (TEP) members, peer reviewers or that arise from the public posting process. Any disagreements will be resolved by consensus. A record of studies excluded at the full-text level with reasons for exclusion will be maintained.

We will consider gray literature searches for additional information on barriers, facilitators and strategies for guideline promotion and implementation and on patient financial burden/distress with a focus on radiation oncology for palliation of bone metastasis to answer the contextual questions.

### **Data Abstraction and Data Management**

To capture information related to intervention heterogeneity and complexity and heterogeneity across enrolled populations, we will create an organization framework and tailor detailed data abstraction tools following principles from the Template for Intervention Description and Replication (TIDieR) checklist.<sup>31</sup> Using standardized templates, data from included studies will be abstracted into categories that include but are not limited to: study design, year, setting, country, funding, sample size, eligibility criteria, attrition, radiation therapy delivery (type, dose, frequency/fractions, prior and additional radiation), prior and concurrent treatments, population and clinical characteristics including key subgroups (gender, age), primary tumor histology, characteristics (e.g., size), location (spine, non-spine and specific location including weightbearing structures) and numbers of metastatic lesions treated, effectiveness-related outcomes (e.g., validated pain, function and quality of life measures), local tumor control and overall survival as well as treatment-related side effects/harms. Information on confounders (in addition to those already identified for abstraction related to patient and MBD characteristics such as presence of fracture, performance status) and methods of adjustment for them will also be abstracted as will data on followup. Information relevant for assessing applicability will be abstracted, including the characteristics of the population, interventions and the number of patients enrolled relative to the number assessed for eligibility. All extracted study data will be verified for accuracy and completeness by a second team member.

## Assessment of Methodological Risk of Bias of Individual Studies

We will use predefined criteria to assess the quality of included studies. We will focus on studies with the least potential for bias and the fewest limitations. RCTs will be assessed based on criteria and methods established in the *Cochrane Handbook for Systematic Reviews of Interventions (Chapter 8.5 Risk of Bias Tool)*<sup>32</sup> and precepts for appraisal developed by the Cochrane Back and Neck Group.<sup>33</sup> Because nonrandomized studies are at increased risk of selection bias and confounding, we will assess risk of bias using instruments tailored to observational studies<sup>34</sup> that consider methods of patient selection (e.g., consecutive patients, use of an inception cohort) and appropriate control for confounding of relevant prognostic factors. We will downgrade studies that do not provide randomization, allocation, and/or blinding details, have a high rate of study loss-to-followup, or demonstrate selective reporting or other bias accordingly. These criteria and methods will be used in concordance with the approach recommended in the chapter, *Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions*,<sup>35</sup> from the *AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.<sup>30</sup> Studies will be rated as being “good,” “fair,” or “poor” quality as described below in Table 2:

**Table 2. Criteria for grading the quality of individual studies**

Rating	Description and Criteria
<b>Good</b>	<ul style="list-style-type: none"> <li>Least risk of bias, results generally considered valid</li> <li>Employ valid methods for selection, inclusion, and allocation of patients to treatment; report similar baseline characteristics in different treatment groups; clearly describe attrition and have low attrition; use appropriate means for preventing bias (e.g., blinding of patients, care providers, and outcomes assessors); and use appropriate analytic methods (e.g., intention-to-treat analysis)</li> </ul>
<b>Fair</b>	<ul style="list-style-type: none"> <li>Susceptible to some bias but not enough to necessarily invalidate results</li> <li>May not meet all criteria for good quality, but no flaw is likely to cause major bias; the study may be missing information making it difficult to assess limitations and potential problems</li> <li>Category is broad; studies with this rating will vary in strengths and weaknesses; some fair-quality studies are likely to be valid, while others may be only possibly valid</li> </ul>
<b>Poor</b>	<ul style="list-style-type: none"> <li>Significant flaws that imply biases of various kinds that may invalidate results; “fatal flaws” in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems with intervention delivery</li> <li>Studies are at least as likely to reflect flaws in the study design or execution as the true difference between the compared interventions</li> <li>Considered to be less reliable than higher quality studies when synthesizing the evidence, particularly if discrepancies between studies are present</li> </ul>

Each study evaluated will independently be dual reviewed for quality by two team members. Any disagreements will be resolved by discussion and consensus.

## Data Synthesis

We will construct evidence tables identifying the study and patient characteristics (as discussed above), results of interest, and quality ratings for all included studies, as well as summary tables and/or figures to highlight the main findings. We will review and highlight studies by using a hierarchy-of-evidence approach, where the best evidence is

the focus of our synthesis for each Key Question. We will analyze randomized trials and NRSI separately and report them separately unless findings are very consistent across study designs and the studies are clinically homogeneous. Studies with the least risk of bias will be summarized separately and compared with summarized results from poorer-quality studies.

Findings will be synthesized qualitatively (e.g., ranges and descriptive analysis, with interpretation of results) and quantitatively (meta-analysis) when appropriate. To address anticipated heterogeneity in reported outcomes, variation in their definitions and criteria for what constitutes response, we will focus on validated outcomes for pain, function, and quality of life. We will also seek TEP input regarding outcomes and their prioritization. We will consider classifying the magnitude of effects for continuous measures of pain and function using a similar system as in prior AHRQ reviews on pain<sup>36-40</sup> and will evaluate the proportion of patients meeting thresholds for clinically important differences (e.g., >30% pain relief) when reported. For analysis of continuous measures across the same outcome measures (e.g., VAS for pain) we will report mean differences and use standardized mean differences for outcomes measures with similar constructs together with 95% confidence intervals.

We will consider pooling studies if there are two to five clinically and methodologically comparable studies.<sup>41,42</sup> For NRSI, pooled estimates will be based on author-reported effect estimates that adjust for key confounders. Sensitivity and subgroup analyses will be performed to explore statistical heterogeneity and differences by study quality, study design, intervention differences, patient characteristics (e.g., age, sex, primary tumor histology, use of additional therapies), and outcome measurement as data permit. Sensitivity analyses related to publication date will be considered. We will summarize within-study analyses of subgroup differences and perform study-level analyses on key demographic, intervention, and clinical factors as data permit in attempt to evaluate differential effectiveness and harms as data permit. Applicability to U.S. practice settings will be assessed based on the Evidence-based Practice Center (EPC) Methods Guide, using the PICOTS framework.<sup>43</sup>

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

Outcomes to be assessed for strength of evidence were prioritized as primary based on input from the Technical Expert Panel. Based on this prioritized list, the strength of evidence for comparison-outcome pairs within each KQ will be initially assessed by one researcher for each clinical outcome (see PICOTS) by using the approach described in the *Methods Guide for Effectiveness and Comparative Effectiveness Review*.<sup>30</sup> To ensure consistency and validity of the evaluation, the initial assessment will be independently reviewed by at least one other experienced investigator using the following criteria:

- Study limitations (low, medium, or high level of study limitations)
  - This is the degree to which studies for a given outcome are likely to have reduced bias based on study design, analysis, and conduct. The aggregate risk of bias across individual studies reporting an outcome is considered.
- Consistency (consistent, inconsistent, or unknown/not applicable)

- This is the degree to which studies report similar magnitudes of effect (i.e., range sizes are similar) or same direction of effect (i.e., effect sizes have the same sign)
- Directness (direct or indirect)
  - This is degree to which the outcome is directly or indirectly related to health outcomes of interest. Patient centered outcomes are considered direct
- Precision (precise or imprecise)
  - Describes the level of certainty of the effect estimate for a particular outcome with a precise estimate being one that allows a clinically useful conclusion. This may be based on sample size sufficiency and number of events. If these are adequate, the interpretation of the confidence interval is also considered. When quantitative synthesis is not possible, sample size and assessment of variance within individual studies will be considered.
- Reporting bias (suspected or undetected)
  - Publication bias, selective outcome reporting, and selective analysis reporting are types of reporting bias. Reporting bias is difficult to assess as systematic identification of unpublished evidence is challenging. If sufficient numbers of RCTs (>10) are available, quantitative funnel plot analysis may be done.

The strength of evidence will be assigned an overall grade of high, moderate, low, or insufficient according to a four-level scale (Table 3) by evaluating and weighing the combined results of the above domains.

**Table 3. Description of the strength of evidence grades**

<b>Strength of Evidence</b>	<b>Description</b>
<b>High</b>	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
<b>Moderate</b>	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
<b>Low</b>	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
<b>Insufficient</b>	We are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. The body of evidence has unacceptable deficiencies which precludes reaching a firm conclusion. If no evidence is available, it will be noted as “no evidence”

Bodies of evidence consisting of RCTs are initially considered as high strength while bodies of comparative observational studies begin as low-strength evidence. The strength of the evidence may be downgraded based on the limitations described above. There are also situations where the observational evidence may be upgraded (e.g., large magnitude of effect, presence of dose-response relationship or existence of plausible unmeasured confounders), if there are no downgrades on the primary domains, as described in the

AHRQ Methods Guide.<sup>30,35</sup> Where both RCTs and observational studies are included for a given intervention-outcome pair, we follow the additional guidance on weighting RCTs over observational studies, assessing consistency across the two bodies of evidence, and determining a final rating.<sup>30</sup>

Summary tables will include ratings for individual strength of evidence domains (risk of bias, consistency, precision, directness) based on the totality of underlying evidence identified.

### **Assessing Applicability**

Applicability will be assessed in accordance with the AHRQ's Methods Guide,<sup>30</sup> using the PICOTS framework. Applicability refers to the degree to which outcomes associated with the intervention are likely to be similar across patients and settings relevant to the care of patients undergoing palliative radiation therapy for MBD based on the populations, interventions comparisons and outcomes synthesized across included studies. Multiple factors identified a priori that are likely to impact applicability include primary tumor histology, patient prognosis and life expectancy, lesion characteristics (number, location, whether they are osteolytic, osteoblastic, or mixed), characteristics of enrolled patient populations (e.g., sex, age, social determinants of health, health and functional status, comorbidities) and methods of radiation delivery. Review of abstracted information on these factors will be used to assess situations for which the evidence is most relevant and to evaluate applicability to real-world clinical practice in typical U.S. settings. We will provide a qualitative summary of our assessment.

### **Contextual Questions**

We plan to follow the methods of the USPSTF to evaluate the contextual questions.<sup>28</sup> A targeted search will be designed by a medical librarian with experience in searching for contextual question evidence for USPSTF reviews, including searching for systematic and narrative reviews. The team will also identify any information relevant to these questions opportunistically, while reviewing comprehensive literature searches for KQs, and will incorporate relevant information from TEP calls.

### **V. References**

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## VI. Definition of Terms

None

## VII. Summary of Protocol Amendments

**Table 4. Summary of Protocol Amendments**

Date	Section	Original Protocol	Revised Protocol	Rationale
08/10/2022	I. Background and Objectives for the Systematic Review.	No wording related to treatment response	The following paragraph was added: In addition to the complexity and heterogeneity of patients, clinical conditions and tumor characteristics, a lack of consensus on how response	Provides context regarding how treatment response is defined. It will set the stage for discussing how treatment response



	<i>Radiotherapy and Management of Bone Metastases</i>		to palliative treatment for MBD is best defined presents a challenge for this review. A variety of criteria and composite outcomes have been suggested. We will focus on pain, function and quality-of-life metrics, acknowledging that systematic reviews comparing dose and fractionation schemes for palliative radiation of MBD have noted heterogeneity in definitions used in included studies for pain response. <sup>1,2</sup> Criteria involving use of imaging (e.g., CT, MRI, PET, plain radiography) for lesion characterization and quantification have been suggested for evaluating treatment response. <sup>3-5</sup> A recent guideline, however, discourages routine imaging assessment following treatment of uncompleate MBD. <sup>6</sup> Anecdotaly, in clinical practice there is substantial variability in how and whether imaging may be used to assess treatment response.	may be reported in the included studies
08/10/2022	II. The Key Questions	<p>Original ordering and wording of Key Questions:</p> <p><b>KQ 1:</b> What is the effectiveness and what are the harms of EBRT in the palliative treatment of bone metastases in symptomatic adults when combined with additional therapies (e.g., surgery, radionuclide therapy, bisphosphonate therapy, ablation kyphoplasty/ vertebroplasty) compared with EBRT alone?</p> <p><b>KQ 2:</b> For symptomatic adults with bone metastases who will receive initial radiation for palliation, what is the comparative effectiveness and what are the comparative harms of dose-fractionation schemes and techniques for delivery (e.g., three-</p>	<p>Reordering and wording revisions to Key Questions:</p> <p><b>KQ 2 and 3</b> from the original protocol were reordered to become <b>KQ 1 and 2</b> respectively. No wording was changed.</p> <p><b>KQ 1</b> from the original protocol was reordered to be <b>KQ 3</b> and was reworded as follows:</p> <p><b>KQ 3:</b> What is the effectiveness and what are the harms of EBRT in the palliative treatment of bone metastases in symptomatic adults for the following:</p> <p>a) EBRT compared with another single MBD treatment modality (e.g., surgery, radionuclide therapy, bisphosphonate therapy, ablation kyphoplasty/ vertebroplasty)</p> <p>b) EBRT combined with another treatment modality (e.g., surgery,</p>	<p>Reordering of the questions was felt to provide additional clarity and focus on the primary decisional dilemmas to be addressed.</p> <p>The rewording of reordered KQ3 better reflects the non-sponsoring partner's intended question and provides additional clarity for operationalization for the review.</p>

		dimensional conformal radiation therapy, stereotactic body radiation)?  <b>KQ 3:</b> For symptomatic adults with bone metastases who will receive re-irradiation for palliation, what is the comparative effectiveness and what are the comparative harms of dose-fractionation schemes and techniques for delivery (e.g., three-dimensional conformal radiation therapy, stereotactic body radiation)?	radionuclide therapy, bisphosphonate therapy, ablation kyphoplasty/vertebroplasty) compared with EBRT alone?  c) EBRT combined with another treatment modality (e.g., surgery, radionuclide therapy, bisphosphonate therapy, ablation kyphoplasty/vertebroplasty) compared with the other (same) treatment modality alone?	
08/10/2022	III. Analytic Frameworks	Original ordering and wording of Analytic Frameworks:  <b>Figure 1.</b> Draft analytic framework for Key Question 1 The paragraph under “Treatments”: External beam radiation therapy (EBRT) for palliative management of bone metastasis with co-interventions or additional therapies compared with EBRT alone  <b>Figure 2.</b> Draft analytic framework for Key Questions 2 and 3	Reordering and wording revisions to Analytic Frameworks:  <b>Figure 1</b> from the original protocol was reordered to <b>Figure 2</b> and retitled “ <b>Draft analytic framework for Key Question 3</b> ” and was reworded as follows: <ul style="list-style-type: none"> <li>• The paragraph under “Treatments” was changed to the following: External beam radiation therapy (EBRT) for palliative management of bone metastasis compared with another bone metastasis treatment; EBRT combined with a co-intervention or additional therapy compared with EBRT alone or the co-intervention or additional treatment alone.</li> <li>• KQ 1 was changed to KQ 3 above each arrow in the flow chart.</li> </ul> <b>Figure 2</b> was changed to <b>Figure 1</b> and retitled “ <b>Draft analytic framework for Key Questions 1 and 2</b> ”. No wording was changed other than changing KQ 2, 3 to KQ 1, 2, respectively, in the paragraph describing the patient population and above each arrow in the flow chart.	These changes were made for consistency with/to reflect the reordering of and the edits to the Key Questions.
08/10/2022	IV. Methods; Table 1. PICOTS:	<b>Population:</b>	<b>Population:</b>	This change was made for consistency with/to

	Inclusion and exclusion criteria.	<p><b>KQ 1:</b> Symptomatic adults with bone metastases who will receive initial palliative radiation</p> <p><b>KQ 2:</b> Symptomatic adults with bone metastases who will receive re-radiation for palliation</p> <p><b>KQ 3:</b> Symptomatic adults with cancer that has metastasized to the bone.</p> <p><b>For all KQ:</b> Patients with either complicated or uncomplicated bone metastases will be included</p> <p>Consider patient and clinical characteristics (e.g., age, sex, social determinants of health, primary tumor histology, site of metastases)</p>	<p>The KQs were reordered to reflect the changes made in the Key Question section (as above): KQ 1 was changed to KQ 3, KQ 2 to KQ 1, and KQ 3 to KQ 2. No wording was changed.</p> <p>Under the heading “For all KQ”, the following sentence was added: Patients with either complicated or uncomplicated bone metastases will be included</p>	<p>reflect the reordering of the Key Questions.</p> <p>The addition of the sentence about complicated and uncomplicated bone metastases was added for clarity.</p>
08/10/2022	IV. Methods; Table 1. PICOTS: Inclusion and exclusion criteria.	<p><b>Interventions:</b></p> <p><b>KQ 1:</b> External beam radiation therapy for the palliative management of bone metastasis <i>with co-interventions</i>, additional therapies (e.g., surgery, radionuclide therapy, bisphosphonate therapy, ablation, kyphoplasty/vertebroplasty)</p> <p><b>KQ 2 and KQ 3:</b> Comparisons of dose-fractionation schemes for EBRT, comparisons of EBRT techniques (e.g., conventional RT vs. SBRT, SBRT vs. IMRT)</p> <p><b>Comparators:</b></p> <p><b>KQ 1:</b> No cointervention (i.e., EBRT alone)</p> <p><b>KQ 2 and KQ 3:</b> Comparisons of dose-</p>	<p><b>For all KQs for both Interventions and Comparators:</b></p> <p>The KQs were reordered to reflect the changes made in the Key Question section (as above): KQ 1 was changed to KQ 3 and KQs 2 and 3 were changed to KQs 1 and 2, respectively.</p> <p><b>For KQs 1 and 2 (previously KQs 2 and 3) for both interventions and comparators:</b> no wording was changed.</p> <p><b>For KQ 3 (previously KQ 1),</b> the wording was changed to reflect the revisions made in the Key Question section (as above).</p> <p><b>For Interventions:</b></p> <p><b>KQ 3:</b> External beam radiation therapy for the palliative management of bone metastasis a) alone, or b) and c) <i>with co-interventions</i>, additional therapies (e.g., surgery,</p>	<p>These changes were made for consistency with/to reflect the reordering of and the edits to the Key Questions.</p>

		fractionation schemes, comparisons of EBRT modalities/techniques	radionuclide therapy, bisphosphonate therapy, ablation kyphoplasty /vertebroplasty)  <b>For Comparators</b> <b>KQ 3:</b> a) another single MBD treatment, b) EBRT alone c) the same cointervention /additional therapy alone	
08/10/2022	IV. Methods; Table 1. PICOTS: Inclusion and exclusion criteria.	<b>Study design</b>  Inclusion criteria states that only studies with ≥10 patients per treatment arm will be included.  Exclusion criteria states that studies with <10 patients per arm or single arm studies (if used) with <10 patients total will be excluded.	<b>Study design</b>  For both the inclusion and exclusion criteria, the cut-off of 10 patients was increased to 20 patients	Increasing the sample size was felt to improve representativeness of included populations, and to enhance the precision and potential to detect effects and harms

CT = computed tomography; EBRT = external beam radiation therapy; IMRT = intensity modulated radiation therapy; KQ = key question; MBD = metastatic bone disease; MRI = magnetic resonance imaging; NRSI = nonrandomized studies of intervention; PET = positron emission tomography; PICOTS = population, intervention, comparator, outcome, timing, setting; RCT = randomized controlled trial; RT = radiation therapy; SBRT = stereotactic radiation therapy.

## References for Protocol Amendments

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## **VIII. Review of Key Questions**

The Agency for Healthcare Research and Quality (AHRQ) will post the Key Questions on the AHRQ Effective Health Care Website for public comment. The Evidence-based Practice Center (EPC) will refine and finalize the Key Questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). All input is intended to ensure that the key questions are specific and relevant.

## **IX. Key Informants**

Key Informants are the end users of research, including 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 identifying the Key Questions for research that will inform healthcare decisions. The EPC will solicit input from Key Informants when developing questions for the systematic review. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed 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. They are 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 results in 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 nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts 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.

TEP input will be sought to hone and re-affirm methods in the draft protocol, including perspectives on proposed KQ and PICOTS changes and managing challenges and reporting to enhance usability and inform meaningful presentation of the report.

## **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 preparation of 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 three months after the 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 may not have any financial conflict of interest greater than \$5,000. Peer reviewers who disclose potential business or professional conflicts of interest may 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. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

## **XIII. Role of the Funder**

This project was funded under Contract No. 75Q80120D00006 from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ Task Order Officer reviewed 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 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. Sample Search Strategies: Radiation Therapy for Bone Metastases

Strategies will be adapted for data bases to be searched.

**KQ1:** ("bone metastases"[Title/Abstract] OR "bone neoplasms/radiotherapy"[MeSH Terms]) AND ("external beam radiation therapy"[Title/Abstract] OR "EBRT"[Title/Abstract] OR "Radiotherapy"[MeSH Terms]) AND ("combined"[Title] OR "additional"[Title] OR "plus"[Title] OR "Combined Modality Therapy"[MeSH Terms])

**KQ2/3:** (((("Technique"[Title] OR "techniques"[Title] OR "Dose fractionation scheme"[Title/Abstract] OR "dose fractionation schemes"[Title/Abstract] OR "three-dimensional conformal radiation"[Title/Abstract] OR "methods"[MeSH Subheading] OR "methods"[MeSH Terms]) AND "dose fractionation, radiation"[MeSH Terms]) OR "radiation dose hypofractionation"[MeSH Terms] OR "radiation dosage"[MeSH Terms] OR "radiotherapy dosage"[MeSH Terms] OR "radiotherapy, computer assisted"[MeSH Terms]) AND (("bone metastases"[Title/Abstract] OR "bone neoplasms/radiotherapy"[MeSH Terms]) AND ("external beam radiation therapy"[Title/Abstract] OR "EBRT"[Title/Abstract] OR "Radiotherapy"[MeSH Terms])))

**SR hedge:** systematic[sb]

**RCT hedge:** (((((((groups[tiab]) OR (trial[tiab])) OR (randomly[tiab])) OR (drug therapy[sh])) OR (placebo[tiab])) OR (randomized[tiab])) OR (controlled clinical trial[pt])) OR (randomized controlled trial[pt]))

**NSRI hedge:** (((("Cohort Studies"[Mesh]) OR "Controlled Clinical Trial"[Publication Type]) OR "Case-Control Studies"[Mesh])) OR (("Evaluation Studies"[Publication Type]) OR "Comparative Study"[Publication Type])) OR (("Comparative Study"[Publication Type]) OR "Follow-Up Studies"[Mesh])