# Health Evidence Review Commission (HERC)

# Coverage Guidance:

# Single Fraction Radiotherapy for Palliation of Bone Metastases

**Approved 10/4/2018**

## HERC Coverage Guidance

Single fraction radiotherapy for palliation of bone metastases is recommended for coverage *(strong recommendation)*. Single fraction radiotherapy should be given strong consideration for use over multiple fraction radiotherapy when clinically appropriate (e.g., not contraindicated by risk of imminent pathologic fracture, worsening neurologic compromise or radioresistant histologies such as sarcoma, melanoma, and renal cell carcinoma).

Note: Definitions for strength of recommendation are in Appendix A. *GRADE Table Element Descriptions*.

Rationales for each recommendation appear below in the GRADE table.

Oregon Health Authority

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## Rationale for development of coverage guidances and multisector intervention reports

Coverage guidances are developed to inform coverage recommendations for public and private health plans in Oregon as plan administrators seek to improve patient experience of care, population health, and the cost-effectiveness of health care. In the era of public and private sector health system transformation, reaching these goals requires a focus on maximizing the benefits and minimizing the harms and costs of health interventions.

HERC uses the following principles in selecting topics for its reports to guide public and private payers:

- Represents a significant burden of disease or health problem
- Represents important uncertainty with regard to effectiveness or harms
- Represents important variation or controversy in implementation or practice
- Represents high costs or significant economic impact
- Topic is of high public interest

HERC bases its reports on a review of the best available research applicable to the intervention(s) in question. For coverage guidances, which focus on clinical interventions and modes of care, evidence is evaluated using an adaptation of the GRADE methodology. For more information on coverage guidance methodology, see Appendix A.

Multisector interventions can be effective ways to prevent, treat, or manage disease at a population level. In some cases, HERC has reviewed evidence and identified effective interventions, but has not made formal coverage recommendations when these policies are implemented in settings other than traditional health care delivery systems because effectiveness may be dependent on the environment in which the intervention is implemented.

## GRADE-Informed Framework

HERC develops recommendations by using the concepts of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for performing the steps involved in developing recommendations. The table below lists the elements that determine the strength of a recommendation. HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Estimates of effect are derived from the evidence presented in this document. Assessments of confidence are from the published systematic reviews and meta-analyses, where available and judged to be reliable.

In some cases, no systematic reviews or meta-analyses encompass the most current literature. In those cases, HERC may describe the additional evidence or alter the assessments of confidence in light of all available information. Such assessments are informed by clinical epidemiologists from the Center for Evidence-based Policy. Unless otherwise noted, estimated resource allocation, values and preferences, and other considerations are assessments of HERC.

### Should single fraction radiotherapy be recommended for coverage for painful bone metastases?

| Outcomes | Estimate of Effect for Outcome/ *Confidence in Estimate* | Resource Allocation | Values and Preferences | Other Considerations |
|---|---|---|---|---|
| **Pain** *(Critical outcome)* | Overall response 61% for single fraction vs. 62% for multiple fraction<br>ARD = 1%<br>NNT = 100<br>OR 0.98 (95% CI 0.95 to 1.01)<br>●●●● *(High confidence, based on 26 RCTs, n = 6,099)* | Single fraction radiotherapy is less costly than multiple fraction treatment. In addition to direct savings in procedure costs, there are | Many patients with painful bone metastases (and their caregivers) would highly value the decreased burden of time, | Professional society guidelines emphasize the comparable efficacy and side effects of single fraction compared to |

## Should single fraction radiotherapy be recommended for coverage for painful bone metastases?

| Outcomes | Estimate of Effect for Outcome/ *Confidence in Estimate* | Resource Allocation | Values and Preferences | Other Considerations |
|---|---|---|---|---|
| **Morbidity associated with bone metastases** *(Critical outcome)* | Pathologic fracture occurred in 3.6% of single fraction patients vs. 3.0% of multiple fraction patients<br>ARD = 0.6%<br>NNH = 166<br>OR 1.21 (95% CI 0.76 to 1.95)<br>●●●○ *(Moderate confidence, based on 12 RCTs, n = 4,437)*<br><br>Spinal cord compression occurred in 2.8% of single fraction patients vs. 1.9% of multiple fraction patients<br>ARD = 0.9%<br>NNH = 111<br>OR 1.44 (95% CI 0.9 to 2.3)<br>●●●○ *(Moderate confidence, based on 6 RCTs, n = 2,886)* | potential savings in travel costs (and other costs borne by patients and families). These savings are moderated somewhat by the increased need for retreatment after single dose therapy.<br><br>Single fraction radiotherapy is nonetheless an expensive intervention that is a challenge to cover under prevailing hospice care payment methodology. | travel, and cost that is associated with single fraction radiotherapy. Preference for single dose treatment might be highest for patients with limited life expectancy. | multiple fraction radiotherapy.<br><br>European Association of Urology guidelines state that single fraction radiotherapy "remains the treatment of choice for alleviating bone pain." This treatment option might be underutilized in the U.S. |
| **Quality of life** *(Critical outcome)* | No significant differences in quality of life ratings at up to 2 years, except for a small temporary decline in physical health domain scores during the first month after treatment for patients receiving multiple fractions (Cohen's *d* effect size 0.12 to 0.17)<br>●●●● *(High confidence, based on 1 RCT, n = 1,115)* | | | |

## Should single fraction radiotherapy be recommended for coverage for painful bone metastases?

| Outcomes | Estimate of Effect for Outcome/ *Confidence in Estimate* | Resource Allocation | Values and Preferences | Other Considerations |
|---|---|---|---|---|
| **Need for retreatment** *(Important outcome)* | Retreatment rate of 20% for single fraction vs. 8% for multiple fraction<br>ARD = 12%<br>NNH = 8<br>OR 2.42 (95% CI 1.87 to 3.12)<br>●●●● *(High confidence, based on 16 RCTs, n = 4,950)* | | | |
| **Harms** *(Important outcome)* | No significant differences in rates of acute radiation toxicities<br>●●●○ *(Moderate confidence, based on 26 RCTs, n = 6,099)* | | | |

| |
|---|
| **Balance of benefits and harms:** Single fraction radiotherapy has efficacy comparable to multiple fraction treatment, with no significant differences noted in pain relief, quality of life measurements, or morbidity associated with uncomplicated bone metastases. Rates of acute radiation toxicity show no significant differences. Single fraction radiotherapy is associated with a higher need for retreatment (although retreatment with another single fraction is not inferior to retreatment with multiple fraction therapy). |
| **Rationale:** Our recommendation for coverage of single fraction radiotherapy is based on a substantial body of evidence demonstrating comparable results to multiple fraction treatment. Single dose treatment is less costly and more convenient, making it the preferred option for many patients, and most valued by patients with limited life expectancy. Our recommendation is strong, and utilization of single fraction radiotherapy for painful bone metastases is encouraged. |
| **Recommendation:** Single fraction radiotherapy for palliation of bone metastases is recommended for coverage (strong recommendation). Single fraction radiotherapy should be given strong consideration for use over multiple fraction radiotherapy when clinically appropriate (e.g., not contraindicated by risk of imminent pathologic fracture, worsening neurologic compromise or radioresistant histologies such as sarcoma, melanoma and renal cell carcinoma). |

Note: GRADE table elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.

# Background

When cancer has metastasized to the bones, the cancer can rarely be cured, but often can be treated to slow its growth (Macedo et al., 2017) and reduce pain. Bone metastases can have important effects on a patient's quality of life and are characterized by severe pain, impaired mobility, pathologic fractures, spinal cord compression, bone marrow aplasia, and hypercalcemia (Macedo et al., 2017). Prostate and breast cancers cause up to 70% of bone metastases because of the high incidence and relatively long clinical course of these cancers (Macedo et al., 2017).

Treatment decisions for bone metastases depend on patient and cancer characteristics, such as the type of index cancer, whether bone metastases are localized or widespread, evidence of extraskeletal metastases, treatment history, symptoms, and the patient's general state of health (Macedo et al., 2017). Treatments for bone metastases include bisphosphonates, denosumab, ablation, surgery, and radiotherapy (Macedo et al., 2017). Radiotherapy is an effective treatment for patients with painful bone metastases: the pain response rate is more than 60% (Westhoff et al., 2016).

## Indications

Single fraction or multiple fraction radiotherapy is used as a palliative treatment for patients with painful bone metastases. Uncomplicated bone metastases (i.e., not at risk for imminent pathologic fracture and not causing neurologic compromise due to spinal cord compression) can often be treated effectively with radiotherapy (Rich et al., 2018). When radiotherapy is indicated for the treatment of uncomplicated painful bone metastases, the most common single fraction treatment regimen is 8 Gy; common multiple fraction regimens generally deliver 20 to 30 Gy in five to ten fractions.

## Technology Description

Single fraction radiotherapy involves one application of external radiation treatment, and multiple fraction radiotherapy involves multiple applications of external radiation treatment over time. Multiple fraction radiotherapy is generally at lower doses than single fraction radiotherapy, although the total radiation dose is higher with multiple fraction versus single fraction radiotherapy.

# Evidence Review

## Rich et al., 2018

Rich et al. (2018) published a recent fair-quality systematic review and meta-analysis of 29 randomized controlled trials (RCTs) comparing single and multiple fraction radiotherapy regimens for the treatment of uncomplicated painful bone metastases. This article updated a previous systematic review published in 2012 with five additional studies. Studies involving complicated bone metastases and those that used nonconventional radiotherapy modalities were excluded. The authors noted that the majority of patients in the included studies had breast or prostate cancer. Most studies compared a single treatment of 8 Gy to 30 Gy in 10 fractions, or 20 Gy in five fractions. For trials with three arms (i.e., single fraction compared to different multiple fractionation regimens), each comparison to single fraction was considered separately. The primary outcomes of interest for this review were complete response rate and overall response rate (as defined in the individual trials), and secondary outcomes included retreatment rates, pathologic fracture rates, spinal cord compression rates, and acute toxicities. Overall response was commonly defined as a two-point improvement in pain scores; complete

response was commonly defined as complete relief of pain at the treated site. The main limitation of this review is the absence of risk of bias assessments for the included studies.

In the intention-to-treat analysis for the primary outcome of overall response rate, 26 trials with more than 6,000 participants contributed to the meta-analysis. The meta-analytic odds ratio for overall response was not statistically significantly different between the single fraction and multiple fraction arms (61% for single fraction vs. 62% for multiple fraction, OR 0.98, 95% CI 0.95 to 1.01, p = 0.25). Similarly, in the 21 trials with more than 5,000 participants that contributed to the meta-analysis for complete response rate, there were no statistically significant differences between the two arms (23% for single fraction vs. 24% for multiple fraction, OR 0.97, 95% CI 0.89 to 1.06, p = 0.55).

For the secondary outcome of retreatment, 16 trials with approximately 5,000 patients showed that retreatment rates were statistically significantly greater in the single fraction arm compared to the multiple fraction arm (20% vs. 8%, OR 2.42, 95% CI 1.87 to 3.12, p < 0.01). For the 12 studies reporting on pathologic fractures (n = 4,437), there were no statistically significant differences between the two arms (3.6% for single fraction vs. 3.0% for multiple fractions, OR 1.21, 95% CI 0.76 to 1.95, p = 0.08). Similarly, for six studies reporting on spinal cord compression (n = 2,886), there were no statistically significant differences between the two arms (2.8% for single fraction vs. 1.9% for multiple fractions, OR 1.44, 95% CI 0.90 to 2.3, p = 0.13). The authors noted that there were no significant differences between the arms in the rates of acute toxicity, but cautioned that the applicable data were not collected using standardized definitions.

The authors observed that because patients with breast and prostate cancer and longer life expectancy were included in trials with longer-term follow-up, the results are applicable to patients with more favorable prognoses. In the two included trials that followed patients to 26 and 52 weeks, the durability of pain relief was similar between the single fraction and multiple fraction regimens. The authors noted that although some clinicians have expressed concern that single fraction treatment to spinal metastases could result in greater toxicity, such a selected patient population has not been prospectively studied, and the extant data does not corroborate those concerns.

The authors concluded that, consistent with previous systematic reviews on this subject, single fraction regimens produce response rates similar to multiple fraction regimens without an increase in acute toxicity, pathologic fractures, or spinal cord compression, but that patients who received single fraction treatments are more likely to require retreatment.

## Chow et al., 2017

The Chow et al. (2017) fair-quality systematic review analyzed studies that compared single fraction regimens with differing doses. The authors did not perform a meta-analysis and noted that the small number of studies that used single fraction doses other than 8 Gy mean that the results must be interpreted cautiously. Only three studies directly compared single fraction regimens using differing doses. In the studies that made direct comparisons, 8 Gy single fraction regimens performed better than 4 Gy or 6 Gy single fraction regimens with respect to response rates and need for retreatment. The authors concluded that 8 Gy should be the standard dose for most single fraction regimens for painful bone metastases.

## Westhoff et al., 2016

Westhoff et al. (2016) analyzed long-term quality of life outcomes derived from the Dutch Bone Metastasis Study, an RCT that compared 8 Gy single fraction radiotherapy to six fractions of 4 Gy in 1,157 patients with painful bone metastases between 1996 and 1998. Most patients in this trial had breast, prostate, or lung cancer. Participants completed quality of life questionnaires weekly for 13 weeks after treatment and then monthly for up to two years. The questionnaires were the Rotterdam Symptom Checklist, three questions on side effects of radiation therapy, and two items taken from the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire. Quality of life data were evaluable for 1,115 participants (96%). Components of the various questionnaires were divided into domains of physical, psychosocial, and functional quality of life. When comparing single fraction and multiple fraction regimens, the authors found comparable quality of life outcomes, except for a temporary worsening of physical domain scores in the multiple fraction group in the first month after treatment. However, the magnitude of the difference in the physical domain score (Cohen's *d* effect size of 0.12 to 0.17 lower than in the single fraction group) was not regarded as clinically relevant.

## Chow et al., 2014

Chow et al. (2014) conducted a multicenter randomized controlled noninferiority trial comparing a single 8 Gy radiotherapy treatment to a 20 Gy multiple fraction regimen for the retreatment of previously irradiated painful bone metastases. The trial was not blinded. Of the 850 patients randomly assigned (1:1) to treatment groups, only 258 patients in the single fraction arm and 263 patients in the multiple fraction arm received the assigned treatment and had evaluable data at the two month follow-up. Approximately two-thirds of the enrolled patients had previously been treated with a single fraction regimen. The two groups were similar with respect to baseline characteristics. Most patients had breast, prostate, or lung cancer. In the intention-to-treat analysis of overall pain response at two months, 28% of the patients in the single fraction arm and 32% of patients in the multiple fraction arm reported an overall pain response ($p = 0.21$, upper bound of the 95% CI 9.2%, which was within the prespecified noninferiority margin of 10%). In the per-protocol analysis (which was limited to patients with evaluable data), 45% of patients in the single fraction arm and 51% of patients in the multiple fraction arm reported overall pain response ($p = 0.17$, upper bound of the 95% CI 13.2%, which exceeded the prespecified noninferiority margin of 10%). There were not statistically significant differences in quality of life between the two arms as assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 at up to six months. There were no statistically significant differences between the two arms with respect to in-field pathologic fractures or spinal cord compression. Acute toxicities (lack of appetite, vomiting, diarrhea, skin redness) assessed at 14 days after treatment were more common in patients in the multiple fraction arm, but the only serious adverse event observed in the trial was an episode of myocardial ischemia that occurred in one patient in the single fraction arm 166 days after treatment. In a logistic regression analysis of the per-protocol model, there was no significant interaction between prior treatment fractionation regimen and overall pain response during retreatment.

## Rudzianskiene et al., 2017

Rudzianskiene et al. (2017) conducted a single-center RCT comparing 8 Gy single fraction radiotherapy to a 30 Gy 10 fraction regimen for the treatment of multiple myeloma. Eligible patients were over age 18, had a verified diagnosis of multiple myeloma with painful bone lesions, and had a Karnofsky

performance score greater than 40%. Of the 101 patients enrolled, 58 patients were randomized to the control arm (30 Gy in 10 fractions) and 43 were randomized to the experimental arm (8 Gy single fraction). The groups were generally similar at baseline, although there were differences between the groups with respect to age, baseline pain scores, and the anatomic site of the planned treatment. For the primary outcomes of pain relief, there were no statistically significant differences between the arms for overall response (74.4% for single fraction vs. 84.5% for multiple fraction, p = 0.2), or for complete pain response (68.8% for single fraction vs. 69.4% for multiple fraction, p = 0.952). Quality of life indices, as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30, only showed significant improvements over baseline in the multiple fraction arm, but the authors cautioned that the imbalance in patient characteristics at baseline might explain this observation. Acute toxicities did not vary between the two groups.

### Evidence Summary

Compared to multiple fraction treatment regimens, single fraction radiotherapy for the treatment of uncomplicated painful bone metastases results in similar outcomes with respect to pain relief, acute toxicity, pathologic fractures, and spinal cord compression. However, patients treated with single fraction radiotherapy are more likely to require retreatment. An analysis from one of the larger RCTs comparing multiple and single fraction regimens found no significant differences in quality of life outcomes.

## Policy Landscape

### Payer Coverage Policies

#### Medicaid

No Washington Medicaid coverage policy was found for single fraction radiotherapy for bone metastases.

#### Medicare

No National Coverage Determinations or Local Coverage Determinations were found for single fraction radiotherapy for bone metastases.

#### Private Payers

No coverage policies for single fraction radiotherapy for bone metastases were found for Aetna, Cigna, Moda, or Regence.

### Recommendations from Others

Four guidelines were identified that include recommendations about the use of single fraction radiation for bone metastases:

- American Society for Radiation Oncology (ASTRO) guidelines on palliative radiotherapy for bone metastases (Lutz et al., 2017)
- American College of Radiology ACR Appropriateness Criteria® on non-spine bone metastases (American College of Radiology, 214)
- American College of Chest Physicians on symptom management for lung cancer patients (Simoff et al., 2013)

- European Association of Urology published on pain management and palliative care for patients with urologic cancers (Paez Borda et al., 2014)

All four of these guidelines state that single fraction radiotherapy is equivalent to multiple fraction radiotherapy in relieving pain, retreatment rates are higher for single fraction versus multiple fraction radiotherapy, and single fraction radiotherapy is more convenient for patients. More details on these guidelines are provided below.

The ASTRO guidelines conclude that:

- An updated review of high-quality data continues to show pain relief equivalency following a single 8 Gy fraction, 20 Gy in 5 fractions, 24 Gy in 6 fractions, and 30 Gy in 10 fractions for patients with previously unirradiated painful bone metastases. Patients should be made aware that single fraction radiotherapy is associated with a higher incidence of retreatment to the same painful site than is fractionated treatment.
- A single 8 Gy fraction provides noninferior pain relief compared with a more prolonged radiotherapy course in painful spinal sites and may therefore be particularly convenient and sensible for patients with limited life expectancy.
- There continues to be no suggestion from available high-quality data that single fraction radiotherapy produces unacceptable rates of long-term side effects that might limit its use for patients with painful bone metastases. The evidence regarding an association between higher risk for pathologic fracture after single fraction radiotherapy versus fractionated therapy remains equivocal.
- The panel reiterates that the use of surgery, radionuclides, bisphosphonates, or kyphoplasty/vertebroplasty does not obviate the need for radiotherapy for patients with painful bone metastases, although 2 recent trials have suggested the potential for similar, albeit less rapid, bone pain relief in prostate cancer patients following an infusion of ibandronate when compared with a single fraction radiotherapy.

The strength of evidence for each of these recommendations from the ASTRO guidelines is either moderate or high, and the strength of recommendation is strong for all of the recommendations.

The American College of Radiology last reviewed the guidelines on non-spine bone metastases in 2014 and concluded that:

- Prospective randomized trials have proven equivalent pain relief with varied fractionation schemes, including 8 Gy in 1 fraction, 20 Gy in 5 fractions, 24 Gy in 6 fractions, or 30 Gy in 10 fractions. Prolonged courses are associated with a lower incidence of retreatment, although shorter courses maximize patient and caregiver convenience by reducing the number of trips to the radiation department.
- Patients who undergo surgical stabilization for impending or completed pathologic fracture of a long bone may be treated with postoperative radiotherapy to 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, or 8 Gy in a single fraction.

The American College of Chest Physicians published guidelines in 2013 that recommended external radiation therapy for lung cancer patients who have pain due to bone metastases. The guidelines concluded that a single fraction of 8 Gy is equally effective for immediate relief of pain as higher fractionated doses of external radiation therapy. In addition, single-fraction radiotherapy is less

expensive than multiple fraction radiotherapy, more cost-effective, and more convenient from the patient's perspective.

The European Association of Urology 2014 guidelines on pain management and palliative care for patients with urologic cancers rated the level of evidence (LE) for recommendations using these categories:

1a: Evidence obtained from meta-analysis of randomized trials
1b: Evidence obtained from at least one randomized trial
2a: Evidence obtained from one well-designed controlled study without randomization
2b: Evidence obtained from at least one other type of well-designed quasi-experimental study
3: Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies, and case reports
4: Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

The European Association of Urology guidelines include these recommendations on treatment for bone metastases:

- Single-fraction radiotherapy is as effective as multiple fraction radiotherapy in relieving metastatic bone pain (LE: 1a).
- The rates of retreatment and pathologic fractures are significantly higher after single fraction radiotherapy (LE: 1a).
- Single-fraction radiotherapy remains the treatment of choice for alleviating bone pain because of its greater convenience for patients (LE: 1a), faster patient turnover for the radiotherapy unit, and lower costs (LE: 3); the recommended dose is 8 Gy (LE: 1a).
- Pain relief can be achieved with lower doses (LE: 1b), and these lower doses should be borne in mind if a third retreatment is necessary, or if there is concern about radiation tolerance (LE: 2b).

## Quality Measures

Two quality measures were identified when searching the National Quality Measures Clearinghouse for single fraction radiotherapy for bone metastases.

In 2017, the American Society of Radiation Oncology developed a quality measure on the use of radiotherapy for bone metastases: the percentage of patients, regardless of age, with a diagnosis of bone metastases and no history of previous radiation who receive external beam radiotherapy with any of the recommended fractionation schemes (i.e., 30Gy/10fxns, 24Gy/6fxns, 20Gy/5fxns, 8Gy/1fxn).

The RAND Corporation quality measure developed in 2010 recommended offering single fraction radiation: percentage of patients with advanced cancer who received radiation treatment for painful bone metastases for whom single fraction radiation was offered, or there was documentation of a contraindication to single fraction treatment.

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Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

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Suggested citation: Obley, A., Mosbaek, C., King, V., & Shaffer, W. (2018). *Coverage guidance: Single fraction radiotherapy for palliation of bone metastases*. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University

# Appendix A. GRADE Table Element Descriptions

| Element | Description |
|---|---|
| Balance of benefits and harms | The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. An estimate that is not statistically significant or has a confidence interval crossing a predetermined clinical decision threshold will be downgraded. |
| Quality of evidence | The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted |
| Resource allocation | The higher the costs of an intervention—that is, the greater the resources consumed in the absence of likely cost offsets—the lower the likelihood that a strong recommendation is warranted |
| Values and preferences | The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted |
| Other considerations | Other considerations include issues about the implementation and operationalization of the technology or intervention in health systems and practices within Oregon. |

## Strong recommendation

***In Favor:*** The subcommittee concludes that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors.

***Against:*** The subcommittee concludes that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors.

## Weak recommendation

***In Favor:*** The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors., but further research or additional information could lead to a different conclusion.

***Against:*** The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the balance of benefits and harms, cost and resource allocation, and values and preferences, but further research or additional information could lead to a different conclusion.

## Confidence in estimate rating across studies for the intervention/outcome

Assessment of confidence in estimate includes factors such as risk of bias, precision, directness, consistency and publication bias.

***High:*** The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.

***Moderate:*** The subcommittee is moderately confident in the estimate of effect: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical

sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

***Low:*** The subcommittee's confidence in the estimate of effect is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

***Very low:*** The subcommittee has very little confidence in the estimate of effect: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

## Appendix B. GRADE Evidence Profile

| Quality Assessment (Confidence in Estimate of Effect) | | | | | | | |
|---|---|---|---|---|---|---|---|
| **No. of Studies** | **Study Design(s)** | **Risk of Bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other Factors** | **Quality** |
| **Pain** | | | | | | | |
| 26 | RCT | Unclear[1] | Not serious | Not serious | Not serious | | High ●●●● |
| **Morbidity** | | | | | | | |
| 12 (pathologic fracture)<br>6 (spinal cord compression) | RCT | Unclear[1] | Not serious | Not serious | Serious[2] | | Moderate ●●●◌ |
| **Quality of life** | | | | | | | |
| 1 | RCT | Low | N/A | Not serious | Not serious | | High ●●●● |
| **Need for retreatment** | | | | | | | |
| 16 | RCT | Unclear[1] | Not serious | Not serious | Not serious | | High ●●●● |
| **Harms** | | | | | | | |
| 26 | RCT | Unclear[1] | Not serious | Not serious | Not serious | | High ●●●● |

[1]The systematic review that informed this estimate did not provide individual or overall risk of bias assessments.

[2]The 95% confidence interval cannot exclude clinically meaningful benefits or harms.

# Appendix C. Methods

## Scope Statement

### Populations

Patients receiving palliative radiotherapy for painful bone metastases

*Population scoping notes: None*

### Interventions

Single fraction radiotherapy

*Intervention exclusions: None*

### Comparators

Multiple fraction radiotherapy

### Outcomes

Critical: Pain, morbidity associated with bone metastases (e.g., pathologic fractures, spinal cord compression), quality of life

Important: Need for retreatment, harms

*Considered but not selected for the GRADE table: None*

### Key Questions

KQ1: What is the comparative effectiveness of single fraction radiotherapy for palliation of painful bone metastases?

KQ2: Does the effectiveness of single fraction radiotherapy for painful bone metastases vary by:

a. Patient characteristics (e.g., expected length of life)
b. Type of cancer
c. Total planned dose of radiotherapy
d. Number of treatment sites
e. Location of sites

KQ3: What are the harms of single fraction radiotherapy for palliation of painful bone metastases?

## Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, and technology assessments that met the criteria for the scope described above. Searches of core sources were limited to citations published after 2013.

The following core sources were searched:

Agency for Healthcare Research and Quality (AHRQ)
Canadian Agency for Drugs and Technologies in Health (CADTH)
Cochrane Library (Wiley Online Library)
Institute for Clinical and Economic Review (ICER)
Medicaid Evidence-based Decisions Project (MED)

National Institute for Health and Care Excellence (NICE)
Tufts Cost-effectiveness Analysis Registry
Veterans Administration Evidence-based Synthesis Program (ESP)
Washington State Health Technology Assessment Program

A MEDLINE® search was also conducted to identify systematic reviews, meta-analyses, and technology assessments, using the search terms for single fraction and bone metastases. The search was limited to publications in English published since 2013. In addition, a MEDLINE® search was conducted for randomized controlled trials published after the search dates of the most recent systematic review selected for each indication.

Searches for clinical practice guidelines were limited to those published since 2013. A search for relevant clinical practice guidelines was also conducted using MEDLINE® and the following sources:

Australian Government National Health and Medical Research Council (NHMRC)
Canadian Agency for Drugs and Technologies in Health (CADTH)
Centers for Disease Control and Prevention (CDC), Community Preventive Services
National Guidelines Clearinghouse
National Institute for Health and Care Excellence (NICE)
Scottish Intercollegiate Guidelines Network (SIGN)
United States Preventive Services Task Force (USPSTF)
Veterans Administration/Department of Defense (VA/DoD) Clinical Practice Guidelines

## Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessments, randomized controlled trials, or clinical practice guidelines.

## Appendix D. Applicable Codes

| CODES | DESCRIPTION |
|---|---|
| **CPT Codes** | |
| 77261-77263 | Therapeutic radiology treatment planning |
| 77280, 77285, 77290 | Therapeutic radiology simulation-aided field setting |
| 77300 | Basic radiation dosimetry calculation |
| 77306-77307 | Teletherapy isodose plan |
| 77331 | Special dosimetry |
| 77332-77334 | Treatment devices, design and construction |
| 77336,77370 | Medical physics consultation |
| 77401-77416 | Radiation treatment delivery |
| 77417 | Port verification films/electronic portal imaging for verification |
| 77431 | Radiation therapy management, complete course of therapy consisting of one or two fractions |
| **HCPCS Level II Codes** | |
| G6003-G6014 | Radiation treatment delivery |
| **ICD-10-PCS Codes** | |
| DP00-DP0C | Beam radiation of bone |
| **ICD-10-CM Codes** | |
| C79.51 | Secondary malignant neoplasm of bone |
| Z51.5 | Encounter for palliative care |

Note: Inclusion on this list does not guarantee coverage.