Topic Brief: Radiation Therapy for Bone Metastases

Date: 11/20/2020
Nomination Number: 0933

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

Issue: There is practice variation in the use of radiation for the management of cancer that has metastasized to the bone (bone metastasis). The nominators for this topic intend to update existing 2016 guidelines to reflect current evidence.

Program Decision:
The scope of this topic met all EHC Program selection criteria and was considered for a systematic review. However, it was not selected.

Key Findings
We identified sufficient evidence to recommend a systematic review for key questions (KQs) 1 and 2, but not KQ 3.

Background

Metastasis is the spread of cancer from its origin to distal parts of the body.[1] Bone metastasis is the third most common type of metastasis. In the United States, around 350,000 people die each year as the result of bone metastases. A 2020 population-based study of patients with bone metastases found that the incidence of bone metastases in individuals with prostate cancer, breast cancer, and renal cancer was approximately 89, 54, and 39 percent, respectively.[2] The median survival from diagnosis of bone metastasis ranges from 6 months in melanoma to 48 months in thyroid cancer. Bone metastasis is characterized by severe pain and represents the most common type of pain from cancer.

External radiation therapy provides palliation for localized metastatic bone pain.[3] The goals of radiation therapy are to improve the patient's quality of life, reduce analgesic requirements, and maintain or ameliorate skeletal function.[4] The 2016 guidelines from the American Society for Radiation Oncology[5] on bone metastasis provide recommendations surrounding the delivery of radiation therapy for bone metastases. The nominator's current request is for a systematic review that would aid in updating these guidelines. The review would cover the effectiveness and harms of initial radiation therapy for bone metastases and reirradiation[6] for cases of reoccurring cancer. Consideration for factors that may influence the effectiveness and harms of the identified treatment such as patient characteristics, additional therapies, and specifications as to how radiation is delivered would also be reviewed. The nominator was actively engaged in

developing the questions for this assessment and ensuring that the scope would match the scope of their planned guideline.

Scope

1. What is the effectiveness and what are the harms of radiation therapy in the palliative treatment of bone metastases?
    a. Which patient characteristics (e.g., age, sex, socioeconomic status, histology of the primary tumor) are associated with effectiveness of radiation therapy in the palliative treatment of bone metastases?
    b. Do additional therapies (i.e., surgery, radionuclide therapy, bisphosphonate therapy, or kyphoplasty/vertebroplasty) affect outcomes?
2. For adults with bone metastases who will receive initial radiation, what is the comparative effectiveness and what are the comparative harms of dose-fractionation schemes, dose-constraints, and techniques (e.g., three-dimensional conformal radiation therapy, stereotactic body radiation)?
3. For adults with bone metastases who will receive re-irradiation, what is the comparative effectiveness and harms of dose-fractionation schemes, dose constraints, and techniques (e.g., three-dimensional conformal radiation therapy, stereotactic body radiation)?

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

Questions	1. Effectiveness and harms of RT	2. Dose fractionation, dose constraints, RT techniques in initial radiation	3. Dose fractionation, dose constraints, RT techniques in re-irradiation
Population	Adults with cancer that has metastasized to the bone. Consider patient characteristics (e.g., age, sex, socioeconomic status, histology of the primary tumor site of metastases)	Adults with cancer that has metastasized to the bone who will receive initial RT.	Adults with cancer that has metastasized to the bone who will receive re-irradiation.
Interventions	RT for the palliative management of bone metastases Subgroups: additional therapies (i.e., surgery, radionuclide therapy, bisphosphonate therapy, or kyphoplasty/vertebroplasty)	-Different dose-fractionation schemes -Dose-constraints -Techniques (e.g., three-dimensional conformal RT, SBR).	-Different dose-fractionation schemes -Dose-constraints -Techniques (e.g., three-dimensional conformal RT, SBR).
Comparators	-No radiation -Other type of radiation treatment -Other treatment for palliative treatment	-Other dose-fractionation scheme -Other dose constraint -Other technique	-Other dose-fractionation scheme -Other dose constraint -Other technique

Questions	1. Effectiveness and harms of RT	2. Dose fractionation, dose constraints, RT techniques in initial radiation	3. Dose fractionation, dose constraints, RT techniques in re-irradiation
Outcomes	Quality of life, pain (level and duration), use of pain medication, skeletal function, need for other intervention for pain relief, harms, (e.g., rate of radiation/treatment toxicity, fracture rates, reduced mobility, reduced independence, financial harm)	Quality of life, pain (level and duration), use of pain medication, skeletal function, need for other intervention for pain relief, skeletal function, harms, (e.g., rate of radiation/treatment toxicity, fracture rates, reduced mobility, reduced independence, financial harm)	Quality of life, pain (level and duration), use of pain medication, skeletal function, need for other intervention for pain relief, skeletal function, harms, (e.g., rate of radiation/treatment toxicity, fracture rates, reduced mobility, reduced independence, financial harm)

Abbreviations: RT=radiation therapy; SBR= stereotactic body radiation.

Assessment Methods

See Appendix A.

Summary of Literature Findings

We found sufficient primary evidence to address two of the three KQs posed by the nominators.

For KQ1, several studies measured the effect of radiation therapy on existing pain,[7-13] and two studies examined prophylactic pain management with radiation therapy.[14, 15] Additionally, several studies addressed KQ1a, examining sex or age differences in predominately pain outcomes.[16-23]

The majority of the studies addressing KQ2 compared different dose fractionation schemes, [24-39] and a few compared different radiation therapy techniques.[40-43]

We did not find any studies to address KQ3.

Table 2. Literature identified for each KQ

Question	Systematic reviews (11/2017-11/2020)	Primary studies (11/2015-11/2020)
Question 1: Effectiveness and harms of RT.	Total: 0	Total: 17, from a sample of 200 • RCT: 0 • Pre-post: 15 Clinicaltrials.gov: 2
Question 2: Dose fractionation, dose constraints, RT techniques in initial radiation	Total: 0	Total: 20, from a sample of 200 • RCT: 8 • Pre-post: 4 Clinicaltrials.gov: 8
Question 3: Dose fractionation, dose constraints, RT techniques in re-irradiation	Total: 0	Total: 0

Abbreviations: KQ=key question; RCT=randomized controlled trial; RT=radiation therapy.

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

Summary of Selection Criteria Assessment

This nomination meets all selection criteria. We estimate 98 primary studies for KQs 1 and 2 together. While we did not find primary studies addressing KQ 3 on radiation specifications for re-irradiation, the yield for KQs 1 and 2 was substantial, and studies for KQ 3 may be identified

as part of a more comprehensive evaluation of the literature. A systematic review of these KQs would serve to inform the development of an updated guideline on radiation therapy for bone metastases.

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

References

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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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Appendix A: Methods

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

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Absence of Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years November 19, 2017 to November 19, 2020 on the questions of the nomination from these sources:

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

Impact of a New Evidence Review

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

Feasibility of New Evidence Review

We conducted a limited literature search in PubMed for the last five years November 19, 2015 - November 19, 2020. Because a large number of articles were identified, we reviewed a random sample of 200 titles and abstracts for each question for inclusion. We classified identified studies by question and study design, to assess the size and scope of a potential evidence review. We then calculated the projected total number of included studies based on the proportion of studies included from the random sample.

Search strategy

Ovid MEDLINE(R) ALL 1946 to November 19, 2020

Date searched: November 20, 2020

1 bone neoplasms/sc (19257)
2 bone metastas*.ti,ab,kf. (17492)
3 or/1-2 (27965)
4 bone neoplasms/rt or (dose fraction/ and (radiation or radiotherap*).ti,ab,kf.) (3570)
5 ((dose adj3 (constrain* or fraction* or technique*)) or ((body or conformal or gray or grey or dose* or dosage* or palliative or stereotactic) adj3 (radiation or radiotherap*)) or reirradiat* or re-irradiat*).ti,ab,kf. (81906)
6 or/4-5 (84725)
7 and/3,6 (2589)
8 7 not ((exp Animals/ not Humans/) or (animal or animals or cat or cats or dog or dogs or mice or mouse or rat or rats or rattus).ti.) (2542)
9 limit 8 to english language (2132)
10 Cochrane database of systematic reviews.jn. or (meta-analysis or "systematic review").pt. or (metaanalysis or meta-analysis or ((evidence or systematic) adj3 (review or synthesis))).ti. (267458)
11 and/9-10 (55)
12 limit 11 to yr="2018 -Current" (14)
13 ("randomized controlled trial" or "controlled clinical trial").pt. or (control* or placebo* or random* or trial).ti,ab. (4899688)
14 and/9,13 (671)
15 limit 14 to yr="2016 -Current" (215)
16 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or (case-control or cohort or cross-sectional or follow-up* or longitudinal or observational or prospective or retrospective).ti,ab. (4356976)
17 and/9,16 (921)
18 limit 17 to yr="2016 -Current" (313)

EBM Reviews - Cochrane Central Register of Controlled Trials October 2020

Date searched: November 20, 2020

1 (bone adj metastas*).ti,ab. (2141)
2 ((dose adj3 (constrain* or fraction* or technique*)) or ((body or conformal or gray or grey or dose* or dosage* or palliative or stereotactic) adj3 (radiation or radiotherap*)) or reirradiat* or re-irradiat*).ti,ab. (9184)
3 and/1-2 (239)
4 3 not (animal or animals or cat or cats or dog or dogs or mice or mouse or rat or rats or rattus).ti. (238)
5 limit 4 to yr="2016 -Current" (120)

EBM Reviews - Cochrane Database of Systematic Reviews 2005 to November 13, 2020

Date searched: November 20, 2020

1 (bone adj metastas*).ti,ab. (8)
2 ((dose adj3 (constrain* or fraction* or technique*)) or ((body or conformal or gray or grey or dose* or dosage* or palliative or stereotactic) adj3 (radiation or radiotherap*)) or reirradiat* or re-irradiat*).ti,ab. (42)
3 and/1-2 (1)

PROSPERO
Date searched: November 20, 2020
bone AND metasta* AND (radiation OR radiotherapy OR radiotherapies OR reirradiation OR re-irradiation)

ClinicalTrials.gov
Date searched: November 20, 2020
[EXPERT SEARCH] (bone AND (metastases OR metastatic OR secondary) AND AREA[InterventionSearch] (radiation OR radiotherapy OR radiotherapies OR reirradiation OR re-irradiation) OR AREA[TitleSearch] (bone AND (metastases OR metastatic OR secondary) AND (radiation OR radiotherapy OR radiotherapies OR reirradiation OR re-irradiation))) AND AREA[OverallStatus] EXPAND[Term] COVER[FullMatch] ("Active, not recruiting" OR "Completed") AND AREA[StdAge] EXPAND[Term] COVER[FullMatch] ("Adult" OR "Older Adult") AND AREA[StudyFirstPostDate] EXPAND[Term] RANGE[01/01/2016, 11/20/2020] (52)
ClinicalTrials link

Value

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

Appendix B. Selection Criteria Assessment

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the US?	Yes.
1b. Is the nomination a request for an evidence report?	Yes.
1c. Is the focus on effectiveness or comparative effectiveness?	Yes.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Yes. In the US, around 350,000 people die each year from bone metastases. In a 2020 population-based study of patients with bone metastases, the incidence of bone metastasis in individuals with prostate, breast, and renal cancers was 88.7%, 53.7% and 38.7%, respectively.[2]
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes. In the US, around 350,000 people die each year from bone metastases. In a 2020 population-based study of patients with bone metastases, the incidence of bone metastasis in individuals with prostate, breast, and renal cancers was 88.7%, 53.7% and 38.7%, respectively.[2]
2c. Incorporates issues around both clinical benefits and potential clinical harms	Yes.
2d. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes. The cost of RT can range from $18,368 to $399,056.[44]
3. Desirability of a New Evidence Review/Absence of Duplication	
3. A recent high-quality systematic review or other evidence review is not available on this topic	Yes. We did not identify a recent systematic review.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Unclear, the consensus guideline on RT for bone metastasis from the American Society of Radiation Oncology was published in 2016 and a systematic review would inform the development of an updated guideline. The consensus guideline indicated that almost all their recommendations were “strong” and supported by high-quality evidence. The guidance indicated that areas of uncertainty remained related to areas such as combinations of external beam RT with bisphosphonates and radiopharmaceuticals, definition of uncomplicated bone metastases, value of intensity modulated RT and image guided RT, and proper use of stereotactic body RT for newly discovered and recurrent spine bone lesions.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes, there is practice variation across settings and socioeconomic variables.

Selection Criteria	Assessment
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	Size/scope* of review: KQ 1: 18 studies KQ 2: 20 studies KQ 3: 0 studies. *These studies were taken from a sample of 200 studies. The estimated size of a new systematic review is medium.
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change	Yes, a new systematic review would inform an updated guideline.
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	Yes, the nominator will use the systematic review to update their existing guidelines.

Abbreviations: KQ=key question; RT=radiation therapy; US=United States.