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.
Link to nomination

Recommendation

x Systematic review
□ Technical brief
□ Evidence map
□ Rapid review
□ Rapid response
□ Expanded topic brief

Key Findings

We identified sufficient evidence to recommend a systematic review. We found studies addressing 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.

This nomination was submitted in July 2020, and while a new systematic review was feasible this topic was not prioritized. After consultation with ASTRO and confirming their continued interest it is being reconsidered for FY2022 funding for the EPC Program.

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
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.

Since a significant period of time had passed since the original search for existing evidence reviews, we conducted an updated search for existing systematic reviews on August 6, 2021 and did not find any.

Table 2. Literature identified for each KQ

Question	Systematic reviews (11/2017-8/2021)	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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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. Additionally, we conducted an updated search on August 6, 2021 to detect any evidence reviews published between November 19, 2020 and August 6, 2021:

- 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.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes, the most recent 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.
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.
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.

Appendix C. Topic Nomination
Radiation Therapy for Bone Metastases Topic Nomination

A topic nomination was submitted on the EHC website:
Submitted on Friday, July 17, 2020 - 14:43

==Topic Suggestion==

1. What is the decision or change you are facing or struggling with where a summary of the evidence would be helpful?
The use of radiation therapy in the management of cancer that has metastasized to the bone, referred to as bone metastases, has shown significant variation in care across different clinical settings, and among patients of different socioeconomic status and race. For these reasons and the high incidence and clinical need for palliative radiation for bone metastases, the first guideline produced by the American Society of Radiation Oncology (ASTRO) in 2011 focused on addressing variation in radiation therapy for bone metastases. It was followed by an update to the guideline in 2016. In accordance with the National Academy of Medicine (formerly Institute of Medicine) standards for the development of high quality, evidence-based clinical practice guidelines, ASTRO intends to use the evidence report developed by AHRQ as the basis to replace the previous version of this guideline to ensure that current guidance provided to clinicians is accurate, and reflects current evidence.

The following key questions will be addressed:
KQ 1: What are the appropriate indications for radiation therapy in the palliative treatment of bone metastases?
KQ 2: What is the impact of surgery, radionuclide therapy, bisphosphonate therapy, or kyphoplasty/vertebroplasty on the appropriate indications for radiation therapy in the palliative treatment of bone metastases?
KQ 3: What radiation therapy dose-fractionation schemes, dose-constraints, and techniques are appropriate for the initial palliative treatment of bone metastases?
KQ 4: What radiation therapy dose-fractionation schemes, dose-constraints, and techniques are appropriate for palliative re-irradiation of bone metastases?
KQ 5: In patients with bone metastases receiving palliative radiation therapy, how do the different dose-fractionation schemes and techniques impact on treatment toxicity and quality of life?
The population of patients that will be assisted by this guideline are those with cancer that has metastasized to the bone. These patients frequently experience morbidity from bone metastases, including pain, bone fracture, reduced or lack of mobility, reduced independence and/or quality of life, financial toxicity, challenges with transportation, and side effects related to the need for pain and other supportive care medications.
The intervention that will be evaluated in this guideline is the use of radiation treatment for the palliative management of bone metastases.
The comparison groups that will be utilized in this guideline will include patients who do not receive radiation treatment, patients who are treated with different radiation techniques or treatment dose/fractionation schemes, and patients who receive other interventions such as medications or procedure intended to palliate bone metastases.
The outcomes that will be examined in this guideline include rate and duration of pain relief, dependence on pain medication, need for further pain intervention, quality of life, rate of musculoskeletal event (such as bone fracture), and rate of radiation-related toxicity.

2. Why are you struggling with this issue?
The use of palliative radiation therapy to manage symptoms related to bone metastases is an essential component of supportive care in cancer patients. This patient population is particularly vulnerable given the presence of disseminated, typically incurable cancer, and the high frequency of comorbid conditions as well as psychosocial and emotional challenges related to living with metastatic cancer. It is critical that these patients are offered the most effective, safe, evidence-based, and patient-centered recommendations to optimize the likelihood of benefit and minimize the potential for treatment-related toxicity, whether physical, financial, psychological, or otherwise. Studies have demonstrated substantial variation in the use of palliative radiation therapy for bone metastases, so much so that the first guideline produced by ASTRO focused on addressing this variation in care disparity. Despite an evidence base with findings that support strong, evidence-based recommendations, contemporary studies continue to demonstrate significant variation in care. Clinicians face difficult patient presentations where numerous factors related to estimated life expectancy, patient-specific values and expectations, and varied imaging and clinical features that must be considered, all of which appear to make it more difficult to provide care that is frequently consistent with guideline recommendations. Given the multifactorial issues that face the patient and their healthcare providers, in realizing the benefits of treatment while reducing risk and adhering to evidence-based standards, it is critically important to educate both groups to empower good medical decision-making in the face of metastatic cancer and the myriad of challenges that come with it.

3. What do you want to see changed? How will you know that your issue is improving or has been addressed?
By replacing the clinical practice guideline on the treatment of bone metastases, ASTRO aims to provide current, evidence-based recommendations that will impact practice patterns and increase the rate of guideline concordance for radiation treatment courses used in this setting to optimize patient care. There are several groups that regularly measure patterns of care and publish on adherence with ASTRO guidelines. ASTRO will collaborate and support patterns of care studies to measure and compare rates of concordance with evidence-based recommendations for the palliative treatment of bone metastases to evaluate whether this issue is improving or has been addressed.

4. When do you need the evidence report? Mon, 08/01/2022

5. What will you do with the evidence report?
ASTRO intends to use the evidence report developed by AHRQ as the basis for a replacement of their evidence-based, clinical practice guideline on Radiation Therapy in the Management of Bone Metastases. An AHRQ report, with a literature search, data extraction, and analysis according to the highest standards of systematic reviews, would significantly aid in the completion of a guideline to provide timely, current, evidence-based recommendations to clinicians in an area of great clinical importance and incidence, with high variation and known potential for disparity in care. ASTRO guidelines are scientifically and methodologically rigorous and are published in high impact journals. They are also widely read and cited by cancer care providers, as demonstrated by citation frequency and quantitative measurement of downloads from the journal website. Once an AHRQ report is available, the ASTRO Guidelines Subcommittee will convene a panel of disease-site experts and general cancer care practitioners from academic, community, and government-run practice settings, including a patient representative and physician-in-training representative, to complete this important guideline. We will be inclusive such that our panel reflects a wide geographic and demographic representation. ASTRO staff with expertise in clinical practice guideline development will support this process.

==Supporting Document==
Upload Document:
https://effectivehealthcare.ahrq.gov/sites/default/files/webform/docs/Bone%20Mets%202017%20guideline.pdf
Title or short description: Evidence review request on radiation therapy for bone metastases
Comments or notes about this file: ASTRO has worked with AHRQ on previous reviews in support of clinical practice guidelines and has an understanding regarding the timelines involved with these processes. This guideline topic was selected based on a high level of confidence that an anticipated timeline of 2 years for completion is appropriate, and our disease-site experts believe there is adequate flexibility based on the recent literature and clinical trial publications, at this timeline will be appropriate for this guideline project.

==(Optional) About You==
What is your role or perspective? Radiation therapy professional society
If you are you making a suggestion on behalf of an organization, please state the name of the organization: American Society of Radiation Oncology
May we contact you if we have questions about your nomination? Yes
First and Last Name: Lisa Bradfield
Title: Senior Manager of Guidelines and QI
Email Address: Lisa.bradfield@astro.org
The results of this submission may be viewed at:
https://effectivehealthcare.ahrq.gov/node/16119/submission/19158