Public Comment Draft

Radiation Therapy for Palliation of Symptomatic Bone Metastases: An ASTRO Clinical Practice Guideline

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Disclosures: All task force members' disclosure statements were reviewed before being invited and were shared with other task force members throughout the guideline's development. Those disclosures are published within this guideline. Where potential conflicts were detected, remedial measures to address them were taken.

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Abstract

Purpose: This guideline provides evidence-based recommendations for palliative radiation therapy (RT) in symptomatic bone metastases.

Methods: The American Society for Radiation Oncology (ASTRO) convened a task force to address 5 key questions regarding palliative RT in symptomatic bone metastases. Based on a systemic review by the Agency for Health Research and Quality, recommendations using predefined consensus-building methodology were established; evidence quality and recommendation strength were also assessed.

Results: For palliative RT for symptomatic bone metastases, RT is recommended for managing pain from bone metastases and spine metastases with or without spinal cord or cauda equina compression. Regarding other modalities with RT, for patients with spine metastases causing spinal cord or cauda equina compression, surgery and postoperative RT are conditionally recommended over RT alone. Furthermore, dexamethasone is recommended for spine metastases with spinal cord/cauda compression. Patients with non-spine bone metastases requiring surgery are recommended postoperative RT. Recommendations for dose-fractionation, constraints, and techniques include symptomatic bone metastases treated with RT are recommended 800 cGy in 1 fraction (800 cGy/1fx), 2000 cGy/5fx, 2400 cGy/6fx, or 3000 cGy/10fx. Spinal cord or cauda equina compression in patient's ineligible for surgery and receiving conventional RT are recommended 800 cGy/1fx, 1600 cGy/2fx, 2000 cGy/5fx, or 3000 cGy/10fx. Symptomatic bone metastases in selected patients with good performance status without surgery or neurological symptoms/signs are conditionally recommended SBRT over conventional palliative RT. Spine bone metastases re-irradiated with conventional RT are recommended 800 cGy/1fx, 2000 cGy/5fx, 2400 cGy/6fx, or 2000 cGy/8fx; non-spine bone metastases re-irradiated with conventional RT are recommended 800 cGy/1fx, 2000 cGy/5fx, or 2400 cGy/6fx. Determination of an optimal RT approach/regimen requires whole person assessment, including prognosis, previous RT dose if applicable, risks to normal tissues, quality of life, cost implications, and patient goals and values. Relatedly, for patient-centered optimization of treatment-related toxicities and quality of life, shared decision-making is recommended.

Conclusions: Based on published data, the ASTRO task force's recommendations inform best clinical practices on palliative RT for symptomatic bone metastases.

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Preamble

As a leading organization in radiation oncology, the American Society for Radiation Oncology (ASTRO) is dedicated to improving quality of care and patient outcomes. A cornerstone of this goal is the development and dissemination of clinical practice guidelines based on systematic methods to evaluate and classify evidence, combined with a focus on patient-centric care and shared decision making. ASTRO develops and publishes guidelines without commercial support, and members volunteer their time.

Disclosure Policy—ASTRO has detailed policies and procedures related to disclosure and management of industry relationships to avoid actual, potential, or perceived conflicts of interest. All task force members are required to disclose industry relationships and personal interests from 12 months before initiation of the writing effort. Disclosures for the chair and vice chair go through a review process with final approval by ASTRO's Conflict of Interest Review Committee. For the purposes of full transparency, task force members' comprehensive disclosure information is included in this publication. Peer reviewer disclosures are also reviewed and included (Supplementary Materials, Appendix E1). The complete disclosure policy for Formal Papers is online.

Selection of Task Force Members—ASTRO strives to avoid bias and is committed to creating a task force that includes a diverse and inclusive multidisciplinary group of experts considering race, ethnicity, gender, experience, practice setting, and geographic location. Representatives from organizations and professional societies with related interests and expertise are also invited to serve on the task force.

Methodology—ASTRO's task force uses evidence-based methodologies to develop guideline recommendations in accordance with the National Academy of Medicine standards.[1,2] The evidence identified from key questions (KQs) is assessed using the **P**opulation, **I**ntervention, **C**omparator, **O**utcome, **T**iming, **S**etting (PICOTS) framework. A systematic review of the KQs is completed, which includes creation of evidence tables that summarize the evidence base task force members use to formulate recommendations. Table 1 describes ASTRO's recommendation grading system. See Appendix E2 in Supplementary Materials for a list of abbreviations used in the guideline.

Consensus Development—Consensus is evaluated using a modified Delphi approach. Task force members confidentially indicate their level of agreement on each recommendation based on a 5-point Likert scale, from "strongly agree" to "strongly disagree". A prespecified threshold of ≥75% (≥90% for expert opinion recommendations) of raters who select "strongly agree" or "agree" indicates consensus is achieved. Recommendation(s) that do not meet this threshold are removed or revised. Recommendations edited in response to task force or reviewer comments are resurveyed before submission of the document for approval.

Annual Evaluation and Updates—Guidelines are evaluated annually beginning 2 years after publication for new, potentially practice-changing studies that could result in a guideline update. In addition, ASTRO's Guideline Subcommittee will commission a replacement or reaffirmation within 5 years of publication.

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Table 1 ASTRO recommendation grading classification system

ASTRO's recommendations are based on evaluation of multiple factors including the QoE and panel consensus, which among other considerations, inform the strength of recommendation. QoE is based on the body of evidence available for a particular key question and includes consideration of number of studies, study design, adequacy of sample sizes, consistency of findings across studies, and generalizability of samples, settings, and treatments.

Strength of Recommendation	Definition	Overall QoE Grade	Recommendation Wording
Strong	• Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits. • All or almost all informed people would make the recommended choice.	Any (usually high, moderate, or expert opinion)	"Recommend/ Should"
Conditional	• Benefits are finely balanced with risks and burden or appreciable uncertainty exists about the magnitude of benefits and risks. • Most informed people would choose the recommended course of action, but a substantial number would not. • A shared decision-making approach regarding patient values and preferences is particularly important.	Any (usually moderate, low, or expert opinion)	"Conditionally Recommend"

Overall QoE Grade	Type/Quality of Study	Evidence Interpretation
High	• 2 or more well-conducted and highly generalizable RCTs or meta-analyses of such trials.	The true effect is very likely to lie close to the estimate of the effect based on the body of evidence.
Moderate	• 1 well-conducted and highly generalizable RCT or a meta-analysis of such trials **OR** • 2 or more RCTs with some weaknesses of procedure or generalizability **OR** • 2 or more strong observational studies with consistent findings.	The true effect is likely to be close to the estimate of the effect based on the body of evidence, but it is possible that it is substantially different.
Low	• 1 RCT with some weaknesses of procedure or generalizability **OR** • 1 or more RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes **OR** • 2 or more observational studies with inconsistent findings, small sample sizes, or other problems that potentially confound interpretation of data.	The true effect may be substantially different from the estimate of the effect. There is a risk that future research may significantly alter the estimate of the effect size or the interpretation of the results.
Expert Opinion*	• Consensus of the panel based on clinical judgment and experience, due to absence of evidence or limitations in evidence.	Strong consensus (≥90%) of the panel guides the recommendation despite insufficient evidence to discern the true magnitude and direction of the net effect. Further research may better inform the topic.

Abbreviations: ASTRO = American Society for Radiation Oncology; QoE = quality of evidence; RCTs = randomized controlled trials.

*A lower quality of evidence, including expert opinion, does not imply that the recommendation is conditional. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials, but there still may be consensus that the benefits of a treatment or diagnostic test clearly outweigh its risks and burden.

ASTRO's methodology allows for use of implementation remarks meant to convey clinically practical information that may enhance the interpretation and application of the recommendation. While each recommendation is graded according to recommendation strength and QoE, these grades should not be assumed to extend to the implementation remarks.

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1. Introduction

Bone metastases are common among patients with advanced cancer and can substantially worsen quality of life (QoL) through associated skeletal related events such as pain, fracture, and spinal cord or cauda equina compression.[3] Radiation therapy (RT) is a particularly effective modality for managing bone metastases, with evidence supporting its efficacy for reducing pain and other symptoms from local progression as well as potentially preventing new skeletal events and providing long-term disease control in select patients with expected prolonged survival.[4-6] Correspondingly, RT dose and technique—ranging from single- and multifraction conventional palliative RT to highly conformal stereotactic body radiation therapy (SBRT) regimens—may vary according to patient and disease factors and treatment intent.

This systematic evidence review and guideline serves to update previous ASTRO recommendations by incorporating new high-quality evidence for the management of symptomatic bone metastases.[7,8] To do so, ASTRO assigned task force members to formulate and provide guidance on 5 key clinical questions central to the use of RT in this context. Whenever possible, data was included and analyzed to consider factors known to be associated with disparities in health access, use, and outcomes.

2. Methods

2.1. Task force composition

The task force consisted of a multidisciplinary team of radiation, medical, and surgical oncologists, palliative care specialists, and a patient representative. This guideline was developed in collaboration with the American Society of Clinical Oncology and the Musculoskeletal Tumor Society, who provided representatives and peer reviewers.

2.2. Document review and approval

The guideline was reviewed by XX official peer reviewers (Appendix E1) and revised accordingly. The modified guideline was posted on the ASTRO website for public comment from November to December 2023. The final guideline was approved by the ASTRO Board of Directors and endorsed by the TBD.

2.3. Evidence review

In July 2020, ASTRO submitted a proposal for the Agency for Healthcare Research and Quality (AHRQ) to develop a comparative effectiveness evidence review on RT for bone metastases, which was accepted and funded by the Patient-Centered Outcomes Research Institute.[9] This review aimed to support a replacement of

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the prior ASTRO 2017 bone metastases guideline.[8] AHRQ performed a systematic search of the databases Embase® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE® Daily, MEDLINE®, Cochrane Central Register of Controlled Trials, Ovid® Cochrane Database of Systematic Reviews, and Scopus® from January 1, 1985 to January 30, 2023. Eligible study designs included randomized controlled trials (RCTs) and comparative nonrandomized studies that controlled for confounding if no or very few RCTs were available. At least one arm in each comparative study was comprised of external beam RT. In total, 53 RCTs and 31 nonrandomized studies were included for data abstraction. Given the high clinical relevance of RTOG 0631,[10] the latest cooperative group study on the management of bone metastases relevant to this guideline, this trial was additionally evaluated by AHRQ after its publication in April 2023 and added to the AHRQ report as an addendum.[9] The systematic review was not otherwise extended past January 30, 2023. For details on the AHRQ methodology and systematic review explanation, including the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram showing the number of articles screened, excluded, and included in the evidence review, see Appendix B of the AHRQ systematic review report.[9]

References selected and published in this document are representative and not all-inclusive. Additional ancillary articles not in the AHRQ evidence tables or report are included in the text but were not used to support the recommendations. The outcomes of interest are pain (level and duration), skeletal function (overall function), relief of spinal cord or cauda equina compression, and QoL. Additional secondary outcomes examined include re-irradiation, local recurrence, fracture, use of pain medication, need for non-RT pain interventions, and overall survival. Given variability in the definitions and modes of assessment for the outcomes of interest, caution should be used when comparing results across studies.

2.4. Scope of the guideline

RT has long been an integral component of the management of symptomatic bone metastases, given its effectiveness in reducing pain and other local sequelae of metastatic bone disease. Historically, 2-dimensional (2-D) RT (ie, based on orthogonal radiographs with simple RT field arrangements) was the mainstay of RT delivery. However, over the past few decades, increasingly advanced technologies have emerged such as 3-D conformal RT (3-D CRT; ie, CT-based imaging for planning with the potential for more complex beam arrangements) and intensity modulated radiation therapy (IMRT; ie, an advanced form of 3-D CRT that uses nonuniform beam intensity, with additional planning, quality assurance, and imaging approaches). Adoption of SBRT (ie, the use of advanced immobilization and imaging techniques to deliver highly conformal, high dose per fraction RT to the tumor target) has enabled further dose escalation and retreatment strategies to be employed. Concurrent with these technological advancements within RT are the improvements in patient systemic therapies resulting in greater longevity with many metastatic cancer diagnoses, raising questions regarding the efficacy of more conventional forms of palliative RT (ie, 2-D and 3-D

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techniques delivered without dose escalation) in a more modern population in terms of outcomes, such as pain control and local control. Furthermore, greater longevity with a metastatic cancer diagnosis has also rendered more salient questions about the role of RT for re-irradiation in the setting of symptomatic bone metastases, including both its efficacy and safety.

With the aforementioned clinical questions in mind, the scope of this guideline is to provide updated evidence of clinical recommendations regarding dose-fractionation and techniques of delivery of RT both in the up front and re-irradiation settings. Furthermore, this guideline compares the effectiveness and harms of RT in conjunction with additional therapies (eg, bisphosphonates, surgery, vertebroplasty) compared with RT alone. Also addressed in this guideline is if and how effectiveness and harms of RT vary by patient and clinical characteristics, with the aim of determining if certain subsets of patients may benefit from specific palliative RT regimens and advanced techniques.

This guideline addresses only the subjects specified in the KQs (Table 2), specifically symptomatic bone metastases in adult patients; management of pediatric symptomatic bone metastases is beyond the scope of this guideline. For the purposes of this guideline, the term *symptomatic bone metastases* refers to osseous metastatic lesions directly resulting in pain or other symptoms. The term *palliative RT* refers to RT delivered with the goal of ameliorating symptoms associated with target lesions. Studies involved patients with symptomatic osseous lesions across a range of clinical scenarios, including varying histologies and extent of disease — from widely metastatic to oligometastatic states. However, a majority of studies limited inclusion to solid malignancies. As such, caution should be used when applying recommendations for hematologic and other potentially radiosensitive tumors, which may be adequately palliated by lower doses or alternative fractionation regimens. Outside the scope of this guideline are many other important questions that may be subjects of other guidelines, including SBRT in the setting of *asymptomatic* metastatic disease.

Table 2 KQs in PICO format

KQ	Population	Intervention	Comparator	Outcomes for all KQs
1	**In adult patients with symptomatic bone metastases, what are the appropriate indications for RT in the palliative treatment of bone metastases?**			Primary Outcomes: • Pain • Skeletal function • Improvement of neurological symptoms from spinal cord or cauda equina compression • QoL Secondary Outcomes: • Local recurrence
	Adult patients with symptomatic bone metastases	• Palliative RT	• Comparisons of symptoms before and after palliative RT	
2	**In adult patients with symptomatic bone metastases, what is the impact of surgery, radiopharmaceutical therapy, bisphosphonate therapy, or kyphoplasty/vertebroplasty on the appropriate indications for RT in the palliative treatment of bone metastases?**			
	Same as KQ1	• Palliative RT	• Comparison of addition (or omission) of RT to other bone metastases interventions (eg, surgery, radiopharmaceuticals,	

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			and bisphosphonate therapies, vertebroplasty)	• Fracture prevention • Need for re-irradiation • Use of pain medication or other interventions for pain relief • Overall survival Adverse Events: • Treatment toxicities • Pain flare
3	**In adult patients with symptomatic bone metastases, what RT dose-fx regimens, dose-constraints, and techniques are appropriate for the initial palliative treatment of bone metastases?**			
	Same as KQ1	• Dose-fx • Target volumes • Motion management • Treatment techniques • Optimal planning parameters	• Comparisons of RT dose-fx regimens • Comparisons of RT techniques (eg, conventional palliative RT vs SBRT)	
4	**In adult patients with symptomatic bone metastases, what RT dose-fx regimens, dose-constraints, and techniques are appropriate for palliative re-irradiation of bone metastases?**			
	Same as KQ1	• Dose-fx • Target volumes • Motion management • Treatment techniques • Optimal planning parameters	• Comparisons of dose-fx regimens for conventional palliative RT • Comparisons of RT techniques (eg, conventional palliative RT vs SBRT)	
5	**In adult patients with symptomatic bone metastases receiving palliative RT, how do the different dose-fx schemes and techniques impact on treatment toxicity and QoL?**			
	Same as KQ1	• Dose-fx • Target volumes • Motion management • Treatment techniques • Optimal planning parameters	• Comparisons of dose-fx regimens for conventional palliative RT • Comparisons of RT techniques (eg, conventional palliative RT vs SBRT)	

Abbreviations: fx = fractionation; KQs = key questions; PICO = Population, Intervention, Comparator, Outcome; QoL = quality of life; RT = radiation therapy; SBRT = stereotactic body radiation therapy.

3. Key Questions and Recommendations

3.1. KQ1: Indications for RT in palliative treatment for symptomatic bone metastases (Table 3)

In adult patients with symptomatic bone metastases, what are the appropriate indications for RT in the palliative treatment of bone metastases?

Table 3 Indications for RT in palliative treatment

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with symptomatic bone metastases, RT is recommended to reduce pain from osseous metastasis.	Strong	High (Overall pain)

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		[11,12] Moderate (Neuropathic pain) [13]
2. For patients with symptomatic spine bone metastases, including those causing compression of the spinal cord or cauda equina, RT is recommended to improve ambulatory status, sphincter function, and reduce pain. Implementation remark: Before initiating RT, evaluation for spine stability and surgery are necessary.	Strong	High [14-19]
3. For patients with symptomatic bone metastases and an anticipated life expectancy of ≥4 weeks, RT is conditionally recommended to improve quality of life (eg, functional status, mobility).	Conditional	Low [20-23]

Abbreviations: KQ = key question; RT = radiation therapy.

Despite the number of RCTs evaluating RT among patients with symptomatic bone metastases, no RCTs have compared RT to no therapy or best supportive care. Furthermore, it is unlikely that such RCTs would be performed in the future given ethical considerations. As such, the evidence supporting appropriate indications for RT in patients with symptomatic bone metastases are gleaned from RCTs comparing different conventional palliative RT dose-fractionation regimens with a focus on whether there are differences in measured outcomes across randomization arms before and after RT. Accordingly, this limited evaluable endpoints. For example, the effect of RT versus no RT on bone fracture risk could not be commented on using these data, whereas differences in pain response, medication use, and ambulatory function before and after RT could be evaluated if they were reported as proportions. Whereas descriptive summary statistics such as mean and median values could not readily be combined across randomization arms post-hoc (eg, mean pain score), trial data that was reported as a proportion (ie, with numerator and denominator, such as complete pain response rate) could be summarized across randomization arms and compared before and after RT. However, it should be noted that differences in an outcome before and after RT could be confounded by other interventions that were not recorded or measured between baseline and response assessment (eg, systemic therapy, bisphosphonate use, analgesics). Therefore, proportions (when given) may overestimate the effect of RT. While response rates for the evaluable outcome measures did not significantly vary between fractionation regimens compared in RCTs of conventional palliative RT regimens only, there were potential differences in these outcomes in RCTs comparing palliative RT to dose-escalated RT approaches (eg, SBRT). As such, only trials of different conventional palliative RT fractionation regimens were included for this KQ to ensure that

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values could be appropriately combined across treatment arms when comparing pre- versus post-RT outcomes.

Palliative RT and pain

Measurement of pain varied across RCTs, ranging from categorical (eg, no pain, pain controlled with minor analgesics, pain requiring minor opiates, and pain requiring major opiates)[16] to continuous (eg, visual analog scale).[20] Not surprisingly, definition of pain response, which was the primary endpoint for most RCTs also varied. These heterogeneous definitions make it challenging to quantify rates of pain response after RT, though allowing for these caveats, overall pain response rates of 52% to 86% were noted up to 4 weeks after RT,[16,20,24-30] 60% to 81% between 4 to 12 weeks after RT[11,12,20,26,28,30,31] and 56% to 66% more than 12 weeks after RT.[20,30] Although statistically significant differences between groups cannot be established on the basis of the available data, overall response rates by primary tumor type reported ranged from 76% to 90% for breast, 60% to 67% for lung, 78% to 88% for prostate, and 60% to 62% for other tumors in 2 RCTs reporting data by tumor type at 12 weeks after RT.[11,32] In 1 RCT evaluating overall pain response at 8 weeks by metastatic site, response rate was 91% for spine, 93% for pelvis, 73% for limbs, and 71% for other metastatic sites after RT.[30] Only 1 RCT evaluated RT in patients with pain with a neuropathic component, demonstrating an overall pain response across the 2 randomized arms of 58% after RT.[13]

Palliative RT and spine bone metastases causing compression of the spinal cord/cauda equina

Multiple RCTs evaluated conventional palliative RT in patients with spine bone metastases causing compression of the spinal cord or cauda equina: 4 comparing single- versus multifraction RT,[14-16,19] 1 comparing different regimens of multifraction RT,[18] and 1 comparing multifraction RT with or without surgical decompression.[17] Most of these studies required radiographic evidence of spinal cord or cauda equina compression.[15-19] Rates of improved or regained sphincter control ranged widely between studies (13% - 71%) after RT,[14,16] while rates of regained ambulation (non-ambulatory to ambulatory) ranged from 8% to 26%.[14-16,19] While RT is indicated for patients with spinal cord or cauda equina compression, this does not obviate the need for surgical evaluation for either stabilization and/or to improve functional status.[17,33]

Palliative RT and quality of life

QoL was variably included as a secondary outcome in RCTs and was challenging to interpret across available randomized studies given varied questionnaires (eg, EORTC, Spitz index) and endpoints (eg, mobility, performance status). Several studies did not report when QoL was reassessed after RT. However, among those that did, the earliest time point was 4 weeks after RT.[20,22] Qualitatively, there appears to be stable or improved

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QoL measurements after RT.[20] For example, in 1 RCT evaluating RT dose (single vs multifraction), global QoL as measured by a visual analog scale was noted to improve at 4 weeks after RT by ≥25% in 34% of patients, ≥50% in 21% of patients, and ≥75% in 11% of patients.[20] It is unknown whether improvements in QoL may be noted sooner (ie, <4 weeks).

3.2. KQ2: Impact of other treatments for bone metastases on indications for RT in palliative treatment (Table 4)

In adult patients with symptomatic bone metastases, what is the impact of surgery, radiopharmaceutical therapy, bisphosphonate therapy, or kyphoplasty/vertebroplasty on the appropriate indications for RT in the palliative treatment of bone metastases?

Table 4 Impact of other treatments for bone metastases on indications for RT in palliative treatment

KQ2 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with spine bone metastases causing compression of the spinal cord or cauda equina, surgery with postoperative RT is conditionally recommended over RT alone.	Conditional	Low [17,34-37]
2. For patients with non-spine bone metastases and spine metastases without spinal cord or cauda compression who have undergone surgery, postoperative RT is recommended.	Strong	Low [38]
3. For patients with spine bone metastases causing compression of the spinal cord or cauda equina, RT combined with dexamethasone is recommended over RT alone.	Strong	Low [39]

Abbreviations: KQ = key question; RT = radiation therapy.

Similar to findings of the 2017 and 2011 ASTRO guidelines concerning the roles of surgery, radiopharmaceuticals, bisphosphonates, kyphoplasty and vertebroplasty, the present task force found that none of these therapies obviate the need for palliative RT for patients with painful bone metastases.[7,8]

Surgery and postoperative RT for compression of the spinal cord/cauda equina

In the setting of spinal metastases causing compression of the spinal cord or cauda equina, decompressive surgery should be considered for eligible patients followed by postoperative RT. Multidisciplinary collaboration is encouraged to optimize patient selection for surgical decompression. Factors that should influence decision-making include performance status; spinal stability;[40] character, duration, and pace of development of neurologic symptoms; location and number of discrete levels of compression; extent and distribution of metastatic disease in the spine; primary tumor site and radiosensitivity; alternative treatment options; prior RT; patient preferences and goals; and expected survival. The RCT of direct

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decompressive surgery and postoperative RT compared with RT alone showed that among a select patient population with compression of the spinal cord, the combination of surgery and RT (3000 cGy in 10 fractions) improved the ability of patients to retain and regain ambulatory status.[17] Other series most commonly report the use of multifraction courses of RT in the postoperative setting; however, an optimal dose-fractionation regimen could not be determined from the available data.[17,34-37] The use of SBRT in the postoperative setting is evolving, and participation in available clinical trials is encouraged for eligible patients.[41,42]

Surgery and postoperative RT for bone metastases

No RCTs have compared surgery alone with surgery and postoperative RT for non-spine bone metastases and spine metastases without cord or cauda equine compression. Supported by retrospective series, expert opinion, and acknowledging long-held ubiquitous practice patterns, RT after surgery for bone metastases is recommended, whether surgery is prophylactic or reactionary after a pathologic fracture.[38,43-47] The optimal sequencing and timing of surgery and RT are open questions, as are the ideal dose-fractionations and target volumes. Reported regimens range from 800 cGy in 1 fraction to 3000 to 4500 cGy in conventionally fractionated and hypofractionated regimens, with multifraction regimens such as 3000 cGy in 10 fractions being most common. Reported target volumes and field sizes vary, with a bias towards more inclusive coverage of all surgical hardware and the suggestion that this may reduce the risk of local recurrence.[38,44,47,48]

Palliative RT and dexamethasone for compression of the spinal cord/cauda equina

The addition of dexamethasone to RT compared with RT alone showed an improvement in ambulatory status among patients with compression of the spinal cord or cauda equina in a small single-center RCT trial.[39,49] However, the dose of dexamethasone was high, with an initial 96 mg intravenous (IV) bolus followed by oral therapy at 96 mg daily (given in 4 divided doses), for 3 days, followed by a 10-day taper.[39] The panel acknowledges the potential detrimental consequences of prolonged high dose corticosteroid therapy, and although the optimal dosing of dexamethasone in this setting is unknown. While high-quality dose finding data was not captured in the literature review, expert opinions have suggested an initial 10 mg IV bolus followed by a maintenance dose of 4 to 6 mg IV/by mouth every 6 to 8 hours or 8 mg every 12 hours, consideration of gastrointestinal prophylaxis, *pneumocystis jiroveci (*previously *pneumocystis carinii)* pneumonia prophylaxis in those receiving dexamethasone ≥3 mg per day (equivalent of prednisone 20 mg per day) for ≥4 weeks,[50] careful monitoring of clinical response and toxicities, a plan for tapering safely and expeditiously, and where feasible, moving doses to earlier hours in the day to avoid insomnia.[49,51-54]

Palliative RT and radiopharmaceutical therapy

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Radiopharmaceutical therapy does not obviate the routine need for palliative external beam RT for patients with localized painful bone metastases. The panel reviewed a variety of randomized and nonrandomized studies including those comparing radiopharmaceutical therapy (with or without concomitant RT) to RT alone, and studies comparing the 2 modalities directly. As such, studies that evaluated radiopharmaceutical therapy alone are out of the scope of this guideline. Specifically, for 2 RCTs comparing RT to strontium-89 chloride for prostate cancer, there was no significant difference in pain outcomes measured between treatment arms.[55,56] While 2 RCTs comparing RT plus strontium-89 versus RT plus placebo similarly showed no significant difference in primary pain outcomes for prostate cancer,[57,58] 1 reported significant reduction of analgesic use over time for the radiopharmaceutical arm.[57] The use of radiopharmaceutical therapy (mostly among patients with metastatic prostate cancer) continues to expand due to observed benefits including preventing skeletal-related events and improving survival,[8] specifically when considering radium-223[59] and Lutetium-177-PSMA.[60] However, the use of radiopharmaceutical therapy for endpoints aside from pain response at the site of index (irradiated) bone metastases is beyond the scope of this guideline.[55-59,61-63]

Palliative RT and bisphosphonate therapy

Bone modifying agents such as bisphosphonate therapies do not obviate the routine need for palliative RT for patients with localized painful bone metastases. The task force reviewed a variety of RCTs and nonrandomized studies, including those comparing bisphosphonates to RT directly and studies comparing combined RT and bisphosphonates to RT alone.[64-67] A UK trial (n=470) randomized patients with metastatic prostate cancer to local conventional palliative RT (800 cGy in 1 fraction) or a single 6 mg infusion of ibandronate and found no difference in overall pain response at 4 or 12 weeks; however, a more rapid initial response with RT was observed.[64]

Palliative RT and kyphoplasty, vertebroplasty, cryoablation, hyperthermia, and radiofrequency ablation

Though data are limited, none of the available evidence suggests that local interventional treatments - including kyphoplasty, vertebroplasty, cryoablation, radiofrequency ablation, or hyperthermia - obviate the need for RT for patients with localized symptomatic bone metastases.[68,69]

3.3. KQ3: Dose-fractionation, dose-constraints, and techniques for initial palliative treatment (Table 5)

In adult patients with symptomatic bone metastases, what RT dose-fractionation regimens, dose-constraints, and techniques are appropriate for the initial palliative treatment of bone metastases?

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Table 5 Dose-fractionation, dose-constraints, and techniques for initial palliative treatment of bone metastases

KQ3 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with symptomatic bone metastases treated with conventional palliative RT, 800 cGy in 1 fraction, 2000 cGy in 5 fractions, 2400 cGy in 6 fractions, or 3000 cGy in 10 fractions are recommended.	Strong	High 11,12,20,22,28,32,70,71
2. In patients with spine bone metastases causing compression of the spinal cord or cauda equina who are not eligible for initial surgical decompression and are treated with conventional palliative RT, 800 cGy in 1 fraction, 1600 cGy in 2 fractions, 2000 cGy in 5 fractions, or 3000 cGy in 10 fractions are recommended. Implementation remark: Consider patient and disease factors in dose-fractionation selection (eg, prognosis and radiosensitivity).	Strong	High 14-16,18,19,72
3. For patients with spine bone metastases causing compression of the spinal cord or cauda equina treated with dose escalated palliative RT, the use of highly conformal planning and delivery techniques (eg, IMRT) is conditionally recommended.	Conditional	Low 73
4. For patients with symptomatic bone metastases treated with SBRT, 1200 to 1600 cGy in 1 fraction (non-spine) and 2400 cGy in 2 fractions (spine) are recommended.	Strong	Moderate 10,74-76
5. For patients with symptomatic bone metastases with ECOG PS 0-2, receiving no surgical intervention, and absent neurological symptoms, SBRT is conditionally recommended over conventional palliative RT. Implementation remark: Other factors to consider include good prognosis/life expectancy, tumor radiosensitivity, and metastatic disease burden.	Conditional	Moderate 10,74-76

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; IMRT = intensity modulated radiation therapy; KQ = key question; SBRT = stereotactic body radiation therapy.

While the role of RT in the treatment of symptomatic bone metastases is widely accepted, the optimal dose-fractionation regimen has been debated for decades, ranging from single- to multifraction delivery using a range of regimens. Studies have also sought to evaluate the role of dose escalation using IMRT or SBRT as compared with conventional palliative RT doses and techniques.[10,73-78] In general, inclusion criteria for RCTs comparing various RT doses and techniques have been broad and overlapping between studies, and most RCTs did not provide statistical analyses for the differential effectiveness of interventions based on patient and disease characteristics. In addition to limiting conclusions regarding appropriate patient selection, this also hindered the ability to comment on how specific RT regimens may have interacted with factors known to be

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associated with disparities in health access, use, and outcomes. As such, the following factors to guide decision making are suggested when considering selection of regimens with higher biological effective dose (BED), advanced planning techniques, or both: better estimated prognosis, radioresistant tumor type, limited metastatic disease, receipt of prior RT, and ability to delay treatment to afford time for advanced planning when appropriate.[79] As described in KQ1, the primary outcome reported for most RCTs was pain response. Heterogeneity in both the definitions used as well as in the timing of assessment of this outcome impaired direct comparisons across studies.

Conventional palliative RT fractionation

Multiple RCTs evaluated the most effective single-fraction dose of palliative RT. The consensus of these studies determined that 800 cGy in 1 fraction was superior to other single-fraction dose regimens (eg, 400 cGy).[71,80] Similarly, more than 10 RCTs set out to determine the most effective multifraction regimen, with regimens of 2000 cGy in 5 fractions and 3000 cGy in 10 fractions among the most commonly used.[21,22,70,81,82]

To further understand the effects of fractionation on palliation of painful bone metastases, there have been many RCTs and nonrandomized studies comparing single-fraction versus multifraction regimens of RT. Most of these studies included spine and non-spine metastases and many included metastases from a variety of malignant tumors; the majority were limited to “uncomplicated” bone metastases without existing or impending fracture, spinal cord or cauda equina compression, or history of prior RT. Almost all the studies used 800 cGy for the single-fraction arm. Conversely, there were a variety of multifraction regimens used throughout these studies. The most common regimens were 2000 cGy in 5 fractions and 3000 cGy in 10 fractions. Other multifraction regimens that were used include: 2250 cGy in 5 fractions, 4000 cGy in 20 fractions and 2400 cGy in 6 fractions.[11,24,30] The recommendation of multifraction regimens of 2000 cGy in 5 fractions and 3000 cGy in 10 fractions is based on the breadth of studies using these fractionation regimens.[11-13,20,25-29,31,70] The regimen 2400 cGy in 6 fractions is additionally included given it was tested as part of the largest (n=1171) multisite RCT of single versus multifraction RT.[11] Although the rates for overall pain response tended to be slightly lower at 4 weeks for single-fraction regimens as compared with multifraction regimens (ranging from 49%-83% vs 53%-89%, respectively across 9 RCTs),[16,20,24-30] after 4 weeks post-treatment, there was no statistically significant difference in pain reduction when comparing the single to the multifraction arms.[11,12,20,26,28,30,31] Despite lack of consistent difference in pain control between the single and multifaction arms, a number of studies showed that patients receiving single-fraction RT were more than 2 times as likely to receive re-irradiation than those who received multifraction regimens.[11-13,15,19,20,25,28,30,70,83,84] Given the lack of systematic imaging follow-up in these studies, it is unclear if retreatment with RT was due to true

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symptomatic disease progression versus a greater willingness to retreat when the prior RT dose intensity was low.

Palliative RT for bone metastases causing spinal cord or cauda equina compression

There are several palliative RT fraction regimens to consider for patients with bone metastases causing spinal cord or cauda equina compression who are not candidates for initial surgical decompression. Across studies, commonly used conventional palliative single- and multifraction RT regimens were (1) 800 cGy in 1 fraction,[14-16,19] and (2) 2000 cGy in 5 fractions, and (3) 3000 cGy in 10 fractions, respectively.[14-16,18,19,72] Multiple RCTs compared the efficacy of single- versus multifraction regimens in maintaining or improving ambulation after RT and demonstrated no differences in ambulatory outcomes at any point between fractionation schemes.[14-16,19] Sphincter, bladder, and bowel control outcomes were also similar for single- and multifraction regimens. Similarly, an RCT comparing 2000 cGy in 5 fractions to 3000 cGy in 10 fractions reported no significant difference in ambulatory outcomes between fractionation arms.[18] Notably, median overall survival was 3 to 4 months across patients in the above noted RCTs reporting this outcome,[15,16,18,19] and 2 studies specifically limited inclusion to patients with estimated median survival of ≤6 months.[16,18] As such, shorter course, lower BED regimens may be most appropriate for patients with limited prognosis. Multifraction regimens with higher doses could be considered if survival is estimated on the order of many months given the potential impact of higher BED on maintenance of ambulatory status.[14,85] In addition to estimated prognosis, relative radio-resistance of tumor type and prior overlapping radiation should be considered in regimen selection.

Dose escalated RT for spine bone metastases causing compression of the spinal cord/cauda equina

There are limited studies on advanced treatment planning and delivery techniques (eg, IMRT) to dose escalate (ie, doses approaching spinal cord/nerve tolerance) for patients with metastatic epidural spinal cord or cauda equina compression who did not undergo surgical resection.[73,77,86,87] In a single institutional study where dose escalated RT (IMRT in 59.3% of the patients) delivering 2500 cGy in 5 fractions was used to treat metastatic epidural spinal cord or cauda equina compression, partial or complete pain relief was achieved in 75.7% of the patients for a median duration of 6 months.[77] In a multicenter phase 2 trial using volumetric modulated arc therapy or SBRT delivering 2500 cGy in 5 fractions for metastatic epidural spinal cord or cauda equina compression, authors reported improvement in motor function in 60% of patients, with 82.5% noted to be ambulatory after treatment.[73] Fifty percent of patients with sensory deficits noticed improvement after treatment. Relief of pain and distress were reported by 61.9% and 54.2% of patients, respectively, at 1 month after treatment. When compared with the historic control group of patients receiving conventional palliative

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RT with 2000 cGy in 5 fractions, local progression free survival (defined as no worsening of motor deficits during and no in-field recurrence of spinal cord compression after RT) was improved with highly conformal dose escalated RT (95% vs 76% at 6 months), but motor function was not appreciably different.[73] No RT myelopathy events were observed.

SBRT for symptomatic bone metastases

Numerous single-arm retrospective and prospective studies on SBRT for symptomatic bone metastases showed promising results in terms of pain control.[88-94] Five RCTs comparing SBRT and conventional palliative RT for symptomatic bone metastases without associated neurological symptoms and not requiring surgical intervention have been completed.[10,74-76,78] For the 3 trials that included only patients with spinal bone metastases, 2 demonstrated statistically significant differences in pain control in favor of SBRT.[74,75] Specifically, an RCT of SBRT using 2400 cGy in 2 fractions reported significantly higher rates of complete pain response at 3 months as compared with conventional palliative RT of 2000 cGy in 5 fractions (35% vs 14%, respectively), with this significant difference persisting >6 months post-treatment.[75] Although the trial of SBRT to 2400 cGy in 1 fraction versus conventional palliative RT to 3000 cGy in 10 fractions did not find an appreciable difference in the primary endpoint (pain relief of >2 points on the visual analog scale at 3 months), pain by this metric was significantly lower in the SBRT group by 6 months. New pathologic fracture rates at 6 months were 27.7% in the SBRT arm and 5.0% in the conventional RT arm (p=0.054); no fractures required surgical intervention.[74] The third trial, RTOG 0631, compared SBRT using 1600 to 1800 cGy in 1 fraction versus conventional palliative RT using 800 cGy in 1 fraction and did not detect a difference between the SBRT and conventional palliative RT in pain control in patients with spine metastases.[10] However, this trial was developed prior to the inception of the use of spinal instability neoplastic score (SINS), reflecting the degree of mechanical instability of the spinal segment which might be a confounder affecting the pain score.[40] Furthermore, more patients in the SBRT arm had a Zubrod score of ≥2, which was identified as a significant predictor of reduced pain response to RT. As compared with the other trials, RTOG 0631 used a non-standard definition of pain response of at least 3 points of pain reduction.[10] In contrast, the others studies employed standardized, rigorous assessment of pain response at the index lesion.[74,75] Additionally, the dosing regimen of 1600 cGy in 1 fraction was used in 55% of the patients in the SBRT arm and is regarded as a lower BED regimen compared with doses used in the other 2 RCTs showing superior pain control with SBRT.[74,75] It is unclear if this also contributed to the negative results. RTOG 0631 is the largest RCT evaluating the role of SBRT for spinal bone metastases. As such, until further data on SBRT for painful bone metastases are available, its results would be expected to dominate meta-analyses inclusive of these data toward a nonsignificant impact of SBRT over conventional RT approaches. However,

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given the limitations of this study as compared to the 2 RCTs demonstrating significant improvements in pain outcomes with SBRT, the task force elected to conditionally recommend SBRT in this context.[74,75]

Two additional RCTs evaluated SBRT versus conventional palliative RT in symptomatic non-spine or combined spine and non-spine bone metastases.[76,78] For painful non-spine bone metastases, an RCT comparing 1200 cGy (for lesions >4 cm) to 1600 cGy in 1 fraction (for lesion ≤4 cm) with SBRT to 3000 cGy in 10 fractions with conventional palliative RT found that SBRT yielded superior pain control.[76] For combined spine and non-spine bone metastases associated with pain, a randomized phase 2 trial from the Netherlands compared SBRT (1800 cGy in 1 fraction, 3000 cGy in 3 fractions or 3500 cGy in 5 fractions) and conventional palliative RT (800 cGy in 1 fraction, 2000 cGy in 5 fractions or 3000 cGy in 10 fractions).[78] In this trial, SBRT did not improve pain response. However, as a result of the high dropout rate in the SBRT arm, the trial was regarded as underpowered to detect any difference in pain response.[78]

Two of the 3 RCTs assessed local recurrence after SBRT versus conventional palliative RT as a secondary outcome. A decrease in local recurrence following SBRT was noted in the RCT of SBRT versus conventional palliative RT for symptomatic spine metastases (2.6% vs 10.4%).[75] In the RCT of SBRT versus conventional palliative RT for non-spine bone metastases, there was a lesser likelihood of local recurrence in the SBRT arm, though not statistically significant in the intention-to-treat analysis.[76]

The recommendations for SBRT dose regimens in Table 5 are specifically drawn from RCTs that provide the highest quality evidence of safety and efficacy for this approach. However, a host of other dose regimens with promising outcomes have been described, including, 1600 to 2400 cGy in 1 fraction, 2800 cGy in 2 fractions, 2400 to 3000 cGy in 3 fractions, and 3000 to 4000 cGy in 5 fractions.[88-92,95,96] Table 6 provides dose constraints for SBRT used in 3 RCTs for treatment of spinal bone metastases.[10,74,75] Additional references for SBRT dose constraints are available, including those derived from consensus groups, SBRT trials performed in other clinical contexts, and radiobiological models.[97-101] Caution should be exercised when applying these dose constraints to the management of symptomatic bone metastases.

Table 6 SBRT dose constraints (based on trial protocols)

Organs at Risk	1 fraction [10,74]	2 fractions[75]	Endpoint
Spinal cord*	≤0.35 cc ≤1000 cGy ≤10% of partial spinal cord ≤1000 cGy ≤0.03 cc ≤1400 cGy	N/R	Myelopathy
Spinal cord PRV/ Thecal sac	N/R	Max point dose ≤1700 cGy	Myelopathy
Cauda equina	≤0.03 cc ≤1600 cGy ≤5 cc ≤1400 cGy	Max point dose ≤1700 cGy	Neuropathy
Sacral plexus	≤0.03 cc ≤1800 cGy ≤5 cc ≤ 1440 cGy	Max point dose ≤2600 cGy	Plexopathy

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Organs at Risk	1 fraction [10,74]	2 fractions[75]	Endpoint
Esophagus†	≤0.03 cc ≤1600 cGy ≤5 cc ≤1190 cGy	Max point dose ≤2000 cGy	Stenosis/ fistula
Ipsilateral brachial plexus	≤0.03 cc ≤1750 cGy ≤5 cc ≤1400 cGy	N/R	Plexopathy
Heart/pericardium	≤0.03 cc ≤2200 cGy ≤15 cc ≤1600 cGy	N/R	Pericarditis
Great vessels†	≤0.03 cc ≤3700 cGy ≤10 cc ≤3100 cGy	N/R	Aneurysm
Trachea† and larynx	≤0.03 cc ≤2020 cGy ≤4 cc ≤1050 cGy	Max point dose ≤2000 cGy Larynx: Mean ≤900 cGy	Stenosis/ fistula
Skin	≤0.03 cc ≤2600 cGy ≤10 cc ≤2300 cGy	N/R	Ulceration
Stomach	≤0.03 cc ≤1600 cGy ≤10 cc ≤1120 cGy	Max point dose ≤2000 cGy	Ulceration/fistula
Duodenum†	≤0.03 cc ≤1600 cGy ≤5 cc ≤1120 cGy	Max point dose ≤2000 cGy	Ulceration
Jejunum/Ileum†	≤0.03 cc ≤1540 cGy ≤5 cc ≤1190 cGy	Max point dose ≤2000 cGy	Enteritis/obstruction
Colon†	≤0.03 cc ≤1840 cGy ≤20 cc ≤1430 cGy	Max point dose ≤2000 cGy	Colitis/fistula
Rectum†	≤0.03 cc ≤1840 cGy ≤20 cc ≤1430 cGy	Max point dose ≤2000 cGy	Proctitis/fistula
Renal hilum/vascular trunk	<2/3 <1060 cGy	N/R	Malignant hypertension
Lungs (right and left)	≥1000 cc ≤740 cGy	V10 <10%, V5 <35%, and V20 <3% and a mean dose of ≤500 cGy for each lung	Pneumonitis
Renal cortex (right and left)	≥200 cc ≤840 cGy	Max point dose ≤2600 cGy Mean dose for each kidney ≤600 cGy	Basic renal function
Liver	N/R	Max point dose ≤2600 cGy Mean dose ≤800 cGy	Liver dysfunction
Pharynx	N/R	Max point dose ≤2000 cGy Mean ≤900 cGy	Stenosis/fistula
Parotids	N/R	Mean dose ≤700 cGy for each parotid	Xerostomia

Abbreviations: Max = maximum; N/R = not reported; PRV = planning organ at risk volume; SBRT = stereotactic body radiation therapy.

* The partial spinal cord should be contoured starting from 5-6 mm above the superior extent of the target volume to 5-6 mm below the inferior extent of the target volume; greater spinal cord volume should be contoured to well-encompass cord dose from beams (eg, noncoplanar beams).

† Avoid circumferential irradiation.

Note: Constraints included are based on trial protocols.[10,74,75] See text for discussion about additional sources for dose constraints available for SBRT.

3.4. KQ4: Dose-fractionation, dose-constraints, and techniques for palliative re-irradiation (Table 7)

In adult patients with symptomatic bone metastases, what palliative RT dose-fractionation regimens, dose-constraints, and techniques are appropriate for palliative re-irradiation of bone metastases?

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Table 7 Dose-fractionation, dose-constraints, and techniques for palliative re-irradiation

KQ4 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with spine bone metastases that would benefit from re-irradiation to the same site, conventional palliative RT regimens of 800 cGy in 1 fraction, 2000 cGy in 5 fractions, 2400 cGy in 6 fractions, or 2000 cGy in 8 fractions are recommended. Implementation remark: Consider prior RT dose, time interval, and total spinal cord tolerance when determining RT dose-fractionation.	Strong	Moderate 102-105
2. For patients with spine bone metastases that would benefit from re-irradiation to the same site, treatment with SBRT is conditionally recommended. Implementation remarks: • Consider patient factors (eg, urgency of treatment, prognosis, and radioresistance) when determining if SBRT is indicated. • Consider prior RT dose, time interval and total spinal cord tolerance when determining RT dose-fractionation.	Conditional	Expert Opinion
3. For patients with symptomatic non-spine bone metastases that would benefit from re-irradiation to the same site, single fraction (800 cGy in 1 fraction) or multifraction conventional palliative RT (2000 cGy in 5 fractions or 2400 cGy in 6 fractions) is recommended.	Strong	Moderate 102,103,105

Abbreviations: KQ = key question; RT = radiation therapy; SBRT = stereotactic body radiation therapy.

With improvements in systemic therapies leading to patients living longer, re-irradiation of a previously irradiated site (including the setting where a bone site requiring palliative RT is immediately proximate to a previously irradiated site) is becoming more common. When considering re-irradiation, the physician's goals are to safely provide relief of symptoms. For re-irradiation of the spine, there are data to support the use of both conventional palliative RT as well as SBRT. There are no data directly comparing conventional palliative RT to SBRT for re-irradiation. For re-irradiation of non-spine sites, there are data supporting the use of conventional palliative RT in re-irradiation but no prospective data using SBRT or comparing SBRT versus conventional palliative RT.

The data supporting conventional palliative RT included 2 RCTs and 2 nonrandomized studies comparing single-fraction to multifraction regimens. Importantly, these studies differed in the pain scales used, the initial dose of RT, how the patients were randomized and/or the re-irradiation regimens applied. In terms of the initial dose received, this varied from 800 cGy in 1 fraction, 1800 cGy in 4 fractions, 2000 cGy in 5 fractions, 3000 cGy in 10 fractions, or unknown dose.[102-105] All of the studies used 800 cGy as the single-fraction

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re-irradiation arm. In terms of the multifraction re-irradiation arms these included: 2000 cGy in 8 fractions, 2000 cGy in 5 fractions, 2400 cGy in 6 fractions, or 1500 cGy in 5 fractions.[102-105] The re-irradiation fractionation was based on anatomic location as well as initial RT dose and fractionation. After prior multifraction RT, 2000 cGy in 8 fractions was used in re-irradiation and 2400 cGy in 6 fractions was used after prior low-dose intensity RT (eg, 800 cGy in 1 fraction).[102,103]

Regardless of the different regimens of these studies, their results were comparable: there was no difference between the single-fraction and multifraction arms for either overall pain response (defined as the sum of complete response and partial response) or complete pain response. Data informing skeletal function, general function, and relief of spinal cord or cauda equina compression were minimal. Two studies found no difference in improvement in walking ability (due to pain) between single-fraction and multifraction RT regimens.[103,104]

Equally important, these studies demonstrated that toxicity was similar between the different regimens with low rates of pathologic fractures (single fraction 800 cGy: 7% vs multifraction 2000 cGy in 5 fractions: 5%).[103] The risk of side effects from RT varied with 1 RCT[103] reporting increased toxicity with multifraction RT compared with single fraction, but the other RCT[102] and 2 nonrandomized studies[104,105] revealed no differences in toxicity rates.

In summary, conventional re-irradiation is a well-supported option with either a single or multifraction dose palliative RT. No consistent significant differences were found comparing different fractionation regimens for pain relief, improvement in walking or motor function, QoL, or toxicity. For single-fraction treatment, 800 cGy is recommended. For multifraction, the recommended re-irradiation doses are 2000 cGy in 5 fractions and 2400 cGy in 6 fractions.[102-105] However, keeping in mind cumulative critical normal tissue (ie, spinal cord, brachial plexus) dose and tolerance, in select situations it can be reasonable to give more dose intense regimens (eg, 3000 cGy in 10 fractions) as re-irradiation, if the initial dose intensity was low and time interval has been sufficiently long (≥6 months).[106,107] Finally, to ensure re-irradiation normal tissue constraints are met, more conformal planning techniques (eg, IMRT) to deliver conventional palliative RT dose regimens may be required.

The data reporting on SBRT in re-irradiation of the spine are limited to retrospective nonrandomized studies.[95,108] One study reported on a multi-institutional series of spine metastases patients treated with SBRT, of which 56% were in the re-irradiation setting (initial RT dose parameters were not detailed).[95] Patients were treated with either single-fraction SBRT (eg, 1630 cGy) or multifraction SBRT (eg 2060 cGy in 3 fractions, 2380 cGy in 4 fractions, and 2540 cGy in 5 fractions). Of symptomatic patients, 71% to 73% had pain improvement (self-reported by patients) at 4 to 6 months. There was no difference in pain response between fractionation regimens. Toxicity was low and similar between the arms with the exception of 1 grade 3 complication in the

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single-fraction arm. Another single institution study employed SBRT to re-irradiate spines previously treated with a median of 3000 cGy in 10 fractions of conventional palliative RT.[108] SBRT re-irradiation dosing was 2500 cGy to 3000 cGy in 5 fractions or 2400 cGy in 3 fractions. Of symptomatic patients, 65% had pain improvement with SBRT, and 93% of patients had stable or improved disease at last follow-up. Toxicities included fatigue (40%) and nausea (20%); of the 4 patients who had persistent or worsening neurological symptoms, all had evidence of disease progression. No RT myelopathies were observed. Because of the paucity and low-quality evidence, SBRT for re-irradiation of the spine is conditionally recommended. Patient and disease factors, such as urgency of treatment (ie, SBRT may not be feasible if RT is urgently indicated), radiosensitivity, and prognosis should be used in determining if conventional palliative RT versus SBRT is indicated. Furthermore, together with sufficient interval of time to retreatment (≥6 months), it is critical to consider the prior spinal cord and nerve root dose in determining the re-irradiation planning and delivery approach and dose and fractionation (see Table 8).[100,109]

Regarding the use of SBRT for re-irradiation of non-spine lesions, there is no prospective data to support it. However, a retrospective study that included patients with non-spine bone metastases treated to 3000 to 3500 cGy in 5 fractions showed complete pain response in 52% of the patients, which is significantly higher compared with previously reported rates in trials using conventional palliative RT.[110] However, given the lack of prospective data, further study of the use of SBRT in this setting is warranted.

Table 8 Spinal cord re-irradiation considerations for spine SBRT

Prior Radiation Details		SBRT Re-Irradiation Dose Recommendations		
Prior spinal cord total dose	Prior EQD2-2	Planned # of fractions	Acceptable range of re-irradiation total dose	Recommended thecal sac constraint (Dmax)
2000 cGy/5 fx - 3000 cGy/10 fx	3000 - 3750 cGy	1	1600 - 1800 cGy	900 cGy
4000 cGy/20 fx - 5000 cGy/25 fx	4000 - 5000 cGy	1	Not recommended	Not recommended
2000 cGy/5 fx - 4500 cGy/25 fx	3000 - 4300 cGy	2	1600 - 2400 cGy	1220 cGy
5000 cGy/25 fx	5000 cGy	2	1600 - 2000 cGy	1100 cGy
2000 cGy/5 fx - 4500 cGy/25 fx	3000 - 4300 cGy	3	1800 - 2700 cGy	1450 cGy
5000 cGy/25 fx	5000 cGy	3	1500 - 2400 cGy	1250 cGy
2000 cGy/5 fx - 4500 cGy/25 fx	3000 - 4300 cGy	4	2400 - 3000 cGy	1620 cGy
5000 cGy/25 fx	5000 cGy	4	2000 - 2600 cGy	1400 cGy
2000 cGy/5 - 4500/25 fx	3000 - 4300 cGy	5	2500 - 3000 cGy	1800 cGy
5000 cGy/25 fx	5000 cGy	5	2000 - 2500 cGy	1550 cGy

Abbreviations: Dmax = maximum point dose to an organ or tumor target; EQD2-2 = dose calculation to an equivalent dose of 2 Gy with an α-to-β ratio of 2; SBRT = stereotactic body radiation therapy.

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3.5. KQ5: Impact of dose-fractionation and techniques on treatment toxicity and QoL (Table 9)

In adult patients with symptomatic bone metastases receiving palliative RT, how do the different dose-fractionation regimens and techniques impact on treatment toxicity and QoL?

Table 9 Impact of dose-fractionation and techniques on toxicity and QoL

KQ5 Recommendation	Strength of Recommendation	Quality of Evidence
1. For patients with bone metastases receiving palliative RT, a shared decision-making approach is recommended to determine dose, fractionation, and use of supportive measures to optimize quality of life.	Strong	Expert Opinion

Abbreviations: KQ = key question; RT = radiation therapy.

The scope of KQ5 focused on the impact of various palliative RT dose-fractionation regimens and techniques on physical toxicity and other harms derived from the treatment itself that may affect QoL. For information regarding the impact of different dose-fractionation regimens, constraints, and techniques on pain response, relief of spinal cord or cauda equina compression, and motor/neurologic function, see KQ3. In the available literature, QoL metrics were not uniformly collected and variably reported, with a frequent absence of patient-reported outcomes. There were 3 RCTs that compared single-fraction and multifraction palliative RT that either had insufficient evidence to characterize QoL, or found physical toxicity between both modalities was relatively low and not significantly different.[15,19,84] One trial used the validated EORTC QLQ-C30 QoL assessment tool, but overall there was insufficient high-quality evidence allowing assessments of patient-reported outcomes and QoL according to treatment dose and technique.[84] This was also true of the trials that compared conventional palliative RT and SBRT.

Rates of acute physical toxicity across different modalities were generally reported to be low, and there were no statistically significant differences seen across all RT dose-fractionation regimens and techniques. Of note, pain flares are commonly seen after palliative RT, but only 1 RCT identified a difference in experiencing a pain flare with single or multifraction RT (10% vs 4%).[13] For patients experiencing pain flare, 1 RCT of patients receiving 800 cGy in 1 fraction for painful bone metastases were randomized to receive dexamethasone 8 mg every day for 5 days with 800 cGy in 1 fraction versus usual care. This showed a decrease in pain flare incidence by 9% among patients receiving dexamethasone.[111] Notably, this trial collected QoL and dexamethasone symptom data using patient-reported, validated instruments (EORTC QLQ-C15 PAL, EORTC QLQ-BM22, and the Dexamethasone Symptom Questionnaire). At day 10, patients receiving dexamethasone

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had significantly reduced nausea and functional interference and improved appetite as compared with placebo.[111] Other domains were not significantly different.

For other acute side effects, there was no difference in the measured physical symptoms across different treatment types, including nausea (approximately 40%), vomiting (approximately 20%), bowel, bladder, or other symptoms. Grade 3 to 4 toxicities were rare among patients receiving single-fraction and multifraction palliative RT, and among those receiving SBRT.[9]

Regarding skeletal-related events including impaired ambulation, pathologic fracture, development of cord compression, the rates were also low and found to be no different between the various dose-fractionation regimens. Specifically, there was no difference in the risk of pathologic fractures between conventional palliative RT with single-fraction and multifraction regimens, with rates measured to be approximately 2% to 10%.[11-13,20,25,30,84] In the RCTs comparing SBRT to conventional palliative RT in symptomatic spine metastases, vertebral fracture rates were similar – from 9 to 20% in the SBRT arms versus 4% to 22% in the conventional palliative RT arms.[10,74,75] One RCT comparing SBRT to conventional palliative RT in non-spine bone metastases reported on fracture rates at 1% in the SBRT versus 0% in the conventional RT arm.[76] Regarding subsequent re-irradiation, conventional palliative RT RCTs in aggregate suggest that single-fraction palliative RT results in higher rates of re-irradiation, with reported retreatment rates ranging from 11% to 29% following single-fraction RT and from 2% to 12% after multifraction RT.[11-13,19,20,25,28,30,70,83,84] However, these studies did not measure whether retreatment later versus upfront multifraction treatment resulted in any difference in a patient's QoL.

Considering the absence of robust high-quality data, it is the consensus of the task force to recommend patient preference-sensitive and shared decision-making for palliative RT in symptomatic bone metastases. No studies captured a large, diverse cohort with detailed report of race, ethnicity, comorbidities, and social determinants of health. This hindered our ability to evaluate QoL relative to factors known to be associated with health disparities. Moreover, evaluated studies may not represent global patterns of delivery of palliative RT. No studies captured patient-reported outcomes comprehensively, such as psychosocial symptoms, time spent receiving treatment, and financial distress. Future studies should consider these outcomes as primary and secondary endpoints when comparing various dose-fractionation regimens and techniques and should ensure adequate assessment of patient demographics, prognosis, and access to care.

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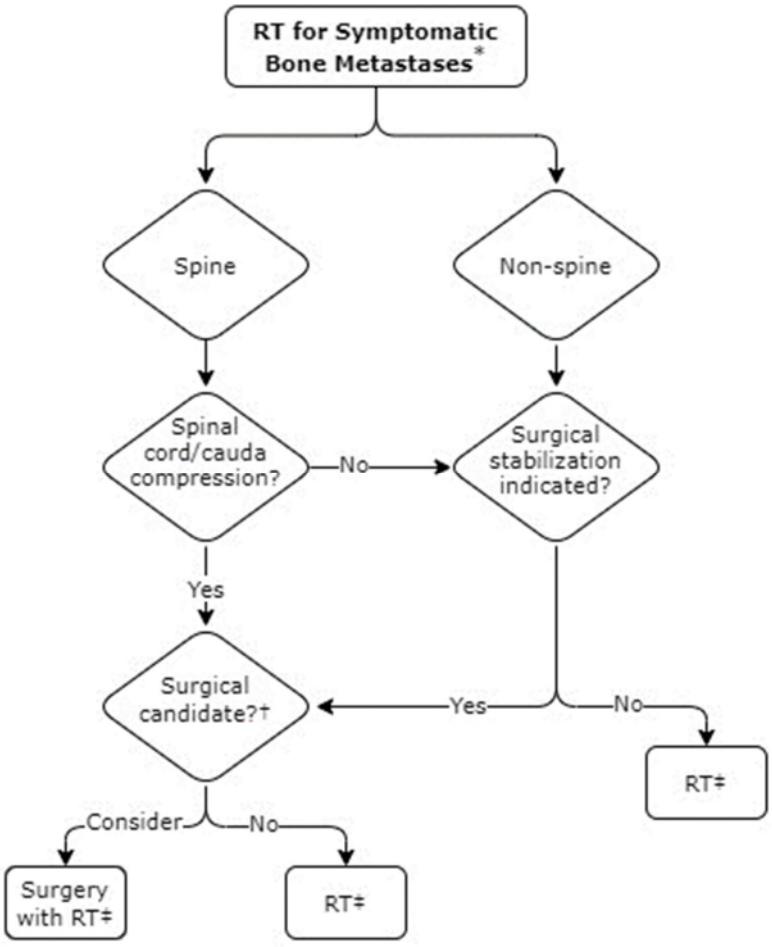
Figure 1 RT for symptomatic bone metastases



Abbreviations: KQ = key question; RT = Radiation Therapy; SBRT = stereotactic body radiation therapy.
*Algorithm applies to all symptomatic bone metastases either in the setting of no prior RT or after a prior course of RT (ie, reirradiation). Further details pertinent to symptomatic bone metastases in the setting of reirradiation are found in the KQ4 recommendations.
†Patients with metastatic spinal cord or cauda compression should receive dexamethasone as part of their up-front management.
‡RT = Selection of treatment dose intensity and planning modality (eg, conventional palliative RT vs SBRT) are discussed in the recommendations section.

4. Conclusions and Future Directions

Over the past few decades, significant shifts in the imaging, immobilization, and treatment delivery technologies available in the management of symptomatic bone metastases (eg, 3-D CRT, IMRT, SBRT) have emerged. Furthermore, advances in systemic therapies have improved life expectancies for many patients with metastatic cancers, rendering such issues as durability of palliative RT, local control, and re-irradiation more

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682 salient. Additionally, advances in other therapies addressing symptomatic bone metastases (eg, surgery,
683 bisphosphonates, radiopharmaceutical, vertebroplasty) have also occurred in this timeframe. Long-term data
684 continue to support the use of short-course, conventional palliative RT regimens for patients with symptomatic
685 bone metastases. However, evidence for conformal and dose-escalation approaches has moved from the
686 experimental toward the standard of care for select patients. These dramatic shifts in the management of
687 patients with metastatic cancer highlight the crucial role of personalized and comprehensive patient
688 assessment – including consideration of metastatic site, global disease characteristics and patient goals and
689 values – together with multidisciplinary input when selecting appropriate interventions for patients with
690 symptomatic bone metastases. Other consensus statements based on expert opinion have been developed for
691 the management of bone metastases with palliative RT;[112,113] the recommendations within the present
692 guidelines are unique in that they are based on a systematic review of the available high-quality data informing
693 this topic.

694 Future studies are needed to address uncertainties in the current evidence base. Randomized studies that
695 seek to delineate patient and disease characteristics that would most benefit from single- versus multifraction
696 regimens, dose escalation, and advanced planning strategies would aid in optimizing patient selection.
697 Attempts to standardize measurements of outcomes including pain response, local control, QoL, impact of
698 differences in cost and resultant financial burden across treatment approaches, and other patient-centered
699 outcomes in the context of palliative RT are required to facilitate comparisons between interventions. Studies
700 should also address the role of combining RT with other modalities (eg, systemic therapies,
701 radiopharmaceutical, local interventions such as vertebroplasty, radiofrequency ablation, and cryotherapy) to
702 define efficacy and safety in the management of symptomatic bone metastases. Finally, studies of methods of
703 identifying metastatic bone sites at-risk of developing skeletal related events (eg, radiomics-based prediction
704 tools) should be developed, with interventions potentially applying RT to at-risk lesions to prevent skeletal
705 related events, an approach suggested as beneficial for patients with asymptomatic metastatic bone disease in
706 a randomized phase II trial.[6] Arguably, the optimal approach to palliative RT is the prediction and prevention of
707 symptoms and other QoL-compromising skeletal related events of bone metastases. Future studies should also
708 make dedicated efforts to ensure diversity of patients in clinical trial enrollment such that study results remain
709 valid and interpretable across patient populations.

710

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Appendix E1. Peer Reviewers and Disclosures (Comprehensive)

- Table is added to the draft prior to publication.

Appendix E2. Abbreviations

3-D CRT = 3-dimensional conformal radiation therapy
AHRQ = Agency for Healthcare Research and Quality
cGy = centigray
EORTC = European Organisation for Research and Treatment of Cancer
IMRT = intensity modulated radiation therapy
KQ = key question
PICOTS = Population, Intervention, Comparator, Outcome, Timing, Setting framework
QoL = quality of life
RCT = randomized controlled trial
RT = radiation therapy
SBRT = stereotactic body radiation therapy

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