Comparative Effectiveness Review
Number 265

Radiation Therapy for Metastatic Bone Disease: Effectiveness and Harms

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(with addendum)

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This report is based on research conducted by the Pacific Northwest Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 75Q80120D00006). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report. Dr. Eric Chang is a physician with specialty expertise in radiation oncology and related clinical research, and served as a clinical expert and co-investigator for this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

A representative from AHRQ served as a Contracting Officer's Representative and reviewed the contract deliverables for adherence to contract requirements and quality. AHRQ did not directly participate in the literature search, determination of study eligibility criteria, data analysis, interpretation of data, or preparation or drafting of this report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States.

The American Society for Radiation Oncology (ASTRO) requested this report from the EPC Program at AHRQ. AHRQ assigned this report to the following EPC: Pacific Northwest Evidence-based Practice Center (Contract Number: 75Q80120D00006).

The reports and assessments provide organizations with comprehensive, evidence-based information on common medical conditions and new healthcare technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for healthcare quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as the healthcare system as a whole by providing important information to help improve healthcare quality.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers. AHRQ may also seek comments from other Federal agencies when appropriate.

Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Radiation Therapy for Metastatic Bone Disease: Effectiveness and Harms

Structured Abstract

Objectives. To evaluate the comparative effectiveness and harms of external beam radiation therapy (EBRT) for palliative treatment of metastatic bone disease (MBD).

Data sources. Four electronic databases from 1985 to January 30, 2023; a targeted search for re-irradiation through January 30, 2023; reference lists; and a Federal Register notice.

Review methods. Using predefined criteria and dual review, we selected randomized controlled trials (RCTs) and nonrandomized studies of interventions (NRSIs) comparing dose-fractionation schemes and EBRT delivery techniques (for initial radiation and re-irradiation, i.e., retreatment for recurrent or persistent pain) and EBRT alone versus in combination with other palliative treatments. Study risk of bias was assessed using predefined criteria. Strength of evidence (SOE) was assessed for the primary outcomes of pain, function, spinal cord compression relief, quality of life, and harms.

Results. We included 53 RCTs and 31 NRSIs; most were fair quality. In patients receiving initial radiation for MBD there was a small increase in the likelihood of overall pain response (improved pain measures with stable or decreased analgesic use) for multiple fraction (MF) EBRT versus single fraction (SF) EBRT up to 4 weeks post-radiation therapy (SOE: moderate) and for higher dose (6 or 8 Gy) SF EBRT versus lower dose (4 Gy) SF EBRT up to 52 weeks post-radiation therapy (SOE: low). SF and MF EBRT did not differ at later followup (SOE: moderate) nor did comparisons of MF EBRT dose/fractions (SOE: moderate ≤12 weeks; low >12 weeks). Re-irradiation was more common with SF versus MF EBRT. Stereotactic body radiation therapy (SBRT) (SF or MF) was associated with a slightly higher (up to 20 weeks, SOE: low) and moderately higher (30 weeks; SOE: moderate) likelihood of overall pain response versus MF EBRT. For re-irradiation, SF and MF SBRT had a similar likelihood of overall pain response, as did SF versus MF EBRT (SOE: low for all). Harms may be similar across dose/fraction schemes and techniques; serious harms were rare. Comparative effectiveness evidence for EBRT was sparse.

Conclusions. In patients with uncomplicated MBD receiving initial palliative radiotherapy, the likelihood of overall pain response for SF and MF EBRT is probably similar, particularly after 4 weeks; re-irradiation was more common with SF-EBRT. SF and MF SBRT may provide slightly greater likelihood of overall pain response versus MF EBRT; evidence is limited. SF and MF EBRT may have similar likelihoods of overall pain response in patients receiving re-irradiation. High-quality evidence comparing SBRT with EBRT is needed in populations with complicated and uncomplicated MBD, as is research on effectiveness of EBRT versus other treatments.

Update: An addendum is located at the end of the main report, before the appendixes.

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Executive Summary

Main Points

- In patients having initial palliative radiation for metastatic bone disease (MBD), multiple fraction (MF) external beam radiation therapy (EBRT) probably slightly increases the likelihood of overall pain response (pain improvement) within 4 weeks of treatment versus single fraction (SF) EBRT. Both probably provide similar likelihood of overall pain response at longer followup. Re-irradiation is more common with SF EBRT.
- For SF EBRT, overall pain response may be slightly more likely with higher doses versus lower doses in patients having initial palliative radiotherapy.
- Stereotactic body radiation therapy (SBRT) (SF or MF) may slightly improve the likelihood of overall pain response versus EBRT for initial radiation.
- In patients receiving re-irradiation, both SF and MF EBRT may have similar likelihood of overall pain response.
- Harms may be similar across dose/fraction schemes and techniques, and serious harms were rare for initial radiation and re-irradiation.
- Information on comparative effectiveness is limited.

Background and Purpose

Bone metastases are common in advanced cancers and result in severe pain and complications that compromise quality of life. Palliative treatment is the focus for symptomatic MBD and EBRT is an integral component of care as it provides pain relief. However, there is variation in palliative EBRT delivery and lack of consensus on indications for use of advanced techniques (e.g., SBRT). **We assessed the effectiveness and harms of EBRT for palliative treatment of MBD, comparing dose-fractionation schemes and delivery techniques for initial radiation and re-irradiation and for EBRT use in conjunction with additional therapies.** The intended audiences for this review are those seeking to update clinical guidelines and clinicians, policymakers, patients, their caregivers, and researchers. The American Society for Radiation Oncology (ASTRO) is the partner for this review.

Methods

We employed methods consistent with those outlined in the Agency for Healthcare Research and Quality Evidence-based Practice Center Program methods guidance (https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview). We describe these in the full report. Our searches covered publication dates from 1985 up to January 30, 2023. We sought studies in patients with symptomatic bone metastases undergoing palliative EBRT, including advanced techniques such as SBRT. Study risk of bias (i.e., quality) was assessed using predefined criteria. We analyzed effects and assessed strength of evidence (SOE) for the primary outcomes of pain, function, relief of spinal cord compression, quality of life, and harms.

Results

We included 53 mostly fair-quality randomized controlled trials (RCTs) and 31 mostly fair-quality comparative nonrandomized studies of interventions (NRSIs). The most evidence was identified for Key Question 1 (initial radiation) (40 RCTs, 18 NRSIs), specifically the comparison of dose-fractionation schemes (34 RCTs, 11 NRSIs). For Key Question 2 (re-irradiation), two RCTs

and three NRSIs met inclusion criteria; for Key Question 3a (EBRT vs. single modality), three RCTs and two NRSIs; for Key Question 3b (EBRT plus another modality vs. EBRT alone), nine RCTs and seven NRSIs; and for Key Question 3c (EBRT plus another modality vs. the same modality alone), three NRSIs. Key findings with at least low SOE are summarized for Key Questions 1 and 2 in Tables A through C. Overall pain response is used to reflect pain improvement. Studies defined pain response based on achieving a threshold for pain reduction; many studies also included stable or reduced analgesic use as part of the definition.

Key Question 1 compared EBRT dose-fraction schemes and delivery of initial palliative radiation for MBD. Our findings suggest that MF EBRT probably slightly increases the likelihood of overall pain response (pain improvement) within 4 weeks of treatment versus SF EBRT but there was no difference at longer followup. Overall pain response may be slightly more likely with higher SF doses versus lower SF doses but no difference between higher and lower MF doses was seen. (Table A). There was no difference between SF and MF EBRT for harms. Regarding delivery techniques, SBRT was associated with increased likelihood of overall pain response verses EBRT, but no differences were seen between IMRT and 3DCRT (Table B).

Table A. Summary of evidence of conventional EBRT fractionation schemes for *initial radiation* for MBD: Key Question 1 (pain, function, QOL, harms)

Outcome	Time Point	SF Vs. MF EBRT	LDSF Vs. HDSF	LDMF Vs. HDMF
Pain, Overall Response (Effect Size/SOE)[a]	*Post-RT to 4 weeks*	Small favoring MF ++	Small favoring HDSF +	No difference ++
	>4 weeks to 12 weeks	No difference ++	Small favoring HDSF +	No difference ++
	>12 weeks	No difference ++	Small favoring HDSF +	No difference +
	Timing NR or unclear	No difference ++	No evidence	No difference +
Relief of SCC (Ambulatory) (Effect Size/SOE)[a]	*Post-RT to 4 weeks*	No difference ++	No evidence	No difference ++
	>4 weeks to 12 weeks	No difference +	No evidence	No difference ++
	>12 weeks	No evidence	No evidence	No difference ++
Relief of SCC (Motor Function; Regain Sphincter Control) (Effect Size/SOE)[a]	*Any time (≤26 weeks)*	No evidence	No evidence	No difference +
Quality of Life (Effect Size/SOE)[a]	*Various (post-RT to 30 weeks)*	No difference +	No evidence	No evidence
Harms/AEs – Pathological Fracture; New SCC (Effect Size/SOE)[a]	*Any time*	No difference +	No evidence	No difference + (fracture)[b]
	≤8 weeks and >8 weeks	No evidence	No difference +	No evidence
Harms/AEs – Skeletal-related Events[c] (Effect Size/SOE)[a]	*Any time*	Insufficient evidence	No difference +	No evidence
Harms/AEs – Adverse Events or Reactions Not Otherwise Specified (Effect Size/SOE)[a]	*Any time*	No evidence	No difference +	No evidence
Harms/AEs – Toxicity, Acute Grade 3, 4 (Effect Size/SOE)[a]	*Any time*	Insufficient evidence	No evidence	No difference +

Outcome	Time Point	SF Vs. MF EBRT	LDSF Vs. HDSF	LDMF Vs. HDMF
Harms/AEs – Toxicity, Acute Nausea/Vomiting; Impaired Bladder or Bowel Function; Pain Flare; Withdrawals due to AEs (Effect Size/SOE)[a]	*Any time*	No difference +	No evidence	No evidence

AEs = adverse events; HDMF = higher total dose multiple fraction; HDSF = higher total dose single fraction; LDMF = lower total dose multiple fraction; LDSF = lower total dose single fraction; MBD = metastatic bone disease; MF = multiple fraction EBRT; QOL = quality of life; RT = radiation therapy; SCC = spinal cord compression; SF = single fraction EBRT; SOE = strength of evidence.
[a] Effect size: No, small, moderate, or large difference favoring SF, LDSF or LDMF (unless otherwise stated); SOE: + = low, ++ = moderate, +++ = high.
[b] Evidence for new SCC was considered insufficient (i.e., not included in summary table).
[c] Re-irradiation or pathologic fracture, cord compression.

Table B. Summary of evidence of delivery techniques for EBRT for *initial radiation* for MBD: Key Question 1 (pain, function, QOL, harms)

Outcome	Time Point	SBRT Vs. EBRT	IMRT Vs. 3DCRT
Pain, Overall Response (Effect Size/SOE)[a]	*4 weeks*	Small +	No evidence
	12 weeks and 26 weeks	Small ++	No difference +
	36 weeks	Moderate +	No evidence
Pain, VAS Pain and Neuropathic Pain Scores[b] (Effect Size/SOE)[a]	*26 weeks*	Large +	Insufficient
Skeletal Function (SINS) (Effect Size/SOE)[a]	*≥12 weeks*	No difference +	No evidence
Quality of Life (Effect Size/SOE)[a]	*Post-RT to 26 weeks*	No difference +	No difference +
Harms/AEs – Pathological Fracture (Effect Size/SOE)[a]	*≤12 weeks*	No difference +	Insufficient
Harms/AEs – SCC; Pain Flare (Effect Size/SOE)[a]	*Post-RT and 26 weeks*	No difference +	No evidence

3DCRT = three-dimensional conformal radiation therapy; AEs = adverse events; EBRT = external beam radiation therapy; IMRT = intensity modulated radiation therapy; MBD = metastatic bone disease; QOL = quality of life; RT = radiation therapy; SBRT = stereotactic body radiation therapy; SCC = spinal cord compression; SINS = Spinal Instability in Neoplasia Score; SOE = strength of evidence; VAS = visual analog scale.
[a] Effect size: No, small, moderate, or large difference favoring SBRT or IMRT; SOE: + = low, ++ = moderate, +++ = high.
[b] Neuropathic pain scores reported for IMRT vs. 3DCRT only.

Evidence for Key Question 2 on dose-fraction schemes and delivery for re-irradiation was sparse. There may be no differences in pain response, function, or harms for SF versus MF EBRT (Table C).

Table C. Summary of evidence of conventional EBRT and SBRT fractionation schemes for *re-irradiation* for MBD: Key Question 2 (pain, function, QOL, harms)

Outcome	Time Point	SF Vs. MF EBRT	SF Vs. MF SBRT
Pain, Overall Response (Effect Size/SOE)[a]	*8 weeks*	No difference +	No evidence
	8 to 26 weeks	No evidence	No difference +
General/Overall Function (Walking on BPI) (Effect Size/SOE)[a]	*8 weeks*	No difference +	No evidence
Quality of Life (Effect Size/SOE)[a]	*8 weeks*	No difference +	No evidence
Harms/AEs – Pathological Fracture; SCC or Cauda Equina Compression (Effect Size/SOE)[a]	*Timing NR*	No difference +	No evidence

AEs = adverse events; BPI = Brief Pain Inventory; EBRT = external beam radiation therapy; MBD = metastatic bone disease; MF = multiple fraction; QOL = quality of life; SBRT = stereotactic body radiation therapy; SCC = spinal cord compression; SF = single fraction; SOE = strength of evidence.
[a] Effect size: No, small, moderate, or large difference favoring SF scheme; SOE: + = low, ++ = moderate, +++ = high.

Comparative evidence for Key Question 3 on EBRT in conjunction with additional therapies was sparse. Comparisons of EBRT versus strontium and versus bisphosphonates alone indicated no differences in pain response or harms between treatments. EBRT combined with surgery may confer more improvement in neurologic outcomes related to spinal cord compression relief versus EBRT alone. Use of dexamethasone with EBRT may improve pain and quality of life and reduce pain flare and acute Grade ≥3 toxicities versus EBRT alone. There may be no differences in pain response or serious adverse events between concomitant use of EBRT with radioisotopes versus EBRT alone (See full report).

Strengths and Limitations

We focused on the best quality evidence directly comparing dose/fractionation schemes for initial radiation and re-irradiation for palliation of MBD and for evaluating comparative effectiveness. We provide updated evidence comparing SBRT with EBRT. Our review appears to be the most complete summary of the highest-quality evidence on benefits and harms of palliative radiotherapy for MBD.

There are limitations to the review and the evidence. Studies used various definitions of pain response. We focused on overall pain response as this was most consistently reported across studies. Primary tumor type, bone metastasis location, and patient characteristics also differed across included studies precluding evaluation of specific patient, clinical, or bone metastasis characteristics that might impact response to palliative radiotherapy. It is not possible to capture the nuances of clinical decision making related to individual patient circumstances or clinical factors that might inform use of specific doses or number of fractions. Most patients studied had uncomplicated MBD (i.e., did not have fractured bone or compression of the spinal cord).

Implications and Conclusions

Our findings suggest that SF and MF EBRT probably provide similar likelihood of overall pain response for palliative radiotherapy of symptomatic MBD for initial treatment and re-irradiation, and there may be no differences in serious harms. Re-irradiation was more common with SF EBRT, however. These findings support clinical guidelines that suggest a preference for SF EBRT over multiple fractions as single fraction use may reduce financial and other burdens experienced by patients receiving palliative care. SBRT (SF or MF) may provide slightly greater likelihood of overall pain response compared with MF EBRT, however evidence is limited. RCT evidence comparing SBRT with EBRT continues to emerge; studies focused on palliative treatment of MBD are needed for spine and nonspine applications and in populations with complicated and uncomplicated MBD. Research evaluating EBRT in combination with other therapies is also needed.

1. Introduction

1.1 Background

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

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

Historically, conventional, two-dimensional external beam radiotherapy (2D-EBRT) has been used for treatment of bone metastasis. Advances in three-dimensional imaging, computerization, and use of linear accelerators or cyclotrons have improved the precision and consistency of radiation delivery techniques, potentially decreasing the radiation impact on healthy or sensitive tissue around the lesions. Newer techniques include three-dimensional conformal radiation therapy (3DCRT), which has largely replaced 2D-EBRT for most applications and is generally considered the current standard, as well as intensity modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT). These advances may allow delivery of higher radiation doses, influencing frequency (fractionation) of treatment for initial palliative radiotherapy[7] and for re-irradiation[8] of MBD, particularly for spinal lesions. There is also emerging evidence for use of these newer techniques in nonspine MBD.[9]

MBD is a heterogeneous disease. Planning for initial MBD radiotherapy (dose, fractionation) is complex. It involves consideration of primary tumor histology, patient prognosis and life expectancy, existing or predicted bone pathology, lesion characteristics (number, location, whether they are osteolytic, osteoblastic, or mixed), the mechanical stability of the affected bones, patient characteristics (e.g., sex, age, health and functional status, comorbidities), and the use of additional therapies.[10,11] These may include bone-modifying agents (e.g., bisphosphonates), bone-targeting radionuclides,[3] surgery including minimally invasive surgery,

or minimally invasive procedures such as ablation, kyphoplasty, vertebroplasty or sacroplasty.[12,13] Commonly, such therapies are planned for use in concert with radiotherapy and are in addition to systemic anticancer therapies (cytotoxic agents, molecular therapies, and immunotherapies). As cancer treatment advances have enhanced patient survival, recurrence and the need for retreatment of previously irradiated areas have become more common.[10,14] Additional considerations related to re-irradiation planning include the acuity and urgency, prediction of tissue recovery based on prior radiation dose fractionation, time since prior radiation, and volume treated to evaluate re-irradiation related toxicity and dose tolerance.[14] Side effects may be greater in patients undergoing re-irradiation. Patients with recurrent pain after initial prior response, ongoing pain following a partial response, or no pain response may be considered for re-irradiation.[14] Decision making in all scenarios involves multidisciplinary input and consideration of patient prognosis and preferences as well as the potential benefits and harms of treatment. It should seek to balance the impact of the frequency of radiation treatments in the remaining months of life with potential for optimal clinical outcomes such as complete pain control. Treatment is tailored to individual patient circumstances.

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

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

Evidence-based clinical guideline recommendations are intended to promote and improve healthcare quality by reducing variations in care and promoting effective therapy while discouraging ineffective and potentially hazardous interventions.[26,27] However, in order to impact clinical decision making, clinical practice, cost-conscious utilization, and patient outcomes,

information on strategies, barriers and facilitators for guideline promotion and implementation are important to consider. Clarity regarding patient financial distress and hardship related to the clinical options for palliative radiotherapy for MBD would also be of value.

1.2 Purpose and Scope of the Systematic Review

To facilitate resolution of the decisional dilemmas identified above and provide updated evidence for clinical recommendations and shared decision making, this systematic review compared dose-fractionation schemes and techniques of delivery for both initial palliative radiation therapy and re-irradiation. We also compared the effectiveness and harms of EBRT for palliative treatment of MBD in conjunction with additional therapies compared with EBRT alone. We also sought to assess how effectiveness and harms may be modified by patient and clinical characteristics (e.g., age, sex, tumor histology) in an effort to identify subsets of patients who may most benefit from specific palliative radiotherapy regimens and advanced techniques. Intended audiences for this review are those seeking to update clinical recommendations or guidelines as well as other stakeholders including clinicians, policymakers, patients, their caregivers, and researchers. ASTRO is the partner for this review.

2. Methods

2.1 Review Approach

The methods for this systematic review followed the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (https://effectivehealthcare.ahrq.gov/products/cer-methods-guide/overview). This systematic review is in accordance with the Preferred Items for Reporting in Systematic Reviews and Meta-Analyses (PRISMA).[28]

2.1.1 Key Questions

A Technical Expert Panel provided comments on the scope of the review. The following Key Questions and inclusion criteria reflect suggestions received and are in the final protocol. The final protocol was posted on the Effective Health Care website on June 23, 2022 (https://effectivehealthcare.ahrq.gov/products/radiation-therapy-bone-metastases/protocol) and registered on PROSPERO (CRD42022340073).

Key Question 1. For symptomatic adults with bone metastases who will receive initial radiation for palliation, what is the comparative effectiveness and what are the comparative harms of dose-fractionation schemes and techniques for delivery (e.g., three-dimensional conformal radiation therapy, stereotactic body radiation)?

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

Key Question 3. What is the effectiveness and what are the harms of external beam radiation therapy (EBRT) in the palliative treatment of bone metastases in symptomatic adults for the following:

a. EBRT compared with another single metastatic bone disease(MBD) treatment modality (e.g., surgery, radionuclide therapy, bisphosphonate therapy, ablation kyphoplasty/ vertebroplasty)
b. EBRT combined with another treatment modality (e.g., surgery, radionuclide therapy, bisphosphonate therapy, ablation kyphoplasty/vertebroplasty) compared with EBRT alone?
c. EBRT combined with another treatment modality (e.g., surgery, radionuclide therapy, bisphosphonate therapy, ablation kyphoplasty/vertebroplasty) compared with the other (same) treatment modality alone?

2.1.2 Contextual Questions

Following the methods of the U.S. Preventive Services Task Force (USPSTF),[29] contextual

questions represent issues in a review for which a valid, but not necessarily systematic, summary of current research is needed in order to provide context on the issue. See Appendix A, Methods, for more details.

Contextual Question 1. What are common barriers and facilitators to implementing guidance in radiation oncology, specifically related to palliative radiation for MBD?

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

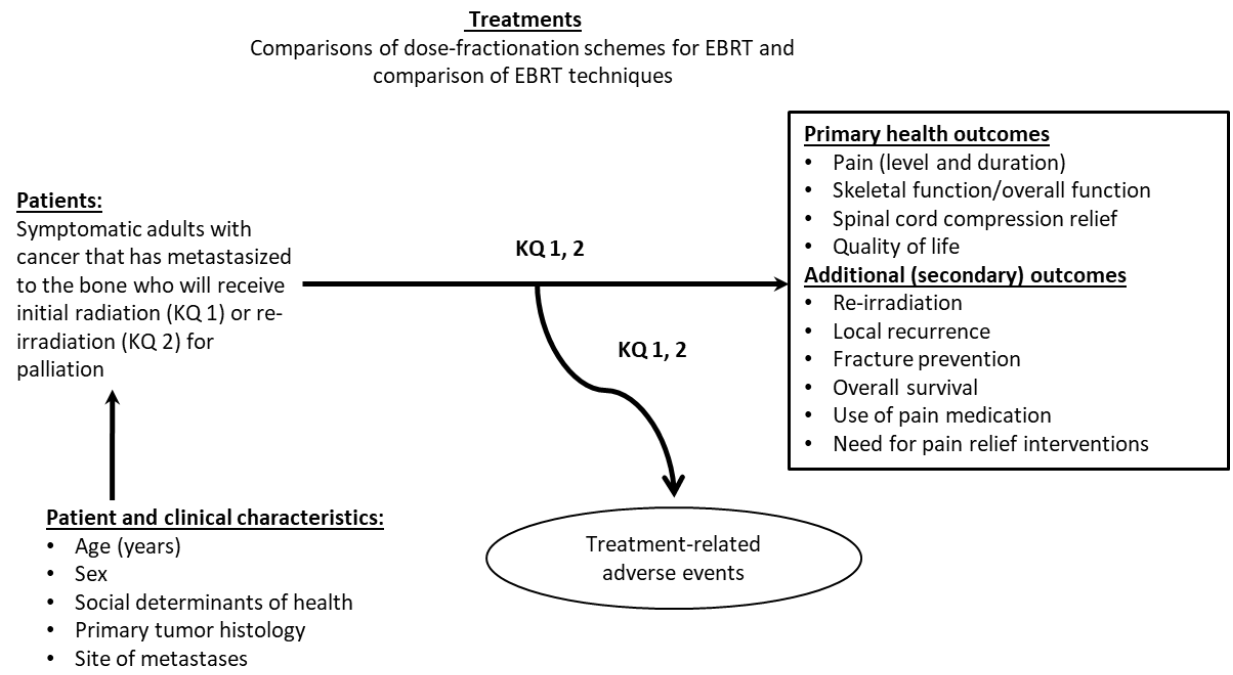
Contextual Question 3. In symptomatic patients considered for palliative radiation therapy for MBD, to what extent does patient financial distress/hardship differ between EBRT dose/fraction schemes or technique?

2.1.3 Analytic Framework

The analytic framework (Figures 1 and 2) illustrates the population, interventions, outcomes, and adverse effects that guided the literature search and synthesis.

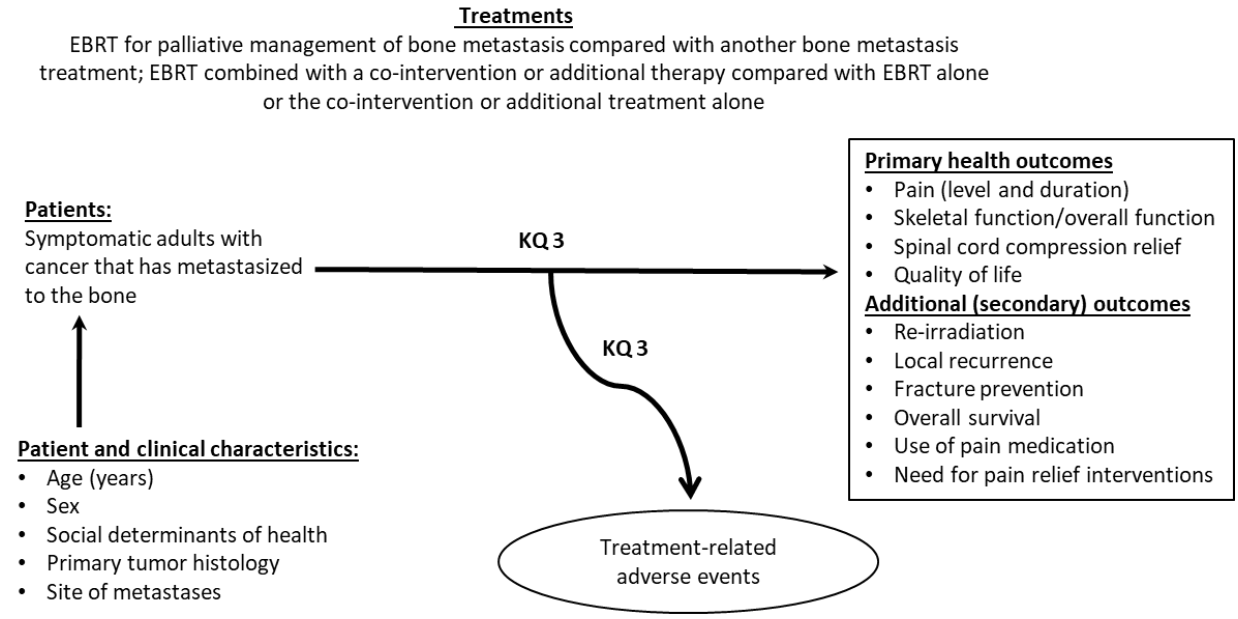
2. Methods

Figure 1. Analytic framework for Key Questions 1 and 2



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

Figure 2. Analytic framework for Key Question 3



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

2.2 Study Selection

We searched Ovid® MEDLINE®, Embase®, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews from 1989 to June 22, 2022. A second, targeted search focusing on terms related to "re-irradiation" was completed from 1985 through August 23, 2022. All searches were conducted by a qualified medical librarian and were peer reviewed (See Methods, Appendix A).

In accordance with the *Methods Guide for Effectiveness and Comparative Effectiveness Review*,[30] we used the pre-established criteria in Table 1 to identify studies eligible for this review. For all Key Questions, we focused on randomized controlled trials (RCTs), as well-conducted RCTs have the least risk of bias. Nonrandomized studies of interventions (NRSIs) in pain can be misleading, due to the subjective nature of pain, which may exacerbate effects of confounding, selection bias, and attentional and other nonspecific effects. We included comparative NRSIs that controlled for confounding to evaluate effectiveness only if no or very few RCTs were available. For comparisons with sufficient RCT data, comparative NRSIs that controlled for confounding were considered for inclusion for evaluation of harms only. We excluded children/adolescents and asymptomatic patients, proton beam therapy and brachytherapy interventions, and studies with less than 20 patients per treatment arm. (See Methods, Appendix A, Table A-1 for detailed exclusion criteria). We did not receive any responses to a Federal Register notice requesting Supplemental Evidence and Data for Systematic review (SEADS). We used dual review to select studies. Appendix A, Methods, contains full details on review methods, including complete search strategies.

Table 1. Criteria for population, intervention, comparison, and outcomes of eligible studies

PICOTS	Inclusion
Population	**KQ 1:** Symptomatic adults with bone metastases who will receive initial palliative radiation **KQ 2:** Symptomatic adults with bone metastases who will receive re-irradiation for palliation **KQ 3:** Symptomatic adults with cancer that has metastasized to the bone. **For all KQs:** Patients with either complicated or uncomplicated bone metastases will be included. Consider patient and clinical characteristics (e.g., age, sex, social determinants of health, primary tumor histology, site of metastases).
Intervention	**KQ 1 and KQ 2:** Comparisons of dose-fractionation schemes for EBRT, comparisons of EBRT techniques (e.g., conventional RT vs. SBRT, SBRT vs. IMRT) **KQ 3:** External beam radiation therapy for the palliative management of bone metastasis a) alone, or b) and c) *with co-interventions*, additional therapies (e.g., surgery, radionuclide therapy, bisphosphonate therapy, ablation kyphoplasty/vertebroplasty)
Comparator	**KQ 1 and 2:** No cointervention (i.e., EBRT alone) **KQ 3:** a) another single MBD treatment, b) EBRT alone, c) the same cointervention/additional therapy alone

PICOTS	Inclusion
Outcome	**Effectiveness:** Primary outcomes • Pain (level and duration) • Skeletal function • Relief of spinal cord compression • Quality of life Additional (secondary) outcomes • Local recurrence • Fracture prevention • Overall survival • Need for re-irradiation • Use of pain medication, need for other interventions for pain relief **Harms and adverse events** Harms (e.g., rate of radiation/treatment toxicity, radiation-induced fracture rates, reduced mobility, reduced independence), adverse events (pain flare, radiation recall, fatigue, skin changes, etc.)
Timing	Any (timing may depend on treatments provided and outcomes assessed)
Setting	Any
Study design, publication type	**All KQs:** Focus will be on the best evidence available that permits direct comparisons to answer Key Questions RCTs will be initially sought; in the absence of RCTs, prospective comparative studies that control for confounding will be considered; if no comparative prospective studies are available, retrospective comparative studies that control for confounding will be considered. In the absence of comparative studies, single arm (e.g., case series, pre-post studies) may be considered For evaluation of harms, comparative cohort and case-control studies will be included; we will focus on studies specifically designed to evaluate harms. Studies of at least 20 patients per treatment arm

EBRT = external beam radiation therapy; IMRT = intensity modulated radiation therapy; KQ = Key Question; MBD = metastatic bone disease; PICOTS = population, intervention, comparator, outcome, timing, setting; RCT = randomized controlled trial; RT = radiation therapy; SBRT = stereotactic radiation therapy.

2.3 Data Extraction and Risk of Bias Assessment

Data were abstracted from included studies into evidence tables based on the organizational framework to include study, patient, and MBD characteristics, primary tumor histology, and study results (including harms), with data verified for accuracy and completeness by a second team member. The risk of bias of included studies was assessed according to established methods,[30,31] with RCTs assessed based on criteria established in the *Cochrane Handbook for Systematic Reviews of Interventions*[32] and precepts for appraisal developed by the Cochrane Back and Neck Group.[33] Because nonrandomized studies are at increased risk of selection bias and confounding, we assessed risk of bias using instruments tailored to observational studies[34] that considered methods of patient selection (e.g., consecutive patients, use of an inception cohort) and appropriate control for confounding of relevant prognostic factors. Based on the risk of bias assessment, individual included studies were rated as being "good," "fair," or "poor" quality. It was not possible for studies to effectively blind participants (or providers) with regard to EBRT regimen for many comparisons. Studies were downgraded to fair for lack of blinding in these instances, as bias from patient expectations of treatment, attentional affects, and performance bias was possible; this is consistent with the approach used in prior AHRQ reviews

of nonpharmacological treatments for pain.[35-37] Full details on data abstraction, data management, and risk of bias assessment (i.e., quality determination) can be found in Appendix A, Methods.

2.4 Data Synthesis and Analysis

We analyzed the evidence according to Key Question, using both narrative (qualitative) and quantitative (meta-analysis) methods where possible. We reviewed and highlighted studies by using a hierarchy-of-evidence approach, focusing our synthesis on the highest quality data for each Key Question. Summary tables were constructed when appropriate to highlight the main findings.

Meta-analyses, using profile-likelihood random effects models, were conducted to summarize data and obtain more precise estimates where there were at least two studies reporting outcomes that were homogeneous enough to provide a meaningful combined estimate.[38,39] We considered clinical and methodological diversity and assessed statistical heterogeneity using Cochran's χ^2 test and the I^2 statistic.[40] For binary outcomes, a risk ratio was used as the effect measure. Both complete pain response and overall pain response were meta-analyzed. Overall pain response included both complete pain response and partial pain response or was defined as an improvement in pain after radiation therapy.[41-46] For continuous outcomes, mean difference (MD) was used as the effect measure as the studies reported outcomes using the same scale, or the outcomes could be converted to the same scale (e.g., pain, converted to 0-10 scale). MD was calculated using the followup score if reported and the change score from baseline if followup scores were not reported.[47] Sensitivity analyses were performed to explore statistical heterogeneity and differences by study quality. There were insufficient data to do subgroup analyses based on intervention differences, patient characteristics, primary tumor type, or other factors. Appendix A, Methods, contains additional detail of our meta-analysis methods. We classified the magnitude of effects for continuous measures of pain and function using the same system as in prior AHRQ reviews on pain.[35-37,48,49] Effects below the threshold for small were categorized as no effect. For analyses with at least 10 trials, we constructed funnel plots and performed the Egger test to detect small sample effects (a marker for potential publication bias).[50]

2.5 Grading the Strength of the Body of Evidence

The strength of evidence (SOE) of primary outcome-intervention pairs were evaluated using AHRQ methods.[30] Details on the methods used are presented in the Methods Appendix A, and primary outcomes are delineated in Table 1, above. The SOE was assigned an overall grade of high, moderate, low, or insufficient by evaluating and weighing the combined results of the following five domains: study limitations, consistency, directness, precision, and reporting bias. RCT evidence was initially considered high, with possible downgrades for any of these domains. For NRSIs, the strength started at moderate for harms outcomes, and low for benefit outcomes. While AHRQ guidance allows for upgrading NRSI evidence in certain circumstances, no upgrading was considered as none of the included studies were considered good. When both RCTs and NRSIs were included for a given outcome, we followed AHRQ guidance for consideration of consistency and weighing of RCTs over observational studies after evaluating each study type separately. We considered NRSI evidence to supplement RCT evidence to arrive at a final rating. We primarily used RCT evidence as that from NRSIs was of lower strength. For bodies of evidence with only a single study, we rated consistency as unknown (rather than not applicable). In these cases, we did not automatically downgrade the evidence to "insufficient"

but considered the sample size or number of events available for analysis. If only poor-quality trials were available for a given outcome, SOE was considered insufficient.

3. Results

A total of 9,784 abstracts were identified, 9,625 from electronic database searches and an additional 159 from hand searching and bibliography review of included studies and systematic reviews. After dual review of titles and abstracts, 604 articles were selected for full-text review, of which 84 studies (in 98 publications) were ultimately included in this review: 53 randomized controlled trials (RCTs) (in 67 publications)[9,22-24,41-47,51-106] and 31 comparative nonrandomized studies of interventions (NRSIs).[107-137] The most evidence was identified for Key Question 1 and the comparison of dose-fractionation schemes (for external beam radiation therapy [EBRT] and stereotactic body radiation therapy [SBRT]). An overview of the number of trials included by Key Question and comparison can be found in Appendix B (Table B-1). Two RCTs were rated good quality (4%),[57,78] 36 fair quality (68%),[9,22,23,41-46,52-55,58,59,63-67,69,70,72-74,81,83,85-87,91,93,94,97,102,106] and 15 poor quality (28%).[51,56,60-62,76,79,80,82,84,88,92,96,98,105] Twenty-one NRSIs were rated fair quality (68%)[107,108,110-113,116,117,120-126,130-133,136,137] and 10 were rated poor quality (32%).[109,114,115,118,119,127-129,134,135] Search results and selection of studies are summarized in the literature flow diagram in Appendix B, Results Overview (Figure B-1). In addition, three Contextual Questions were addressed. Additional information on the Contextual Questions is available following the results to the Key Questions and in Appendix C. Appendix D provides a list of all included studies.

Detailed evidence tables for included studies and quality assessments are available in Appendixes E and F. Appendix G contains details on the strength of evidence (SOE), and Appendix H lists excluded studies along with reasons for exclusion. Appendix I contains additional forest plots (i.e., pooled analyses) not presented in the full report. The definitions of magnitude of effects for continuous measures of pain and function are presented in Appendix J. Appendix K lists all references cited in the appendixes.

Only data for the primary outcomes of interest to this report are summarized in the Results section below, except for re-irradiation. Data for all other secondary outcomes can be found in Results Appendix B and are organized by Key Question then intervention and comparator. In addition, summary tables for select outcomes can be found in the same Appendix (Tables B-3 to B-17).

Definitions of pain responses varied across trials, particularly definitions of complete response (Appendix B, Table B-2). Definitions of pain response included achievement of pain reduction by a specific threshold (e.g., ≥2 points decrease in visual analog score [VAS] compared with baseline) with many trials also including decreased or stable analgesic use in the response definition. Overall pain response encompasses complete and partial response in most trials. We focused on overall pain response in the results to denote the general concept of improvement in pain.

3.1 Key Question 1. Effectiveness and Harms of Dose-Fractionation Schemes and Techniques for Delivery: Initial Radiation

3.1.1 Single Versus Multiple Dose-Fractionation Schemes: Conventional EBRT

3.1.1.1 Key Points

- Single-fraction (SF) EBRT is probably associated with a small decrease in the likelihood of achieving overall pain response compared with multiple-fraction (MF) EBRT up to 4 weeks post-treatment (9 RCTs, N=1280, 67.5% vs. 71.9%, risk ratio [RR] 0.93, 95% confidence interval [CI] 0.88 to 0.99, I^2=0%) (SOE: moderate), but no clear differences between groups at >4 to 12 weeks (7 RCTs, N=2173, 69.4% vs. 68.3% RR 1.01, 95% CI 0.95 to 1.07, I^2=0%) (strength of evidence [SOE]: moderate) or >12 weeks (2 RCTs, N=214, RR 0.87, 95% CI 0.68 to 1.12, I^2=0%) (SOE: moderate) were seen. This was consistent across trials in populations with mixed spine/nonspine metastatic bone disease (MBD), however no difference was seen between SF EBRT and MF EBRT in analysis confined to patients with spinal metastases (2 RCTs, N=356, 56% vs. 58%, RR 0.96, 95% CI 0.78 to 1.16, I^2=0%). Reported pain response likely included data for initial radiation therapy and re-irradiation. Results slightly favoring MF EBRT over SF EBRT at up to 4 weeks may in part reflect patients having received only initial radiation and/or a proportion of patients whose improvement occurred later than 4 weeks.
- There may be no difference between SF EBRT and MF EBRT in pain scores (0–10 scale) or in quality of life (various measures) across trials at any time frame (SOE: low for both).
- Evidence on overall function from two poor-quality trials was insufficient.
- There was probably no difference between SF EBRT and MF EBRT on maintenance or improvement in ambulation as an indicator of spinal cord compression relief up to 4 weeks post-treatment (SOE: moderate) and may be no difference at >4 to 12 weeks (SOE: low).
- Across RCTs, there may be no differences in pathologic fractures between SF EBRT and MF EBRT in patients with mixed spine/nonspine MBD or in one trial in patients with spine metastasis without cord compression (9 RCTs, N=4,086, 4.1% vs. 3.4%, RR 1.18, 95% CI 0.68 to 2.08, I^2=53.1%); similarly, there were no differences between SF EBRT and MF EBRT in the likelihood of developing spinal cord compression (5 RCTs, N=2774, 2.9% vs. 2.0%, RR 1.41, 95% CI 0.87 to 2.30, I^2=0%) (SOE: low for both outcomes).
- There may be no differences between SF EBRT and MF EBRT on the risk of developing the following adverse outcomes (SOE: low for all): pain flare, impairment of bladder or bowel function, Grade 3 and Grade 4 toxicities, and withdrawal due to adverse events.
- There was insufficient evidence for the following composite measures: skeletal events (re-irradiation and/or fracture) and skeletal adverse events (hospitalization for uncontrolled pain, symptomatic vertebral fracture, interventional procedure, salvage surgery, new or deteriorated neurologic symptoms, and spinal cord or cauda equina compression).

3.1 Key Question 1: Effectiveness and Harms of Dose-Fractionation Schemes and Techniques for Delivery, Initial Radiation

- Across RCTs, SF EBRT was associated with an over 2-fold higher likelihood of re-irradiation compared with MF EBRT (13 RCTs, N=5040, 19.8% vs. 8.2%, RR 2.44, 95% CI 1.79 to 3.66, I^2=68.4%). This remained true across RCTs in populations with mixed spine/nonspine MBD (10 RCTs, N= 5040, RR 2.81, 95% CI 2.19 to 3.94, I^2=37.5%), but analyses confined to populations with spine MBD (with or without metastatic spinal cord compression [MSCC]), showed no difference between single and multiple fraction (3 RCTs, N=1,031, 17.7% vs. 13.5%, RR 1.28, 95% CI 0.96 to 2.09, I^2=35.4%).

3.1.1.2 Description of Included Studies

Twenty-two RCTs (in 29 publications)[41,43-47,51,53-55,59-62,66,68,70,71,74,75,79,82,87,93,95,96,102-104] and four NRSIs[111,118,121,122] compared SF EBRT versus MF EBRT for the palliative treatment of bone metastases (Appendix E, Tables E-1 and E-2).

Across the RCTs, sample sizes ranged from 40 to 1,171 (total N=6,623). The average study mean (13 trials)[43,46,53,55,59-62,68,70,71,74,75,79,82,87,95,103,104] or median (7 trials)[41,44,45,47,54,66,93,102] age of participants was 65 years across 20 RCTs (range 52 to 70 years); two RCTs did not report patient age.[51,96] The average proportion of males across 21 RCTs was 54 percent (range 30% to 83%); one trial did not report patient sex.[87] Few trials reported race or ethnicity, comorbidities, or social determinants of health, with one trial reporting nationality (53% Norwegian, 47% Swedish)[70] and another trial reporting race (76% White, 17% Black, 5% Hispanic/Latino, ≤1% Asian, or other).[62] The primary tumor types included breast (range, 8% to 49%), lung (range, 1% to 33.5%), and prostate (5% to 80%). One RCT (in 3 publications) did not report primary tumor type.[62,68,71] In two trials, primary tumors were recorded as favorable (10% to 30%), intermediate (70%, only available in one trial),[51] and/or unfavorable (20% to 70%).[51,74]

Bone metastases were present at multiple sites in 13 to 86 percent of patients across seven trials; the proportion with metastases to other nonbone/visceral sites ranged from 20 to 41 percent across three trials. Across three trials, the metastatic bone lesions were lytic in 60 to 88 percent, sclerotic in 8 to 33 percent, and mixed in 3 to 7 percent. The site of bone metastases was mixed (i.e., spine and nonspine) in most RCTs (15 trials; spine, 29% to 89% and nonspine, 11% to 71%);[41,43-47,51,53,54,59-62,66,68,70,71,74,75,79,82,87,93,95,96,102,104] spinal cord compression and pathologic fracture were exclusion criteria in most of the mixed trials. Five trials included bone metastases to the spine only (4 of MSCC and 1 which did not report spinal cord compression), and no trials included bone metastases to nonspine sites only. Pathological fractures were present at baseline in 0 to 15 percent of patients across the 10 trials that reported this information. In the four trials specifically evaluating MSCC, 45 to 67 percent of participants were ambulatory and 9 to 26 percent of participants reported abnormal bladder function at baseline. Most trials did not describe bone metastases as either complicated or uncomplicated; however, many trials did report spinal cord or cauda equina compression, or pathologic fracture at study entry, the presence or absence of which has been used to define complicated and uncomplicated bone metastases.

The single fraction dose was 8 Gy in all but two trials, which used 10 Gy.[47,60,102] The most common multiple fraction doses were 30 Gy (3 Gy x 10) and 20 Gy (4 Gy x 5) over 1 to 2 weeks across 18 trials;[41,44,45,47,51,53-55,59,61,62,66,68,70,71,79,82,87,93,95,96,102] one trial used 16 Gy (8 Gy x 2) over 1 week,[74] one trial used 22.5 Gy (4.5 Gy x 5) over 1 week,[60] one trial used 24 Gy (4 Gy x 6) over an undisclosed time period,[46,75,104] and two used 40 Gy (2 Gy x 20) over 4 weeks.[43,51] Most trials did not clearly report the specific type of EBRT employed but it was most likely two-dimensional (2D) or three-dimensional conformal radiation therapy (3DCRT) as these are the most commonly available techniques. Common concomitant treatments included analgesics (16% to 70%), opioids (35% to 81.2%, one outlier trial at 2.8%), and steroids (19% to 100%).

3.1 Key Question 1: Effectiveness and Harms of Dose-Fractionation Schemes and Techniques for Delivery, Initial Radiation

Previous treatments included systemic therapy (37% to 54%, includes primarily chemotherapy and hormone therapy), surgery (2% to 7%), and analgesics (16% to 70%). Most trials excluded patients who had chemotherapy or recent changes in systemic therapy, prior radiation therapy (RT) to the treatment site, prior vertebral fracture, and poor prognosis (generally life expectancy under 6 weeks). Followup periods ranged from 1 to 64.4 months.

One trial was conducted in the United States,[62,68,71] 13 in Europe,[41,45-47,55,59,60,66,70,74,75,82,87,93,95,102,104] three in Australia and New Zealand,[41,66,93] three in Egypt,[43,51,54] two in India,[44,79] one in Iran,[53] and two did not report the countries in which they were conducted.[61,96] Most were single center trials and the most common source of funding across the trials was government, followed by university and undisclosed funding.

Fifteen trials were fair quality[41,43-47,53-55,59,66,70,74,75,87,93,95,102,104] and seven were poor quality.[51,60-62,68,71,79,82,96] Common limitations included inability to blind patients and providers, lack of assessor blinding, unclear randomization and allocation concealment methods and high attrition (Appendix F, Table F-1). In many cases, the high attrition was due to high mortality (7.1% to 92.3%, longer followups generally above 20%), which is to be expected in this patient population.

Given the number of RCTs that compared SF EBRT versus MF EBRT, the four eligible NRSIs were included for evaluation of harms only (as specified in the Methods) and are described in Appendix B.

3.1.1.3 Detailed Synthesis

3.1.1.3.1 Pain

Definitions of pain responses varied across trials (Appendix B, Table B-2). We focused on overall response below, which encompasses complete and partial response in most trials (Appendix E, Table E-1).3.1.1.3.1.1 Overall Pain Response

Fourteen RCTs[41,43-46,53,54,59,60,62,74,87,93,96] comparing SF EBRT with MF EBRT contributed data to meta-analyses of overall pain response. Three RCTs were in patients with spinal metastasis[44,74,93] and 11 included patients with spine or nonspine MBD.[41,43,45,46,53,54,59,60,62,87,96]

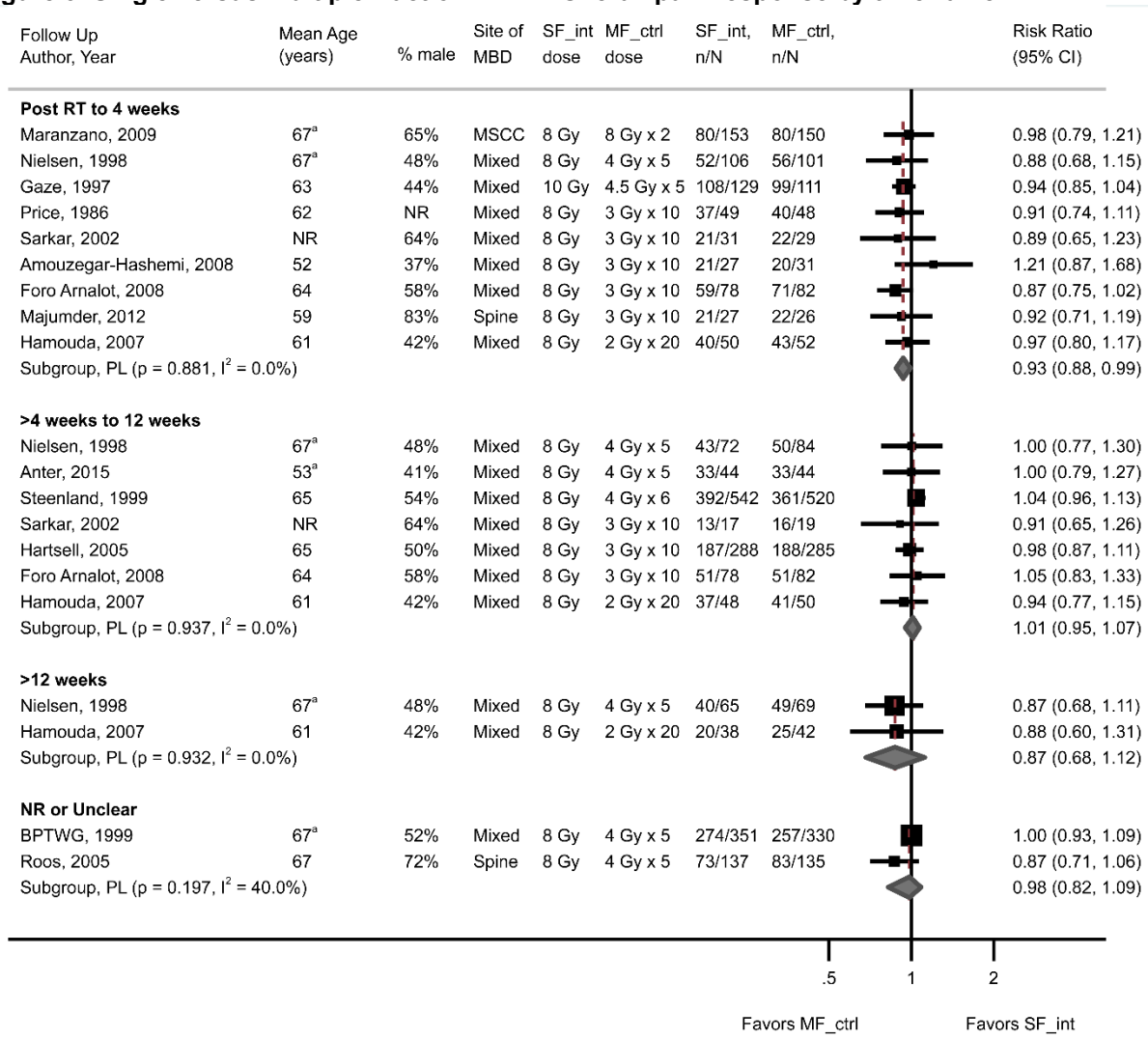
SF EBRT was associated with a small decrease in the likelihood of achieving overall pain response compared with MF EBRT up to 4 weeks post-treatment (9 RCTs, N=1280, 67.5% vs. 71.9%, RR 0.93, 95% CI 0.88 to 0.99, I^2=0%)[43-45,53,59,60,74,87,96] (Figure 3). Exclusion of two poor-quality trials[60,96] did not change the effect estimates (7 RCTs, N=980, 63.3% vs. 67.8%, RR 0.93, 95% CI 0.86 to 1.01, I^2=0%),[43-45,53,59,74,87] with the proportions of patients with overall response slightly lower in each group. The small overall decrease in pain response at 4 weeks was consistent across trials in populations with mixed spine/nonspine metastases (7 RCTs, N=924, 71.9% vs. 77.3%, RR 0.93, 95% CI 0.87 to 0.99, $I^{2=}$0%),[43,45,53,59,60,87,96] however no difference was seen between SF EBRT and MF EBRT in analysis confined to patients with spinal metastases across two fair-quality trials (2 RCTs, N=356, 56% vs. 58%, RR 0.96, 95% CI 0.78 to 1.16, I^2=0%)[44,74] that included one trial in patients with MSCC.[74] We found no clear difference in the likelihoods of achieving overall pain response between SF EBRT and MF EBRT from 4 to 12 weeks (7 RCTs, N=2173, 69.4% vs. 68.3%, RR 1.01, 95% CI 0.95 to 1.07, I^2=0%)[43,45,46,54,59,62,96] or at >12 weeks (2 RCTs, N=214, RR 0.87, 95% CI 0.68 to 1.12, I^2=0%);[43,45] all trials were in patients with mixed spine/nonspine MBD. No difference was seen across two trials where followup time was not reported or unclear (2 RCTs, N= 953, 71.1% vs. 73.1%, RR 0.98, 95% CI 0.82 to 1.09, I^2=40%).[41,93] In one trial, 89 percent of patients had spinal metastasis, while the other trial was conducted in a mixed population (Figure 3). Exclusion of

poor-quality trials for >4-week to 12-week results did not influence estimates or heterogeneity at the later time frames.

Across trials, results for pain response at all timeframes likely combined response data for initial radiation therapy and re-irradiation. Results slightly favoring MF EBRT over SF EBRT at up to 4 weeks may in part reflect patients having received only initial radiation and/or a proportion of patients whose improvement occurred later than 4 weeks.

There was no difference in overall pain response between SF EBRT and MF EBRT in analysis based on longest followup across trials (14 RCTs, N=3837, 69.4% vs. 70.0%, RR 0.99, 95% CI 0.94 to 1.03, I^2=0%)[41,43-46,53,54,59,60,62,74,87,93,96] or when trials of mixed spine/nonspine MBD (11 RCTs, N=3209, 72.2% vs. 72.0%, RR 0.99, 95% CI 0.95 to 1.03, I^2=0%)[41,43,45,46,53,54,59,60,62,87,96] were considered separately from those in patients with spine metastases (3 RCTs, N=628, 54.9% vs. 59.5%, RR 0.92, 95% CI 0.80 to 1.06, I^2=0%)[44,74,93] (Appendix I, Figures I-1 and I-2). There was no indication of publication or small study bias based on funnel plot analysis and Egger's test (p= 0.405) (Appendix I, Figure I-3).

Figure 3. Single versus multiple fraction EBRT: Overall pain response by timeframe



BPTWG = Bone Pain Trial Working Group; CI = confidence interval; EBRT = external beam radiation therapy; MBD = metastatic bone disease; MF_ctrl = multiple fraction is the control; MSCC = metastatic spinal cord compression; NR = not reported; PL = profile likelihood; RT = radiation therapy; SF int = single fraction is the intervention.

[a] Median age

3.1 Key Question 1: Effectiveness and Harms of Dose-Fractionation Schemes and Techniques for Delivery, Initial Radiation

One fair-quality prospective NRSI (N=968)[111] found no difference in the probability of achieving overall pain response (adjusted odds ratio [OR] 0.86, 95% CI 0.63 to 1.19) for SF EBRT versus MF EBRT or when analyses were confined to patients with complicated MBD (N=335, adjusted OR 0.90, 95% CI 0.51 to 1.61). When patients were asked if bone pain interfered with their ability to care for themselves, SF EBRT was less likely than MF EBRT to improve this ability (adjusted OR 0.62, 95% CI 0.42 to 0.92); this was also true in analyses confined to patients with complicated MBD (adjusted OR 0.49, 95% CI 0.23 to 0.98).

3.1.1.3.1.2 Complete Pain Response and Pain Scores

Across studies for which complete response was reported or could be inferred, there were no differences between SF EBRT and MF EBRT based on data from last followup (14 RCTs, N= 3821, 34.6% vs. 23.1%, RR 1.01, 95% CI 0.92 to 1.10, I^2=0%),[41,43-46,53,54,59,60,62,74,87,93,96] at any time frame, or by population (mixed spine/nonspine MBD, spine only) (Appendix I, Figures I-4 to I-6).

Six trials[44,46,47,66,70,79] reported pain based on VAS, numerical rating scale (NRS) or European Organisation for Research and Treatment of Cancer (EORTC) scores which were converted to a 0-10 scale for pooled analysis. There was no difference between SF EBRT and MF EBRT for pain posttreatment up to 4 weeks (4 RCTs, N=1854, mean difference [MD] 0.29, 95% CI -0.03 to 0.65, I^2=54%);[44,46,66,70] the estimated difference was below the threshold for a small effect of 0.5 (Appendix I, Figure I-7). Sensitivity analyses using VAS data for one trial[47] and NRS data for another[70] reduced the heterogeneity and slightly increased the effect size, but the estimate remained below the threshold for a small effect (4 RCTs, N= 1854, MD 0.35, 95% CI -0.17 to 0.56, I^2=0%). No differences between SF EBRT and MF EBRT were seen at >4 to 12 weeks (5 RCTs, N=1837, MD 0.03, 95% CI -0.42 to 0.41, I^2=66%) or >12 weeks (3 RCTs, N= 1395, MD -0.07, 95% CI -0.46 to 0.29, I^2=0%)[46,47,66,70,79] (Appendix I, Figure I-7). Sensitivity analyses excluding the one poor-quality trial[79] from the latter two time frames did not impact effect size or reduce heterogeneity. MF EBRT was associated with small pain improvement in two fair-quality trials in patients with MSCC versus SF EBRT post-treatment up to 4 weeks (2 RCTs, N=390, MD 0.53, 95% CI 0.12 to 1.08, I^2=0%, 0-10 scale),[44,66] however there were no differences at longer times in this patient population or in trials of populations with mixed spine/nonspine MBD[46,70,79] (Appendix I, Figure I-8). There was no difference between SF EBRT and MF EBRT in analyses based on longest followup time (Appendix I, Figure I-9).

3.1.1.3.2 Function

Two poor-quality trials[61,79] in patients with mixed spine and nonspine metastases (MSCC excluded in one trial[61]) reported general function outcomes and found no differences between fractionation schemes. One trial reported the proportion of patients with improvement in performance status (SF EBRT: 10% [2/20] vs. MF EBRT: 15% [6/40]; RR 0.67, 95% CI 0.45 to 3.01) but the measure used (unclear if Karnofsky Performance Scale [KPS] or EORTC performance scale was reported) and the timing of measurement (up to 6 months) were unclear.[79] The second trial reported time to improvement of one grade of functionality (SF EBRT: mean 4.8 months [95% CI 3.3 to 6.4 months] vs. MF EBRT: 5.4 months [95% CI 3.9 to 6.9 months], p=0.339) and time to performance of activities of daily living independently and without pain (mean 7 months [95% CI 5 to 9] vs. mean 5 months [95% CI 4 to 7 months], respectively, p=0.549) according to the Barthel Index.[61]

3.1.1.3.3 Relief of Spinal Cord Compression/Neurological Outcomes

Four trials[51,66,74,102] which enrolled only patients with MSCC assessed ambulatory status using slightly different measures: a 4-point scale, consistent with the World Health Organization (WHO) performance status, based on the validated Medical Research Council muscle power criteria[138] (Grade 1 = ambulatory without aids and grade 5 of 5 muscle power in all muscle groups; Grade 2 = ambulatory with aids or grade 4 of 5 muscle power in any muscle group; Grade 3 = unable to walk with no worse than grade 2 of 5 power in all muscle groups or grade 2 of 5 power in any muscle group; and Grade 4 = absence [0/5 muscle power] or flicker [1/5 muscle power] of motor power in any muscle group);[66] Tomita's functional motor grading system[139] (Grade 1= ambulatory without aids; Grade 2 = ambulatory with aids; Grade 3 = inability to walk; Grade 4 = paraplegic);[74] and an author-modified Tomita 3-point scale for mobility (Grade 1= ambulatory without aids; Grade 2 = ambulatory with aids; and 3 = bed-bound).[102] The fourth trial only reported the outcome as "ambulatory" (authors mention evaluating motor function using the Medical Research Council muscle power criteria, scale 0 [complete paralysis] to 5 [normal power], but how this was applied is unclear).[51]

There were no differences between SF EBRT and MF EBRT in the proportion of patients who were ambulatory at any timepoint across all four RCTs (Table 2),[51,66,74,102] both when considering patients who either maintained or improved their ambulation status compared with baseline and only patients who improved their ambulation status.

Table 2. Relief of spinal cord compression: ambulatory status in patients with MSCC

Outcome[a]	Author, Year	Followup[b]	SF EBRT % (n/N)	MF EBRT % (n/N)	RR (95% CI)[c]
Ambulation: maintained or improved[e] from baseline	Abu Hegazy, 2011[d]	Post-RT	86.3% (82/95)	86.8% (165/190)[d]	0.99 (0.90 to 1.10)
	Maranzano, 2009	Post-RT	62.1% (95/153)	69.3% (104/150)	0.90 (0.76 to 1.05)
	Hoskin, 2019	4 weeks	66.8% (143/214)	67.6% (152/225)	0.99 (0.87 to 1.13)
	Thirion, 2020	5 weeks	61.1% (22/36)	54.1% (20/37)	1.13 (0.76 to 1.68)
	Hoskin, 2019	8 weeks	69.3% (115/166)	72.7% (128/176)	0.95 (0.83 to 1.09)
	Hoskin, 2019	12 weeks	71.8% (102/142)	67.7% (107/158)	1.06 (0.91 to 1.23)
Ambulation: improved[e] from baseline	Abu Hegazy, 2011[d]	Post-RT	26.3% (25/95)	25.8% (49/190)[d]	1.02 (0.67 to 1.54)
	Maranzano, 2009	Post-RT	5.9% (9/153)	8.7% (13/150)	0.68 (0.30 to 1.54)
	Thirion, 2020	5 weeks	8.3% (3/36)	10.8%(4/37)	0.77 (0.19 to 3.20)
	Hoskin, 2019	8 weeks	7.2% (12/166)	10.2% (18/176)	0.71 (0.35 to 1.42)

CI = confidence interval; EBRT = external beam radiation therapy; MF = multiple fraction; MSCC = metastatic spinal cord compression; RD = risk difference; RR = risk difference; RT = radiation therapy; SF = single fraction.

[a] Except for one trial which did not clearly report criteria used to define ambulation (Abu Hegazy, 2011), trials considered patients ambulatory after treatment if they achieved a Grade 1 or 2 (able to walk with or without walking aids) on the trial measures (WHO performance status/Medical Research Council muscle power criteria, Tomita's functional motor grading system, author-modified Tomita's scale for mobility).

[b] Post-RT = unclear timing after therapy/timing not otherwise specified.

[c] Calculated by Evidence-based Practice Center unless otherwise indicated.

[d] The 30 Gy (3 Gy x 10) and the 40 Gy (2 Gy x 20) arms were combined into one multiple fraction arm. There were no differences between groups when compared separately with the single fraction arm.

[e] Regained ambulation (nonambulatory at baseline) or ability to walk unaided (walking with aids at baseline).

One trial reported a mobility score using the authors' own modified Tomita mobility scale (1–3 scale; 1 = unaided, 2 = with walking aid, and 3 = bed-bound) and found no differences between SF EBRT versus MF EBRT in change scores from baseline to 5 weeks: mean change 0.06 (standard deviation [SD] 0.75) versus 0.3 (0.78), adjusted difference in change scores -0.28 (95% CI -0.6 to 0.03).[102]

Sphincter, bladder, and bowel control were reported a variety of ways (i.e., improvement, normal, abnormal) across the four RCTs with no differences between fractionation schemes at any timepoint, with one exception (Results Appendix B, Table B-3): one fair-quality trial[74] found

SF EBRT associated with a large increase in the likelihood of achieving good/normal sphincter control post-RT compared with MF EBRT (N=303, 5.9% vs. 1.3%, RR 4.41, 95% CI 0.97 to 20.1), however the estimate was imprecise. When considering only those patients with poor/abnormal sphincter control at baseline (i.e., likelihood of regaining control only as opposed to maintaining or regaining control), there was no statistical difference between groups though the rate with SF EBRT was higher (34.6% vs. 13.3%, RR 2.60, 95% CI 0.64 to 10.5). One trial reported a bladder score using the authors' own scale for bladder function (1-3 scale; 1 = continent, 2 = incontinent, and 3 = catheterized) and found no differences between SF EBRT versus MF EBRT in change scores from baseline to 5 weeks: mean change 0.17 (SD 0.71) versus 0.22 (0.96), adjusted difference in change scores -0.05 (95% CI -0.45 to 35).[102] In two trials, patients with good baseline bladder function developed poor function requiring an indwelling catheter: 0.8 percent (n=2/258, 1 poor-quality RCT[51]) and 4.6 percent (n=12/262, 1 fair-quality RCT[74]). Results were not reported by treatment group.

One poor-quality trial reported no difference between SF EBRT and MF EBRT in the proportion of patients who had sensory deficit at baseline (19% [18/95] vs. 20.5% [39/190] of the total population, respectively) who recovered after treatment (27.8% [5/18] vs. 30.8% [12/39], RR 0.90, 95% CI 0.37 to 2.18).[51]

3.1.1.3.4 Quality of Life

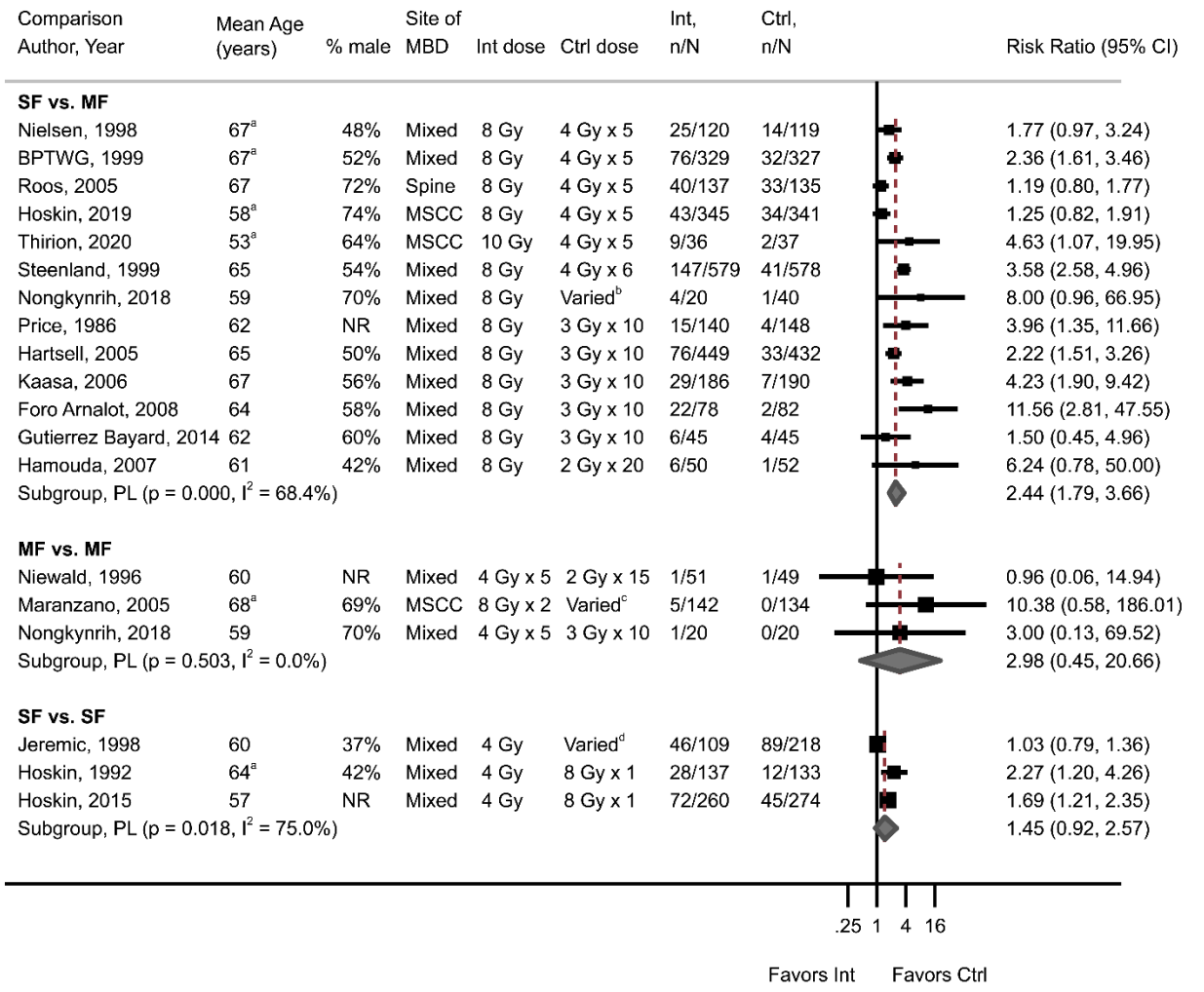
Quality of life was variably measured and reported (Results Appendix B, Table B-4). Three RCTs reported no differences between SF EBRT and MF EBRT in quality of life based on the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).[66,70,102] One RCT reported no differences between dose/fraction schemes using a global VAS (0-100) quality of life (QOL) scale.[45] Another RCT reported no difference between fractionation schemes based on the Spitzer QOL index post-RT.[60] One trial reported no significant differences for the two treatment groups based on the Rotterdam Symptom Check List but provided no data.[46]

3.1.1.3.5 Secondary Outcomes

Thirteen RCTs comparing SF EBRT and MF EBRT reported rates of re-irradiation. SF EBRT was associated with an over 2-fold higher likelihood of re-irradiation compared with MF EBRT, consistent with a large effect (13 RCTs, N=5040, 19.8% vs. 8.2%, RR 2.44, 95% CI 1.79 to 3.66, I^2=68.4%);[41,43,45,46,59,61,62,66,70,79,87,93,102] substantial heterogeneity was noted (Figure 4). The effect size and statistical heterogeneity were slightly increased with the exclusion of three poor-quality trials[61,62,79] (10 RCTs, RR 2.55, 95% CI 1.73 to 4.21, I^2=75%).[41,43,45,46,59,66,70,87,93,102] The heterogeneity may have in part been due to variation in criteria for performing re-irradiation across studies. The funnel plot for this analysis showed some visual asymmetry, which raises the possibility of publication bias. It may be due to the substantial heterogeneity for the pooled estimate (I^2=68%) given variability in decision making criteria for performing re-irradiation across trials. The Egger's test was not significant (p=0.221) (Appendix I, Figure I-10).

3.1 Key Question 1: Effectiveness and Harms of Dose-Fractionation Schemes and Techniques for Delivery, Initial Radiation

Figure 4. Re-irradiation across fractionation schemes for EBRT



BPTWG = Bone Pain Trial Working Group; CI = confidence interval; Ctrl = control group; EBRT = external beam radiation therapy; Int = intervention group; MBD = metastatic bone disease; MF = multiple fraction is control; MSCC = metastatic spinal cord compression; NR = not reported; PL = profile likelihood; RT = radiation therapy; SF = single fraction is intervention.

[a] Median age

[b] 4 Gy x 5 (20 Gy) or 3 Gy x 10 (30 Gy)

[c] 5 Gy x 3 & 3 Gy x 5 (30 Gy)

[d] 6 Gy or 8 Gy

Across RCTs in patients with mixed spine/nonspine MBD, SF EBRT was associated with an over 2-fold higher likelihood of re-irradiation compared with MF EBRT, consistent with a large effect (10 RCTs, RR 2.81, 95% CI 2.19 to 3.94, I^2=37.5%),[41,43,45,46,59,61,62,70,79,87] however analyses confined to studies in patients with spine MBD, found no difference between dose/fraction schemes (3 RCT, N=1,031, 17.7% vs. 13.5%, RR 1.28, 95% CI 0.96 to 2.09, I^2=35.4%).[66,93,102] Two of the RCTs were in patients with MSCC.[66,102] In the RCT of patients without MSCC,[93] there was no difference between dose fractionation schemes on the likelihood of re-irradiation (N=272, 29.2% vs. 24.4%, RR 1.19, 95% CI 0.80 to 1.77). In contrast, one NRSI[121] designed to evaluate clinically relevant adverse spinal events in patients with uncomplicated spinal metastases reported that re-irradiation was more common following SF EBRT versus MF EBRT (N=299, 18.2% vs. 6.0%, p=0.004).

One fair-quality prospective NRSI (N=968) found no difference in re-irradiation between SF EBRT and MF EBRT (17% versus 14%).[111]

Data for other secondary outcomes (local control, medication use, need for additional intervention, and overall survival) can be found in Results Appendix B.

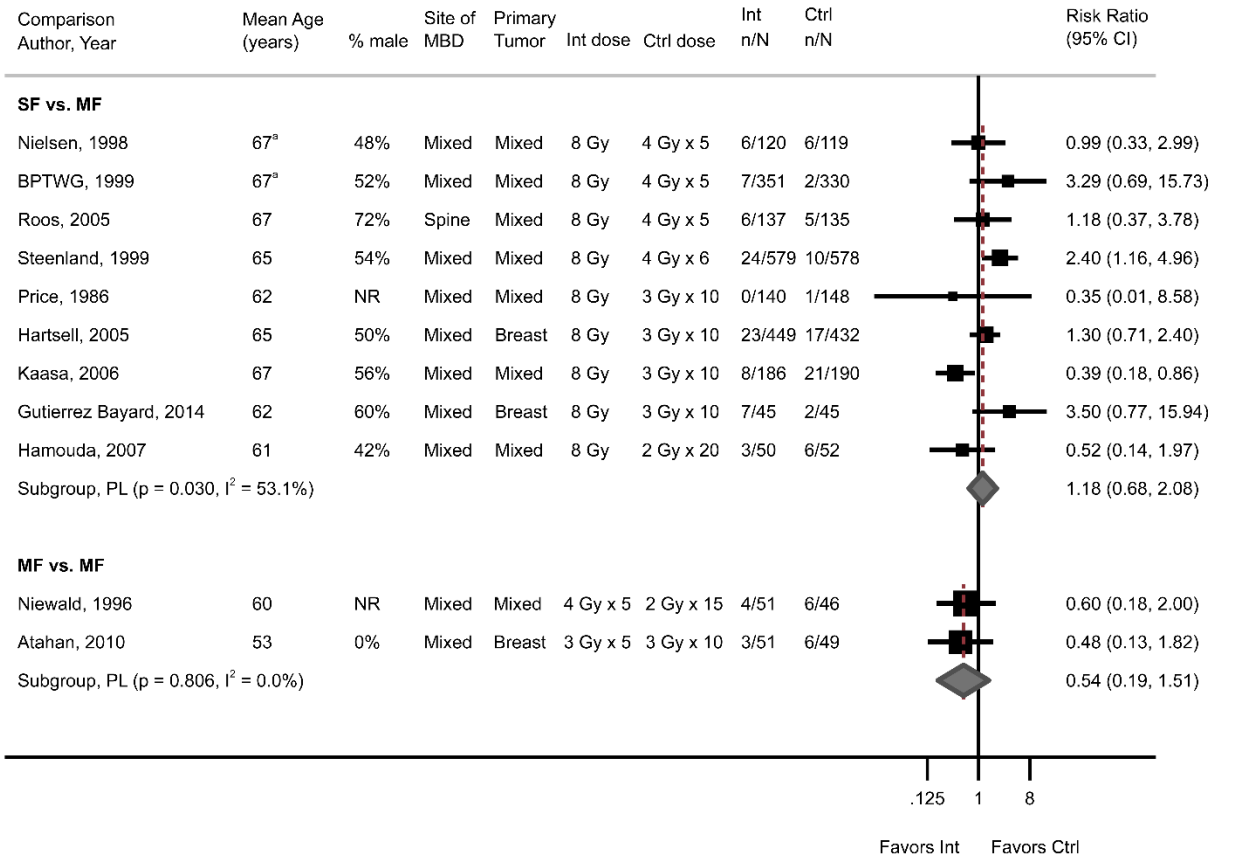
3.1.1.3.6 Harms and Adverse Events

Toxicity, adverse events, and harms were inconsistently reported across included studies.

3.1.1.3.6.1 Pathologic Fracture

There was no difference in pathologic fractures between SF EBRT and MF EBRT (9 RCTs, N=4086, 4.1% vs. 3.4%, RR 1.18, 95% CI 0.68 to 2.08, I^2=53.1%)[41,43,45,46,61,62,70,87,93] (Figure 5). Exclusion of two poor-quality trials[61,62] reduced the effect estimate but heterogeneity was similar (7 RCTs, N=3115, RR 1.02, 95% CI 0.50 to 2.07, I^2=59%).[41,43,45,46,70,87,93] One fair-quality trial in patients with spinal metastases who did not have cord compression at baseline reported new or progressive vertebral fractures;[93] no difference between radiation schemes was seen (N=272, 4.4% vs. 3.7%, RR 1.18 95% CI 0.37 to 3.78). All trials enrolled patients with various primary tumors.

Figure 5. Pathologic fractures across fractionation schemes for EBRT



BPTWG = Bone Pain Trial Working Group; CI = confidence interval; Ctrl = control group; EBRT = external beam radiation therapy; Int = intervention group; MBD = metastatic bone disease; MF = multiple fraction; NR = not reported; PL = profile likelihood; SF = single fraction.
[a] Median age

In contrast to the RCT findings, one fair-quality NRSI (N=299)[121] designed to evaluate clinically relevant adverse spinal events in patients with uncomplicated spinal metastases reported greater odds of fracture with SF EBRT (13.6% vs. 3.0%, OR 3.73, 95% CI 1.61 to

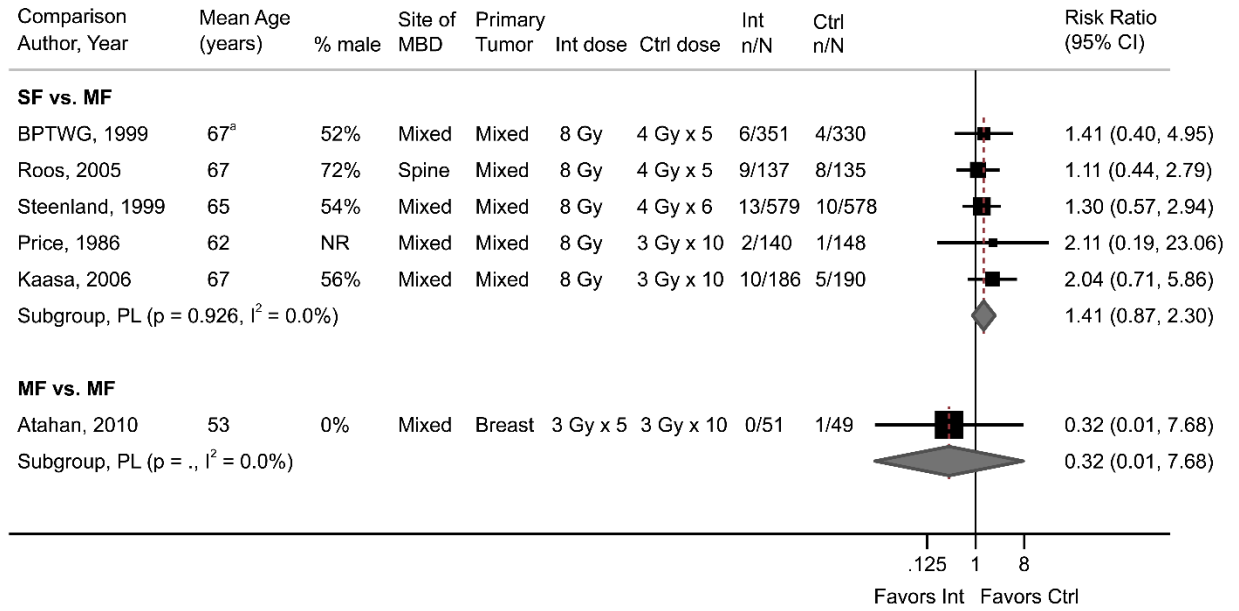
8.63). It is unclear if this is an adjusted estimate. In the propensity-matched cohort, symptomatic vertebral fracture risk was also higher with SF EBRT versus MF EBRT (N=132, 13.6% vs 1.5%).[121]

See Results Appendix B, Table B-10 for pathological fracture outcomes.

3.1.1.3.6.2 Spinal Cord Compression

There was no difference in the development of spinal cord compression following treatment between SF EBRT and MF EBRT (5 RCTs, N=2774, 2.9% vs. 2.0%, RR 1.41, 95% CI 0.87 to 2.30, I^2=0%).[41,46,70,87,93] All trials were fair quality. All but one trial was in patients with mixed spine/nonspine MBD and had excluded patients with MSCC at recruitment (Figure 6). One trial was primarily in patients with spine metastases (89%), but only one patient had MCSS prior to radiation therapy[93] and found no difference in the likelihood of spinal cord compression by dose/fractionation scheme (N=272, 6.6% vs. 5.9%, RR 1.1, 95% CI 0.44 to 2.79) posttreatment. One additional poor-quality trial reported no spinal cord compression in either group.[82]

Figure 6. New spinal cord compression across fractionation schemes for EBRT



BPTWG = Bone Pain Trial Working Group; CI = confidence interval; Ctrl = control group; EBRT = external beam radiation therapy; Int = intervention group; MBD = metastatic bone disease; MF = multiple fraction; NR = not reported; PL = profile likelihood; SF = single fraction.

[a] Median age

One fair-quality propensity score matched cohort NRSI[121] designed to evaluate clinically relevant adverse spinal events in patients with uncomplicated spinal metastases reported that cord or cauda equina compression was more common with SF EBRT than with MF EBRT (N=132, 10.6% vs. 0%, p=0.002).

See Results Appendix B, Table B-10, for spinal cord compression outcomes.

3.1.1.3.6.3 Other Adverse Events

Pain Flare. One fair-quality RCT found no difference between SF EBRT and MF EBRT in the likelihood of experiencing a pain flare in patients with spine MBD (N=233, 10% vs. 4%, RR 2.0, 95% CI 0.91 to 5.81).[93] There was no clear difference between dose/fraction schemes across two small NRSIs using different definitions of pain flare. All effect estimates were imprecise.

Risk of pain flare was similar with SF EBRT and MF EBRT in one NRSI (N=111, 38.6% vs. 39%, RR, 1.35, 95% CI 0.87 to 2.11). The other NRSI evaluated a subset of patients enrolled in the Canadian Bone Metastasis Trial (N=44)[122] who agreed to complete a 14-day pain diary (MBD sites not reported). It used two different pain flare definitions. Results using both definitions suggest that pain flare may be more common with SF EBRT compared with MF EBRT, however, estimates were imprecise (Tannock definition, 43.5% vs. 23.8%, RR 1.83, 95% CI 0.75 to 4.47; Chow Definition, 56.5% vs. 23.8%, RR 2.37, 95% CI 1.02 to 5.53).

Skeletal Events and Spinal Adverse Events. There was no difference in skeletal-related events, defined as at least one instance of re-irradiation or pathologic fracture, between SF EBRT and MF EBRT in one poor-quality RCT (N=90, 28.8% vs. 13.3% RR 2.17, 95% CI 0.90 to 5.19).

One fair-quality NRSI[121] designed to evaluate clinically relevant adverse spinal events in patients with uncomplicated spinal metastases reported that SF EBRT was associated with higher likelihood of any spinal adverse event (N=299, 27.3% vs. 14.2%, adjusted hazard ratio (HR) 2.78, 95% CI 1.51 to 5.15). Cumulative incidence of any spinal adverse event was consistently higher with SF EBRT: 4 weeks (6.8% vs. 3.5%), 12 weeks (16.9% vs. 6.4%) and 26 weeks (23.6% vs. 9.2%). SF EBRT was associated with higher rate of first spinal adverse event at 12 weeks (N=132, 22.5% vs. 7.7%, HR 3.2, 95% CI 1.3 to 7.5) based on propensity score matched analysis. Spinal adverse events included hospitalization for uncontrolled pain, symptomatic vertebral fracture, interventional procedure, salvage surgery, new or deteriorated neurologic symptoms, and spinal cord or cauda equina compression.

Various Adverse Events. There were no differences between SF and MF EBRT for new impairment of bladder or bowel function in one fair-quality RCT[66] in patients with MSCC. No differences were seen in bladder impairment prior to 8 weeks (N=638, 43.7% vs. 34.5%, adjusted OR 1.31, 95% CI 0.87 to 1.97) or at 8 weeks (N=317, 31.1% vs 20.5% [34/166], adjusted OR 1.78, 95% CI, 0.93 to 3.39) or in bowel impairment at any time (N=637, 64.4% vs. 63.4%, OR 1.05, 95% CI 0.76 to 1.45) or at 8 weeks (39.1% [59/151] vs. 36.7% [61/166], OR 1.10, 95% CI 0.70 to 1.74).

One fair-quality RCT (N=303)[74] in patients with MSCC reported no occurrences of radiation induced myelopathy for either dose/fraction scheme. Another fair-quality RCT reported that one patient who received SF EBRT experienced radiation enteritis due to retreatment and one patient in the MF EBRT group experienced a small bowel ileus. Two RCTs reported no adverse event-related study withdrawals.[44,96] One NRSI[121] in patients with uncomplicated spine MBD reported that new or deteriorated neurologic symptoms were more common following SF EBRT versus MF EBRT in a matched propensity score cohort (N=132, 12.1% vs. 4.5%, p=0.10).

3.1.1.3.6.4 Toxicity

Toxicity type, severity, and frequency were variably reported across studies. Some studies reported toxicities by numbers of sites versus number of patients. We focused on Grades 3 and 4 toxicities here; detail on other grades is found in Results Appendix B, Table B-7.

In patients with mixed spine/nonspine MBD, Grade 4 toxicities were rare, ranging from 0 percent to 3 percent, with no differences between SF EBRT and MF EBRT across three RCTs,[54,60,62] however, this may in part be attributed to small sample size given the rare nature of these events. Similarly, Grade 3 toxicities were similar between SF SBRT and MF SBRT for any toxicity (<1% to 3% vs. <1% to 4%) across one fair- and one poor-quality RCT,[54,62] and for specific toxicities of nausea and vomiting (11% vs. 15%) and tiredness/lassitude (10% vs. 14%)

in another poor-quality trial.[60] Two other trials reported that no grade 3 or 4 toxicities occurred.[59,82] There was no difference between SF and MF EBRT for "quite a bit or very much" nausea (39% vs. 40%) or vomiting (20% vs. 21%) in a subset of patients (N=124) from the Bone Trial Working Group RCT[41] based on pain diaries up to 14 days post-treatment (Results Appendix B, Table B-7).

There was limited data comparing toxicities for SF EBRT versus MF EBRT in patients with spine metastasis. Retrospective analysis[68] of the Radiation Therapy Oncology Group 97-14 trial[62] in patients with painful spine metastases reported low frequency of acute or late Grade 4 toxicities and no difference by dose/fraction scheme (N= 135, 0% vs. 1% for both acute and late). Results were similar for Grade 3 toxicities (N=124, acute <1% vs. 3%, late 2% vs. 0%). Sample sizes may have been inadequate to identify differences. One fair-quality RCT (N=686)[66] reported similar risk of Grade 3 or 4 toxicity (20.5% vs. 20.6%) and of death unrelated to treatment (0.9% vs. 1.5%). Small individual trials report no difference in Grade 3 acute gastrointestinal toxicities (N=59, 0% vs. 6%)[44] or late upper thigh pain (N=52, 0% vs. 0.5%).[102] One of these RCTs[102] reported somewhat lower risk of any Grade 2 or 3 toxicity with SF SBRT versus MF EBRT (N=100) 11.1% vs. 26.1%, RR 0.43, 95% CI 0.14 to 1.05); the estimate is imprecise.

3.1.1.3.7 Differential Effectiveness or Safety

There is insufficient information from included trials on differential effectiveness or harms for all comparisons of SF EBRT and MF EBRT based on patient characteristics, tumor characteristics, baseline function or other factors. Five RCTs (across 8 publications)[43,46,62,66,68,71,95,104] reported various subgroup analyses for such factors, but only one reported tests for interaction (range of p-values, 0.08 to 0.96; Results Appendix B, Tables B-28 to B-30).[66] While substantial overlap in confidence intervals may suggest that the factors did not differentially impact effectiveness or harms, trials were underpowered to effectively evaluate modification. Thus, conclusions are not possible. Data are found in Results Appendix B, Tables B-18 to B-30.

3.1.2 SF EBRT: Lower Dose Single Fraction (LDSF) Versus Higher Dose Single Fraction (HDSF) EBRT

3.1.2.1 Key Points

- LDSF (4 Gy) may be associated with slightly lower likelihood of overall pain response compared with HDSF (6 to 8 Gy) up to 4 weeks posttreatment (2 RCTs, N= 861, RR 0.80, 95%CI 0.58 to 1.02, I^2= 76%), >4 to 12 weeks (2 RCTs, N=743, 74.3% vs. 83.3% RR 0.89, 95%CI 0.72 to 1.0, I^2=63.9%) and 12 weeks (1 RCT N=180, 82.3% vs. 93.1%, RR 0.88, 95% CI 0.79 to 0.99) (SOE: low).
- There was insufficient evidence to evaluate the impact of different SF doses on function or quality of life from one cluster RCT (SOE: insufficient).
- No patients had pathologic fractures or spinal cord compression within the first 8 weeks of radiation and there may be no differences between LDSF and HDSF for either of these outcomes at >8 weeks in one trial (SOE: low).
- There may be no differences between LDSF (6 Gy) and HDSF (8 Gy) for skeletal events (pathologic fracture, re-irradiation, cord compression), adverse events (not specified) or adverse reactions (not specified) in a cluster RCT in which all patients received zoledronic acid, calcium, and vitamin D (SOE: low for all).

- Two trials found that re-irradiation was more common with LDSF (4 Gy) versus HDSF (8 Gy), however a third trial found no difference in re-irradiation risk for 4, 6, or 8 Gy single fractions.

3.1.2.2 Description of Included Studies

Four RCTs[64,67,69,72] compared different doses of SF schemes for conventional EBRT for the palliative treatment of bone metastases (Appendix E, Table E-1). We reported the lowest doses as the intervention (LDSF) and higher dose as the control (HDSF).

Across the RCTs, sample sizes ranged from 139 to 655 (total N=1391). The average study median (3 trials)[64,67,69] or mean (1 trial)[72] age of participants was 61 years (range 57 to 64 years). The average study proportion of males across three RCTs was 48 percent (range 37% to 65%); one trial did not report patient sex.[64] None of the trials reported race, comorbidities, or social determinants of health. Primary tumor types included breast (range, 21% to 46%), lung (range, 19% to 35%), and prostate (range, 13% to 17%); no trial reported primary tumor histology in terms of favorable or unfavorable. All four RCTs included patients with bone metastases at mixed sites. Across three RCTs, spinal metastases accounted for 37 to 59 percent of lesions, and nonspine metastases accounted for 41 to 63 percent;[64,67,69] one RCT did not provide further details.[72] Pathological fracture and MSCC were exclusion criteria in two trials,[64,67] and just pathological fracture in one[69] (the fourth trial[72] did not report these characteristics). The presence or absence of these characteristics have been used to define complicated and uncomplicated bone metastases. No trial reported whether bone metastases were lytic or sclerotic or if concomitant nonbone/visceral metastases were present. One trial included patients with a single bone metastasis[64] and another included patients with ≤2 bone metastases;[72] the remaining two trials did not report the number of metastases treated.

The lower dose in three RCTs was 4 Gy;[64,67,69] 6 Gy was used in the fourth RCT.[72] All patients in the latter trial received six 4 mg doses of zoledronic acid (infusion) in addition to daily doses of 500 mg calcium supplement and 400 IU of oral vitamin D during treatment. The higher dose was 8 Gy in 3 RCTs;[64,67,72] the remaining RCT contained two higher dose arms: 6 Gy and 8 Gy.[69] For purposes of meta analyses, data from these two higher dose arms were combined to form the high dose group. Most trials did not clearly report the specific type of EBRT employed but it was most likely 2D- or 3DCRT as these are most used.

All four RCTs reported baseline analgesic use with most patients taking opioids/narcotics (range, 46% to 64%); in three trials, 17 to 22 percent of patients were not on any analgesics.[64,67,69] Prior RT to the same site was an exclusion criterion in three trials.[64,69,72] One trial each excluded patients with previous surgery[69] and pretreatment bisphosphonate use[72] while another trial[64] included patients with a history of chemotherapy (35%), hormone therapy (25%), and bisphosphonate use (34%) (unclear if concurrent or past treatments). Followup periods ranged from 12 to 156 weeks.

Three trials were conducted in Europe[67,69,72] and one was multinational without specifying details.[64] Two were single center trials[67,69] and two were multicenter.[64,72] One of the multicenter trials did not report the number of hospitals but used hospital site as the unit of randomization.[72] The source of funding was reported in one trial as government[64] and was not reported in the other trials.

All trials were fair quality.[64,67,69,72] Three trials were unable to blind care providers, patients, or outcome assessors[64,67,69] one trial masked care providers and patients but was less clear in whether it blinded outcome assessors.[72] Other common limitations included unclear randomization and allocation concealment methods (Appendix F, Table F-1). High levels of

attrition were common across trials, particularly as followup time increased, due to high mortality rates in this patient population.

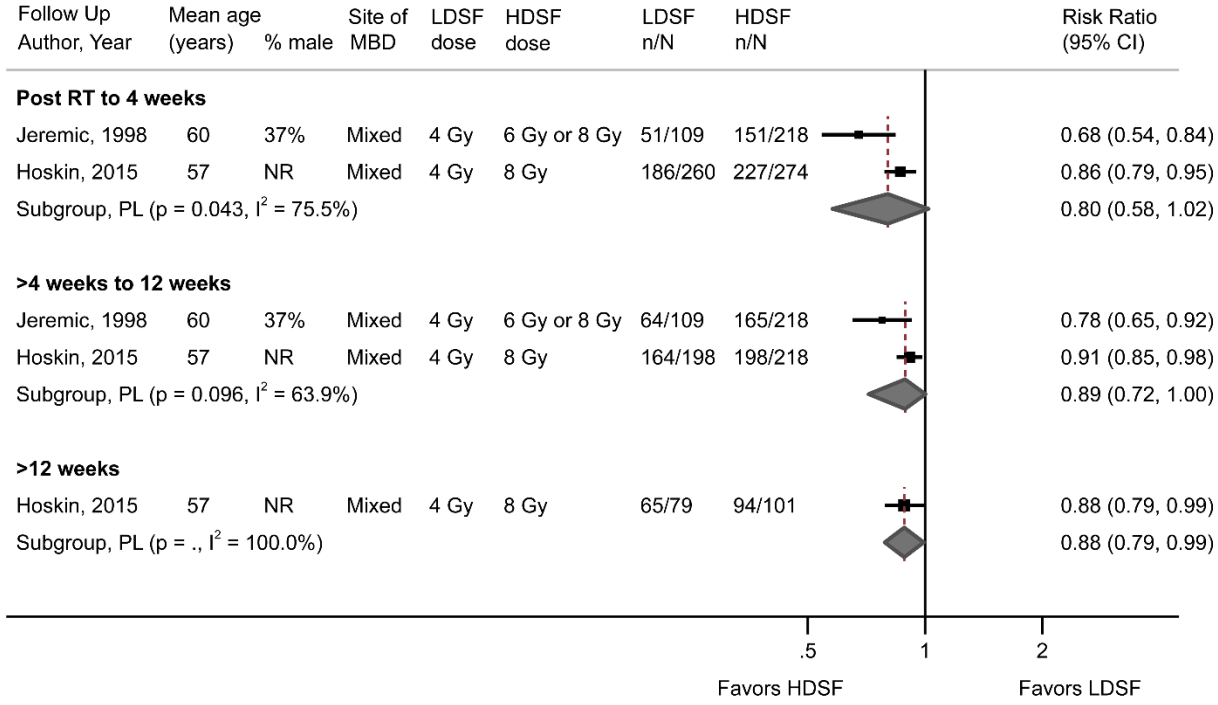
3.1.2.3 Detailed Synthesis

3.1.2.3.1 Pain

Definitions of pain responses varied across the four trials (Results Appendix B, Table B-2), as did measures for reporting pain. We focused on overall response below, which encompasses complete and partial response in most trials (Appendix E, Table E-1).

LDSF was associated with a slightly lower likelihood of achieving overall response compared with HDSF up to 4 weeks posttreatment (2 RCTs, N= 861, 64.2% vs. 76.8%, RR 0.80, 95% CI 0.58 to 1.02, I^2= 76%),[64,69] which persisted >4 to 12 weeks (2 RCTs, N=743, 74.3% vs. 83.3%, RR 0.89, 95% CI 0.72 to 1.0, I^2=64%)[64,69] and to >12 weeks (1 RCT, N=180, 82.3% vs. 93.1%, RR 0.88, 95% CI 0.79 to 0.99).[64] LDSF was 4 Gy for all trials. HDSF was 8 Gy in one trial. Two HDSF arms, 6 Gy and 8 Gy, were used in one trial; the arms were combined for this meta-analysis (Figure 7).[69] Analysis confined to the 8 Gy higher dose for this trial increased heterogeneity, accentuated the differences between LDSF and HDSF and decreased precision posttreatment up to 4 weeks (2 RCTs, N=753, 64.2% vs. 10.2%, RR 0.77, 95% CI 0.52 to 1.07 I2= 83%); use of the 8 Gy dose had little impact on estimates, while heterogeneity remained high >4 weeks to 12 weeks (2 RCTs, N= 635, RR 0.89, 95% CI 0.67 to 1.03, I^2=72%). LSDF was also associated with slightly lower likelihood of overall pain response compared with HDSF in analyses based on longest followup time (2 RCTs, N=507, 68.5% vs. 81.2%, RR 0.85, 95% CI 0.71 to 0.97, I^2= 33%).[64,69]

Figure 7. Comparison of lower and higher dose single fractions of EBRT: Overall pain response by timeframe



CI = confidence interval; EBRT = external beam radiation therapy; Gy = Gray; HDSF = higher total dose single fraction EBRT (control); LDSF = lower total dose single fraction EBRT (intervention); MBD = metastatic bone disease; NR = not reported; PL = profile likelihood.

3.1 Key Question 1: Effectiveness and Harms of Dose-Fractionation Schemes and Techniques for Delivery, Initial Radiation

In analyses of complete pain response as defined by authors, there was no difference between LDSF and HDSF post-treatment up to 4 weeks (3 RCTs, N= 1055, 27.4% vs. 28.6% RR 0.93, 95% CI 0.67 to 1.19, I^2=30%) but LDSF was associated with slightly lower likelihood of complete pain response >4 weeks up to 12 weeks compared with HDSF across the same trials (3 RCTs, N=844, 36.8% vs. 42.3%, RR 0.82, 95% CI 0.68 to 0.98, I^2 = 0%)[64,67,69] (Appendix I, Figure I-11). There was no difference between SF doses at >12 weeks in one trial (1 RCT, N=180, 68.3% vs. 76.2% RR 0.90, 95% CI 0.74 to 1.08).[64] Definitions of complete response varied (Results Appendix B, Table B-2).

One trial (N=270) reported lower prevalence of pain improvement by ≥1 category (categories of no pain, mild, moderate, severe) with LDSF (4 Gy) compared to HDSF (8 Gy) at 4 weeks (44% vs. 69%, data not available for effect size calculation).[67] The authors also reported lower response rate in LDSF recipients versus HDSF recipients at this time frame (53% vs. 76%, p<0.01) based on actuarial analysis. The differences between lower and higher doses was less at 8 and 12 weeks (70% vs. 80% for both times as estimated from graphs). A cluster trial, which randomized treatment by hospital, reported higher mean VAS pain scores (0–10 scale) at 30 weeks for LDSF (6 Gy) compared with HDSF (8 Gy) for pain while supine (3.69 vs. 1.79, p=0.067), while seated (1.67 vs. 0.96, p=0.123) and while standing (2.34 vs. 1.27, p=0.006) suggesting small improvement in pain favoring HDSF; authors did not provide sufficient data to calculate effect sizes with confidence intervals. All patients in this trial received six, 4 mg doses of zoledronic acid (infusion) in addition to daily doses of 500 mg calcium supplement and 400 IU of oral vitamin D during this treatment.

3.1.2.3.2 Function

A cluster RCT (N=117) reported lower KPS scores (0–100 scale, higher score indicates better function) for LDSF versus HDSF at 30 weeks (mean 77.27 vs. 84.62, p=0.1635), however this trial did not provide sufficient information to evaluate effect size and related precision.[72] None of the other trials reported function.

3.1.2.3.3 Relief of Spinal Cord Compression/Neurological Outcomes

None of the included studies reported relief of spinal cord compression or other neurological outcomes.

3.1.2.3.4 Quality of Life and Functional Status

A cluster RCT (N=115) used the EORTC QLQ-C30 questionnaire to evaluate quality of life and functional status based on three parts: Part 1 with five yes/no questions on daily activities, part 2 with 21 questions on daily symptoms (1-4 scale for each question) and part 3 consisting of two questions on patient general health (1–7 scale).[72] Authors reported that there were no differences between LDSF and HDSF at 30 weeks for any of the EORTC QLQ-C30 parts based on analysis of covariance (ANCOVA) modeling, and provided the following means: Part 1, mean 6.67 versus 6.08; Part 2, mean 33.15 versus 30.81; and Part 3, mean 9.24 versus 9.62. Variability of the means was not described.

3.1.2.3.5 Secondary Outcomes

The frequency of re-irradiation following LDSF and HDSF varied across three trials (see Figure 4 above). One older trial reported substantially higher re-irradiation following LDSF compared with HDSF (N=270, 20% vs. 9%, RR 2.27, 95% CI 1.20 to 4.26).[67] Another older trial reported no difference across three SF schemes (N= 327, 42%, 44% and 38% for 4 Gy, 6 Gy, 8 Gy doses respectively, RR combining the two higher doses 1.03, 95% CI 0.79 to 1.36).[69] The

third trial reported that more retreatments were given after LDSF compared with HDSF (72 vs. 45, p=0.01), but it is unclear if these are retreated sites or numbers of patients.[64]

Data for overall survival can be found in Results Appendix B.

3.1.2.3.6 Harms and Adverse Events

Adverse events and toxicity were summarized in two trials (Results Appendix B, Table B-8).

3.1.2.3.6.1 Pathologic Fracture and Spinal Cord Compression

No pathologic fractures were reported in one older trial at any of three SF doses (4 Gy, 6 Gy, 8 Gy) up to 8 weeks post-treatment (N=327) and no difference between doses was seen at >8 weeks (N=137, 6% vs. 7% vs. 7%, RR combining 2 HDSF groups 0.92, 95% CI 0.24 to 3.54)[69] (Results Appendix B, Table B-11). No differences in development of spinal cord compression were reported in the same trial for any dose up to 8 weeks (N=327) post-treatment and no difference between doses was seen at >8 weeks (N=190, 7% vs. 8% vs. 6%, RR combining 2 HDSF groups 0.94, 95% CI 0.30 to 2.93).

3.1.2.3.6.2 Other Adverse Events

The cluster RCT, in which all patients received zoledronic acid, calcium, and vitamin D supplements, reported no difference in skeletal events, which included pathological fracture, re-irradiation, or compression, between LDSF and HDSF (N=137, 23.5% vs. 19.4%, RR 1.31, 95% CI 0.68 to 2.49).[72] Authors reported that pathologic fractures and re-irradiation due to pain or fracture were the most common skeletal events and both had similar overall incidence of 4.24%. The time to the onset of experiencing a skeletal event or disease progression was shorter for the SDSF versus HDSF (81.6 days vs 122 days). This trial also reports that fewer patients in the LDSF group had one or more adverse events (not specified) compared with the HDSF group (47.4% vs. 61.2%, RR 0.77, 95% CI 0.56 to 1.07); LDSF recipients also less commonly had at least one adverse reaction (not specified, 14.0% vs. 21.2%; RR 0.66, 95% CI 0.31 to 1.42). The most frequent adverse reactions were fever (4.4%) and nausea (3.7%).

3.1.2.3.6.3 Toxicity

No trial reported specifically on Grade 3 or 4 toxicities. Grade 1 and 2 toxicities were reported in one trial (N=327) evaluating three SF doses (4 Gy, 6 Gy, 8 Gy).[69] There were no differences between arms for nausea/vomiting (19% vs. 18% vs. 22%) or diarrhea (13% vs. 11% vs. 15%); there were no other gastrointestinal toxicities in any group (Results Appendix B, Table B-8).

3.1.2.3.7 Differential Effectiveness or Safety

There was insufficient information on differential effectiveness from one RCT that compared single fraction schemes for EBRT based on subanalyses of primary tumor type and metastatic site.[69] The trial did not report tests for interaction. While substantial overlap in confidence intervals may suggest that the factors did not differentially impact effectiveness or harms, the trial was underpowered to effectively evaluate modification. Thus, conclusions are not possible. Data are found in Results Appendix B, Tables B-35 to B-36.

3.1.3 MF EBRT: Lower Dose Multiple Fraction (LDMF) Versus Higher Dose Multiple Fraction (HDMF)

3.1.3.1 Key Points

- There was probably no differences between total LDMF and HDMF schemes in overall pain response post-treatment up to 4 weeks (6 RCTs, N= 788, 64.1% vs. 67.0%, RR 0.96, 95% CI 0.87 to 1.06, I^2=0%), from >4 to 12 weeks (3 RCTs, N=275, 79.6% vs. 80.4%, RR 1.02, 95% CI 0.89 to 1.12, I^2=0%) (SOE: moderate), and maybe no difference at >12 weeks (2 RCTs, N=114, 78.6% vs. 72.4%, RR 1.10, 95% CI 0.86 to 1.38, I^2=0%) (SOE: low), with mixed spine and nonspine MBD or in patients with MSCC.
- There was insufficient evidence on overall function reported in three poor-quality RCTs (SOE: insufficient).
- There were no differences between LDMF versus HDMF schemes for any outcomes related to relief of spinal cord compression in patients with MSCC including improvement on the following: ambulatory status (SOE: moderate), walking capacity (SOE: low), motor function (SOE: low), regain of sphincter control (SOE: low).
- There may be no differences in pathologic fractures (SOE: low) or in Grade 3 toxicities (SOE: low) between LDMF versus HDMF schemes.
- Evidence was considered insufficient to compare multiple fraction schemes on risk of radiation induced myelopathy in patients with MSCC or on risk of new spinal cord compression (SOE: insufficient).
- There was no difference in frequency of re-irradiation by multiple fraction scheme.

3.1.3.2 Description of Included Studies

Ten RCTs (in 12 publications)[42,51,63,73,76,79,80,82,89-92] and one retrospective NRSI[132] compared different multiple fraction EBRT schemes (Appendix E, Tables E-1 and E-2). We reported the lower total dose multiple fraction EBRT as the intervention (LDMF), which generally had fewer fractions (dose per fraction generally higher) and higher total dose EBRT fractions as the control (HDMF), which generally represented more lower-dose fractions. Given the large number of RCTs, one NRSI was included for information on harms only.[132]

Across the 10 RCTs, sample sizes ranged from 60 to 300 (total N=1,615). Mean or median ages range from 53 to 68. The average proportion of males in trials was 55 percent (range, 0% to 87%). No trial reported race or ethnicity. Four trials[51,73,76,91] reported some patients as nonambulatory or severely mobile-impaired (range 27% to 62%). Primary tumor types included breast (range 10% to 100%), lung (range 20% to 33%), and prostate (range 5% to 12%). One trial included only breast cancer[92] and another reported 89 percent of patients had hepatocellular carcinoma.[63] One trial reported the primary tumor histology in terms of favorable (10%) or unfavorable (20%) with the remaining classified as "intermediate".[51] The site of bone metastases was mixed (i.e., spine and nonspine) in six RCTs (spine 27% to 89% and nonspine 11% to 73%)[42,63,76,80,82,92] (spinal cord compression and pathologic fracture were exclusion criteria in most of these trials), spine only in one RCT (presence or absence of cord compression not report),[79] and three RCTs included patients with MSCC only.[51,73,91] The proportion of patients with multiple bone metastases ranged from 58 to 86 percent (3 RCTs)[63,82,91] and the proportion with metastases to nonbone/visceral sites ranged from 20 to 77 percent (3 RCTs).[51,73,91] One trial reported lesions in terms of lytic (88%) and sclerotic (8%).[82]

The total dose in the LDMF arms ranged from 15 Gy to 40 Gy with 20 Gy (4 Gy in 5 fractions), the most common dose-fractionation scheme,[76,79,80,82,91] followed by 15 Gy (3 Gy in 5

fractions).[42,92] Across the HDMF arms, total dose ranged from 30 Gy to 60 Gy and the most common dose-fractionation scheme was 30 Gy (3 Gy in 10 fractions)[42,51,79,82,91,92] followed by 30 Gy (2 Gy in 15 fractions).[76,80] Most trials did not clearly report the specific type of EBRT employed but it was most likely 2D or 3DCRT as these are most commonly used. Prior radiation therapy to the site, surgery, and/or chemotherapy were generally exclusion criteria in the trials. However, small proportions of patients had concomitant surgery in two trials,[76,82] and concurrent chemotherapy was common in two trials.[63,76] Other concomitant treatments included dexamethasone in two trials,[51,73] and antiemetic prophylaxis[73] and bisphosphonates[91] in one each. One trial gave all patients zoledronic acid in conjunction with EBRT and excluded those with pretreatment bisphosphonates.[42] The proportion of patients using narcotics at baseline ranged from 4 to 52 percent across three trials.[79,82,92] Median or mean followup periods ranged from 12 to 156 weeks.

Two trials were conducted in Germany,[76,89-91] two in Turkey,[42,82] and one each in Italy,[73] India,[79] China,[63] Egypt,[51] Japan,[80] and Denmark;[92] most were either single center or did not report how many centers were involved. None of the trials reported funding sources.

Four trials were fair quality[42,63,73,89-91] and six were poor quality.[51,76,79,80,82,92] No trial blinded care providers, patients or outcome assessors. Allocation concealment, high attrition, and lack of intention-to-treat analyses were other common limitations (Appendix F, Table F-1).

Given the number of RCTs that compared different multiple fraction EBRT schemes, the eligible NRSI was included for evaluation of harms only (see Methods Appendix A, Process for Selecting Studies) and is described in Appendix B.

3.1.3.3 Detailed Synthesis

3.1.3.3.1 Pain

Definitions of pain responses varied across trials, particularly with regard to definitions of complete response (Appendix B, Table B-2). We focused on overall response below, which encompasses complete and partial response in most trials (Appendix E, Table E-1).

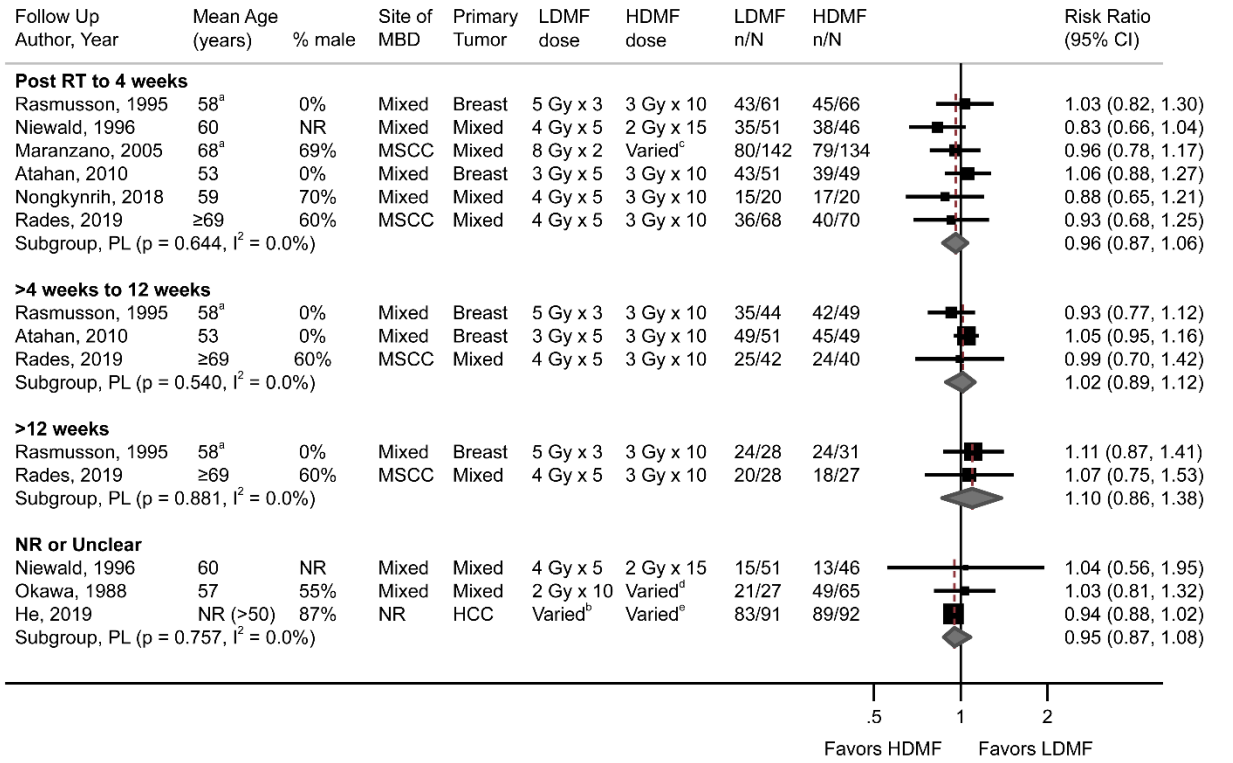
Eight RCTs[42,63,73,76,79,80,90,92] comparing LDMF with HDMF contributed data to meta-analyses of overall pain response. Five trials[42,76,79,80,92] were in patients with mixed spine and nonspine MBD, two trials[73,90] were in patients with spinal cord compression and one trial[63] in patients with hepatocellular carcinoma did not report on MBD site.

There were no differences between schemes using LDMF versus HDMF in overall pain response posttreatment up to 4 weeks (6 RCTs, N= 788, 64.1% vs. 67.0%, RR 0.96, 95% CI 0.87 to 1.06, I^2=0%),[42,73,76,79,90,92] from >4 to 12 weeks (3 RCTs, N=275, 79.6% vs. 80.4%, RR 1.02, 95% CI 0.89 to 1.12, I^2=0%),[42,90,92] at >12 weeks (2 RCTs, N=114, 78.6% vs. 72.4%, RR 1.10, 95% CI 0.86 to 1.38, I^2=0%),[90,92] or in studies where time of assessment was unclear or not reported (3 RCTs, N=372, 70.4% vs. 74.4%, RR 0.95, 95% CI 0.87 to 1.08, I^2=0%)[63,76,80] (Figure 8). Exclusion of poor-quality trials did not substantially change effect estimates, heterogeneity, or conclusions at any timeframe. There was no difference in overall response between LDMF and HDMF in analyses based on longest followup (8 RCTs, N= 902, 70.1% vs. 72.0%, RR 0.99, 95% CI 0.93 to 1.07, I^2=0%)[42,63,73,76,79,80,90,92] or when patients with mixed MBD were considered separately from those with MSCC (Appendix I, Figures I-12 and I-13).

Similarly, there were no differences in complete response between multiple fraction schemes at any timeframe or for analyses based on longest followup (Appendix I, Figures I-14 to I-16).

3.1 Key Question 1: Effectiveness and Harms of Dose-Fractionation Schemes and Techniques for Delivery, Initial Radiation

Figure 8. Comparison of multiple fraction EBRT schemes: Overall pain response by timeframe



CI = confidence interval; EBRT = external beam radiation therapy; HCC = hepatocellular carcinoma; HDMF = higher total dose multiple fractions (control); LDMF = lower total dose multiple fraction (intervention); MBD = metastatic bone disease; MSCC = metastatic spinal cord compression; NR = not reported; PL = profile likelihood.

[a] Median age

[b] 4 Gy x 7 or 4 Gy x 10

[c] 5 Gy x 3 & 3 Gy x 5 (30 Gy)

[d] 4.5 Gy x 5 (22.5 Gy) or 2 Gy x 15 (30 Gy)

[e] 2 Gy x 20 (40 Gy) or 2 Gy x 30 (60 Gy)

3.1.3.3.2 Function

Various measures of overall function were reported in three poor-quality RCTs in patient with mixed spine/nonspine MBD.[76,79,92] All reported that no differences between LDMF and HDMF were found for any measure at any time point. One trials (N= 100)[76] found no difference in mobility improvement immediately post treatment (70% vs. 71%, RR 0.99, 95% CI 0.77 to 1.27) or at last followup (time not reported, 26% vs. 24%, RR 1.04, 95% CI 0.53 to 2.05). Similarly, another trial[92] reported no differences between multiple fractionation schemes for moderately to severely reduced activity versus slightly reduced or no limitation at weeks: 4 (N=126, 42% vs. 42%, RR 0.98, 95% CI 0.65 to 1.48), 12 (N=92, 33% vs. 35%, RR 0.92, 95% CI 0.52 to 1.67), 26 (N=59, 25% vs. 26%, RR 1.11, 95% CI 0.44 to 2.76) or 52 (N=27, 23% vs. 36%, RR 0.65, 95% CI 0.19 to 2.18) posttreatment; there were baseline differences between groups in the proportions of patients with moderate to severe activity reduction (N=166, 64% vs. 80%) and substantial loss of participants with time. The third trial[79] reported no difference in the proportion of patients with improved KPS scores between LDMF and HDMF (65% [13/20] in each group); at baseline 60 percent of patients in both groups had KPS ≥60.

3.1.3.3.3 Relief of Spinal Cord Compression/Neurological Outcomes

Two RCTs found no differences between LDMF and HDMF groups in ambulatory status at any timepoint. In the fair-quality trial,[91] approximately 57 percent of patients in both groups were

ambulatory (32% did not require aid prior to treatment). There were no differences between multiple fraction schemes in the proportions of patients who were ambulatory shortly posttreatment (63.5% vs. 64.6%), 4 weeks (71.8% vs. 74.0%), 12 weeks (80.9% vs. 73.3%), or 16 weeks (81.8% vs. 83.3%). Those who were ambulatory at 4 weeks (44.9% vs. 42.9%) walked without aid. The poor-quality trial (N=190)[51] also found no difference between multiple fraction schemes following treatment (timing not reported). Of the 39 percent of patients in both multiple fraction groups who were nonambulatory pretreatment (39/100 vs. 35/90), similar proportions were ambulatory after treatment (66.7% vs. 65.7%). Patients who were ambulatory at baseline remained ambulatory thus, posttreatment overall ambulation was similar (87% vs. 86.7%).

Two fair-quality trials[73,92] in patients with MSCC reported no difference between LDMF and HDMF schemes in motor function improvement following treatment. The largest trial (N=276) graded motor function based on Tomita's groups[139] as group I, ability to walk without support, group II, ability to walk with support, group III inability to walk, or group IV, paraplegic. Pretreatment, one-third of patients in each fractionation group were not walking (49/142 vs. 43/144). There was no difference between multiple fraction schemes for regain of walking capacity (29%,14/49 vs. 28%, 12/43) posttreatment. Across treatment groups none of the patients with paraplegia (n=17) improved. The other trial (N=203)[91] used an 8-point scale (0 being complete paraplegia to 7, normal strength) based on the American Spinal Injury Association and International Medical Society of Paraplegia (ASIA)[140] criteria to evaluate each leg separately, resulting in total points of 0 to 14. A change of ≥2 points indicated improvement or deterioration. There were no differences in patients experiencing improvement between LDMF and HDMF posttreatment (N=192, 24.0% vs. 28.1% , RR 0.85, 95% CI 0.53 to 1.38), at 4 weeks (N=155, 38.5% vs. 44.2%, RR 0.87, 95% CI 0.60 to 1.27), 12 weeks (N=92, 42.6% vs. 48.9%, RR 0.87, 95% CI 0.56 to 1.36) and 26 weeks (N=63, 57.6% vs. 60.0%, RR 0.96, 95% CI 0.63 to 1.45). At 12 weeks the proportion of patients without further progression was higher in the LDMF versus HDMF group (55.3% (26/47) vs. 44.4% (20/45), RR 2.49, 95% CI 1.36 to 4.55).

Two RCTs in patients with MSCC found no difference in LDMF versus HDMF in improved sphincter control posttreatment. In the fair-quality trial (N=276),[73] 11 percent and 10 percent of patients respectively had abnormal control pretreatment. Similar proportions of patients with abnormal control pretreatment regained control post-treatment (12% vs. 15%) and the remainder continued to have poor control (88% vs. 85%). The poor-quality RCT (N=190)[51] reported that 10 percent and 7.8 percent in the LDMF and HDMF groups respectively had abnormal control pretreatment and of those, similar proportions in each group returned to normal function post-treatment (7/10 and 5/7). This same trial reported that there was no difference between groups in sensory function recovery (31.6% vs. 30%) but did not provide detail.

3.1.3.3.4 Quality of Life and Functional Status

Quality of life and functional status based on validated measures were not reported in any of the trials.

3.1.3.3.5 Secondary Outcomes

There was no difference in frequency of re-irradiation by multiple fraction scheme across one fair-quality RCT[73] in patients with MSCC and two small, poor-quality RCTs[76,79] in patients with mixed MBD (3 RCTs, N=403, 3.5% vs. 0.5%, RR 2.98, 95% CI 0.45 to 20.66, I^2=0%); however effect estimates are very imprecise (Figure 4 above).

Data for other secondary outcomes (local control, medication use, need for additional intervention, and overall survival) can be found in Results Appendix B.

3.1.3.3.6 Harms and Adverse Events

Adverse events and toxicity were variably reported across RCTs and NRSIs for this comparison, with many stating that no events or toxicities occurred.

3.1.3.3.6.1 Pathologic Fracture

There was no difference in pathologic fractures between multiple fraction schemes across trials in patients with mixed spine, nonspine MBD that could be pooled (2 RCTs, N=197, 6.9% vs. 12.6%, RR 0.54, 95% CI 0.19 to 1.51, I^2=0%)[42,76] (Figure 5 above). One of these trials (N=100) reported vertebral fractures (4% vs. 2%) separately from other pathologic factures (2% vs. 10%, RR 0.19, 95% CI 0.02 to 1.96; effect estimate is imprecise).[42] Another fair-quality trial (N=202)[91] reported that no vertebral fractures occurred in patients with MSCC and a fourth poor-quality trial[82] reported an overall fracture rate of 2.3% across schemes. One fair-quality NRSI (N=105)[132] reported low risk of pathologic fracture and no difference based on fraction schemes (0% vs. 2%) at 4 months. Given the low frequency of pathologic fracture, studies may have been underpowered to detect a difference between groups (Results Appendix B, Table B-12).

3.1.3.3.6.2 Spinal Cord Compression

Development of new spinal cord compression was reported in two RCTs. One fair-quality trial (N=100)[42] in patients with metastatic breast cancer reported no events with LDMF and one event in the HDMF group (0% vs. 2%, RR 0.32, 95% CI 0.01 to 7.68) (see Figure 6 above). The other, poor-quality trial (N=87)[82] reported that no new MSCC occurred. Given the low frequency of new cord compression, studies may have been underpowered to detect this (Results Appendix B, Table B-12).

3.1.3.3.6.3 Toxicity

Four RCTs in patients with MSCC provided information on toxicity (Results Appendix B, Table B-9). There were no differences between LDMF and HDMF in one fair-quality RCT (N=276)[73] up to 52 weeks for the following Grade 3 toxicities: esophagitis (1% in both groups), pharyngeal dysphagia (0% vs. 1%), and diarrhea (1.4% vs. 1.5%). One fair-quality RCT[91] in patients with MSCC reported that acute toxicities as nausea, diarrhea, and radiation dermatitis did not exceed grade 2 for either multiple fraction scheme. One poor-quality RCT (n=190)[51] found no difference by multiple fraction scheme for Grade 1 and 2 toxicities which ranged from 0 percent to 4.4 percent.

Three RCTs reported that spinal cord morbidity[73] and late radiation toxicity such as myelopathy[91,92] were not observed. Three fair-quality NRSIs in patients with MCSS with overlap in authors and institutions, provided limited information on toxicities and focused evaluation on prognostic factors for various outcomes. Two of these were retrospective (N=1304 and 521)[141,142] and it is unclear whether there may be overlap in patients across them; the other two NRSIs (N=265 and 214)[143,144] were prospective. All reported that acute toxicities did not exceed Grade 1 and that no late toxicities such as radiation-related myelopathy occurred but do not provide further information.

No RCTs in populations with mixed MBD reported on Grade 3 or higher toxicities. One fair-quality RCT (N=183)[63] found no difference in Grade 1 or 2 gastrointestinal (17.5% vs. 11%) or hematological (9% vs. 7%) toxicities by fractionation schemes. One poor-quality RCT[92] found no differences in toxicities between multiple fraction schemes but did not report severity of toxicities. Toxicities were more common at 4 weeks post-treatment (N=167, nausea 20% vs. 21%, diarrhea 5.9% vs. 7.3 %, slight erythema 6.1% vs. 5.9%) than at 12 weeks (N=131, nausea 6% vs. 10%, diarrhea 4.8% vs. 1.4%) or 26 weeks (N=97, nausea 4% vs. 2%, diarrhea 2.25% vs.

1.9%). One fair-quality NRSI (N=105)[132] reported that no Grade 3 or 4 toxicities occurred in the LDMF group and one patient in the HDMF group experienced acute Grade 4 diarrhea, thus their finding of substantially lower frequency of any toxicity with LDMF compared with HDMF (2.6% vs. 23.8%) seems to be for Grade ≤2 toxicities.

3.1.3.3.7 Differential Effectiveness or Safety

There is insufficient information from included trials on differential effectiveness for all comparisons of multiple fraction schemes for EBRT based on subanalyses of primary tumor type and histology and metastatic site (1 RCT)[80] and survival prognosis (1 RCT).[89] Neither trial reported tests for interaction. While substantial overlap in confidence intervals may suggest that the factors did not differentially impact effectiveness or harms, studies were underpowered to effectively evaluate modification. Thus, conclusions are not possible. Data are found in Results Appendix B, Tables B-31 to B-34.

3.1.4 Single Versus Multiple Dose-Fractionation Schemes: SBRT

3.1.4.1 Key Points

- Studies meeting inclusion criteria did not report primary outcomes of interest
- There may be no differences in pathologic fractures between SF SBRT and MF SBRT in one RCT and one NRSI, both rated fair quality (SOE: low).
- There may be no differences between SF SBRT and MF SBRT in Grade ≥3 toxicities or in Grade ≥2 toxicities in one RCT and one NRSI, both studies were rated fair quality (SOE: low).
- There was insufficient evidence from NRSI regarding the following adverse events: pain flare, transesophageal fistula and Grade 3 or 4 toxicities.

3.1.4.2 Description of Included Studies

One multicenter RCT[106] and four NRSIs[113,114,120,136] compared single (SF) versus multiple (MF) dose-fractionation schemes of SBRT for the palliative treatment of MBD. Aside from toxicity and harms, primary outcomes of interest for this review were not reported in any of these studies. The primary focus of each study was local control and overall survival, and palliative intent was generally not clear from study descriptions. Study details can be found in the data abstraction (Appendix E, Tables E-1 and E-2).

In the RCT (N=117), median age was 64 years (32–89 years). Most patients were male (71%) with solitary (80%) bone only lesions (3% had bone plus nodal lesions and 9% had nodal only lesions); patients with >5 metastatic lesions were excluded. Inclusion appears to have been based on imaging findings of spinal metastasis, not symptomatic status. Most lesions involved the spine (62%), but authors do not report spinal cord compression. The most common primary cancer was prostate (47%) followed by lung (9%), colorectal (9%) and renal (7%) cancer. A single fraction dose of 24 Gy was compared with a three fractions of 9 Gy delivered every other day (27 Gy total) MF SBRT scheme. Concurrent systemic or hormonal therapy (not specified) was common (61%). Pretreatment with dexamethasone (4 mg twice daily) was primarily given to the SF EBRT group and was selective in patients receiving the 3-fraction scheme. Posttreatment adjuvant therapies were at the physician's discretion. Baseline pain was not reported.

Across four NRSIs, samples sizes ranged from 43 to 127 (total N=363). The average study mean age ranged from 45 to 64 years and the proportion of males ranged from 40 to 79 percent. One NRSI enrolled patients with renal cell carcinoma with 56 percent of lesions occurring in the

spine, 21 percent in pelvic bone structures, 9 percent in the femur and 13 percent in other bones.[136] Three other studies were in patients with spine metastasis; MSCC was present in all patients in one study,[120] one study excluded patients with MSCC,[114] and the third did not report spinal cord compression.[113] One NRSI enrolled patients with metastatic lesions (56% were to the spine) from renal cell carcinoma;[136] another NRSI from the same institution enrolled patients with proven high-grade sarcoma metastases to spine.[113] One additional NRSI enrolled patients with spinal metastases from renal cell caricinoma.[114] The most common primary tumors in the other NRSI of spine metastases were from breast (21%) and lung (20%). Most spine segment lesions in this study were radiosensitive (58%) and were primarily carcinoma from breast or prostate. Radioresistant lesions (42% of segments) were primarily carcinomas from colon, renal cell, uterine, or thyroid origin (Appendix E, Table E-2). Single fraction doses of 18 to 24 Gy were used in three NRSIs[113,114,136] with 16 or 18 Gy reported in one NRSI.[120] Various dose and multiple fraction schemes were reported in NRSIs including 20 to 30 Gy (3–5 fractions),[136] median 28.5 Gy dose (3–6 fractions),[113] 30 Gy (5 fractions),[114] and in one NRSI 21 Gy, 24 Gy, 25.5 Gy or 27 Gy (3 fractions) or 30 Gy (5 fractions).[120]

All studies were conducted in the United States. The RCT was partially funded by government sources.[106] The funding source was not reported for three NRSIs[113,114,136] and one NRSI reported that no funding was received.[120] The RCT was fair quality due to unclear reporting of attrition or assessor blinding (Appendix F, Table F-1). The trial was stopped early due to slow enrollment. Two NRSIs were fair quality[113,136] and two were poor quality[114,120] (Appendix F, Table F-2). Lack of assessor blinding was noted across studies. Other methodological limitations included concerns about patient selection and unclear reporting of attrition. Data on toxicities and adverse events in most studies were based on numbers of lesions or sites versus number of patients and most analyses did not adjust for correlated data.

3.1.4.3 Detailed Synthesis

The included RCT and NRSIs did not provide information by dose/fraction for the primary outcomes of interest for this review except for toxicities and harms. The primary focus of these studies was to evaluate local control/local failure and/or overall survival, the results for which can be found in Results Appendix B. Risk of re-irradiation was not reported in any included study.

3.1.4.3.1 Harms and Adverse Events

There was no difference between SF SBRT and MF SBRT for Grade ≥2 fractures in the RCT (2.6% vs. 2.6% of lesions)[106] in a population with mixed spine and nonspine metastasis or for vertebral body fractures in one fair-quality NRSI (3% vs. 4% of patients).[136] One poor-quality NRSI reported a higher proportion of vertebral body fractures for SF SBRT compared with MF SBRT based on assessable sites (46.2% or 6/13 sites vs. 9.1% or 1/11sites, p=0.11) in patients with spine metastases.[114] Two other NRSIs (one fair and one poor quality) in patients with spine metastases did not report fracture risk by treatment group (Results Appendix B, Table B-13). The fair-quality study reported chronic (≥90 days) Grade 1 insufficiency fracture of 2.3%, but did not report numbers of patients.[113] The poor-quality study reported that vertebral fractures occurred in 9.1% (26/287) of treated lesions and that no radiation-related myelitis occurred.[120]

The RCT found no differences between SF SBRT and MF SBRT in Grade ≥3 toxicities based on number of lesions (7.8% vs. 3.9%) or Grade ≥2 toxicities (11.7% vs. 6.5%).[106] Specific Grade ≥2 toxicities included pain (9.1% vs. 3.9%) and neuropathy (2.6% vs. 0%). One fair-quality NRSI reported Grade ≥2 neuropathy (8% vs. 2%).[136] One fair-quality NRSI reported low risk of Grade 4 erythema (2% vs. 0%);[136] another poor-quality study reported that no patient in

either treatment groups experienced any Grade 4 toxicity.[120] One fair-quality NRSI reported that tracheoesophageal fistulae occurred in two patients receiving SF SRBT (3% vs. 0%); both cases occurred after radiation recall esophagitis following use of doxorubicin and iatrogenic manipulation (biopsy, dilatation or both).[113] One poor-quality NRSI reported similar instances of pain flare between SF and MF SBRT groups based on assessable sites (7/20 vs. 6/20 sites).[114] See Results Appendix B, Table B-14 for further details.

3.1.5 Multiple Versus Multiple Dose-Fractionation Schemes: SBRT

3.1.5.1 Key Points

- There is insufficient evidence on primary outcomes of interest or harms from one poor-quality NRSI to compare multiple SBRT fraction schemes.

3.1.5.2 Description of Included Studies

Two NRSIs comparing different multiple dose-fractionation SBRT schemes were identified and provide insufficient information (Appendix E, Table E-2).[107,115] One study of post-operative SBRT (N=80) in patients with spinal metastases provided limited comparison of SBRT dose-fractionation schemes as part of multivariate analysis evaluating predictors of local control.[107] Primary outcomes were not reported. Mean patient age was 59 years and 55 percent were male. Primary cancer for 44 percent of patients was listed as "other". Common population characteristics included presence of baseline vertebral compression fracture (55%), presence of paraspinal extension (78%), prior EBRT (75%, mean 20 Gy/5 fractions), and ECOG score of -1 (88.7%). Most patients had surgical decompression alone (36%) or with instrumented stabilization (50%). Three patients (3.7%) received a single fraction 24 Gy SBRT dose, 40 percent received 18 to 26 Gy in two fractions, and 56 percent received 18 to 40 Gy (3–5 fractions). Population characteristics were not provided by dose/fractionation scheme. The study was conducted in Canada; no funding was received. It was rated poor quality based on inadequate information on how patients receiving different dose/fractionation schemes compared at baseline, no reporting of attrition, and unclear assessor blinding (Appendix F, Table F-2).

Another small, prospective NRSI (N=57) in patients with spinal metastases did not control for potential confounding and was of poor quality and is included here for completeness.[115] Mean patient age was 64 years, and the majority were male (56%). The most common primary tumors were breast (22%), non-small cell lung cancer (20%), prostate (20%) and other (19%); the majority of patients had oligometastases (56%). Most patients had KPS >70 (80%), fourteen patients (26%) had vertebral compression fractures at enrollment and 30 percent of patients had surgical treatment of spinal lesions prior to SBRT. SBRT of 35 Gy (5 fractions) was compared to 48.5 Gy (10 fractions) SBRT. The study, conducted in Sweden, received partial government funding. It was rated poor quality based on unclear criteria for patient selection, high attrition, unclear comparability between treatment groups on baseline characteristics and failure to control for potential confounding (Appendix F, Table F-2).

3.1.5.3 Detailed Synthesis

3.1.5.3.1 All Outcomes

The NRSI of post-operative SBRT (N=80) in patients with spinal metastases did not report primary effectiveness outcomes of interest.[107] Authors reported that no patient experienced Grade 4 toxicity, but other harms and toxicities are not reported by dose/fraction. Fractures occurred in 11 percent of patients and pain flare in 9 percent.

The second NRSI in patients with spinal metastases, which did not adjust for confounding (N=57), found that overall pain response was achieved for more lesions in the 5-fraction group than the 10-fraction group (90.5% vs. 84.6%) at 3 months; mean VAS pain scores at 3 months were 1.2 (SD 1.8) versus 2.0 (SD 2.3) respectively.[115] Fewer new fractures developed in patients receiving 5-fraction compared to 10-fraction schemes (9% vs. 17%); information on fracture at baseline was not provided by dose-fractionation scheme. It is unclear if these differences were statistically significant. Information on quality of life and function were also not reported by dose-fractionation scheme. Authors reported that no patient developed radiation-induced myelopathy, there were no Grade 4 or higher toxicities and that one patient experienced acute Grade 3 pain.

Secondary outcomes (local control and overall survival) can be found Results Appendix B.

3.1.6 IMRT Versus 3DCRT

3.1.6.1 Key Points

- There may be no differences between IMRT and 3DCRT in overall pain or quality of life outcomes at any timepoint in one small fair-quality RCT of spinal metastases (SOE: low).
- Evidence was insufficient for pathologic fractures, Grade 3 or 4 toxicity or treatment related deaths.

3.1.6.2 Description of Included Studies

One RCT (reported in three publications)[22,24,100] and two NRSIs[125,128] compared image guided intensity modulated radiotherapy (IMRT) to three-dimensional conformal radiotherapy (3DCRT) (Appendix E, Tables E-1 and E-2).

One, small RCT (N=60)[22,24,100] compared IMRT with 3DCRT (both delivered in 3 Gy over 10 fraction) in patients with spine metastases (mostly thoracic and lumbar); authors stated that spinal cord compression was not a specific criterion for exclusion but did not indicate if any patients had cord compression at baseline, though 12 percent had a neurological deficit. Mean patient age was 64 years and 55 percent were male with a mean Karnofsky performance status score of 63 (out of 100). Race, social determinants of health, and comorbidities were not reported. Primary tumor sites were lung (45%), breast (22%), or prostate (11%) primarily; authors did not describe tumor histology in terms of favorable or unfavorable. The number of metastases differed between treatment groups: more patients randomized to IMRT had a single metastasis compared with 3DCRT (57% vs. 33%) and fewer had two metastatic sites (13% vs. 30%); the proportion of patients with three metastases was similar (30% vs. 37%). Distant metastases were present in the viscera (40%), lung (22%), brain (15%) and tissue (15%). The proportion of lytic/sclerotic lesions was not reported, nor was the presence of preexisting fractures. Prior RT was an exclusion criterion, but nearly all other prior and concurrent therapies differ between groups by ≥10%; patients in the IMRT group received more medications across all categories, including opiates (67% vs. 57%) and nonsteroidal anti-inflammatory drugs (NSAIDs) (77% vs. 63%) and received more bisphosphonates (43% vs. 23%). About 30 percent of patients in both groups wore an orthopedic corset. The trial was conducted at one center in Germany and followed patients for a median of 4.3 months (range of 0.5 to 10 months). Authors reported that no funding was received. The trial was rated fair quality due to unclear randomization techniques, lack of blinding, and high attrition rates (Appendix F, Table F-1).

Across the two NRSIs, sample sizes ranged from 179 to 716 (total N=895).[125,128] One study reported median age of 61 years,[128] while the other split age into <65 (65% versus 48%) and >65 years (35% versus 52%).[125] Neither NRSI reported race or social determinants of health. Most

primary tumor sites were lungs (range, 24% to 37%), breast (range, 7% to 19%), and prostate (range, 8% to 21%). Neither study reported tumor histology in terms of favorable or unfavorable or whether lesions were lytic or sclerotic. One study included patients with MSCC only[125] (58% were ambulatory before treatment) but excluded patients with pre-existing fractures, while the other study included patients with mixed spine (59% of lesions) and nonspine (29% of lesions) metastases or both (12% of lesions);[128] patients in the latter trial had a mean ECOG performance status score 1.6. In the study that included MSCC, more patients in the IMRT group had other bone metastases (78% vs. 66%) and visceral metastases (65% vs. 49%) at the time of therapy compared with the 3DCRT group, but further details were not reported.[125] Fewer patients in the IMRT group in this trial had three or more metastases (35% vs. 60% in 3DCRT group). Few to no patients (0% to 4%) had prior RT, no patient had prior surgery and other concurrent treatments (chemotherapy, palliative care management, dexamethasone, corticosteroids) ranged from 39 percent to 78 percent across studies. Neither study reported opioid use at baseline.

One study (mixed site MBD) assessed conformal radiotherapy using a technique designed to mimic IMRT and compared it to nonconformal RT; patients were given a mean total dose of 19.6 Gy over a mean of 4.4 fractions.[128] The other study (MSCC) used precision RT dosed at 5 Gy in five fractions and compared it to a historical control group that received conventional RT with 4 Gy in five fractions.[125]

One study was conducted in the United States[128] and the other in Germany.[125] Followup was 26 weeks in both studies. One study[125] was funded by government, the other was unclear. One study was fair quality[125] and the other poor quality.[128] Common methodological limitations included imbalances in prognostic factors at baseline and lack of blinding (Appendix F, Table F-2); additional concerns in the poor-quality study included unclear attrition.

3.1.6.3 Detailed Synthesis

3.1.6.3.1 Pain

Overall, there were no differences between IMRT and 3DCRT in pain outcomes including overall and complete pain response (Table 3), VAS pain scores, and neuropathic pain (data unclear or not provide for latter two outcomes) immediately after RT or at 12 and 26 weeks in one RCT.[100] The one exception was VAS pain scores at 12 weeks which were slightly better in patients who received IMRT (p=0.04, data not provided).

One NRSI (N=254) found that more patients who received IMRT showed significant improvement in their pain during treatment compared with 3DCRT (30.5% vs. 15.2%, RR 2.04, 95% CI 1.24 to 3.37); however, there was no difference between groups at 8 weeks (28.2% vs. 32.1%).[128]

Table 3. Pain response in one RCT comparing IMRT with 3DCRT

Pain Response	Timing	IMRT, % (n/N)	3DCRT, % (n/N)	RR (95% CI)
Overall Response	12 weeks	70% (14/20)	47.4% (9/19)	1.48 (0.85 to 2.57)
	26 weeks	70.6% (12/17)	58.3% (7/12)	1.21 (0.69 to 2.14)
Complete Response	12 weeks	50% (10/20)	26.3% (5/19)	1.90 (0.80 to 4.54)
	26 weeks	41.2% (7/17)	25% (3/12)	1.65 (0.53 to 5.11)

3DCRT = three-dimensional conformal radiation therapy; CI = confidence interval; IMRT = intensity modulated radiation therapy; RCT = randomized controlled trial; RR = risk ratio.

3.1.6.3.2 Function and Relief of Spinal Cord Compression

One poor-quality NRSI conducted a propensity score-matched analysis of 40 patients who received IMRT versus a historical control group of 664 patients who received 3DCRT; patients were divided into 5 strata defined by the quintiles of the propensity scores resulting in <10

patients per strata for the IMRT arm.[125] All patients had MSCC. There was no statistical difference (p=0.515) between groups for change in motor deficits (i.e., improvement, stable, deterioration); across quintiles, the rate of improvement ranged from 38 to 75 percent with IMRT versus 32 to 45 percent with conventional EBRT. Given the number of strata (quintiles and three strata for motor deficit), authors may not have had sufficient power to detect differences between treatments.

3.1.6.3.3 Quality of Life

There were no differences in quality of life based on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients with Bone Metastases 22 (EORTC-QLQ-BM-22) questionnaire between IMRT and 3DCRT at any timepoint measured in one RCT[24] (Table 4). The NRSIs did not report QOL outcomes.

Table 4. Quality of life outcomes in one RCT comparing IMRT with 3DCRT

EORTC-QLQ-BM-22 Domain	Timing	IMRT, Mean (SD)	3DCRT, Mean (SD)	MD (95% CI)
Painful Sites	Baseline	35.8 (22.5) (n=30)	35.8 (20.5) (n=30)	NA
	Post RT	27.6 (22.0) (n=28)	34.0 (21.7) (n=28)	-6.4 (-18.1 to 5.3)
	12 weeks	24.3 (24.1) (n=20)	32.6 (23.0) (n=19)	-8.3 (-23.6 to 7.0)
	26 weeks	28.6 (22.6) (n=17)	31.1 (25.5) (n=12)	-2.5 (-20.9 to 15.9)
Pain Characteristics	Baseline	43.7 (31.8) (n=30)	56.3 (34.2) (n=30)	NA
	Post RT	36.5 (31.3) (n=28)	39.3 (28.0) (n=28)	-2.8 (-18.7 to 13.1)
	12 weeks	31.1 (42.1) (n=20)	31.0 (25.0) (n=19)	0.10 (-22.5 to 22.7)
	26 weeks	35.3 (35.2) (n=17)	29.6 (29.7) (n=12)	5.70 (-19.9 to 31.3)
Functional Interference	Baseline	51.1 (27.3) (n=30)	51.8 (29.8) (n=30)	NA
	Post RT	38.5 (29.7) (n=28)	44.5 (24.6) (n=28)	-6.0 (-20.6 to 8.6)
	12 weeks	36.9 (31.2) (n=20)	37.1 (26.8) (n=19)	-0.20 (-19.1 to 18.7)
	26 weeks	39.2 (28.5) (n=17)	38.9 (26.1) (n=12)	0.30 (-21.1 to 21.6)
Psychosocial Effects	Baseline	54.8 (23.0) (n=30)	59.8 (18.0) (n=30)	NA
	Post RT	48.0 (25.3) (n=28)	60.9 (23.1) (n=27)	-12.9 (-26.0 to 0.2)
	12 weeks	45.6 (28.7) (n=20)	58.5 (23.3) (n=18)	-12.9 (-30.2 to 4.4)
	26 weeks	39.2 (28.5) (n=17)	52.8 (17.8) (n=12)	-13.6 (-32.7 to 5.5)

3DCRT = three-dimensional conformal radiation therapy; CI = confidence interval; EORTC-QLQ-BM-22 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients with Bone Metastases 22; IMRT = Intensity modulated radiation therapy; MD = mean difference; NA = not applicable; RCT = randomized controlled trial; RT = radiation therapy; SD = standard deviation.

3.1.6.3.4 Secondary Outcomes

None of the included studies reported need for re-irradiation. Secondary outcomes for this comparison (local control, medication use, need for additional treatment and overall survival) can be found in Results Appendix B.

3.1.6.3.5 Harms and Adverse Events

3.1.6.3.5.1 Pathological Fracture

There was no difference between IMRT and 3DCRT in the prevalence of pathological fracture through 26 weeks in one RCT.[100] At baseline the prevalence was 3 percent (1/30) versus 13 percent (4/30), respectively; at 12 weeks, 15 percent (3/20) versus 11 percent (2/19); and at 26 weeks, 17 percent (3/18) versus 17 percent (2/12). None of the fractures required salvage surgical intervention. One NRSI reported that there were no cases of vertebral fracture in the IMRT group (not reported 3DCRT arm).[125]

3.1.6.3.5.2 Toxicity

There were no Grade 4 toxicities and overall the frequency of Grade 3 toxicity was low following IMRT and 3DCRT as reported by one RCT in patients with spinal metastases.[22,24] Frequencies of Grade 3 toxicity, respectively, were: 4 percent (1/27, diarrhea and myalgia) versus 4 percent (1/28, nausea) post RT, 6 percent (1/18, peripheral motor neuropathy) versus 21 percent (3/14, dermatitis, myositis, and paresthesia, radiculitis, peripheral motor neuropathy and myalgia in 1 patient) at 12 weeks,[22] and 6 percent (1/18, radiculitis) versus 0 percent (0/12) at 26 weeks.[24] Grade 1 and 2 toxicities were more common than higher grade toxicities and while the frequency was somewhat lower following IMRT versus 3DCRT, in general, there were no differences between groups at any timepoint (range across toxicities, respectively: post RT, 0% to 29.6% vs. 3.6% to 39.3%; 12 weeks, 0% to 16.7% vs. 0% to 35.7%; and 26 weeks, 0% to 16.7% in both groups).[22,24] The one exception was esophagitis post RT which was much less common (large effect) following IMRT (7.4% vs. 35.8%, RR 0.20, 95% CI 0.05 to 0.86). Across both groups, the most common Grade 1 or 2 toxicities reported post RT were xerostomia (29.6% vs. 35.7%), nausea (29.6% vs. 39.3%), dyspnea (25.9% vs. 35.8%), and myalgia (22.2% vs. 25.0%); these remained the most common toxicities at 12 weeks. At 26 weeks, dyspnea (16.7% vs. 8.3%), brachial plexopathy, radiculitis, myalgia and myositis (5.6% vs. 16.7% for all) were the most frequent toxicities. Results Appendix B, Table B-15 contains details regarding toxicity outcomes.

Consistent with the RCT, one NRSI[125] in patients with MSCC reported no Grade 4 toxicities following IMRT or 3DCRT and one Grade 3 event in the IMRT arm (n=40) (3%; nausea/vomiting). A second NRSI (N=254) in patients with MBD at mixed sites reported similar, low rates (0% to 1%) of Grade 3 or 4 toxicities (dysphagia, vomiting, and diarrhea).[128] Grade 1 or 2 toxicities were again more common than higher-grade toxicities with no difference between groups across both NRSIs (Results Appendix B, Table B-15).

3.1.6.3.5.3 Other Serious Adverse Events

There were no treatment related deaths in the RCT.[22] One NRSI stated that no cases of late myelopathy occurred in the IMRT arm (not reported for 3DCRT).[125]

3.1.7 EBRT Plus Hemibody Irradiation Versus EBRT Alone

3.1.7.1 Key Points

- No primary outcomes of interest were reported by one fair-quality RCT (N=450) comparing the addition of hemibody irradiation (HBI) to EBRT versus EBRT alone.
- Evidence was insufficient for Grade 3 or 4 toxicities and other serious events.

3.1.7.2 Description of Included Studies

One RCT (N=450)[86] compared a single 8 Gy dose of HBI in addition to 30 Gy (3 x 10 Gy) of EBRT versus 30 Gy of EBRT alone given over 2 weeks. Most patients were 60 years of age or older (69%) and male (59%) with a KPS score ≥70 (79%). The trial did not report race or ethnicity, comorbidities or social determinants of health. The most common primary tumor types included prostate (33%), breast (27%) and lung (24%). The study did not report primary tumor histology in terms of favorable or unfavorable or bone metastases in terms of complicated or uncomplicated. Most patients had multiple bone metastases (82%); the trial did not report the metastases sites. In the HBI group, the targeted hemibody area for most patients was the lower third (64%) and HBI was given within 1 week of the local EBRT. Patients on hormonal therapy were enrolled if therapy was stable for the 2 months prior to randomization; chemotherapy

within 2 weeks of entry into the study was an exclusion criterion. This trial was conducted in the United States and was supported by a grant from the Radiation Therapy Oncology Group. It was rated fair quality due to unclear allocation concealment methods and lack of blinding.

3.1.7.3 Detailed Synthesis

3.1.7.3.1 All Outcomes

The RCT did not report any primary effectiveness outcomes of interest to this report. EBRT plus HBI resulted in lower overall rates of re-irradiation (48.9% vs. 58.7%, RR 0.82, 95% CI 0.69 to 0.97) over 52 weeks and delayed time-to-occurrence compared with EBRT alone (Appendix E, Table E-1).[86] Results for secondary outcomes (local control and overall survival) can be found in Results Appendix B.

The addition of HBI to EBRT was associated with increased risk of any Grade 3 (5.3% vs. 1.4%, RR 3.86, 95% CI 1.10 to 13.49), any Grade 2 (16.8% vs. 9.6%, RR 1.75, 95% CI 1.06 to 2.88), and any Grade 1 (17.3% vs. 9.6%, RR 1.79, 95% CI 1.09 to 2.94) toxicity compared with EBRT alone in one RCT.[86] Hematological toxicities specifically (i.e., leukopenia, thrombocytopenia, and anemia) were more common (especially grade 3 and grade 1) with combined EBRT and HBI, as were grade 1 and 2 nausea/vomiting and diarrhea. All events were transitory. Grade 4 events were rare with one occurring in the HBI group (<1%, thrombocytopenia) (Results Appendix B, Table B-16). There were no treatment related deaths reported in either group, and no cases of radiation pneumonitis occurred in the combined EBRT plus HBI arm. Pathological fracture, spinal cord compression and pain flare were not reported.

3.1.8 Advanced Techniques Versus Conventional EBRT

3.1.8.1 Key Points

- SBRT was associated with a small increase in the likelihood of experiencing overall pain response compared with conventional EBRT posttreatment up to 4 weeks (2 RCTs [excluding poor quality], N=325, 60% vs. 48%, RR 1.24, 95% CI 0.98 to 1.57, I^2=0%) (SOE: low), at 12 weeks (4 RCTs, N=408, 59% vs. 44%, RR 1.31, 95% CI 1.05 to 1.61, I^2=0%) (SOE: moderate) and up to 26 weeks (3 RCTs, N=324, 50% vs. 37%, RR 1.32, 95% CI 1.01 to 1.92, I^2=24.3%) (SOE: low). At 36 weeks a small RCT in patients with nonspine MBD found moderate increase in the likelihood of overall response (SOE: low) with SBRT versus EBRT.
- SBRT was also associated with large improvement in VAS pain score (0-10 scale) >12 weeks (SOE: low); evidence was insufficient at other time frames.
- SBRT was associated with improved stability based on the Spinal Instability in Neoplasia Score (SINS) (0-18 scale) at 12 weeks; there was no difference at 26 weeks compared with conventional EBRT (SOE: low).
- There were no differences between SBRT and EBRT on any quality-of-life measures at 12, 26 (SOE: low), or 52 weeks (SOE: insufficient).
- There were no differences between SBRT and EBRT on spinal cord compression by 26 weeks (SOE: low), pathologic fracture at 12 weeks (SOE: low), or pain flare within 2 days of treatment or at 26 weeks (SOE: low).

3.1.8.2 Description of Included Studies

Four RCTs (in 6 publication) [9,23,84,94,99,101] and four NRSIs[108,116,130,133] compared SBRT versus conventional EBRT. Another population based comparative NRSI compared advanced techniques (IMRT, 3DCRT, SBRT) with simple conventional EBRT[124] (Appendix E, Tables E-1 and E-2).

Across the RCTs, sample sizes ranged from 60 to 229 (total N=559). The average age of participants was a mean 62.3 years (range 62 to 63 years) in two trials[9,23,99,101] and a median 64 years in two trials.[84,94] The average proportion of males across trials was 56.2% (range 51% to 62%). Few trials reported comorbidities, social determinants of health or race or ethnicity, with one exception regarding race (79% White, 6% Black, 7% Hispanic/Latino, 3% Asian, and 4% other).[9] The most common primary tumor types across all RCTs included lung (range 26% to 49%) and breast (range 9% to 31%), as well as prostate in two trials (14% to 51%).[9,84] None of the trials reported the primary tumor histology in terms of favorable or unfavorable. Bone metastases were present at multiple sites in 16 percent to 22 percent of patients across two trials;[9,23,99,101] in one of these trials most patients had metastases to other nonbone sites (47% visceral, 27% lung, 18% brain, and 16% tissue).[23,99,101] In one trial, the metastatic bone lesions were lytic in 41 percent, sclerotic in 28 percent, and mixed in 30 percent of participants. The site of bone metastases was limited to the spine in two RCTs,[23,94] mixed spine (55%) and nonspine (45%) in one RCT,[84] and nonspine sites only (pelvis primarily, 59%) in one RCT.[9] Spinal cord compression was an exclusion criterion in all trials including spine metastases. In the two RCTs that included spinal metastases only, 29 percent of patients in one trial had a preexisting pathological fracture[23] and 27 percent in the other had <50 percent vertebral body collapse (2% had ≥50% collapse) 41aselyne.[94] No trials described bone metastases as either complicated or uncomplicated.

The SBRT dose varied among RCTs (12 to 24 Gy in one fraction, 24 Gy total in two fractions, 30 Gy total in three fractions, 35 Gy in five fractions).[9,23,84,94,99,101] The most common EBRT dose was 30 Gy (3 Gy x 10); one trial primarily used single fraction EBRT (8 Gy) and two trials also used 20 Gy (4 Gy x 5).[84,94] Most trials did not clearly report the specific type of EBRT employed but it was most likely 2D or 3DCRT. Concomitant treatments included analgesics and systemic therapies in 41 and 46 percent of participants. Previous treatments included systemic therapy and targeted therapies. Most trials excluded patients who had chemotherapy, prior RT to the treatment site, spinal cord compression, compression fracture, and surgery. The proportion of patients who used opioids at baseline ranged from 38 to 51 percent in two trials that reported this information.[23,84,99,101] Followup periods ranged from 12 to 104 weeks.

One RCT was conducted in the United States,[9] two in Europe, [23,84,99,101] and one in Canada and Australia[94] and most were single center trials. The most common source of funding across the trials was government, followed by industry, private and unclear funding.

Three RCTs were fair quality [9,23,94,99,101] and one was poor quality.[84] Common limitations included unclear randomization and allocation concealment methods, lack of blinding, and high attrition (Appendix F, Table F-1). In many cases, the high attrition was due to high mortality (range 15.7% to 56.9%) which is to be expected in this patient population.

Across the NRSIs of SBRT versus EBRT, sample sizes ranged from 44 to 131 (total N=277). The average study mean age of participants was 64 years (range 59 to 66 years) in two studies[130,133] and the median age was 51 years in two studies (range, 46 to 57).[108,116] The average proportion of males in trials was 61 percent (range 25% to 93%). No studies reported on race or ethnicity, comorbidities or social determinants of health. The primary tumor types reported included breast (range, 24% to 50%), lung (range, 22% to 36%), and prostate (30% in one study[133]); one trial enrolled only patients with hepatocellular carcinoma. None of the NRSIs

reported the primary tumor histology in terms of favorable or unfavorable. Bone metastases were present at multiple sites in 53 to 65 percent of patients across two studies.[130,133] The site of bone metastases was mixed (i.e., spine and nonspine) in two NRSIs (spine, 35.8% to 45% and nonspine, 64.2% to 65%).[108,133] Two NRSIs included bone metastases to the spine only and no trials included bone metastases to nonspine sites only. No studies described bone metastases as either complicated or uncomplicated. The NRSI (N=1,712)[124] of advanced techniques versus EBRT (categorized as simple, parallel opposed pair RT) consisted of mostly males (64%), 50 to 70 years old (50%). The most common primary tumors were prostate, breast, and lung. The most common MBD sites were spine (55%) and pelvis (21%).

Total doses and fractionation schedules varied across the SBRT and EBRT arms across all studies (Appendix E, Table E-2). Most studies did not clearly report the specific type of EBRT employed but it was most likely 2D or 3DCRT; one study reported using 3DCRT.[133] Concomitant treatments reported were surgery, radioisotope injection (samarium), and analgesics in two studies.[116,133] Previous treatments included systemic therapy in one study.[108] Most studies did not report exclusion criteria, but prior treatment and surgery were exclusion criteria in one trial.[116] Followup periods ranged from 4 to 22 weeks. The NRSI of advanced techniques versus EBRT did not report specific doses and fractions; the most used advanced technique was IMRT (67%), followed by 3DCRT (26%) and SBRT (8%).[124]

Two studies were conducted in the United States,[108,116] one in Europe, [133] one in South Korea,[130] and one in Canada[124] and most were single center studies. The most common source of funding across the trials was government, followed by unclear funding. All five NRSIs were fair quality (Appendix F, Table F-2).[108,116,124,130,133] Common limitations included imbalances in prognostic factors between groups at baseline and unclear attrition.

3.1.8.3 Detailed Synthesis

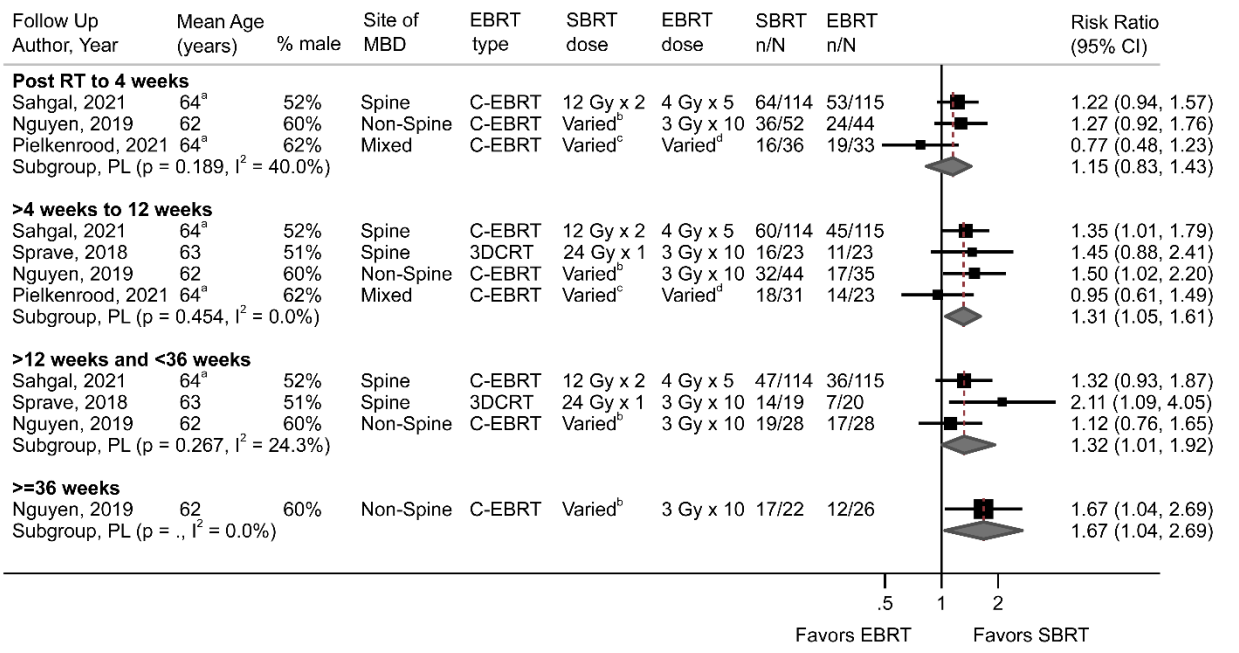
3.1.8.3.1 Pain

All four RCTs contributed data to meta-analyses of overall pain response. There was no difference between SBRT and conventional EBRT in overall response at 4 weeks post-RT (3 RCTs, N=394, 57.4% vs. 50.0%, RR 1.15, 95% CI 0.83 to 1.43, I^2=40%) (Figure 9).[9,84,94] However, exclusion of the one poor-quality trial resulted in a small increase in the likelihood of achieving overall pain response with SBRT at this timepoint and eliminated heterogeneity (2 RCTs, N=325, 60.2% vs. 48.4%, RR 1.24, 95% CI 0.98 to 1.57, I^2=0%).[9,94] SBRT was associated with a small increase in the likelihood of achieving overall pain response compared with EBRT at 12 weeks (4 RCTs, N=408, 59.4% vs. 44.4%, RR 1.31, 95% CI 1.05 to 1.61, I^2=0%)[9,23,84,94] and at 26 weeks (3 RCTs, N=324, 49.7% vs. 36.8%, RR 1.32, 95% CI 1.01 to 1.92, I^2=24.3%),[9,23,94] and a moderate increase at 36 weeks in one trial in patients with nonspine metastases (N=48, 77.3% vs. 46.2%, RR 1.67, 95% CI 1.04 to 2.69) (Figure 9).[9] Exclusion of the poor-quality trial at 12 weeks resulted in a slightly larger but similar estimate (3 RCTs, N=354, 59.7% vs. 42.2%, RR 1.41, 95% CI 1.13 to 1.77, I^2=0%).[9,23,94] Similarly, SBRT was associated with a small increase in the likelihood of achieving overall pain response compared with conventional EBRT in analysis based on longest followup (12 to 36 weeks) across trials (4 RCTs, N= 370, 51.6% vs. 37.5%, RR 1.35, 95% CI 1.02 to 1.95, I^2=39.2%) (Appendix I, Figure I-17);[9,23,84,94] exclusion of the one poor-quality trial resulted in a moderate increase in the likelihood of achieving overall pain response and eliminated heterogeneity (3 RCTs, N=316, 50.3% vs. 34.2%, RR 1.52, 95% CI 1.16 to 2.21, I^2=0%).[9,23,94]

When RCTs were analyzed separately at longest followup based on the site of MBD, SBRT was associated with a small increase in the likelihood of achieving overall pain response

compared with EBRT in populations with spine metastases (2 RCTs, N=268, 45.9% vs. 31.9%, RR 1.46, 95% CI 0.97 to 2.71, I^2=34.9%)[23,94] and a moderate increase in patients with nonspine metastases (1 RCT, N=48, 77.3% vs. 46.2%, RR 1.67, 95% CI 1.04 to 2.69)[9] (Appendix I, Figure I-17); in both populations, these associations were first seen at the 12-week followup and persisted through final followup (Appendix I, Figure I-18). There were no differences between treatment groups at any timepoint in the poor-quality trial that included a population with MBD at mixed (i.e., spine and nonspine) sites.[84]

Figure 9. SBRT versus conventional EBRT: Overall pain response by timeframe



3DCRT = three-dimensional conformal radiation therapy; CI = confidence interval; C-EBRT = conventional external beam radiation therapy; MBD = metastatic bone disease; PL = profile likelihood; SBRT = stereotactic body radiation therapy

[a] Median age

[b] 12 Gy x 1 for lesions >4 cm or 16 Gy x 1 for lesions ≤4 cm

[c] 18 Gy x 1 or 10 Gy x 3 or 7 Gy x 5

[d] 8 Gy x 1 primarily; 4 Gy x 5 or 3G y x 10

There was no difference between SBRT and conventional EBRT in complete pain response at 4 weeks (2 RCTs, N=298, 23.3% vs. 16.9%, RR 1.40, 95% CI 0.65 to 2.44, I^2=0%)[84,94] or 12 weeks (3 RCTs, N=329, 32.1% vs. 15.5%, RR 2.09, 95% CI 0.66 to 4.08, I^2=58.8%).[23,84,94] However, after exclusion of the poor-quality, outlier trial at 12 weeks SBRT was associated with a large increase in the likelihood of achieving complete pain response compared with EBRT across the two trials in patients with spinal metastases (N=275, 36.5% vs. 14.5%, RR 2.52, 95% CI 1.42 to 4.46, I^2=0%);[23,94] this effect persisted at 26 weeks (2 RCTs, N=268, 35.3% vs. 14.8%, RR 2.31, 95% CI 1.25 to 7.15, I^2=35.2%)[23,94] (Appendix I, Figures I-19 to I-21). There was no difference between SBRT and EBRT in complete pain response at any timepoint (4 or 12 weeks) in the poor-quality trial in a population of mixed spine and nonspine bone metastases.

SBRT was associated with a large improvement in pain intensity (on a 0-10 scale) compared with EBRT at 26 weeks in one RCT in patients with spinal metastases (N=39, MD -2.13, 95% CI -3.59 to -0.67);[23] there were no differences between treatment groups at earlier timepoints (up to 4 weeks: 2 RCTs, N=143, MD 0.84, 95% CI -0.45 to 2.31, I^2=0%; and >4 to 12 weeks: 2 RCTs, N=135, MD -0.90, -2.34 to 0.76, I^2=0%) across both RCTs[23,84] (Appendix I, Figure I-22). One of these trials in patients with spine metastases reported no difference between groups in

neuropathic pain at any timepoint up 26 weeks, but it is unclear how this outcome was measured.[23]

Consistent with results from the RCTs, there were no differences between SBRT and EBRT in pain outcomes at 4 weeks in matched-pairs analyses across two NRSIs in patients with spinal metastases.[116,130] In one study in patients with primary hepatocellular carcinoma, complete pain relief (adjusted for pain medication) was reported by 21.4% (6/28) of SBRT versus 10.7% (3/28) of EBRT patients (p=0.83) and the mean change in VAS pain scores was -3.7 (SD 2.7) vs. -2.8 (SD 2.4), respectively, (p=0.13)[130] The second study did not provide data but stated that pain relief (excellent/good: complete relief with or without pain medication) did not differ between treatments (p=0.11).[116] A third NRSI in patients with mixed spine and nonspine MBD from renal cell carcinoma reported significantly better symptom control (i.e., stable disease, partial pain response or complete pain response) with SBRT through 2 years (74.9% vs. 35.7%, p=0.020).[108]

A fourth NRSI in patients with mixed spine and nonspine MBD also found no differences between advanced techniques and simple EBRT based on estimates (adjusted for age, primary histology, sex and treatment region) for partial pain response or complete response. Compared with simple EBRT (referent) adjusted estimates for partial pain response were: 3DCRT (OR 1.08, 95% CI 0.46 to 2.56), IMRT (OR 1.02, 95% CI 0.49 to 2.09) and SBRT (OR 0.64, 95% CI 0.10 to 4.12); adjusted estimates for complete pain response were: 3DCRT (OR 0.74, 95% CI 0.21 to 2.58), IMRT (OR 1.29, 95% CI 0.52 to 3.23), and SBRT (OR 1.16, 95% CI 0.13 to 10.36).[124]

3.1.8.3.2 Function

Skeletal function was reported by one RCT (N=229) that evaluated patients with primarily thoracic and lumbar spinal metastases.[94] At baseline, the median SINS score (0-18 scale, higher score indicates greater instability) was 7 in both groups. SBRT was associated with an improvement in SINS score (i.e., increased stability) at 12 weeks compared with EBRT (mean [SD] change from baseline -0.94 [1.69] vs. -0.49 [1.61]; p=0.03) but there was no difference between groups by 26 weeks (-0.74 [1.99] vs. -0.73 [1.86], p=0.88). None of the other trials reported skeletal or general function outcomes.

None of the NRSIs reported function outcomes.

3.1.8.3.3 Relief of Spinal Cord Compression/Neurological Outcomes

None of the studies comparing SBRT and EBRT reported neurological outcomes or outcomes related to the relief of spinal cord compression.

3.1.8.3.4 Quality of Life

All four trials reported quality-of-life outcomes (see Appendix E, Table E1 for details). Two trials, both in patents with spinal metastases, reported the EORTC-QLQ-BM-22, specifically designed for patients with bone metastases.[94,99] In pooled analyses (Appendix I, Figures I-23 to I-26), there were no differences between SBRT and conventional EBRT across the four domains at any timepoint (post-RT to 4 weeks, 12 weeks and 26 weeks). Mean differences across timepoints ranged from -4.18 to 1.81 for the painful sites domain, from -7.73 to 2.85 for the pain characteristics domain (0-100 scale, lower score mean better QOL for both), from 1.97 to 2.86 for the functional interference domain and from -2.20 to 3.26 for the psychosocial aspects domain (0-100 scale, higher score means better QOL for both). One of these trials also reported the EORTC-QLQ-C30, with no differences between treatments across the various domains at any timepoint except for financial burden: SBRT was associated with a moderate likelihood of achieving improvement in financial burden compared with EBRT at 26

weeks (35.1% vs. 22.9%; RR 1.53, 95% CI 0.97 to 2.41).[94] A third trial in patients with MBD at mixed spine and nonspine sites reported no differences between SBRT and EBRT at any timepoint up to 12 weeks (median 67 vs. 67 on a 0-100 scale) based on the EORTC-QLQ-C15-PAL, designed for use in palliative cancer care.[84] The fourth trial in patients with nonspine metastases reported no difference in the proportion of patients in the SBRT and EBRT groups without severe symptoms on the MD Anderson Symptom Inventory at 4 (60% vs. 63%), 12 (70% vs. 75%), 26 (88% vs. 86%), and 52 (89% vs. 90%) weeks (estimated from graph).[9]

Consistent with the RCTs, one NRSI that compared SBRT versus 3DCRT for the treatment of bone metastases (spine and nonspine) in patients with oligometastatic disease reported no difference between groups on four of the five EORTC-QLQ scales evaluated (C15-PAL global QOL and emotional functioning and BM-22 functional interference and psychosocial effects); the difference between groups on the C15-PAL physical functioning scale was marginally significant favoring SBRT (4 weeks [N=71]: 74 vs. 62; 12 weeks [N=59]: 75 vs. 64; 24 weeks [N=69]: 83 vs. 68; and 52 weeks [N=31]: 91 vs. 60) (Appendix E, Table E-2).[133] All QOL analyses were adjusted for primary tumor, WHO performance status, presence of nonbone metastases, number of metastases, whether all metastases were treated, and pain at baseline. Of note, median followup times differed significantly between the SBRT and EBRT groups: 25 (range, 2 to 52) months versus 46 (range, 9 to 55) months, respectively (p=0.044). One NRSI in patients with mixed spine and nonspine MBD also report no differences between advanced techniques (IMRT, 3DCRT, SBRT) and simple EBRT for the impact of pain interference on quality of life but do not provide adjusted estimates for this outcome.[124]

3.1.8.3.5 Secondary Outcomes

SBRT resulted in a lower likelihood of re-irradiation at 12 weeks compared with conventional EBRT according to intent-to-treat analysis in one trial (N=160) of nonspine metastases, though the difference was not statistically significant and clinical significance is unknown (HR of 0.13, 95% CI 0.004 to 4.01; no other data provided).[9] The rates of re-irradiation at 52 and 104 weeks, were 0% in the SBRT group and 3.3% and 5.3%, respectively, in the EBRT group; loss to followup at these later timepoints was high and available patient numbers were unclear.

There was no difference between SBRT and EBRT in rates of re-irradiation (10.7% vs. 7.1%, respectively; RR 1.50, 95% CI 0.27 to 8.30) at mean of 26 weeks in one NRSI (N=56) of spinal metastases from hepatocellular carcinoma.[130] Similarly, there was no difference between groups in rates of re-irradiation after 4 weeks (SBRT, 9.1% vs. EBRT, 22.7%; RR 0.40, 95% CI 0.09 to 1.85) in a second, small NRSI (N=44) in patients with spinal metastases.[116]

Results for other secondary outcomes (local control, medication use, need for additional treatments and overall survival) are in Results Appendix B.

3.1.8.3.6 Harms

3.1.8.3.6.1 Pathological Fracture and Spinal Cord Compression

There was no differences in the risk of pathological fracture between SBRT and conventional EBRT in pooled analyses at 12 weeks (2 RCTs, 1 spine and 1 nonspine metastases, N=206, 2.9% vs. 1.0%; RR 2.28, 95% CI 0.26 to 21.47, I^2=0%) and at 26 weeks (2 RCT, both spine metastases, N=263, 13.3% vs. 15.6%, RR 0.77, 95% CI 0.18 to 16.75, I^2=74.6%),[94,101] or when the two trials in spinal metastases were considered separately from the trial of nonspine bone metastases (Appendix I, Figures I-29 and I-30). Heterogeneity was high in the pooled analysis at 26 weeks across the two trials in spinal metastases. One RCT (N=225) showed a lower risk of

vertebral compression fractures (VCFs) with SBRT (12 Gy in 2 fractions) versus EBRT (4 Gy in 5 fractions) (10.9% vs. 17.4%)[94] and the other, smaller trial (N=38) showed a higher risk with SBRT (24 Gy in one fraction) versus EBRT (3 Gy in 10 fractions, 27.8% vs. 5%) (the risk at 12 weeks was similar between groups, 8.7% vs. 4.3%). In the latter trial, three of the five fractures seen at 26 weeks in the SBRT arm were progression of existing VCFs (no fracture in either group required salvage surgery). Patients randomized to SBRT in this trial tended to have more preexisting (present at baseline) VCFs than those in the EBRT group (41% vs. 18%; RR 2.28, 95% CI 0.91 to 5.70). Most VCFs in these two trials were Grade 1; one Grade 3 and one Grade 4 VCF occurred after SBRT and EBRT, respectively (0.9% for both). The RCT in patients with nonspine MBD reported one case of radiation-induced fracture in the SBRT arm within 12 weeks (1.2% [1/81] vs. 0% [0/79] with EBRT).[9]

Consistent with the RCTs, no differences between groups in the risk of pathological fracture were reported by either NRSI.[108,130] One study evaluated the treatment of spinal metastases from hepatocellular cancer and reported a higher incidence of Grade 1 or 2 VCF following SBRT but the difference was not statistically significant and the confidence interval was wide: 17.9 percent (5/28) after SBRT versus 3.6 percent (1/28) after EBRT (RR 5.00, 95% CI 0.62 to 40.11).[130] Two SBRT patients required kyphoplasty and one EBRT patient required vertebroplasty to stabilize the VCFs. In the second NRSI in patients with bone metastases at mixed sites (spine and nonspine) from renal cell carcinoma, the incidence of pathological fracture due to tumor progression was 4 percent (2/50 lesions) (1 pelvic, 1 spine) versus 8.9 percent (4/45 lesions) (2 pelvic, 2 spine) following SBRT and EBRT, respectively.[108]

Of the 32 patients who suffered VCFs through 26 weeks in one RCT (see above), two progressed to symptomatic spinal cord compression, both after conventional EBRT (1.7%, n=115).[94] None of the other studies reported on spinal cord compression.

3.1.8.3.6.2 Pain Flare

Two RCTs, both in patients with spinal metastases, reported no difference following SBRT versus EBRT in the incidence of in-field pain flare though the timing of measurement was different. One trial reported pain flare over the first 1 to 2 days, which occurred in two patients in each group (7.4%; 2/27).[23] At 26 weeks in the second trial, 43% (45/110) vs. 34% (35/115) reported pain flare (RR 1.34, 95% CI 0.94 to 1.92).[94]

3.1.8.3.6.3 Other Serious Adverse Events

No serious AEs occurred after SBRT or conventional EBRT across two RCTs and one NRSI in patients with spinal metastases. There were no cases of radiation-related myelopathy, cauda equina injury or late toxicities in one RCT (N=55) over a mean followup of 32.4 weeks;[23] discontinuation due to treatment-related toxicity or treatment-related mortality in one RCT (N=225) with a median followup of 28.6 weeks;[94] or late toxicities in one NRSI (N=38) at followup of less than12 weeks.[116]

3.1.8.3.6.4 Toxicity

There were no Grade 4 toxicities as reported by three RCTs, two in spinal metastases[23,94] and one in mixed spine and nonspine MBD.[84] Grade 3 toxicities were uncommon across all four trials,[9,23,84,94] ranging from 0 to 10 percent following SBRT and 0 to 5 percent following EBRT, with no differences between groups. The most common Grade 3 toxicities in both treatment arms were fatigue (SBRT, 11.1% vs. EBRT, 5.1%) in one trial of nonspine MBD (N=160)[9] and pain (4.5% vs. 4.3%, respectively) in one trial of spine metastases (N=225).[94] Acute Grade 1 and 2 toxicities were more common than higher grade toxicities and occurred with similar frequency

between treatment groups (range from 0% to 24.7% after SBRT and from 0% to 17.9% after EBRT, primarily nausea/vomiting and fatigue) across three RCTs (Results Appendix B, Table B-17).[9,23,94]

Across the NRSIs, toxicity outcomes were generally consistent with those of the RCTs. One NRSI in patients with bone metastases at mixed spine and nonspine sites reported no Grade 4 toxicities and one case of Grade 3 dermatitis which occurred in the SBRT group (2%; 1/50 lesions).[108] Three NRSIs, two in patients with spinal metastases and one in patients with bone metastases at mixed sites, reported similar rates of acute Grade 1 and 2 toxicities which ranged from 0 to 11 percent in the SBRT arms and 0 to 18 percent in the conventional EBRT arms, the most common of which were nausea, fatigue, dermatitis/skin problems, and esophagitis.[108,116,130] The two NRSIs in spine metastases (which used matched pairs analyses) reported that fewer patients overall experienced any acute toxicity after SBRT compared with EBRT (N=100; 20% vs. 46%; RR 0.43, 95% CI 0.23 to 0.82).[116,130] Individually, the study in patients with primary hepatocellular cancer (N=56) reported toxicity rates of 32.1 percent versus 60.7 percent (RR 0.53, 95% CI 0.29 to 0.98) (Results Appendix B, Table B-17).[130]

3.1.8.3.7 Differential Effectiveness or Safety

There is insufficient information on differential harms (risk of new pathological fracture) from one RCT that compared SBRT with 3DCRT based on subanalyses of metastatic bone characteristics.[101] The trial did not report tests for interaction. While substantial overlap in confidence intervals may suggest that the factors did not differentially impact effectiveness or harms, the trial was underpowered to effectively evaluate modification. Thus, conclusions are not possible. Data are found in Results Appendix B, Table B-37.

3.2 Key Question 2. Effectiveness and Harms of Dose-Fractionation Schemes and Techniques for Delivery: Re-Irradiation

3.2.1 Key Points

- There may be no difference between SF EBRT and MF EBRT in overall pain response, improvement in walking ability, and quality of life at 2 months post re-irradiation in one RCT (SOE: low for all).
- Evidence was insufficient from one NRSI for improvement in motor function at any time.
- There may be no difference between re-irradiation with SF EBRT and MF EBRT for the following adverse events: spinal cord or cauda equina compression, pathologic fracture or Grade 4 toxicity in one large RCT (SOE: low for all).
- One NRSI found no difference between SF SBRT and MF SBRT in pain improvement at 4-6 months post re-irradiation (SOE: low) but evidence on toxicity was insufficient.

3.2.2 Single Versus Multiple or Multiple Versus Multiple Dose-Fractionation Schemes: Re-Irradiation With EBRT

3.2.2.1 Description of Included Studies

Two RCTs (N=173 and 850)[58,103] compared re-irradiation SF EBRT with MF EBRT for the palliative treatment of bone metastases in populations with mixed spine/nonspine metastases (Appendix E, Table E-1). One trial[103] was a subsequent publication of the Dutch Bone Metastasis Study and reported on the subgroup of patients who underwent re-irradiation within 1 year of followup. The average study mean age of participants was 65 years for both trials and most were male (59% and 61%). Neither trial reported race or ethnicity, comorbidities or social determinants of health. The primary tumor types included breast (34% and 39%), lung (22% and 28%), and prostate (22% and 23%). Neither trial reported the primary tumor histology in terms of favorable or unfavorable. The proportion of patients with bone metastases at multiple sites was 51 percent in one trial[103] and not reported in the other. The locations of bone metastases were pelvis (36% and 40%); spine (22% and 28%); humerus (7% one trial) or upper limbs (10% one trial); and femur (8%, one trial[103]). The proportion of metastases to nonbone/visceral was not reported in either trial, nor was the proportion of metastatic bone lesions that were lytic or sclerotic or complicated or uncomplicated. Spinal cord compression and pathologic fracture were exclusion criteria for both trials.

The single fraction dose was 8 Gy in both trials. The multiple fraction dose was 24 Gy (4 Gy x 6)[103] and 20 Gy (4 Gy x 5, with some exceptions based on target field and previous radiation therapy).[58] One RCT allowed both 2D- and 3D-EBRT,[58] while the type of EBRT was not reported in the other trial. Concomitant treatments included nonspecified bone-modifying agents and systemic therapy (no proportions provided) at the discretion of the treating physician in one RCT[58] and narcotic and nonnarcotic analgesics in both trials. The proportion of patients who used opioids at baseline was 32 percent at a mean daily dose of morphine equivalence of 44 mg in the trial that reported baseline analgesic use.[58] Previous treatments as reported by one trial included nonspecified systemic therapy in 51 percent of the population which differed according to primary cancer type (79% with breast cancer, 81% with prostate cancer, and 12% of with lung cancer).[103] One trial excluded patients with metastases of renal cell carcinoma, melanoma, and

cervical spine metastasis.[103] Patients with treatment areas associated with previous palliative surgery or who were receiving systematic radiotherapy or half-body irradiation within 30 days of randomization were excluded in the other trial.[58] Median followup was 12.2 months[58] and a maximum of 2 years (mean followup duration not reported).[103]

One trial was conducted at 17 sites in The Netherlands and did not report funding source.[103] The other trial was conducted in Canada, Australia, New Zealand, United States, Israel, Switzerland, United Kingdom, The Netherlands, and France and funded primarily by national cancer institutes.[58]

One trial was rated fair quality[58] and the other poor quality.[103] Methodological limitations included inability to blind care providers or patients, unclear randomization and allocation concealment methods, unclear if randomized groups were similar at baseline, and high attrition, only partly due to high mortality (Appendix F, Table F-1).

Two NRSI compared SF versus MF EBRT for re-irradiation (Appendix E, Table E-2). Sample sizes were 60 and 62 (total N=122).[127,129] The median age of participants was 55 years in one study and 63 years at primary radiation therapy in the other and just over half were male (52% and 56%). Neither study reported race or ethnicity, comorbidities or social determinants of health. The primary tumor types included breast (27% and 37%), lung (8% and 10%), prostate (3% and 35%), and multiple myeloma (13%)[129] or myeloma/lymphoma (7%).[127] Neither study reported the primary tumor histology in terms of favorable or unfavorable or reported the proportion of patient with bone metastases at multiple sites or to nonbone/visceral sites, nor were bone metastases described as complicated or uncomplicated. One NRSI excluded patients with lytic lesions >3 cm or >50% cortical erosion of bone diameter. The site of bone metastases was mixed in one study (55% spine, 45% nonspine)[129] while all patients in the second study had MSCC (36% lumbar spine alone, 34% thoracic spine alone, 24% cervical and thoracic spine, and 6% thoracic and lumbar spine).[127] Spinal cord compression was an exclusion criterion in the mixed spine/nonspine metastases study along with any high-risk lesions for pathological fracture. In the NRSI of patients with spinal cord compression, neurologic outcomes such as pain and incontinence were not studied, although all had motor deficits of the lower limbs with baseline motor function scores of Grade 1 (ambulatory without aid, 10%), Grade 2 (ambulatory with aid, 65%), Grade 3 (not ambulatory, 24%), and Grade 4 (paraplegia, 1.6%).

The single fraction dose was 8 Gy in both NRSIs; the multiple fraction dose was 20 Gy (4 Gy x 5) over 5 days or 8 days (if spine/whole pelvis involved)[129] and 20 Gy (4 Gy x 5) or 15 Gy (3 Gy x5) depending on initial radiation treatment (treatment duration not reported).[127] Neither study reported the specific EBRT used. All patients received concomitant chemotherapy and/or hormonal systemic therapy and bisphosphonates in one study,[129] while concomitant treatment was not described in the other study.[127] Previous treatments such as surgery or chemotherapy for the targeted spinal area were not allowed in one study[127] and not reported in the other.[129] The proportion of patients who used opioids at baseline was 90 percent[129] or not reported.[127] Median followup times were 7 months[129] and 12 months.[127]

The NRSIs were conducted in Europe at one or more sites[127] and at a single site in Egypt.[129] Neither study reported funding source. Both NRSIs were rated poor quality due to unclear blinding of outcome assessors, unclear if comparison groups similar at baseline, and lack of adjustment for prognostic confounding variables (Appendix F, Table F-2).

3.2.2.2 Detailed Synthesis

3.2.2.2.1 Pain

Two RCTs (N=995)[58,103] assessed the effects of re-irradiation EBRT in MBD patients without spinal cord compression. The single fraction dose was 8 Gy in both RCTs. The multiple fraction dose was 24 Gy (4 Gy x 6)[103] and 20 Gy (4 Gy x 5 primarily).[58] One trial found overall response to treatment, defined as the sum of complete and partial responses (complete response was defined as a Brief Pain Inventory (BPI) [scale 0 to 10] worst-pain score of zero with no increase in daily oral morphine equivalent and partial response was defined as persistent pain, with a worst-pain score reduction of at least 2 points and no increase in daily morphine equivalence needed or no increase in pain with a reduction in daily morphine equivalent use of 25% or more) was similar between SF EBRT and MF EBRT at 8 weeks (N=850, 28% vs. 32%, RR 0.87, 95% CI 0.71 to 1.08).[58] There was also no difference in complete response between SF EBRT and MF EBRT (N=850, 8% vs. 7%, RR 1.20, 95% CI 0.75 to 1.91).[58] The other RCT defined response to retreatment as a decrease in pain scores on an 11-point scale after retreatment compared to before retreatment and was not different between the 119 patients who received SF EBRT and the 26 patients who received MF EBRT and had followup pain scores (66% vs. 46%, RR 1.44, 95% CI 0.63 to 2.22).[103]

There was also no difference in overall pain response, defined as the sum of complete response and partial response (based on pain intensity and type of analgesia used), between SF and MF EBRT for re-irradiation (N=60, 93% vs. 88%, RR 1.10, 95% CI 0.95 to 1.28) in one NRSI.[129] While complete response was infrequent in one RCT[58] (N=850, 8% vs. 7%, see above), it occurred more frequently in this NRSI (N=60, 21% vs. 16%, RR 1.37, 95% CI 0.47 to 4.01)[129] but did not favor either single or multiple fractionation treatment for either study.

3.2.2.2.2 Skeletal and General Function

Skeletal function outcomes were not reported by any of the included studies.

One RCT in patients without spinal cord compression found no difference in improvement in walking ability (due to a reduction in pain interference) based on the BPI (2 points or more improved on 0-10 scale) between 8 Gy SF EBRT and 20 Gy MF EBRT (4 Gy x 5) at 2 months (N=720, 28% improved vs. 33% improved, RR 0.85, 95% CI 0.69 to 1.06).[58]

3.2.2.2.3 Relief of Spinal Cord Compression

One NRSI (N=62) in patients with spinal cord compression and motor deficits of the legs undergoing re-irradiation with SF EBRT (8 Gy), LDMF EBRT (15 Gy, 3 Gy x 5) or HDMF EBRT (20 Gy, 4 Gy x 5 primarily) reported no difference between dose-fractionation schemes in improvement in motor function as measured on a Grade 1 to 4 scale:[139] Grade 1=ambulatory without aid; Grade 2=ambulatory with aid; Grade 3=not ambulatory; and Grade 4=paraplegia; improvement=1 or more grades lower.[127] The proportion of patients who improved in motor function after 4 weeks (N=62) was 38 versus 33 versus 54 percent (p=0.69), after 12 weeks (N=57) was 43 versus 36 versus 54 percent (p=0.78), and after 26 weeks (N=38) was 48 versus 57 versus 75 percent (p=0.67), respectively.[127] Six of the 16 patients who were nonambulatory at baseline regained the ability to walk with no between-group difference (3/8, 38% after SF EBRT; 1/3, 33% after LDMF EBRT; 2/5, 40% after HDMF EBRT). Improvement in motor function was most likely to occur in patients with myeloma/lymphoma (50%) and less likely to occur in patients with lung cancer (0%) for primary histology.

3.2.2.2.4 Quality of Life

One RCT found no difference between 8 Gy SF EBRT and 20 Gy MF EBRT (4 Gy x 5 primarily) at 8 weeks on quality of life as assessed with the QLQ-C30 (≥10 points improvement, 0-100 scale) (N=463, 34% vs. 35% improved, RR 0.97, 95% CI 0.78 to 1.24).[58]

3.2.2.2.5 Secondary Outcomes

None of the included studies reported need for re-irradiation. Secondary outcomes for this comparison (medication use, overall survival) can be found in Results Appendix B.

3.2.2.2.6 Harms and Adverse Events

One RCT reported 50 pathological fractures among 7 percent of patients who received 8 Gy/single fraction versus 5 percent who received 20 Gy (4 Gy x 5) in intent-to-treat analysis (N=850, OR 1.54, 95% CI 0.85 to 2.75).[58] The same study reported no difference between fractionation schemes on spinal cord/cauda equina compressions (N=850, 2% vs. <1%, OR 3.54, 95% CI 0.73 to 17.15). At 14 days posttreatment, MF EBRT (4 Gy x 5) was associated with increased likelihood of lack of appetite (66% vs. 56%, RR 1.17, 95% CI 1.04 to 1.32), vomiting (23% vs. 13%, RR 1.79, 95% CI 1.29 to 2.48), diarrhea (31% vs. 23%, RR 1.36, 95% CI 1.07 to 1.75), and skin reddening (24% vs. 14%, RR 1.69, 95% CI 1.21 to 2.36) when compared with SF EBRT in one RCT (N=850).[58] In this study there was one serious adverse event deemed possibly related to study treatment in a patient who received Gy 8 in a single fraction and was admitted to hospital with grade 4 cardiac ischemia or infarction. A second RCT (N=145) reported no difference between 8 Gy in a single fraction and 24 Gy (4 Gy x 6) in the likelihood of experiencing nausea/vomiting, itching, painful skin, or fatigue.[103] Additionally, there were no pathological fractures, spinal cord compression, or toxicity related to re-irradiation, in one NRSI (N=60).[129]

One NRSI (N=62) in patients with spinal cord compression reported only Grade 1 toxicities, not reported by re-irradiation scheme, following treatment (35% with nausea and 21% with dysphagia due to esophagitis) in patients who were irradiated in the thoracic spine.[127]

3.2.3 Single Versus Multiple Dose-Fractionation Schemes: Re-Irradiation With SBRT

3.2.3.1 Description of Included Studies

One retrospective NRSI (N=228; 348 lesions)[117] compared re-irradiation with SF SBRT (mean 16.3 Gy) versus MF SBRT (mean 20.6 Gy in 3 fractions, 23.8 Gy in 4 fractions, and 25.4 Gy in 5 fractions) in patients with primarily (75%) thoracic and lumbar spinal metastases (Appendix E, Table E-2). Individuals with frank spinal cord compression or spinal instability were excluded. Most patients (56%) had previous EBRT and received SBRT due to pain (97%). Primary tumor types included breast (25%), lung (18%), renal cell (15%), and thyroid (8%) cancer. The mean patient age was 59 years and 48 percent were male. Other patient (race/ethnicity, comorbidities, social determinants of health, primary tumor histology in terms of favorable or unfavorable) and bone (number of metastases, metastases to nonbone/visceral sites, lytic or sclerotic lesions, complicated versus uncomplicated lesions) characteristics were not reported. Median followup was 360 days. This study was conducted in the United States and partially funded by industry. It was rated fair quality due to baseline differences between groups, unclear blinding of outcome assessors and lack of adjustment for all prognostic variables, although adjustment was made for initial tumor volume (Appendix F, Table F-2).

3.2.3.2 Detailed Synthesis

3.2.3.2.1 All Outcomes

There was no difference between SF SBRT versus MF SBRT in long-term (after 4-6 months) pain improvement (patients were asked to rate their pain as improved, stable, or worse compared with pretreatment; 71% vs. 73%, RR 0.97, 95% CI 0.83 to 1.14).[117] However, at up to 12 months, patients who received SF SBRT were more likely to experience pain control (pain relief or pain stabilization; 100% vs. 88%, p=0.003). Patients treated with SF SBRT required more frequent re-irradiation compared with those treated with MF SBRT (13% vs. 1%, p<0.001; timing unclear).[117] Results for other secondary outcomes (overall survival) can be found in Results Appendix B.

3.2.3.2.2 Harms and Adverse Events

The rate of adverse events was similar in an NRSI (N=228) of SF SBRT versus MF SBRT (4.6% vs. 5.9%, respectively) with one Grade III complication (details not reported) among patients treated with single-session and no Grade II or Grade III adverse events among patients who received multisession treatment (0.8% vs. 0%, RR 2.52, 95% CI 0.10 to 61.21).[117]

3.3 Key Question 3a. Effectiveness and Harms of EBRT Versus Another Single Treatment Modality

3.3.1 Key Points

- In RCTs comparing EBRT and strontium-89 for palliative care of bone metastasis, evidence was insufficient for pain response (based on composite measures of pain, functional interference and analgesic use) .
- There may be no difference between EBRT and strontium-89 for pain flare or Grade 3 or 4 toxicities (SOE: low) in one RCT.
- Evidence was insufficient for pain response and quality of life with EBRT versus cryoablation in one NRSI.
- There may be no differences in WHO response rate (based on pain medication utilization and average pain score) or quality of life (Functional Assessment of Cancer Therapy-General [FACIT-G]) between EBRT and ibandronate at 4 weeks or at 12 weeks (some patients may have crossed over to other treatment by 12 weeks) based on one RCT (SOE: low for all).
- There may be no difference between EBRT and ibandronate in the likelihood of experiencing a pathological fracture or spinal cord compression (SOE: low). Evidence was insufficient for Grade 3 or 4 toxicity.

3.3.2 EBRT Versus Radioisotopes

3.3.2.1 Description of Included Studies

Two RCTs conducted in patients with metastatic prostate cancer compared EBRT with strontium-89 chloride (a radioisotope that delivers radiation to cancerous areas)[81,88] (Appendix E, Table E-1). Sample sizes were 111 and 203, median ages were 67 and 71, and all patients were male. Neither trial reported race or ethnicity, comorbidities or social determinants of health. One trial reported the median number of hot spots on bone scans was 11 with about 35 percent of patients reporting one painful metastasis and about 44 percent reporting two painful metastases.[81] Neither trial reported the primary tumor histology in terms of favorable or unfavorable or bone metastases in terms of complicated or uncomplicated. One trial required all patients to have sclerotic bone metastases for study entry.[88] Risk of spinal cord compression or pathological fracture were exclusion criteria in one trial.[88] Both trials required patients to have hormone-resistant prostate cancer.

The dose of EBRT was 20 Gy (4 Gy x 5 or a single dose of 8 Gy) for local radiotherapy in one trial[88] or usual radiotherapy regimen per the treatment center (median of 4 Gy x 5) in the other.[81] The type of EBRT (two- or three-dimensional) was not reported in the trials. The dose of Strontium-89 Chloride was 150 MBq in one trial and 200 MBq in the other. Concomitant therapies were not reported. One trial reported about 49 percent of patients were receiving at least 20 mg of morphine equivalents daily at study entry, while the other trial reported 35 percent of patients were receiving level-4 narcotics. One trial followed patients until death,[81] whereas followup was 12 weeks in the other trial.[88] Of note, in this latter trial, patients who failed to achieve pain relief with the treatment assigned at randomization (either EBRT [4 Gy x 5 or 8 Gy x 1] or strontium-89 200 MBq) were offered the other treatment at 8 weeks.

One trial was conducted in the United Kingdom; it is unclear if the other trial was conducted solely in The Netherlands or was multinational. One trial received support from Amersham

Laboratories (strontium), and the Scottish Urological Oncology Group; funding was not reported in one trial. One trial was rated fair quality and other rated poor quality[88] due to lack of blinding, reporting of findings for some patients at 12 weeks and for other patients at 8 weeks (those who crossed over to other treatment), and high attrition (Appendix F, Table F-1).

3.3.2.2 Detailed Synthesis

3.3.2.2.1 Pain and Function

One RCT (N=203) evaluated palliative treatment with EBRT or strontium-89 150 MBq for bone metastases in patients with prostate cancer.[81] The radiotherapy regimen varied by treatment center based on usual care (median EBRT dose was 4 Gy in 5 fractions). There was no difference between EBRT and strontium in subjective response (N=190, 33.3% vs. 34.7%, p=NR) defined as (1) a reduction in pain score of at least one level on a 5-point scale from 0 = no analgesics required to 4 = narcotic analgesics regularly required with no deterioration in WHO performance status (6-point scale from 0 = fully active, able to carry out all pre-disease performance without restriction to 5 = dead), or (2) no change in pain and at least a 25 percent reduction in daily analgesics dose, with no deterioration in performance status, or (3) improvement in performance status by at least one level without an increase in analgesics dose by 25 percent or more or without an increase in pain level.[81] There was also a similar median duration of response between treatments (4.5 months vs. 4.6 months, p=0.6001; HR 1.14, 95% CI 0.70 to 1.85 [favors EBRT]).[81] Another RCT (N=148) in patients with metastatic prostate cancer, rated poor quality, reported no difference between EBRT and strontium in the proportion of participants who experienced dramatic improvement (33% vs. 29%, respectively, RR 1.17, 95% CI 0.67 to 2.04, data from graph)[88] based on a composite outcome that incorporated two pain measures (analgesic intake [increased, unchanged, decreased by 20% to 40%, decreased by 50% to 80%, virtually discontinued] and pain type/severity [increase in pain type and/or severity at most affected sites, increase in pain type and/or severity at some sites, no change, decrease in type and/or severity at some sites, decrease in type/severity at most sites]) and two function measures (general condition [deterioration, unchanged, some improvement, definitely better] and mobility [more restricted, unchanged, less restricted]).

3.3.2.2.2 Secondary Outcomes

None of the included studies reported need for re-irradiation. Secondary outcomes for this comparison (medication use and overall survival) can be found in Results Appendix B.

3.3.2.2.3 Harms and Adverse Events

Pain flare was less common with EBRT (median 5 x 4 Gy) compared with strontium-89 150 MBq in one RCT (N=193, 8.2% vs. 18.4%, RR 0.43, 95% CI 0.20 to 0.95).[81]

One RCT (N=203) reported nonhematologic Grade 3 or 4 toxicities in EBRT (median 5 x 4 Gy) versus strontium-89 150 MBq: nausea/vomiting (1% vs. 4%, RR 0.25, 95% CI 0.03 to 2.17) and diarrhea (8.3% vs. 2%, RR 3.60, 95% CI 0.86 to 18.17).[81] Grade 3 or 4 hematologic toxicities were seen in 2 percent of patients who received EBRT and none in patients who received strontium.[81] One RCT (N=148) reported Grade 3 and Grade 4 platelet toxicity in 3.4 percent who received radiotherapy (5 x 4 Gy or 1 x 8 Gy) versus 6.9 percent of patients who received strontium-89 (200 MBq).[88] However, some of the patients assigned to radiotherapy may have received hemi-body radiotherapy rather than local treatment.

3.3.3 EBRT Versus Cryoablation

3.3.3.1 Description of Included Studies

One NRSI compared EBRT with cryoablation (use of extreme cold to kill cancer cells) (Appendix E, Table E-2).[112] Of 175 participants enrolled, 150 were treated with EBRT (n=125) or cryoablation (n=25). (The remaining 25 patients were treated with a combination of EBRT and cryoablation and are described under Key Questions 3b and 3c.) Patients were matched via propensity score analysis. Mean patient age was 68 years and 49 percent were male. Comorbidities, social determinants of health and race/ethnicity were not reported. Mean Karnofsky score ranged from 70 to 89 in exactly half of the patients and 91 to 100 in the other half. Primary tumors included prostate (33%), lung (29%), breast (23%), kidney (9%), and colorectal (7%). The study did not report primary tumor histology in terms of favorable or unfavorable or bone metastases in terms of complicated or uncomplicated. Tumor metastatic locations included pelvis (40%), sacrum (24%), vertebrae (17%), humerus (7%), and femur (3%). All patients were taking narcotic analgesics at enrolment, 63 percent were receiving chemotherapy, 29 percent bisphosphonates, 28 percent hormonal therapy, and 9 percent immunotherapy. Patients with evidence of spinal cord or cauda-equina compression or pathological fracture were excluded. Treatment with 3D-conformal beams (5 x 20 Gy) or cryoablation (2, 15-minute freezes with a 10-minute thaw in between) were compared. Outcomes were reported at 12 weeks. This study was conducted Italy and rated moderate quality (Appendix F, Table F-2); funding was not reported.

3.3.3.2 Detailed Synthesis

3.3.3.2.1 Pain

This NRSI reported that 3DCRT was associated with a large decrease in the likelihood of achieving complete pain response at 12 weeks (defined as a pain score of 0 on a VAS, [scale not defined but likely 0-10] at the treated site with no increase in analgesic intake) compared with cryoablation (N=150, 11.2% vs. 32%, RR 0.35, 95% CI 0.16 to 0.75) in patients with varied metastatic cancers.[112]

3.3.3.2.2 Quality of Life

Improvement in quality of life was assessed with one question from the McGill Quality of Life Questionnaire (MQOL), consisting of an NRS (0-10) on global quality of life (e.g., physical, emotional, social, spiritual, financial) where 0=very bad to 10=excellent and slightly favored cryoablation: EBRT, MQOL: MD 5 (95% CI 4 to 5) versus cryoablation, MQOL: MD 6 (95% CI 5 to 8).[112]

3.3.3.2.3 Secondary Outcomes

The NRSI did not report need for re-irradiation. Secondary outcomes for this comparison (medication use) can be found in Results Appendix B.

3.3.3.2.4 Harms and Adverse Events

Comparative harms were not reported (only harms associated with cryoablation) (Appendix E, Table E-1).

3.3.4 EBRT Versus Bisphosphonates

3.3.4.1 Description of Included Studies

One RCT[65] compared a single dose of 8 Gy EBRT with ibandronate 6 mg in patients with metastatic prostate cancer (Appendix E, Table E-1). Patients could cross over to the other treatment after 4 weeks whether or not they experienced improvement in pain. Twenty-seven percent of patients (128/470) crossed over to the other treatment (23.8% initially treated with EBRT crossed over to ibandronate and 30.6% initially treated with ibandronate crossed over to EBRT, RR 0.78, 95% CI 0.58 to 1.05). The sample size in the trial was 470; median age was 73 years; all were male. Race/ethnicity, comorbidities, or social determinants of health were not reported. Areas of metastases were not reported, although the primary sites of pain were in the abdomen (78%) and thorax (15%). This trial did not report the primary tumor histology in terms of favorable or unfavorable or complicated or uncomplicated. Ninety percent of patients were receiving or had recently received hormone therapy and 3 percent were receiving chemotherapy. Median followup was 11.7 months. This trial was conducted in the United Kingdom and sponsored by the University College London; funding from Cancer Research UK; Roche Products Limited provided ibandronate; the trial was rated fair quality (Appendix F, Table F-1).

3.3.4.2 Detailed Synthesis

3.3.4.2.1 Pain, Quality of Life and Harms, and Adverse Events

The WHO response rate (based on decrease, stable, or increase in pain medication [nonopioid, weak opioid, strong opioid] and average pain score [no pain, pain reduced by at least 2 points out of 10, pain score stable, or pain score increased by at least 2 points out of 10) was not different between EBRT and ibandronate at 4 weeks or at 12 weeks in one RCT (4 weeks: N= 357, 53.1% vs. 49.5%, RR 1.08, 95% CI 0.88 to 1.32; at 12 weeks: N=313, 49.4% vs. 56.1%, RR 0.88, 95% CI 0.71 to 1.09).[65] Results were similar at 26 and 52 weeks (26 weeks: N=250, 52.8% vs. 48.8%, RR 1.08, 95% CI 0.85 to 1.38; 52 weeks: N=145, 42.3% vs. 45.9%, RR 0.92, 95% CI 0.64 to 1.33).[65] Quality of life was assessed using the FACIT-G v. 4.0, an instrument divided into four sections (physical well-being, social/family well-being, emotional well-being, and functional well-being) with total score between 0 to 108 points. At both 4 weeks and 12 weeks there were no differences on any section or on overall quality of life between treatment with ibandronate 6 mg and single fraction EBRT (8 Gy) (MD -1.0, 95% CI -4.0 to 2.0; MD -0.3, 95% CI -3.8 to 3.3, respectively).[65] Patients could cross over to the other treatment after 4 weeks (27% of patients crossed over); most patients crossed over due to lack of sufficient pain relief.

There was no difference in pathological fracture rates (2.1% vs. 3.0%, RR 0.71, 95% CI 0.23 to 2.22) between patients treated with EBRT versus ibandronate, respectively. The incidence of spinal cord compression in patients with pain in the chest or abdomen was similar with EBRT compared with ibandronate (N=431, 3.3% vs. 5.6%, RR 0.58, 95% CI 0.23 to 1.45).[65] The incidence of spinal cord compression in those with arm, leg, or head and neck pain was not reported. The risk of experiencing any toxicity was also similar between treatments (N=470, 41% vs. 39%, absolute RD -2.6%, 95% CI -11.4% to 6.3%). All but one toxicity was rated grade 1 or 2 (one person treated with EBRT experienced grade 3 nausea).

Results for overall survival (secondary outcome) can be found in Results Appendix B.

3.3.4.2.2 Differential Effectiveness or Safety

There is insufficient information on differential effectiveness from one RCT that compared SF EBRT with ibandronate based on subanalyses of primary tumor type.[65] The trial did not

report tests for interaction. While substantial overlap in confidence intervals may suggest that the factors did not differentially impact effectiveness or harms, the trial was underpowered to effectively evaluate modification. Thus, conclusions are not possible. Data are found in Results Appendix B, Table B-38.

3.3.5 EBRT Versus Androgen Deprivation Therapy

3.3.5.1 Description of Included Studies

One NSRI compared EBRT with androgen deprivation therapy in patients with oligometastatic prostate cancer (Appendix E, Table E-2); only patients with bone metastases are included here.[110] This study reported only secondary outcomes (no harms) and is summarized in Results Appendix B.

3.4 Key Question 3b. Effectiveness and Harms of EBRT Combined With Another Treatment Modality Versus EBRT Alone

3.4.1 Key Points

There was *low strength of evidence* for the following outcomes and comparisons for Key Question 3b:

- **EBRT plus surgery versus EBRT alone:**
  - There may be more improvement in MSCC symptoms with surgery and EBRT, measured by ambulation after treatment (moderate improvement), American Spinal Injury Association (ASIA) Impairment Scale and Frankel scores (large improvements) and continence (large improvement) versus EBRT alone in one fair-quality RCT. NRSIs did not consistently show improvement in MSCC symptoms for EBRT plus surgery versus EBRT alone.
- **EBRT plus dexamethasone versus EBRT:**
  - Results from one good-quality RCT showed that EBRT plus dexamethasone may be associated with a small improvement in pain (overall pain response and VAS pain scores); a small improvement in function and in appetite along with a decrease in nausea according to quality-of-life measures (EORTC-QLQ-BM22, EORTC QLQ-C15-PAL); a small reduction in pain flare; and a moderate decrease in acute grade 3 to 4 bone pain, versus EBRT alone. There were no cases of grade 3 or higher nausea; Grade 3 or 4 fatigue, anorexia, hyperglycemia, constipation, and bloating were infrequent (0% to 2%), with no differences between treatment arms.
- **EBRT plus radioisotopes versus EBRT alone:**
  - There may be no difference between EBRT plus strontium-89 versus EBRT plus placebo in overall pain response at 12 and 26 weeks in one fair-quality RCT.

Evidence was considered *insufficient* for the following comparisons and outcomes:

- **EBRT plus surgery versus EBRT alone:** pain (VAS 0-10), function (KPS), quality of life, and nerve damage across two fair-quality NRSIs.
- **SBRT plus surgery versus SBRT alone:** relief of spinal cord compression (Frankel scores) from one poor-quality NRSI
- **EBRT plus dexamethasone versus EBRT alone:** relief of spinal cord compression (ambulation) posttreatment from one small, poor-quality RCT.
- **EBRT plus bisphosphonates (zoledronate) versus EBRT alone**: pain, risk of skeletal events and pain flare across one RCT and two NRSI's, all rated poor quality.
- **EBRT plus radioisotopes (strontium-89) versus EBRT alone:** quality of life from two moderate-quality RCTs (data was not provided by either trial).
- **EBRT plus cryoablation versus EBRT alone:** overall pain response, quality of life and harms from one fair-quality NRSI
- **EBRT plus hyperthermia versus EBRT alone**: quality of life from one poor-quality RCT
- **EBRT plus capecitabine versus EBRT alone:** overall pain response from one fair-quality RCT

3.4.2 EBRT or SBRT Plus Surgery Versus EBRT or SBRT Alone

3.4.2.1 Description of Included Studies

One RCT[83] and four NRSIs[109,123,126,137] compared either conventional EBRT or SBRT with surgery to EBRT or SBRT alone for the palliative treatment of bone metastases (Appendix E, Tables E-1 and E-2). Results for EBRT and SBRT are presented separately below. In all five studies, spinal metastases were an inclusion criterion. The RCT and two NRSIs,[109,126] including the SBRT study,[109] also required patients to have MSCC.

One RCT[83] included 101 participants with MSCC and a median age of 60 years, 69 percent of whom were male. Race and other patient characteristics were not reported. Lung cancer was the most common primary histology (26%), followed by prostate (19%) and breast cancer (13%). Metastases to nonspine sites were not reported. Many patients were nonambulatory (32%), incontinent (39%), or had spinal instability (38%) at baseline. Surgery for all patients included circumferential decompression, with stabilization including use of cement, metal rods, or bone grafts for those with spinal instability. Patients received EBRT within two weeks after surgery. Total EBRT dose in both treatment groups was 30 Gy (3 Gy x 10). All patients also received dexamethasone. Baseline opioid use was not reported, but post-treatment use was a study outcome. Median followup for surgical patients was 15 weeks, 13 weeks for control patients. The trial was conducted at seven U.S. academic centers, with government funding, and was rated fair quality due to unclear reporting of the following: allocation concealment methods, assessor blinding and attrition (Appendix F, Table F-1).

Three NRSIs of EBRT and surgery (N=534)[123,126,137] in patients with spinal metastases included 67 percent male patients, with mean age 52 years across two studies (not reported for the third). One study included only patients with cancer of unknown origin[123] and one only those with primary lung cancer;[137] most patients (54%) in the third study[126] also had lung cancer, and 19 percent had cancer of unknown origin. Across two studies, 45 percent of patients had nonspine bone metastases, and 42 percent had visceral metastases (not reported in the third). In one study 36 percent of patients were nonambulatory at baseline, 30 percent in another (Frankel grade C or less); the third did not report baseline motor function. Surgical procedures included decompression and/or stabilization. Total EBRT dose was 30 to 45 Gy in 10 to 20 fractions across two studies, not described in the third; none reported treatment duration. Additional reported treatments included chemotherapy (2 studies), bisphosphonates (1 study), erlotinib (1 study), and dexamethasone (1 study). Followup (mean or median) ranged from 22 to 38 weeks. Two studies were conducted in one of two academic centers in China, the third at multiple centers in the U.S., Europe, and Saudi Arabia. Funding sources were unclear. All three studies were rated fair quality, with methodologic limitations including differences in baseline characteristics (2 studies), unclear methods for patient selection and ascertainment of exposures and outcomes, no blinding reported, and no analysis to control for confounding (1 study) (Appendix F, Table F-2).

One NRSI of SBRT and surgery[109] enrolled 57 patients with 69 metastatic lesions and spinal cord compression. Most results were reported by lesion rather than by patient. Mean age was 60 years, and 43 percent of lesions occurred in males. Race and other patient characteristics were not reported. Primary tumors varied widely, including renal cell (26%), breast (25%), lung cancer (16%), and 14 other histologies. Non-spine metastases and baseline function were not reported. Patients with high-grade SCC underwent surgery with decompression and stabilization. Total SBRT dose was 16 to 30 Gy in 1 to 5 fractions, with duration not reported, and some lesions (43%) had previously been treated with EBRT. Median followup was 43 weeks. The setting was a single U.S. academic center, with funding not reported. The study was rated poor

quality (Appendix F, Table F-2): confounding by indication was a concern, as patients with higher-grade MSCC, fracture, or instability were treated with surgery, others with SBRT alone, and the study did not control for confounding. Prior treatment differed across treatment groups, methods for ascertaining exposures and outcomes were unclear, and blinding was not reported.

3.4.2.2 Detailed Synthesis

3.4.2.2.1 Pain

In one fair-quality NRSI (N=46),[137] addition of surgery to EBRT was associated with a small decrease in pain scores at 4 weeks (2.6 vs. 3.6, MD -1.0, 95% CI -1.4 to -0.6) and a moderate decrease at 12 weeks (3.0 vs. 4.3, MD -1.3, 95% CI -2.0 to -0.6, 0 to 10 scales) compared with EBRT alone.

3.4.2.2.2 Relief of Spinal Cord Compression

One RCT (N=101)[83] found surgery associated with greater improvement in MSCC symptoms by several measures. Patients given EBRT alone were less likely to be ambulatory after treatment (56.9% vs. 84.0%, adjusted RR 0.68, 95% CI 0.52 to 0.88, small to moderate effect) than those given surgery with EBRT. There were large effects on both ASIA scores (60% vs. 86% the same or better, adjusted RR 0.30, 95% CI 0.14 to 0.62) and Frankel scores (61% vs. 91% the same or better, adjusted RR 0.26, 95% CI 0.12 to 0.54) for EBRT alone compared with combination therapy. Fewer patients given EBRT alone maintained continence (rates NR, adjusted RR 0.51, 95% CI 0.29 to 0.90, moderate to large effect) than those undergoing surgery along with EBRT.

Among three fair-quality NRSIs, one study reported better relief of MSCC with surgery than without, while two studies reported no effect. In one study (N=287),[123] 53.4 percent of surgical patients had better Frankel scores after 8 weeks, compared with 33.3 percent of those given EBRT alone (RR 1.60, 95% CI 1.17 to 2.19, moderate improvement). However, a smaller study (N=46)[137] found no difference in the number of patients with better Frankel scores (D or E) after treatment (85.7% with surgery vs. 72.0% without, RR 1.19, 95% CI 0.88 to 1.61). In a third study (N=201)[126] there was no effect on improved motor function at 26 weeks (22.4% vs. 16.4%, RR 1.36, 95% CI 0.76 to 2.45) or ambulation after treatment (67.2% vs. 61.2%, RR 1.10, 95% CI 0.89 to 1.36) with surgery and EBRT compared with EBRT alone.

One poor-quality NRSI[109] of SBRT and surgery compared with SBRT alone (N=57) showed no difference in rates of improved Frankel scores (timing NR). Events were few, and the estimate imprecise (SBRT and surgery 14.3% vs. SBRT 10.4%, RR 1.37, 95% CI 0.36 to 5.22).

3.4.2.2.3 Function

One NRSI (N=46)[137] showed a small potential improvement in overall function associated with surgery: 85.7 percent of patients undergoing surgery with EBRT had better scores on the Karnofsky Performance Scale (80 to 100), compared with 60 percent of those given EBRT alone, though the difference was not statistically significant (RR 1.34, 95% CI 0.95 to 1.89).

3.4.2.2.4 Quality of Life

Two NRSIs reported overall quality of life, using the FACIT-G[123] or the EORTC-QLQ-C30.[137] We rescaled both instruments to range 0 to 100, with higher scores reflecting better quality of life. The studies showed moderate improvement in quality of life associated with surgery: mean score after treatment was 46.5 for surgery with EBRT compared with 34.8 for EBRT alone (2 NRSIs, N=333, pooled MD 10.96, 95% CI 9.00 to 13.79, $I^2 = 0.0\%$).[123,126]

3.4.2.2.5 Secondary Outcomes

None of the included studies reported need for re-irradiation. Secondary outcomes for these comparisons (local control, medication use and overall survival) can be found in Results Appendix B.

3.4.2.2.6 Harms and Adverse Events

One NRSI (N=287)[123] reported nerve damage associated with treatment: low-grade postoperative nerve damage in the surgical group, and damage associated with radiation therapy in the group given EBRT alone. Rates of nerve damage were lower with surgery than with radiation therapy (4.7% vs. 12.5%, RR 0.38, 95% CI 0.16 to 0.88); nerve damage association with EBRT in the surgical group was not reported. The most common complications in the EBRT group in this study were post-RT dermatitis (30.7%, 27/88) and hematological problems (25%, 22/88); these complications were not reported for those in the combined EBRT and surgery group.

In one poor-quality NRSI[109] of SBRT and surgery (N=57 patients, 69 lesions), none of the patients treated with SBRT and surgery sustained a pathological fracture; among lesions treated with SBRT alone, five fractures occurred (4 after hypofractionated therapy of 20, 27 or 30 Gy and 1 after single-fraction therapy of 16 to 23 Gy), though the effect estimate was imprecise (0% vs. 10.4%, RR 0.20, 95% CI 0.012 vs. 3.50). There was one case of mild esophagitis (treatment group not reported). There were no cases of radiation induced myelopathy.

3.4.3 EBRT Plus Dexamethasone Versus EBRT

3.4.3.1 Description of Included Studies

Two RCTs[57,98] compared EBRT with dexamethasone to EBRT alone for the palliative treatment of bone metastases (Appendix E, Table E-1). One RCT[98] enrolled patients with MSCC and gave dexamethasone to improve motor deficits. The other trial[57] excluded patients with MSCC and gave dexamethasone to mitigate an adverse effect of EBRT (pain flare).

The first RCT[98] included 57 patients with MSCC, 63 percent of whom were ambulatory at baseline. Median age was 62 years, and 32 percent of patients were male. Most patients (60%) had primary breast tumors, with gastrointestinal (11%) and prostate (9%) tumors next most common. Non-spine metastases were not reported. Total EBRT dose was 28 Gy, given in seven daily 4-Gy fractions; dexamethasone dose started at 96 mg/day and was tapered off over 1.4 weeks. Previous treatment for epidural metastasis was an exclusion criterion. Followup was 104 weeks or until death (actual followup not reported). The trial was conducted at a single center in Denmark, with nonprofit funding, and was rated poor quality for unclear randomization and allocation concealment methods, differences between groups in sex at baseline, lack of blinding and failure to report attrition (Appendix F, Table F-1).

The second trial[57] enrolled 298 patients with painful bone metastases but without MSCC or pathologic fracture. Median age was 69 years, and 57 percent of patients were male. Primary tumor histology was lung (28%), prostate (25%), breast (22%) and other solid tumors (25%). Site of metastasis was mixed, with 35 percent spine and 65 percent nonspine; 78 percent of patients had solitary metastases, and 22 percent had multiple metastases. At baseline most patients (55%) had Karnofsky score of 70 to 80, and worst pain score of 7 to 10 (51%). EBRT was given in a single 8-Gy fraction, and dexamethasone dose was 8 mg/day for 5 days (one dose before EBRT and 4 doses after). Patients had narcotics prescribed at baseline, but prior radiation therapy, recent or concurrent systemic steroids, NSAIDs, and planned chemotherapy were exclusion criteria. Median followup was 6 weeks. The trial was conducted at 23 centers in

Canada, received government and university funding, and was rated good quality (Appendix F, Table F-1).

3.4.3.2 Detailed Synthesis

3.4.3.2.1 Pain

One good-quality RCT (N=298)[57] showed a small potential improvement in overall pain response at 6 weeks in patients treated with dexamethasone compared with EBRT alone (43.2% vs. 34.7%, RR 1.25, 95% CI 0.94 to 1.66), though the result was not statistically significant. Pain score reduction at 1.4 weeks also showed a small potential benefit with dexamethasone (-2.37 vs. -1.85, MD -0.52, p=0.09, 0 to 10 scale), again not statistically significant.

3.4.3.2.2 Relief of Spinal Cord Compression

A small, poor-quality RCT (N=57)[98] showed a small potential improvement in ambulation in MSCC patients after treatment with dexamethasone and EBRT compared with EBRT alone (81.5% vs. 63.3%, RR 1.29, 95% CI 0.93 to 1.78). Dexamethasone was associated with higher rates of survival with ambulation over one year (p=0.046, Kaplan-Meier analysis), but the difference decreased between 26 weeks (59.3% vs. 33.3%, RR 1.78, 95% CI 0.98 to 3.22, moderate improvement) and 52 weeks (29.6% vs. 20%, RR 1.48, 95% CI 0.59 to 3.73, no difference).

3.4.3.2.3 Quality of Life

A good-quality trial (N=298)[57] assessed quality of life using the EORTC-QLQ-C15-PAL, adapted for patients in palliative care, and the EORTC-QLQ-BM-22, a module for patients with bone metastases. Dexamethasone with EBRT was associated with a small reduction in functional interference from bone metastases compared with EBRT alone (BM-22 -10.5 vs. -3.8, MD -6.70, 95% CI -11.75 to -1.65 on a 0 to 100 scale at 1.4 weeks). The C15-PAL showed a decrease in nausea scores with dexamethasone and EBRT compared with EBRT alone; however, the number of patients reporting nausea as an adverse event was similar between groups (reported with adverse events). Increased appetite reported on the Dexamethasone Symptom Questionnaire was greater with dexamethasone (7.2 vs. -0.6, MD 7.80, 95% CI 2.18 to 13.42 on a 0 to 100 scale, small improvement). There was also a small improvement in the change in appetite scores on the EORTC-QLQ-C15-PAL (-2.7 vs. 4.5, MD -7.20, 95% CI -14.71 to 0.32, 0 to 100 scale). This trial found no difference between treatments in C15-PAL scores for physical or emotional scales.

3.4.3.2.4 Secondary Outcomes

None of the included trials reported need for re-irradiation. Secondary outcomes for this comparison (medication use and overall survival) can be found in Results Appendix B.

3.4.3.2.5 Harms and Adverse Events

The primary purpose of dexamethasone in one good-quality RCT (N=298)[57] was to prevent pain flare associated with EBRT. The trial showed a small potential benefit with dexamethasone, but this difference did not reach statistical significance: 26.4 percent of patients treated with dexamethasone experienced pain flare within 1.4 weeks, compared with 35.3 percent of those given EBRT alone (RR 0.75, 95% CI 0.53 to 1.05). There was a moderate potential decrease with dexamethasone in grade 3 to 5 bone pain reported as an adverse event (7.5% vs. 14.0%, RR 0.54, 95% CI 0.27 to 1.08). There was no difference between patients treated with dexamethasone and EBRT compared with EBRT alone in rates of Grade 1 or 2 nausea (23.1%

vs. 23.8% of patients, RR 0.97, 95% CI 0.64 to 1.47), and the estimate was imprecise. (No patient in either group experienced grade 3 or higher nausea.) However, the EORTC-QLQ-C15-PAL showed a small improvement in nausea scores associated with dexamethasone (-0.6 vs. 8.0, MD -8.60, 95% CI -15.37 to -1.83 on a 0 to 100 scale at 1.4 weeks). Grade 3 to 4 fatigue, anorexia, hyperglycemia, constipation, and bloating were infrequent (0% to 2.1%) and did not differ between treatment arms. The second, poor-quality trial[98] only reported significant side effects related to high-dose dexamethasone (Appendix E, Table E-1).

3.4.3.2.6 Differential Effectiveness or Safety

There is insufficient information on differential effectiveness from one RCT that compared MF EBRT plus dexamethasone with MF EBRT alone based on a subanalysis of primary tumor type.[98] The trial did not report tests for interaction. While substantial overlap in confidence intervals may suggest that the factors did not differentially impact effectiveness or harms, the trial was underpowered to effectively evaluate modification. Thus, conclusions are not possible. Data are found in Results Appendix B, Table B-39.

3.4.4 EBRT Plus Bisphosphonates Versus EBRT

3.4.4.1 Description of Included Studies

One RCT[105] and two NRSIs[119,135] (all considered poor quality) compared EBRT with bisphosphonates to EBRT alone for palliation of bone metastases (Appendix E, Tables E-1 and E-2). None of the three studies reported spinal cord compression at baseline.

The RCT enrolled 40 patients, all with bladder cancer.[105] Median age was 54 years (mean not reported), and 78 percent of participants were male. The most common site of metastases was the pelvis (73%), followed by the spine (55%) and the femur, humerus, and ribs (25% for each site). Thirty percent of patients had a single metastasis, 32.5 percent had two or three, and 37.5 percent had four or more. Patients with visceral metastases were excluded. Total EBRT dose was 13 Gy (6.5 Gy x 2 over 24 hours) in 65 percent of patients, and 20 Gy (4 Gy x 5 over 4 days) in 35 percent. Patients were randomized to receive zoledronate (4 mg intravenous) or placebo (i.e., EBRT alone group) given monthly over 6 months. Two patients in the control group received chemotherapy during the study; analgesia was available to all patients, but opioid use was not specified. Eighty percent of patients had prior radical cystectomy. Median followup was 24 weeks. The trial took place at a single academic center in Egypt, and source of funding was unclear. The trial was assessed as poor-quality due to unclear randomization and allocation concealment methods, inadequate data to compare treatment groups at baseline, lack of blinding and failure to report attrition (Appendix F, Table F-1).

Median age was 65 years in one NRSI,[119] and not reported in the other.[135] Across the two studies, 56 percent of participants were male, 41 percent had spine metastases, and 47 percent had visceral metastases. One study included only patients with renal cell carcinoma, who were classified into favorable- (3%), intermediate- (77%), and high (19%) -risk groups.[119] In the other NRSI, breast (32%), colorectal (19%) and lung cancer (15%) were most common primary tumor types; 75 percent of bone metastases were osteolytic, and 25 percent osteoblastic.[135] All patients in the latter study had complete or impending pathologic fractures and were treated with radiation therapy after stabilizing orthopedic surgery. Median total dose was 39 Gy in one study, given in 5 fractions over 5 weeks, and 30 Gy in the other, with 10 fractions in 35 percent and 2 fractions in 19 percent of patients (duration not reported). Zoledronate was given every 3 to 4 weeks at a dose of 4 mg in the study with mixed primary tumor types; the dose was reduced

based on renal function in the study of patients with renal cell carcinoma (actual doses not reported). In this study 77 percent of patients had undergone nephrectomy, and 55 percent had systemic treatment in addition to study drugs, including sunitinib, interferon, interleukin-2, sorafenib, everolimus, and temsirolimus. For patients receiving zoledronate, the effect of treatment with sunitinib was also reported. Median followup was 87 weeks in this study, and 39 weeks in the study of patients undergoing orthopedic surgery. Both were single-center studies, one set in Japan, the other in Germany, and both were rated poor quality because of unclear methods for patient selection and for ascertainment of exposures and outcomes, baseline characteristics that differed across groups or were not clearly reported, retrospective design, blinding not reported, and no control for confounding (Appendix F, Table F-2).

3.4.4.2 Detailed Synthesis

3.4.4.2.1 Pain and Function

One RCT (N=40)[105] reported pain scores at 52 weeks using the BPI. Zoledronate given with EBRT was associated with a moderate benefit compared to EBRT alone (BPI 2.95 vs. 4.37, MD -1.42, 95% CI -1.76 to -1.08, 0 to 10 scale).

None of the included studies reported function outcomes.

3.4.4.2.2 Secondary Outcomes

None of the included studies reported need for re-irradiation separately (see harms below). Secondary outcomes for this comparison (local control and overall survival) can be found in Results Appendix B.

3.4.4.2.3 Harms and Adverse Events

One RCT (N=40)[105] reported the risk of skeletal-related events (SREs), defined as pathologic fractures, spinal cord compression, hypercalcemia of malignancy, or the need for additional radiation or bone surgery. Among patients given zoledronate with EBRT, 60 percent had at least one SRE, compared with 90 percent of those receiving EBRT plus placebo (RR 0.67, 95% CI 0.45 to 0.98, moderate benefit). One NRSI (N=62)[119] reported a composite SRE measure similar to the RCTs (pathologic fracture, spinal palsy with ambulatory disorder, impending fracture or palsy, or pain requiring re-irradiation or surgery), and like the trial found moderate benefit associated with the addition of zoledronate: 73 percent of patients given combination therapy were SRE-free at 104 weeks, compared with 44.4 percent of those given EBRT alone (RR 1.67, 95% CI 1.05 to 2.66). Among patients treated with zoledronate (in addition to EBRT) in this study, SRE-free rates were higher in those also given sunitinib (92% with sunitinib vs. 53% without).

One poor-quality NRSI (N=72)[135] found no difference in pain flare between patients treated with zoledronate and EBRT compared with those given EBRT alone, and the estimate was imprecise (16.1% vs. 18.8%, RR 0.86, 95% CI 0.29 to 2.53). One poor-quality RCT (N=40)[105] only stated that adverse events were similar and that none of the following events occurred in either group: gastrointestinal side effects, uveitis, local reaction at injection site, frozen bone, or jaw osteonecrosis.

3.4.5 EBRT Plus Radioisotopes Versus EBRT Alone

3.4.5.1 Description of Included Studies

Three RCTs (reported in 4 publications)[77,78,85,97] compared EBRT plus a radioisotope versus EBRT alone for the palliative treatment of bone metastases (Appendix E, Table E-1). Across the RCTs, sample sizes ranged from 64 to 126 (total N=221). The average study mean age of participants was 70 years (range 67 to 73 years). Two trials[77,78,85] enrolled only males; the proportion of males was not reported in the remaining trial.[97] None of the trials reported on race or ethnicity, comorbidities, or social determinants of health. In two of the trials, the primary tumor was in the prostate,[77,78,85] and in the remaining trial the primary tumor types were prostate (69%), breast (20%) and other locations (11%).[97] None of the trials reported the primary tumor histology in terms of favorable or unfavorable. None of the trials reported the location or characteristics of bone metastases, though the inclusion criteria of one of the trials[85] required multiple bone metastases at enrollment.

EBRT dosage varied among the trials. One trial[78] utilized a dose-fractionation scheme that included either 8 Gy single fraction or multiple fraction doses of 20 Gy (4 Gy in 5 fractions) over 1 week or 30 Gy (3 Gy in 10 fractions) over 2 weeks. Dosage in the second trial[85]was 30 Gy (3 Gy in 10 fractions) for 14 days or 20 Gy (5 Gy in 4 fractions) for 7 days. In the third trial,[97] the planned dosage was 30 Gy (3 Gy in 10 fractions), although the study reported that some patients received 8 Gy single fraction; the timing of EBRT delivery was not reported in this trial. None of the trials clearly reported the specific type of EBRT employed but it was most likely 2D or 3DCRT. Radioisotopes used in the studies were radium-223[78] or strontium-89.[85,97] Concomitant use of NSAIDs or other pain medication was permitted in all three trials, though the proportion of patients using specific treatments was not reported apart from baseline opioid used which was 50 percent in one trial.[85] One trial[78] excluded patients with previous radiotherapy and prior therapy was unclear in one trial.[85] In the third trial, the proportion of previously treated patients was 28 percent for radiotherapy, 12 percent for chemotherapy and 17 percent for hormone therapy.[97] Duration of followup was 6 months in two trials[85,97] and 2 years in the remaining trial.[77,78]

Two trials were conducted in Europe,[77,78,97] and one in Canada.[85] Two[77,78,85] were multicenter studies and one[97] was a single center study. Funding (by a private source) was only reported in one study.[77,78]

One trial was good quality[77,78] and two were fair quality[85,97] (Appendix F, Table F-1). Limitations of the fair quality studies included unclear randomization and allocation concealment, between-group differences at baseline, and high rates of attrition, which is to be expected in this patient population due to high mortality (range 60% to 78%).

3.4.5.2 Detailed Synthesis

3.4.5.2.1 Pain

Pain outcomes were reported in two trials.[85,97] Overall pain response, reported in one trial of EBRT plus strontium-89 versus EBRT plus placebo (N=70), was not different between groups at 12 or 26 weeks (data not reported).[97] In another trial (N=124), use of EBRT plus strontium-89 resulted in a higher proportion of patients reporting both complete (range of RRs, 1.01 to 2.34) and partial (range of RRs, 1.05 to 2.30) pain response at timepoints ranging from 4 to 26 weeks, although the difference between the treatment and control groups was not always statistically significant.[85] In the same trial, for complete pain response, the addition of strontium-89 to EBRT (vs. EBRT alone) resulted in a moderate increase in the likelihood of achieving response at 12

weeks (50.7% vs. 33.3%; RR 1.52, 95% CI 0.98 to 2.36) and a large increase at 21 weeks (65.7% vs. 28.1%; RR 2.34, 95% CI 1.49 to 3.67; absolute risk difference [ARD] 0.38, 95% CI 0.21 to 0.54). Results for partial pain response were similar, with the combined treatment conferring a small increase in the likelihood of achieving response at 12 weeks (77.6% vs. 59.6%; RR 1.30, 95% CI 1.10 to 1.67; ARD 0.18, 95% CI 0.02 to 0.34) and 21 weeks (80.6% vs. 64.9%; RR 1.24, 95% CI 0.99 to 1.55) and a large increase at 26 weeks (80.6% vs. 35.1%; RR 2.30, 95% CI 1.58 to 3.33; ARD 0.46, 95% CI 0.30 to 0.61).

3.4.5.2.2 Skeletal Function

Skeletal function was not reported in any of the trials, but one trial reported a composite outcome of skeletal-related events.[78] Skeletal-related events comprised a wide range of outcomes, including increased pain, analgesic consumption, palliative treatment for skeletal pain, and new fracture (vertebral or nonvertebral). There was no difference between EBRT plus radioisotope and EBRT alone in either time to first skeletal-related event (14 weeks vs. 11 weeks, adjusted HR 1.75, 95% CI 0.96 to 3.19) or in the proportion of patients with a skeletal-related event at 16 weeks (51.5% vs. 58.1%, RR 0.89, 95% CI 0.57 to 1.39) or at 52 weeks (78.8% vs. 83.9%, RR 0.94, 95% CI 0.74 to 1.19).

3.4.5.2.3 Quality of Life

Quality of life was narratively reported in two trials.[85,97] One trial (N=124)[85] reported that the addition of strontium-89 to EBRT was associated with "superior" quality of life outcomes (p=0.006) and the other trial (N=70)[97] reported no statistically significant difference between treatment and control groups for any domain on the Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer (QLC C-30) at 3-month followup.

3.4.5.2.4 Secondary Outcomes

Patients in the EBRT plus strontium-89 group were less likely to require re-irradiation compared to those treated with EBRT plus placebo in one RCT (N=124); risk estimates consistently favored the combined group from 26 to 74 weeks (RRs ranged from 0.57 to 0.68), and absolute risk differences between groups ranged from 19.3 to 40.3 percent (Appendix E, Table E-1).[85]

Results for other secondary outcomes (local control and overall survival) can be found in Results Appendix B.

3.4.5.2.5 Harms and Adverse Events

Harms and adverse events were inconsistently reported (Appendix E, Table E-1). One trial (N=63) reported no difference between EBRT plus radium-223 and EBRT alone in risk of serious adverse events, hematological toxicity, or most specific adverse events (e.g., diarrhea, vomiting, and nausea).[78] A second trial (N=124) found EBRT plus strontium-89 associated with an increased risk of Grade 3 or 4 thrombocytopenia (34.3% vs. 3.5%) and Grade 1 or 2 leukopenia (55.2% vs. 21.1%) with imprecise risk estimates (RR 9.78, 95% CI 2.41 to 39.72 and RR 2.62, 95% CI 1.52 to 4.53) compared with EBRT alone.[85] EBRT plus a radioisotope was associated with a higher rate of constipation in one trial and a higher rate of hemorrhage in another trial compared with EBRT alone, but for both outcomes there were few events (36% [12/33] vs. 6% [2/31] for constipation and 14.9% [10/67]) vs. 5.2% [3/57] for hemorrhage) and risk estimates were imprecise (RRs 5.64, 95% CI 1.37 to 23.19 and 2.84, 95% CI 0.82 to 9.81). Harms and adverse events were not reported in the third trial.[97]

3.4.6 EBRT Plus Cryoablation Versus EBRT Alone

3.4.6.1 Description of Included Studies

One NRSI[112] compared EBRT plus cryoablation (use of extreme cold to kill cancer cells) with EBRT alone (Appendix E, Table E-2). Of 175 participants enrolled, 150 were treated with EBRT plus cryoablation (n=25) or EBRT alone (n=125). (The remaining 25 patients were treated with cryoablation alone and are described under Key Questions 3a and 3c.) Patients were matched via propensity score analysis. The mean patient age was 68 years and 49 percent were male. Comorbidities, social determinants of health and race/ethnicity were not reported. Mean Karnofsky score ranged from 70 to 89 in about half of the participants (49%) and 91 to 100 in the other half (51%). Primary tumor types included prostate (33%), lung (29%), breast (24%), colorectal (7%), and renal (6%). The study did not report primary tumor histology in terms of favorable or unfavorable or bone metastases in terms of complicated or uncomplicated. Enrollment criteria required the presence of a single, painful bone metastases, which was present primarily in the pelvis (41%), sacrum (24%), or vertebrae (17%). Spinal cord compression and treatment site fracture were exclusion criteria.

The EBRT dose was 20 Gy (4 Gy x 5) over one week and was delivered 15 days after cryoablation. The specific type of EBRT employed was not reported but was most likely 2D or 3DCRT. Percutaneous cryoablation (-100° C) was delivered in two, 15-minute sessions separated by 10 minutes. Concomitant treatments included narcotic analgesics in 100 percent of participants. Previous treatments were not reported. The duration of followup was 12 weeks.

The study was conducted in Italy, in a single center; no funding source was reported. The study was rated fair quality. Limitations included unclear overall and differential attrition and lack of blinding (Appendix F, Table F-2).

3.4.6.2 Detailed Synthesis

3.4.6.2.1 Pain

Pain response was assessed at 12 weeks.[112] EBRT plus cryoablation was associated with a moderate increase in the likelihood of achieving an overall pain response compared with EBRT alone (84% vs. 53.6%, RR 1.57, 95% CI 1.24 to 1.99). Results similarly favored EBRT plus cryoablation for complete response, but the estimate was imprecise (72% vs. 11.2%, RR 6.43, 3.71 to 11.15).

3.4.6.2.2 Quality of Life

Quality of life was assessed using the meaningful existence subscale of the McGill Quality of Life Questionnaire.[112] At 12 weeks, patients in the EBRT plus cryoablation group reported higher quality-of-life scores than those in the EBRT alone group (7, 95% CI 5.4 to 9 vs. 5, 95% CI 4 to 5). While this difference was statistically significant (p=0.003), the clinical significance of this finding is unclear.

3.4.6.2.3 Secondary Outcomes

The NRSI did not report need for re-irradiation. Secondary outcomes for this comparison (medication use) can be found in Results Appendix B.

3.4.6.2.4 Harms and Adverse Events

Comparative harms were not reported (only harms associated with cryoablation) (Appendix E, Table E-1).

3.4.7 EBRT Plus Hyperthermia Versus EBRT Alone

3.4.7.1 Description of Included Studies

One RCT (N=57)[56] compared EBRT plus hyperthermia (n=29) with EBRT alone (n=28). (Appendix E, Table E-1). The mean age was 58 years and 56 percent were male. Race/ethnicity, social determinants of health, and comorbidities were not reported, although trial inclusion criteria required an ECOG score between 0 and 3 at baseline. The primary tumor type was breast or prostate in 19 percent of the population; tumor type was not reported for the remaining 81 percent of the population. A single bone metastasis was present in 44 percent of the population, and 56 percent had multiple bone metastases. Fifty percent of metastases were in the spine, 28 percent were in pelvic bones, and 21 percent were in the sternum, ribs or extremities. Patients with previous radiotherapy at the metastatic site or with a pathologic fracture requiring surgery were excluded from the trial; presence of spinal cord compression was not reported.

The EBRT dose was 30 Gy (3 Gy x 10 fractions) over 2 weeks. The specific type of EBRT employed was 3DCRT. Hyperthermia was delivered over 2 weeks for a total of four sessions of at least 40 minutes per session using targeted heating (median 559 watts) through the Thermatron R-8 device. Concomitant analgesic use was permitted per inclusion criteria, but specific rate of use was reported. The duration of followup was 12 weeks.

The trial was conducted in Taiwan, in a single academic (university) center; funding was through the university. The RCT was rated poor quality due to numerous limitations that included unclear randomization, allocation concealment, reporting of attrition and loss to followup (Appendix F, Table F-1). The trial initially had a planned 3-year duration and an enrollment of at least 152 patients but was stopped early at 3 months due enrollment difficulties and due to the observed complete response in the EBRT plus hyperthermia group. As a result, the trial was underpowered to detect differences between treatment groups.

3.4.7.2 Detailed Synthesis

3.4.7.2.1 Pain

Overall pain response was not reported. Complete response was assessed at 4, 8, and 12 weeks.[56] There was no clear difference between EBRT plus hyperthermia and EBRT alone in the proportion of patients achieving complete response at 4 weeks (24.1% vs. 14.3%, RR 1.69, 95% CI 0.55 to 5.14); however, EBRT plus hyperthermia was associated with large increases in likelihood of complete response at 8 (34.5% vs. 10.7%, RR 3.22, 95% CI 0.99 to 10.49) and 12 weeks (37.9% vs. 7.1%, RR 5.31, 95% CI 1.29 to 21.85). Risk estimates were imprecise at all timepoints. Among patients with a pain response, the median time to progression was not achieved in the EBRT plus hyperthermia group and was 28 days in the EBRT alone group.

3.4.7.2.2 Quality of Life

Quality of life was assessed using the European Organization for Research and Treatment of Cancer C30 (QLC C-30) questionnaire, which includes measures of physical function and global assessment of health. There were no differences between EBRT plus hyperthermia and EBRT alone groups at baseline. Between-group differences favoring EBRT plus hyperthermia were

observed at 4 and 8 weeks for both physical function and global health status, although these differences were not sustained at 12-week followup (Appendix E, Table E-1).[56] Interpretation of these results is challenging, as the study was not adequately powered to detect differences between groups and there was diminishing number of patients available for followup at 4 (EBRT plus hyperthermia n=29; EBRT alone n=24), 8 (EBRT plus hyperthermia n=22; EBRT alone n=7), and 12 weeks (EBRT plus hyperthermia n=18; EBRT alone n=2).

3.4.7.2.3 Harms and Adverse Events

Harms of treatment and adverse events occurred frequently in both groups but were generally mild; there were no Grade 3 or 4 adverse events in either group. About half (48.3%) of the patients in the EBRT plus hyperthermia group experienced local heating pain due to the hyperthermia treatment (Appendix E, Table E-1).[56]

3.4.8 EBRT Plus Capecitabine Versus EBRT Alone

3.4.8.1 Description of Included Studies

One RCT[52] (N=84) compared EBRT plus capecitabine (n=42) with EBRT alone (n=42). (Appendix E, Table E-1). The mean age was 47 years. Sex was not reported, but the trial enrolled only patients with breast cancer so presumably all or most patients were female. Race/ethnicity and social determinants of health were not reported. A single bone metastasis was present in 31 percent of the population, and 69 percent had multiple bone metastases; specific sites were not reported. In addition to bone metastases, 10 percent of patients had lung metastases and 12 percent had liver metastases. Spinal cord compression and treatment site fracture were exclusion criteria.

The EBRT dose was 30 Gy (3 Gy x 10 fractions) for 5 days. The specific type of EBRT employed was not reported. Oral capecitabine (825 mg/m^2) was given twice a day at the time of EBRT. The study group randomized to EBRT alone did not receive a corresponding oral placebo. The duration of followup was 12 weeks, and outcomes were assessed at 1, 2, 4, 8, and 12 weeks.

The trial was conducted in Egypt, in a single hospital radiology center; study funding was not reported. The RCT was rated fair quality due to unclear allocation concealment and blinding of outcome assessors and patients (Appendix F, Table F-1).

3.4.8.2 Detailed Synthesis

3.4.8.2.1 Pain

The addition of capecitabine to EBRT was associated with large increases in likelihood of overall pain response at 1 and 2 weeks, and moderate increases at 4, 8, and 12 weeks compared with EBRT alone; RRs ranged from 2.00 at 1 week to 1.89 at 12 weeks (Appendix E, Table E-1).[52] The proportion of patients in the EBRT plus capecitabine group with an overall pain response was 81.0 percent at 2 weeks and remained stable throughout the 12-week followup, while the proportion with an overall response in the EBRT group peaked at week 4 at 47.6 percent and declined slightly to 42.8 percent at 8 and 12 weeks. Risk estimates similarly favored the EBRT plus capecitabine for complete pain response, with RRs ranging from 3.00 to 2.25, corresponding to a large effect size, at 1 to 12 weeks. Differences between groups were less clear for partial pain response. The addition of capecitabine to EBRT had a moderate to large effect on the proportion of patients with a partial response at week 2 (RR 2.00, 95% CI 1.07 to 3.74) but not at other time points. Median VAS pain score was consistently 2 to 3 points lower with EBRT

plus capecitabine than EBRT alone across all time points; these differences were also statistically significant.

3.4.8.2.2 Secondary Outcomes

None of the included studies reported need for re-irradiation. Secondary outcomes for this comparison (medication use) can be found in Results Appendix B.

3.4.8.2.3 Harms and Adverse Events

No Grade 3 or 4 toxicity was reported in either group during trial followup and there was no difference between EBRT plus capecitabine and EBRT in treatment-related adverse events (e.g., nausea, diarrhea) (Appendix E, Table E-1).[52]

3.5 Key Question 3c. Effectiveness and Harms of EBRT Combined With Another Treatment Modality Versus the Same Treatment Modality Alone

3.5.1 Key Points

All evidence for Key Question 3c was considered *insufficient* to draw conclusions:

- **EBRT plus cryoablation versus cryoablation alone**: overall pain response, quality of life and harms from one fair-quality NRSI
- **EBRT plus radioisotopes (strontium-89) versus radioisotopes (strontium-89) alone**: pain response and harms from one poor-quality NRSI that did not control for confounding.
- **EBRT plus surgery versus surgery alone:** function from one fair-quality NRSI that did not control for confounding.

3.5.2 EBRT Plus Cryoablation Versus Cryoablation Alone

3.5.2.1 Description of Included Studies

One NRSI[112] compared EBRT plus cryoablation (use of extreme cold to kill cancer cells) with cryoablation alone (Appendix E, Table E-2). Of the 175 participants enrolled, 50 were treated with EBRT plus cryoablation (n=25) or cryoablation alone (n=25). (The remaining 125 patients were treated with EBRT alone and are described under Key Questions 3a and 3b.) Patients were matched via propensity score analysis. The mean patient age was 68 years and 50 percent were male. Comorbidities, social determinants of health and race/ethnicity were not reported. Mean Karnofsky score ranged from 70 to 89 in just over half (54%) of the patients and 91 to 100 in the other 46 percent. Primary tumor types included prostate (32%), lung (24%), breast (24%), renal (12%) and colorectal (8%). The study did not report primary tumor histology in terms of favorable or unfavorable or bone metastases in terms of complicated or uncomplicated. Enrollment criteria required the presence of a single, painful bone metastases, which was present in the pelvis (34%), sacrum (26%), vertebrae (17%), rib, humerus, or femur (8% each). Spinal cord compression and treatment site fracture were exclusion criteria.

The EBRT dose was 20 Gy (4 Gy x 5) over 1 week and was delivered 15 days after cryoablation. The specific type of EBRT employed was not reported but was most likely 2D or 3DCRT. Percutaneous cryoablation (-100° C) was delivered in two, 15-minute sessions separated by 10 minutes. Concomitant treatments included narcotic analgesics in 100 percent of participants. Previous treatments were not reported. The duration of followup was 12 weeks.

The study was conducted in Italy, in a single center; no funding source was reported. The study was rated fair quality. Limitations included unclear overall and differential attrition and lack of blinding (Appendix F, Table F-2).

3.5.2.2 Detailed Synthesis

3.5.2.2.1 Pain

Pain response was assessed at 12 weeks.[112] More patients achieved overall pain response after EBRT plus cryoablation compared with cryoablation alone, but the difference was not statistically significant (N=50, 84% vs. 68%, RR 1.24, 95% CI 0.90 to 1.70). However, EBRT

plus cryoablation was associated with a large increase in the likelihood of achieving a complete pain response compared with cryoablation alone (72% vs. 32%, RR 2.25, 95% CI 1.21 to 4.19).

3.5.2.2.2 Quality of Life

Quality of life was assessed using the meaningful existence subscale of the McGill Quality of Life Questionnaire.[112] At 12 weeks, patients in the EBRT plus cryoablation group reported higher quality-of-life scores than those in the cryoablation alone group (7, 95% CI 5.4 to 9 vs. 6, 95% CI 5 to 8) but the difference was not statistically significant (p=0.290).

3.5.2.2.3 Secondary Outcomes

The NRSI did not report the need for re-irradiation. Secondary outcomes for this comparison (medication use) can be found in Results Appendix B.

3.5.2.2.4 Harms and Adverse Events

Comparative harms were not reported (only harms associated with cryoablation) (Appendix E, Table E-1).

3.5.3 EBRT Plus Strontium-89 Versus Strontium-89 Alone

3.5.3.1 Description of Included Studies

One retrospective NRSI[134] compared strontium-89 plus EBRT (n=53) with strontium-89 alone (n=53) for palliation of multiple bone metastases from primarily lung (36%), breast (27%), prostate (17%), and epipharynx (14%) cancer (Appendix E, Table E-2). The sites of the bone metastases and other characteristics were not reported. Mean patient age was 57 years and 64 percent were male. Strontium-89 148 MBq was given once every 3 to 6 months. One month after strontium injection, patients in the combination group received EBRT 30 to 60 Gy (delivery technique and fractionation scheme not reported) over 2 to 4 weeks. The study was conducted in China at a single center and was rated poor quality because of unclear methods for patient selection and for ascertainment of exposures and outcomes, baseline characteristics were not robustly reported, blinding not reported, and no control for confounding, though primary tumor types were balanced across treatment groups (Appendix F, Table F-2).

3.5.3.2 Detailed Synthesis

3.5.3.2.1 Pain

There was no difference between EBRT plus strontium-89 and strontium-89 alone in the proportion of patients who achieved overall pain response, defined as no or improved pain and normal or improved sleep and activities of daily living (90.6% vs. 83.0%, respectively, RR 1.09, 95% CI 0.94 to 1.27), or complete pain response (no pain and normal sleep and activities of daily living) (49.1% vs. 43.4%, RR 1.13, 95% CI 0.75 to 1.71).[134] The timing of measurement was unclear.

3.5.3.2.2 Secondary Outcomes

None of the included studies reported need for re-irradiation. Secondary outcomes for this comparison (local control) can be found in Results Appendix B.

3.5.3.2.3 Harms and Adverse Events

EBRT-related harms were not reported. Authors state that there were no differences (p>0.05) between groups in the incidence of side effects related to strontium-99 immediately after injection (no cases) or at 4 to 6 weeks post injection (decrease of white blood cells and platelets, recovered by 12 weeks) but did not provide comparative data.[134]

3.5.4 EBRT Plus Surgery Versus Surgery Alone

3.5.4.1 Description of Included Studies

One fair-quality NRSI (N=60)[131] compared EBRT plus surgical stabilization versus surgical stabilization alone for palliation of pathological (61%) or impending (39%) fractures due to bone metastases (Appendix E, Table E-2). Patients were selected using inpatient International Classification of Diseases (ICD)-9 and surgical codes. Previous RT to the fracture site was an exclusion criterion. Fracture sites included femoral trochanter (33%), femoral shaft (30%), femoral head/neck (28%), humerus (5%), and other (5%). Primary cancer types were breast (33%), lung (23%) and prostate (13%), primarily. Surgical procedures were classified as either fracture fixation (75%) or an arthroplasty reconstruction (25%). Patients in the combined group received EBRT (median dose 30 Gy, fractions not reported) within a median of 14 days postoperatively. An equal number of patients who received the combine treatment had pathologic (51%) or impending (49%) fracture whereas those treated with surgery alone had primarily pathologic fractures (72%). Several other baseline characteristics differed between the two groups: patients in the combined EBRT plus surgery group were younger (58 vs. 64 years) with a greater proportion of females (69% vs. 55%) as well as with lung cancer as the primary tumor type (31% vs. 14%). Patients in the combined group also had better extremity functional status before fracture (Grade 1 [normal, pain free], 88% vs. 58%). Authors performed multivariate logistic regression analyses to control for these imbalances. The study was conducted in the United States at two sites and was rated fair quality because of concerns around the use of ICD-9 and procedures codes to accurately select patients and lack of blinding (Appendix F, Table F-2).

3.5.4.2 Detailed Synthesis

3.5.4.2.1 Function

Combined EBRT and surgery resulted in a large increase in the likelihood of achieving functional status Grade 1 or 2 (normal use of extremity with or without pain) at any timepoint compared with surgery alone in multivariate analysis: 52.9 percent versus 11.5 percent, RR 4.59, 95% CI 1.51 to 13.93, however the estimate was imprecise.[131] The combined group also had a significantly higher likelihood of achieving Grade 1 or 2 functional status at all time frames measured up to 12 months (1–3, 3–6, and 6–12 months; p<0.04); after 12 months the difference between groups was borderline significant (p=0.06) in favor of the combined group (data not provided).

3.5.4.2.2 Secondary Outcomes

No patient in the combined EBRT plus surgery group underwent re-irradiation compared with 11.5 percent of patients in the surgery only group (at 1, 2, and 27 months postoperatively).[131] Other secondary outcomes (need for additional treatment and overall survival) can be found in Results Appendix B.

3.5.4.2.3 Harms and Adverse Events

The study did not report harms.

3.6 Contextual Questions

The three contextual questions below describe factors impacting guideline implementation, strategies for promoting implementation and considerations related to patient financial distress. Answers to these questions were informed by peer-reviewed literature captured by our search and limited supplemental searches specific to guideline implementation and financial burden, government reports and conversations with our Technical Expert Panel. Additional information is found in Appendix C.

3.6.1 Contextual Question 1. Common Barriers and Facilitators to Guideline Implementation

3.6.1.1 Key Points

- Despite the existence of Clinical Practice Guidelines (CPGs) there is great heterogeneity in application of radiation therapy for MBD with relative underutilization of single fraction RT
- Barriers to implementation of CPGs include healthcare professional factors, guideline-related factors and external factors, including healthcare organizations, communities of practice and patients
- Facilitators include CPGs that are accessible and easy to use, commitment to resources needed to support implementation, accessibility to the multidisciplinary care model, incentives toward education and practice improvement for all care team members
- Palliative medicine professionals value an individualized approach to management of serious illness; they did not view the use of CPGs to be inconsistent with high-quality palliative care
- Patients appreciate the opportunity to participate in creation of their radiation treatment plan.

3.6.1.2 Detailed Synthesis

Clinical Practice Guidelines are created with the intent of maximizing quality and consistency of patient care. The benefit of CPGs to clinicians and patients is contingent on effective implementation. Despite the existence of CPGs for palliative radiation therapy of MBD and general consensus that single fraction radiation treatment (SFRT) offers patients equal equivalent pain-relief with increased convenience and decreased financial burden, there is great heterogeneity in application of guidelines with relative underutilization of single fraction radiotherapy.

We identified two reviews[145,146] that provide a broad framework for understanding the barriers and facilitators to implementing CPGs across healthcare. Two other reviews explore barriers and facilitators specific to cancer care and endorse similar themes.[147,148]

Barriers are organized into the following categories: healthcare professional factors, guideline-related factors and external factors. Amongst healthcare professional factors, the most significant contributors are knowledge deficits around CPGs and attitude toward practice change, including confidence and motivation. Factors related directly to CPGs include strength of evidence, feasibility of implementation and applicability to real-world patients, particularly complex patients. External factors included those associated with healthcare organizations, communities of practice and patients themselves. Clinicians benefit from strong leadership, a culture of continuous learning, support for interprofessional/multidisciplinary practice and

availability of resources. Patient factors were broadly identified by the review articles as lack of knowledge of diagnosis and guidelines as well as lack of trust in or involvement with care team around decisions.

One review[149] sought to understand the attitude toward acceptance of CPGs amongst over a thousand palliative care professionals in Germany. This multidisciplinary cohort included physicians (55.5%) and nurses (30.3%) as well as mental and spiritual health professionals, with 15.2% of physician participants practicing cancer care. This study revealed significant skepticism around the quality of CPGs and concern that they offer a "one-size-fits-all" approach rather than the holistic/patient-centered approach prioritized by palliative care clinicians. Another review[147] similarly identified this concern for "cookbook medicine" amongst cancer care clinicians. Nonetheless, the providers in the first study felt the existence of CPGs for palliative patients was not inherently inconsistent with high-quality palliative care nor palliative care values.[149]

Regarding palliative radiation for MBD, two studies looked at patient preference for single versus multi-fraction treatment regimens. One offered education based on the Dutch Bone Metastasis Study to a cohort of patients at a university hospital system in Singapore.[150] They found that 85 percent of these patients chose multi-fraction. Patients attributed this preference to lower rates of re-treatment and decreased frequency of fractures. For the patients that did elect the single fraction regimen, they credited convenience and cost. The other study evaluated a cohort of patients at a Canadian cancer center and, with aide of a decision tool, 76 percent of this group favored a single fraction regimen.[151] Though outcome differed, the same main factors were most influential: convenience as the reason for SFRT and risk for fracture supporting MF. Regardless of treatment regimen preference, both studies found that patients strongly appreciated the opportunity to participate actively with choosing their own treatment plan. Some of the variability in these studies may relate to difference between Asian and Canadian populations. We did not find any similar studies conducted in American healthcare setting. In addition to the barriers described above, Technical Expert Panel members described additional potential barriers to implementing clinical guidelines on palliative radiation for patients with MBD, including challenges in the referral process, referring provider unawareness of treatment options, general requirement for treatment at local facilities, and financial incentives.

Facilitators for implementation of CPGs are largely intuitive based on the barriers noted above. Clinicians and patients benefit from CPGs that are accessible and easy to use and benefit from the translation of CPGs into practical decision guides and patient communication tools. From institutions and leaders, facilitative factors include commitment to technology and staff needed to support implementation, accessibility to multidisciplinary care model, as well as incentives toward education and practice improvement for all care team members.

Choosing Wisely is an initiative from the American Board of Internal Medicine Foundation aimed at streamlining access to guidelines and improving conversations between physicians and patients to promote evidence-based and truly necessary beneficial care. There is some discrepancy between recommendations by participating body: for instance, the American Society of Radiation Oncology includes "Don't routinely use extended fractionation schemes (>10 fractions) for palliation of bone metastases."[152] In contrast, the Canadian Medical Association and its cancer societies explicitly include: "Don't recommend more than a single fraction of palliative radiation for an uncomplicated painful bone metastasis," and the American Academy of Hospice and Palliative Medicine[153] suggest "Don't recommend more than a single fraction of palliative radiation for an uncomplicated painful bone metastasis." One study[19] found for the 196 patients treated with palliative radiation to MBD across the state of Michigan, 7.7 percent received SFRT and of the 70 patients with simple painful bone metastases, 12.9 percent received

SFRT. Another publication from Canada[16] found 50.2 percent utilization of SFRT, varying from 60 percent in British Columbia to 31 percent in Saskatchewan. While multiple structural factors likely underlie the variation in recommendations between societies, the variation may reflect opportunity for Choosing Wisely recommendations to facilitate changes in practice.

Among the tools found useful in promoting CPG implementation are the creation of algorithms or clinical pathways as explored by two studies[154,155] Toward that end, one of these studies[154] offers guidance for the creation and implementation of a radiation oncology treatment algorithm based on CPGs as well as patient and disease factors. The other study[155] investigates the impact of an electronic clinical pathway for maximizing guideline-concordant care and significantly finds an increase in appropriate SFRT rates from 18 percent pre-pathway to 48 percent post-pathway. Additional strategies are further discussed in Contextual Question 2.

3.6.2 Contextual Question 2. Strategies To Promote the Use and Implementation of Guidance

3.6.2.1 Key Points

- The most effective strategies to promote guideline implementation appear to be the use of online clinical pathways and education-based interventions, particularly when use of peer review/audits were included.
- The least effective appear to be electronic medical record-based interventions; guideline dissemination appears to improve utilization and adherence, but impact may be transient.
- Novel payment care models/incentivized quality metrics provide an intriguing area of research though may benefit from targeting of radiation oncology providers who decide treatment decisions.

3.6.2.2 Detailed Synthesis

We identified 18 studies evaluating strategies intended to improve guideline uptake and adherence (Appendix C, Table C-1). Five evaluated some type of online platform with or without peer review or electronic medical record alert intended to increase use of single-fraction/short-course radiation regimens and reduce use of extended course treatment,[155-159] six focused on provider education followed by peer-review or practice audit,[160-165] two focused on guideline dissemination alone,[26,166] and two described the impact of a payment model or otherwise incentivized implementation of quality metrics.[167,168] One additional publication described clinical algorithm creation, presenting an example case,[154] and another analyzed the influence of physician peer-based groups alone.[169] One additional publication described the implementation of a dedicated palliative radiation oncology service line.[170] Ten studies were conducted in the United States,[155-159,165,167-170] five in Canada,[26,162-164,166] and three were conducted in Europe (United Kingdom, Italy, Switzerland).[154,160,161]

Briefly, with regard to the five studies evaluating online platforms or electronic medical record alerts, the interventions generally consisted of online care pathways designed to assist providers in deciding between fractionation regimens for palliation of bone metastases.[155-159] Clinical pathways were designed based on a variety of different inputs, including national guidelines, expert input, and literature review as well as prognostication scoring systems. Implementation either did or did not include a component of peer review prior to treatment.

The six studies evaluating education-based interventions utilized educational sessions based on literature review and national guidelines describing indications for single-fraction radiation treatment, often including a component of department-level or provider-level audit of single-

fraction radiation therapy rates.[160-165] The two studies focusing on guideline dissemination evaluated use of single-fraction radiation after release or electronic dissemination of clinical practice guidelines.[26,166]

Overall, the most effective interventions appear to be online clinical pathways or targeted educational interventions, which generally demonstrated increase in single-fraction or shorter-course radiation regimens/decrease in extended courses of radiation therapy after implementation.[155,157,158,160,162,163,165] These interventions varied widely in the included components as well as how educational intervention/clinical pathways were constructed, with variation in the degree of impact; degree of change may be influenced by the targeted group/practice environment though with some suggestion of improvement across both academic and community settings. Notably, a key component across effective interventions appears to be a component of peer review or provider auditing. A single study evaluating the impact of prospective peer review alone without pathway/education intervention was effective in changing practice patterns.[158] Furthermore, a single study evaluating electronic medical record-based alerts without peer review found no difference in compliance rates with national quality recommendations.[159]

The importance of leveraging peer review may also be reflected in the studies evaluating guideline dissemination alone. Generally, these studies demonstrated that guideline dissemination alone may not provide long-term changes in utilization. One study reports increased use of single-fraction radiation therapy immediately post-guideline dissemination but a return to pre-guideline levels within a few years, with minimal impact to inter-center variations in fractionation use.[26] The other study indicated no impact of guideline dissemination alone, with use of single-fraction radiation therapy varying widely between individual providers.[166]

Novel payment schemes designed to alter provider incentives in making treatment decisions remain an intriguing area of research, particularly in the United States where alternative payment models are being explored. One study evaluated the impact of the Oncology Care Model, an alternative payment model designed to improve the quality and value of care in oncology practices but found no effect on fractionation patterns;[168] however, this may reflect the design of the model, which focuses on episodes of chemotherapy administration and not directly on radiation oncology providers. A study that provided incentives to facilities meeting quality metrics regarding use of extended courses of radiation therapy for bone metastases found low levels of use followed the intervention.[167] Of note, the development of alternative payment models for radiation oncology providers has been approached in the United States and supported by the American Society for Radiation Oncology, though given debate regarding the components of the model an alternative payment model has not been implemented.

A final study evaluating the impact of a dedicated radiation oncology service line did demonstrate increases in the use of shorter-course radiation therapy regimens.[170] While such programs are gaining in popularity in the United States, implementation may be more restricted to academic settings that promote provider specialization, though community-based programs have been explored.

While these interventions overall suggest clinical pathways may increase uptake of single-fraction or shorter-course radiation regimens in concordance with national guidelines, challenges remain in the ability to handle nuanced individual patient care situations/refinement of necessary components to influence care without increasing unnecessary workflow disruptions. Complete uptake of such regimens may not be clinically appropriate for all patients though this is reflected in national guidelines, which note certain populations that were excluded or less reflected in trial data.

3.6.3 Contextual Question 3. Patient Financial Distress Based on EBRT Dose/Fraction Schemes or Techniques

There is insufficient information to draw firm conclusions about differences in patient financial distress or hardship by dose/fraction schemes or techniques across the four studies identified for this question. Future research is needed on how best to define and measure financial distress/toxicity and how to best measure this in symptomatic patients who are considering radiotherapy options for palliative treatment of MBD.

3.6.3.1 Key Points

- We did not identify any study that focused on, measured, or described patient financial distress or toxicity related to EBRT for palliative treatment of MBD.
- Very limited information across three studies suggests that fewer radiotherapy sessions may be less burdensome on patients. None of these studies were conducted in the United States. Given differences in health systems, insurance and care delivery, the applicability of findings from these studies is unclear.

3.6.3.2 Detailed Synthesis

While studies formally evaluating the costs or cost-effectiveness of radiotherapy techniques or fractionation schemes for palliative treatment of MBD were identified, they did so from a health system or payer perspective and did not assess the direct financial impact on patients.

We identified three studies which provided limited information describing patient financial burden by dose/fraction schemes for palliative radiotherapy for MBD. Three are based on RCTs included in this review.[79,94,171] One trial from Canada,[94] directly asked patients regarding perceptions of financial difficulty. In another study, a subset of patients from the Dutch Bone Metastasis Study answered a questionnaire regarding costs of nonradiotherapy and nonmedical costs as part of a cost-utility analysis.[171] An RCT from India, reported on costs of patient travel.[79] Study and patient information are found in Appendix C, Table C-2.

Only one study directly asked patients about financial difficulty. This fair-quality trial included in this review compared 24 Gy/2 fraction SBRT with 20 Gy/5 fraction conventional EBRT in 299 patients with confirmed spinal MBD who did not have neurological deficit.[94] Patient perception of financial difficulty was assessed based on the question “Has your physical condition or medical treatment caused you financial difficulties?” included in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30, 0-100 scale, higher scores worse difficulty). SBRT was associated with improved perception of financial strain compared with conventional EBRT based on mean change scores at 1 month, (-5.9 vs. 1.5 p=0.03) but the difference was no longer statistically significant at 3 or 6 months and large standard deviations suggest lack of precision (Appendix C, Table C2). More SBRT recipients reported improved perception of financial distress compared with conventional EBRT from baseline to 6 months (35% vs. 22%) and fewer reported worsening of financial distress (15% vs. 29%) with similar proportions of patients in each group reporting stability (50% vs. 48%). Authors conclude that SBRT was associated with improved perception of financial strain versus conventional EBRT and suggest that the finding could reflect more general financial strain in terminally ill patients as well as a differential effect of fewer sessions.

Another study evaluating a subset of patients (N=166) from the Dutch Bone Metastasis Study who completed cost questionnaires suggests that 8 Gy single fraction EBRT may be somewhat less burdensome for patients than 5 fractions of 4 Gy.[171] Authors do not clearly delineate which costs are paid by patients or describe financial distress. Estimated costs (in 2002 USD) for

radiotherapy (time travel, and out-of-pocket expenses) and for nonmedical costs (time/travel, out-of-pocket, domestic help, paid an unpaid labor) are assumed to be patient costs. SFRT was associated with lower estimated radiotherapy costs for time, travel and out-of-pocket expenses compared with multiple fraction radiation treatment (MFRT) ($134, 95% CI $87-$181 vs. $704, 95% CI $396 to $1012, p<0.001). There was no association between nonmedical costs overall or the individual components with fraction scheme however (Appendix C, Table C-2). Authors speculate that although retreatment was more common with SFRT versus MFRT (25% vs. 7%), most patients may find an extra SFRT less burdensome. Similarly, another included poor-quality RCT from India compared 8 Gy/1 fraction, 20 Gy/5 fractions and 30 Gy/10 fractions (N=60).[79] Compared with the SFRT, average travel distance and cost per patient were greater in the MFRT schemes. Formal statistical comparison across fractionation schemes was not reported for distance or cost. Authors concluded that the 20Gy/5 fraction may be more economically feasible than the 30Gy/10 fraction scheme and more favorable than the SFRT given lower frequency of re-irradiation (20% for SFRT vs. 5%). The only study conducted in the US retrospectively evaluated the National Cancer Data Base[172] and reported that in both univariate and multivariate analysis, greater distance to treatment was associated with increased odds of SFRT compared with MFRT use but provides no financial information; conclusions regarding patient financial impact are not possible.

4. Discussion

4.1 Findings in Relation to the Decisional Dilemmas

Planning for palliative radiation of symptomatic metastatic bone disease (MBD) is complex and presents numerous decisional dilemmas. Using a best evidence approach, our synthesis focuses on the best quality evidence directly comparing dose/fractionation schemes and techniques for initial radiation and re-irradiation for palliation of MBD to inform decision-making around these dilemmas.

The key findings and strength of evidence (SOE) for Key Question 1 are summarized in Tables 5–7, for Key Question 2 in Table 8, and for Key Question 3 in Tables 9–12. All focus on primary outcomes and harms. SOE is further detailed in Appendix G. In addition to the Key Questions, three contextual questions are addressed in the previous section, with additional information found in Appendix C.

4.1.1 Evidence Base Available

Evidence on effectiveness of palliative radiation therapy for MBD was available from 83 studies (in 97 publications), 53 randomized controlled trials (RCTs) (in 67 publications) and 30 nonrandomized studies of interventions (NRSIs) published since 1985. Most studies enrolled patients with uncomplicated MBD from a variety of primary tumors, MBD sites and characteristics. Most of the available evidence was for Key Question 1 comparing external beam radiation therapy (EBRT) dose and fraction schemes for initial radiotherapy for symptomatic MBD. The overall SOE for pain outcomes comparing single fraction (SF) EBRT with multiple fraction (MF) EBRT and comparing different MF EBRT doses was moderate, reflecting moderate confidence in the findings. For comparisons of SF EBRT doses, SOE was most often low. Across RCTs comparing stereotactic body radiation therapy (SBRT) with MF EBRT, SOE for most outcomes was low. Evidence was sparse for Key Question 2 on re-irradiation and SOE was low for most outcomes. For comparative effectiveness (Key Questions 3 a, b, c), much of the evidence was insufficient due to methodological limitations, imprecision, and unknown consistency of effects from single studies.

4.1.2 Evidence on Effectiveness

For SF EBRT versus MF EBRT, we found moderate evidence of a small increased likelihood of overall pain response (improvement) favoring MF EBRT post-treatment up to 4 weeks. Reported pain response likely combined data for initial radiation therapy and re-irradiation. We found moderate evidence of no difference in overall pain response at later time periods, however. Results slightly favoring MF EBRT over SF EBRT at up to 4 weeks, may in part reflect patients having received initial radiation only and/or a proportion of patients whose improvement occurred later than 4 weeks. Relief of spinal cord compression was probably similar between SF and MF EBRT as was quality of life posttreatment. We found low-strength evidence that rates of new pathological fracture and spinal cord compression may not be different between treatment groups. There were no differences in Grade 3 or 4 toxicities or other harms between SF and MF EBRT, however many outcomes were rare and estimates imprecise. This, combined with study limitations led to an SOE of insufficient for many harms outcomes (Table 5). SF EBRT was associated with an over 2-fold higher likelihood of re-irradiation compared with MF EBRT. This remained true across RCTs in populations with mixed spine/nonspine MBD, but analyses

confined to populations with only spine MBD (with or without metastatic spinal cord compression [MSCC]), showed no difference between SF EBRT and MF EBRT schemes. Studies rarely described indications or specific criteria for re-irradiation. Some have suggested that higher rates of re-irradiation may in part be due to a greater willingness to retreat SF EBRT recipients versus MF EBRT recipients.[103]

In general, studies did not explicitly identify MBD as complicated or uncomplicated. Uncomplicated MBD has been defined as "painful bone metastases unassociated with impending or existing pathologic fracture or existing spinal cord or cauda equina compression" based on evaluation of RCT exclusion criteria.[173] Using this definition, all RCTs comparing SF EBRT with MF EBRT in patients with mixed spine and nonspine MBD would be considered to have uncomplicated MBD (i.e., excluded fractures, MSCC), except for one poor-quality trial that provided insufficient detail to assess this. In six RCTs of patients with spine metastases, four enrolled only patients with spinal cord compression.[51,66,74,102] There were limited data available to assess consistency of results for outcomes across spine MBD trials that enrolled only patients with MSCC compared with those that did not; no trial provided sufficient information to directly compare the impact of SF EBRT versus MF EBRT in patients with and without MSCC. There was no difference between SF EBRT with MF EBRT for overall pain response in one trial in patients with MSCC[74] or in the two trials[44,93] with uncomplicated MBD.

We found low evidence that patients receiving lower dose SF (4 Gy) had a slightly lower likelihood of achieving overall pain response versus those receiving higher SF doses (6 or 8 Gy) in populations with mixed spine/nonspine MBD, however harms and toxicities may not differ. There was moderate evidence that comparisons of lower versus higher total dose MF EBRT probably have similar likelihood of overall pain response and relief of spinal cord compression.

We found that SBRT (SF or MF) was associated with a slightly higher likelihood (up to 20 weeks, SOE: low) and moderately higher likelihood (30 weeks, SOE: moderate) of overall pain response versus conventional, multiple fraction EBRT without differences in other primary outcomes between techniques (SOE: low). Analysis included one small RCT in patients with nonspine MBD, two RCTs in patients with spine MBD, and one RCT in patients with mixed MBD. Evidence on harms was sparse and mostly insufficient for different SBRT dose/fractionation schemes.

Evidence comparing dose and fraction schemes for re-irradiation was sparse. SF EBRT and MF EBRT may have a similar likelihood of achieving overall pain response following re-irradiation, and there may be no differences between SF and MF for improving quality of life, or the risk of pathological fractures or spinal cord compression.

4.1.3 Evidence for Differential Effectiveness or Harms

There was insufficient information from included trials on differential effectiveness or harms for all comparisons and interventions based on patient characteristics, tumor characteristics or other factors. Studies were underpowered to effectively evaluate this. Data are found in Results Appendix B, Tables B-18 to B-39.

Table 5. Summary of evidence of conventional EBRT fractionation schemes for *initial radiation* for MBD: Key Question 1 (pain, function, QOL, harms)

Outcome	Time Point	SF Vs. MF	LDSF Vs. HDSF	LDMF Vs. HDMF
Pain, Overall Response (Effect Size/SOE)[a]	Post-RT to 4 weeks	Small favoring MF ++	Small favoring HDSF +	No difference ++

4. Discussion

Outcome	Time Point	SF Vs. MF	LDSF Vs. HDSF	LDMF Vs. HDMF
	>4 weeks to 12 weeks	No difference ++	Small favoring HDSF +	No difference ++
	>12 weeks	No difference ++	Small favoring HDSF +	No difference +
	Timing NR or unclear	No difference ++	No evidence	No difference +
Pain, VAS/NRS/EORTC Scores (Effect Size/SOE)[a]	Post-RT to 4 weeks	No difference ++	No evidence	No evidence
	>4 weeks to 12 weeks	No difference +	No evidence	No evidence
	>12 weeks	No difference +	Insufficient evidence	No evidence
General/Overall Function (Effect Size/SOE)[a]	Post-RT to 4 weeks and >4 to 12 weeks	No evidence	No evidence	Insufficient evidence
	>12 weeks	No evidence	Insufficient evidence	Insufficient evidence
	Timing unclear	Insufficient evidence	No evidence	Insufficient evidence
Relief of SCC (Ambulatory) (Effect Size/SOE)[a]	Post-RT to 4 weeks	No difference ++	No evidence	No difference ++
	>4 weeks to 12 weeks	No difference +	No evidence	No difference ++
	>12 weeks	No evidence	No evidence	No difference ++
Relief of SCC (Motor Function) (Effect Size/SOE)[a]	Post-RT to >12 weeks	No evidence	No evidence	No difference +
Relief of SCC (Regain Sphincter Control) (Effect Size/SOE)[a]	Post-RT to 4 weeks	No evidence	No evidence	No difference +
Relief of SCC (Neurological Deficit) (Effect Size/SOE)[a]	Post-RT to 4 weeks	No evidence	No evidence	Insufficient evidence
Quality of Life (Effect Size/SOE)[a]	Post-RT to 30 weeks	No difference +	No evidence	No evidence
	30 weeks	No evidence	Insufficient evidence	No evidence
Harms/AEs – Pathological Fracture (Effect Size/SOE)[a]	Any time	No difference +	No evidence	No difference +
	≤8 weeks and >8 weeks	No evidence	No difference +	No evidence
Harms/AEs – New SCC (Effect Size/SOE)[a]	Any time	No difference +	No evidence	Insufficient evidence
	≤8 weeks and >8 weeks	No evidence	No difference +	No evidence
Harms/AEs – Cord or Cauda Equina Compression, Deterioration of Neural Symptoms (Effect Size/SOE)[a]	Any time	Insufficient evidence	No evidence	No evidence
Harms/AEs – Skeletal-related Events[b] (Effect Size/SOE)[a]	Any time	Insufficient evidence	No difference +	No evidence
Harms/AEs – Serious Adverse Event (Effect Size/SOE)[a]	Any time	Insufficient evidence	No evidence	No evidence
Harms/AEs – Adverse Events or Reactions Not Otherwise Specified (Effect Size/SOE)[a]	Any time	No evidence	No difference +	No evidence
Harms/AEs – Pain Flare (Effect Size/SOE)[a]	Any time	No difference +	No evidence	No evidence

Outcome	Time Point	SF Vs. MF	LDSF Vs. HDSF	LDMF Vs. HDMF
Harms/AEs – Radiation Myelopathy (Effect Size/SOE)[a]	Any time	Insufficient evidence	No evidence	Insufficient evidence
Harms/AEs – Toxicity, Acute Grade 3, 4 (Effect Size/SOE)[a]	Any time	Insufficient evidence	No evidence	No difference +
Harms/AEs – Toxicity, Late Grade 3, 4 (Effect Size/SOE)[a]	Any time	Insufficient evidence	No evidence	No evidence
Harms/AEs – Toxicity, Acute Nausea/Vomiting Quite a Bit or Very Much; Withdrawals due to AEs (Effect Size/SOE)[a]	Any time	No difference +	No evidence	No evidence
Harms/AEs – Impaired Bladder or Bowel Function (Effect Size/SOE)[a]	Any time and 8 weeks	No difference +	No evidence	No evidence
Harms/AEs – Various AEs (Effect Size/SOE)[a]	Any time	Insufficient evidence	No evidence	No evidence

AEs = adverse events; EBRT = external beam radiation therapy; EORTC = European Organisation for Research and Treatment of Cancer; HDMF = higher total dose multiple fraction; HDSF = higher total dose single fraction; LDMF = lower total dose multiple fraction; LDSF = lower total dose single fraction; MBD = metastatic bone disease; MF = multiple fraction; NR = not reported; NRS = numerical rating scale; QOL = quality of life; RT = radiation therapy; SCC = spinal cord compression; SF = single fraction; SOE = strength of evidence; VAS = visual analog scale.
[a] Effect size: No, small, moderate, or large difference favoring SF, LDSF, or LDMF; SOE: + = low, ++ = moderate, +++ = high.
[b] Re-irradiation or pathologic fracture, cord compression

Table 6. Summary of evidence of SBRT fractionation schemes for *initial radiation* MBD: Key Question 1 (pain, function, QOL, harms)

Outcome	Time Point	SF Vs. MF	LDMF Vs. HDMF
Pain, Overall Response; VAS Pain Scores (Effect Size/SOE)[a]	≥12 weeks	No evidence	Insufficient
General/Overall Function; Relief of SCC; Quality of Life (Effect Size/SOE)[a]	Any time	No evidence	No evidence
Harms/AEs – Pathological Fracture (Effect Size/SOE)[a]	Any time	No difference +	Insufficient
Harms/AEs – Serious Adverse Event; Pain Flare (Effect Size/SOE)[a]	Any time	Insufficient	No evidence
Harms/AEs – Radiation Myelopathy (Effect Size/SOE)[a]	Any time	No evidence	Insufficient
Harms/AEs – Toxicity, Acute Grade 3, 4 (Effect Size/SOE)[a]	Any time	No difference + (mixed) Insufficient (spine)	Insufficient

AEs = adverse events; HDMF = higher total dose multiple fraction; LDMF = lower total dose multiple fraction; MBD = metastatic bone disease; MF = multiple fraction; QOL = quality of life; SBRT = stereotactic body radiation therapy; SCC = spinal cord compression; SF = single fraction; SOE = strength of evidence; VAS = visual analog scale.
[a] Effect size: No, small, moderate, or large difference favoring SF or LDMF; SOE: + = low, ++ = moderate, +++ = high.

4. Discussion

Table 7. Summary of evidence of delivery techniques for EBRT for *initial radiation* for MBD: Key Question 1 (pain, function, QOL, harms)

Outcome	Time Point	SBRT Vs. EBRT	IMRT Vs. 3DCRT	EBRT Plus HBI Vs. EBRT Alone
Pain, Overall Response (Effect Size/SOE)[a]	4 weeks	Small +	No evidence	No evidence
	12 weeks and 26 weeks	Small ++	No difference +	No evidence
	36 weeks	Moderate +	No evidence	No evidence
Pain, VAS Pain and Neuropathic Pain Scores[b] (Effect Size/SOE)[a]	Post-RT to 4 weeks and 12 weeks	Insufficient	Insufficient	No evidence
	26 weeks	Large +	Insufficient	No evidence
Skeletal Function (SINS) (Effect Size/SOE)[a]	≥12 weeks	No difference +	No evidence	No evidence
Relief of SCC (Motor Deficits) (Effect Size/SOE)[a]	26 weeks	No evidence	Insufficient	No evidence
Quality of Life (Effect Size/SOE)[a]	Post-RT to 4 weeks, 12 and 26 weeks	No difference +	No difference +	No evidence
	52 weeks	Insufficient	No evidence	No evidence
Harms/AEs – Pathological Fracture (Effect Size/SOE)[a]	≤12 weeks	No difference +	Insufficient	No evidence
	26 weeks	Insufficient	Insufficient	No evidence
Harms/AEs – SCC (Effect Size/SOE)[a]	26 weeks	No difference +	No evidence	No evidence
Harms/AEs – Pain Flare (Effect Size/SOE)[a]	Post-RT and 26 weeks	No difference +	No evidence	No evidence
Harms/AEs – Serious AEs (Treatment Related Death) (Effect Size/SOE)[a]	Any time	Insufficient	Insufficient	Insufficient
Harms/AEs – Toxicity, Acute Grade 3, 4 (Effect Size/SOE)[a]	Post-RT to 12 weeks	Insufficient	Insufficient	Insufficient
	26 weeks	No evidence	Insufficient	No evidence

3DCRT = three-dimensional conformal radiation therapy; AEs = adverse events; EBRT = external beam radiation therapy; HBI = hemibody irradiation; IMRT = intensity modulated radiation therapy; MBD = metastatic bone disease; QOL = quality of life; RT = radiation therapy; SBRT = stereotactic body radiation therapy; SCC = spinal cord compression; SINS = Spinal Instability in Neoplasia Score; SOE = strength of evidence; VAS = visual analog scale.

[a] Effect size: No, small, moderate, or large difference favoring SBRT, IMRT or EBRT + HBI; SOE: + = low, ++ = moderate, +++ = high.

[b] Neuropathic pain was reported only for the IMRT vs. 3DCRT comparison.

Table 8. Summary of evidence of conventional EBRT and SBRT fractionation schemes for *re-irradiation* for MBD: Key Question 2 (pain, function, QOL, harms)

Outcome	Time Point	SF vs. MF EBRT	SF vs. MF SBRT
Pain, Overall Response (Effect Size/SOE)[a]	8 weeks	No difference +	No evidence
	8 to 26 weeks	No evidence	No difference +
	Timing NR	Insufficient	No evidence
General/Overall Function (Walking on BPI) (Effect Size/SOE)[a]	8 weeks	No difference +	No evidence
Relief of SCC (Motor Function Improvement) (Effect Size/SOE)[a]	4, 12, and 26 weeks	Insufficient	No evidence
Quality of Life (Effect Size/SOE)[a]	8 weeks	No difference +	No evidence
Harms/AEs – SCC or Cauda Equina Compression; Pathological Fracture (Effect Size/SOE)[a]	Timing NR	No difference +	No evidence
Harms/AEs – Toxicity, Acute Grade 3, 4 (Effect Size/SOE)[a]	Acute	Insufficient	Insufficient

AEs = adverse events; BPI = Brief Pain Inventory; EBRT = external beam radiation therapy; MBD = metastatic bone disease; MF = multiple fraction; NR = not reported; QOL = quality of life; SBRT = stereotactic body radiation therapy; SCC = spinal cord compression; SF = single fraction; SOE = strength of evidence.
[a] Effect size: No, small, moderate, or large difference favoring SF scheme; SOE: + = low, ++ = moderate, +++ = high.

4.1.4 Evidence on Comparative Effectiveness

We found that evidence was generally insufficient for most comparisons of EBRT with another therapy, of EBRT plus another therapy versus either EBRT alone or the other therapy alone for most outcomes. We found low-strength evidence that EBRT plus surgery may be associated with better relief of spinal cord compression compared with EBRT alone. Use of dexamethasone as part of EBRT (SF or MF) may result in small improvements in pain and quality of life as well as lower risk of pain flare and bone pain versus EBRT alone (SOE low for all). There may be no difference between use of radioisotopes with EBRT versus EBRT alone for overall pain response and frequency of serious adverse events (SOE low).

Table 9. Summary of evidence of EBRT versus another single therapy for MBD: Key Question 3a (pain, function, QOL, harms)

Outcome	Time Point	EBRT Vs. Strontium	EBRT Vs. Cryoablation	EBRT Vs. Bisphosphonates
Pain, Subjective Response (Effect Size/SOE)[a]	Timing NR	Insufficient	No evidence	No evidence
ixPain, Complete Response (Effect Size/SOE)[a]	12 weeks	No evidence	Insufficient	No evidence
Pain, WHO Response Rate[b] (Effect Size/SOE)[a]	4 and 12 weeks	No evidence	No evidence	No difference +
Quality of Life (Effect Size/SOE)[a]	12 weeks	No evidence	Insufficient	No difference +
Harms/AEs – Pain Flare (Effect Size/SOE)[a]	Timing NR	No difference +	No evidence	No evidence
Harms/AEs – Pathological Fracture (Effect Size/SOE)[a]	Timing NR	No evidence	No evidence	No difference +
Harms/AEs – Toxicity, Acute Grade 3, 4 (Effect Size/SOE)[a]	Timing NR	No difference +	No evidence	Insufficient

AEs = adverse events; EBRT = external beam radiation therapy; MBD = metastatic bone disease; NR = not reported; QOL = quality of life; SOE = strength of evidence; WHO = World Health Organization.
[a] Effect size: No, small, moderate, or large difference favoring EBRT; SOE: + = low, ++ = moderate, +++ = high.

[b] WHO response rate based on decrease, stable, or increase in pain medication (nonopioid, weak opioid, strong opioid) plus average pain score (no pain, pain reduced by ≥ 2/10 points, pain stable, or pain score increased ≥ 2/10 points).

Table 10. Summary of evidence of EBRT or SBRT plus another therapy versus EBRT or SBRT alone for MBD: Key Question 3b (pain, function, QOL, harms)

Outcome	Time Point	EBRT Plus Surgery Vs. EBRT	SBRT Plus Surgery Vs. SBRT	EBRT Plus Dexamethasone Vs. EBRT	EBRT Plus Bisphosphonate Vs. EBRT
Pain, Overall Response (Effect Size/SOE)[a]	>4 to 12 weeks	No evidence	No evidence	Small +	No evidence
	>12 weeks	Insufficient	No evidence	No evidence	No evidence
Pain, VAS Pain Scores (Effect Size/SOE)[a]	Post-RT to 4 weeks	Insufficient	No evidence	Small +	No evidence
	>4 to 12 weeks	Insufficient	No evidence	No evidence	No evidence
	>12 weeks	No evidence	No evidence	No evidence	Insufficient
Overall Function (KPS) (Effect Size/SOE)[a]	Post-RT	Insufficient	No evidence	No evidence	No evidence
Relief of SCC (Ambulatory) (Effect Size/SOE)[a]	Post-RT	Moderate +	No evidence	Insufficient	No evidence
Relief of SCC (Frankel Same/Better) (Effect Size/SOE)[a]	Post-RT	Large +	Insufficient	No evidence	No evidence
Relief of SCC (ASIA Same or Better; Continence Maintained) (Effect Size/SOE)[a]	Post-RT	Large +	No evidence	No evidence	No evidence
Quality of Life (Effect Size/SOE)[a]	Post-RT	Insufficient	No evidence	Small +	No evidence
Harms/AEs – SREs (Effect Size/SOE)[a]	>12 weeks	No evidence	No evidence	No evidence	Insufficient
Harms/AEs – Nerve Damage (Effect Size/SOE)[a]	Post-RT	Insufficient	No evidence	No evidence	No evidence
Harms/AEs – Pain Flare (Effect Size/SOE)[a]	Timing NR	No evidence	No evidence	Small +	Insufficient
Harms/AEs – Toxicity, Grade ≥3 Bone Pain (Effect Size/SOE)[a]	Acute, timing NR	No evidence	No evidence	Moderate +	No evidence
Harms/AEs – Toxicity, Grade 3, 4, other (Effect Size/SOE)[a]	Acute, timing NR	No evidence	No evidence	No difference +	No evidence

AE = adverse event; ASIA = American Spinal Injury Association Impairment Scale; EBRT = external beam radiation therapy; KPS = Karnofsky Performance Scale; MBD = metastatic bone disease; NR = not reported; QOL = quality of life; RT = radiation therapy; SBRT = stereotactic body radiation therapy; SCC = spinal cord compression; SOE = strength of evidence; SRE = skeletal-related events; VAS = visual analog scale.

[a] Effect size: No, small, moderate, or large difference favoring EBRT/SBRT plus another therapy; SOE: + = low, ++ = moderate, +++ = high.

Table 11. Summary of evidence of EBRT plus another therapy versus EBRT alone for MBD: Key Question 3b (pain, function, QOL, harms).

Outcome	Time Point	EBRT Plus Radioisotope Vs. EBRT	EBRT Plus Cryoablation Vs. EBRT	EBRT Plus Hyperthermia Vs. EBRT	EBRT Plus Capecitabine Vs. EBRT
Pain, Overall Response (Effect Size/SOE)[a]	>4 to 12 weeks	No difference +	Insufficient	No evidence	Insufficient
	>12 weeks	No difference +	No evidence	No evidence	No evidence
Quality of Life (Effect Size/SOE)[a]	Post-RT	Insufficient	No evidence	No evidence	No evidence
	12 weeks	No evidence	Insufficient	Insufficient	No evidence
Harms/AEs – Serious AEs (Effect Size/SOE)[a]	Timing NR	No difference +	No evidence	No evidence	No evidence
Harms/AEs – Toxicity, Grade 3 or 4 (Effect Size/SOE)[a]	Acute	Insufficient	No evidence	No evidence	No evidence

AEs = adverse events; EBRT = external beam radiation therapy; MBD = metastatic bone disease; NR = not reported; QOL = quality of life; RT = radiation therapy; SOE = strength of evidence.
[a] Effect size: No, small, moderate, or large difference favoring EBRT plus another therapy; SOE: + = low, ++ = moderate, +++ = high.

Table 12. Summary of evidence of EBRT plus another therapy versus the other therapy alone for MBD: Key Question 3c (pain, function, QOL, harms)

Outcome	Time Point	EBRT Plus Cryoablation Vs. Cryoablation	EBRT Plus Radioisotope Vs. Radioisotope	EBRT Plus Surgical Stabilization Vs. Surgical Stabilization
Pain, Overall Response (Effect Size/SOE)[a]	>4 to 12 weeks	Insufficient	No evidence	Insufficient
	Timing NR	No evidence	Insufficient	No evidence
Function, Normal Use of Extremities[b] (Effect Size/SOE)[a]	Any time	No evidence	No evidence	Insufficient
Quality of Life (Effect Size/SOE)[a]	Post-RT	No evidence	No evidence	No evidence
	12 weeks	Insufficient	No evidence	No evidence
Harms/AEs – Serious AEs (Effect Size/SOE)[a]	Timing NR	No evidence	No evidence	No evidence

AE = adverse event; EBRT = external beam radiation therapy; MBD = metastatic bone disease; NR = not reported; QOL = quality of life; RT = radiation therapy; SOE = strength of evidence; w/w/o = with or without.
[a] Effect size: No, small, moderate, or large difference favoring EBRT plus another therapy; SOE: + = low, ++ = moderate, +++ = high.
[b] With or without pain.

4.1.5 Comparison With Other Systematic Reviews

Our review is consistent with other systematic reviews of RCTs directly comparing EBRT single and multiple fraction schemes regarding both effectiveness and harms,[174-176] namely that there are no differences between SF EBRT and MF EBRT in overall pain response (based on longest followup), pathological fracture or new MSCC and higher risk of re-irradiation with SF EBRT. Our review includes recently published RCTs, provides information based on length of followup, and includes additional detail on harms. In contrast to our findings, a recent Bayesian network meta-analysis[177] reports that single 8 Gy EBRT was associated with better pain control, less risk of pathologic fracture and cord compression and reduced need for re-irradiation compared with multiple fractions of 20 Gy or 30 Gy; however, many estimates lacked precision.

Differences in methodological approach to data synthesis in our review at least partially account for the contrast in findings. Our review uses direct head-to-head evidence within RCTs whereas network meta-analyses indirectly compare treatment options across RCTs when there is no direct evidence. Differences in included studies and categorization of pain response also likely contribute to the disparity in findings.

Recent reviews of SBRT for palliation in MBD have focused on spine MBD, relied on NRSI, particularly single arm studies, and provided indirect comparisons of the modalities. Our review provides the most up to date synthesis of RCT evidence comparing SBRT with conventional EBRT and importantly includes one RCT in patients without spine MBD. Our finding that SBRT was associated with slightly higher likelihood of overall pain improvement versus conventional EBRT is consistent with one recent review that included NRSI.[178] Our findings of low frequency of Grade 3 and 4 toxicities and serious harms for all radiation therapy modalities is consistent with other systematic reviews, however studies may have been underpowered to detect rare outcomes.

4.2 Strengths and Limitations

Our review has some notable strengths. Our synthesis focuses on the best quality comparative effectiveness evidence directly comparing dose/fractionation schemes for initial radiation and re-irradiation for palliation of MBD. This review also provides updated information comparing SBRT with conventional EBRT, and describes evidence gaps for both effectiveness and comparative effectiveness of radiation therapy for MBD, which may stimulate additional research.

Our review has some limitations. We were only able to conduct limited analyses for publication bias due to small numbers of RCTs for many analyses. Our review of study bibliographies and clinical trial registries did not reveal unpublished studies meeting our inclusion criteria that would suggest missing publications. We did not include non-English language publications, however, title/abstract review of such publications captured from our search and listed in bibliographies suggests that this number would be few, and they would not meet our inclusion criteria; we are unlikely to have missed studies that would have changed our conclusions.

Using a best evidence approach, we focused on RCTs where possible. When sufficient RCT evidence was available, comparative NRSIs that were designed to evaluate harms, and which controlled for confounding, were considered. We excluded nonrandomized studies focused on effectiveness outcomes in these instances. NRSIs can be misleading due to the subjective nature of pain and the impact of nonspecific effects of patient expectations regarding treatment and attention received on patient reported outcomes. The potential for selection bias and uncontrolled confounding add to the weaknesses of NRSIs. In addition, in populations such as those with MBD, confounding by indication and inclusion of additional therapies with radiation therapy are likely to occur in NRSIs, making specific conclusions regarding radiation therapy effectiveness and adverse events challenging. Information from included NRSIs on harms provided limited additional insight beyond what was available from the RCTs when they were available. For questions where RCT evidence was sparse or not identified, comparative NRSIs were considered. Ideally such studies would have explored the need to control for prognostic factors such as age, sex, primary tumor histology, pain duration, baseline pain severity, and prior treatments for outcomes of interest for this review (e.g., overall pain response). Many NRSIs provided limited information regarding adjustment methods, and many did not adjust for these

prognostic factors and reported adjusted estimates for only selected outcomes. The pool of eligible patients and selection of patients from that pool was general not well described and attrition was frequently unclear, raising concerns regarding confounding by indication and selection bias. While comparative NRSIs provide some information in the absence of RCT evidence, limitations of these studies generally led to determination of insufficient evidence for many outcomes and results should be interpreted cautiously. Inclusion of studies that directly compare interventions is most consistent with best evidence given the comparative intent of this review. Thus, single arm studies, including case series and pre-post studies, were excluded.

Limitations in the evidence base are reflected in the limitations to the review. There is substantial heterogeneity in enrolled populations across studies related to primary tumor types as well as number of sites or lesions. Studies that enrolled patients with spine and nonspine MBD did not report results by MBD sites. Few studies characterized MBD lesions regarding type (e.g., osteolytic, osteoblastic, favorable, unfavorable). RCTs comparing SF EBRT and MF EBRT of populations with mixed spine and nonspine MBD enrolled patients with uncomplicated MBD, based on the suggested definition (no pathological fractures or spinal cord or cauda equina compression);[173] thus, the effectiveness and harms of SF EBRT versus MF EBRT in patients with complicated MBD requires further research. Similarly, no high-quality comparative evidence was identified in patients with complicated MBD for comparisons of single fractions, multiple fractions or in populations having re-irradiation were identified.

Few studies reported pain response based on the visual analog scale (VAS), numeric rating scale (NRS), or similar method to measure pain improvement. Most studies used various definitions of pain response (Results Appendix B, Table B-2). Typically pain response was a composite measure (e.g., use of a pain measure combined with frequency of analgesic use). Some studies used specific thresholds for pain to categorize response (e.g., 20% pain response), and some employed the International Consensus on Palliative Radiotherapy Endpoints.[179] Heterogeneity in definitions has been noted in other systematic reviews. We focused on overall pain response; this was most consistently reported and encompassed complete and partial responses based on authors' descriptions. We may have misclassified pain response in some instances. We did not report composite outcomes that combined aspects of pain response with imaging, given our focus on alleviating pain for this review. Similarly, definitions of pain flare varied across studies.

Some outcomes may not be routinely or systematically assessed either in clinical studies or clinical practice. For example, fractures and cord compression may be asymptomatic and studies may not have routinely confirmed these via imaging. Similarly, outcomes such as pain flare and local recurrence were variably defined across studies and may or may not be symptomatic.

Evidence from methodologically rigorous studies comparing SBRT with conventional EBRT and comparing various SBRT dose/fraction schemes for palliation remains sparse, particularly in patients with MBD not involving the spine. Some included SBRT studies primarily included patients with oligometastases and appeared to focus on aspects of survival and provided limited information on primary outcomes of interest to this review (e.g., pain response). Studies of SBRT compared single or two fraction SBRT with multiple EBRT fractions. Studies comparing dose/fraction schemes for re-irradiation were limited even with the inclusion of comparative NRSIs. This is also true for comparisons of EBRT alone or in combination with other palliative treatments for MBD.

There was insufficient information from included trials on differential effectiveness or harms based on patient characteristics, tumor characteristics or other factors for all comparisons and

interventions. Studies were underpowered to effectively evaluate this. There was also insufficient information from included studies to assess factors that may provide insight into how social determinants of health may impact delivery, effectiveness, and harms of palliative radiation therapy for MBD. Included studies did not provide information on patient sociodemographic characteristics beyond age and sex. Evaluation of the impact of social determinants of health requires a different approach to study design and analysis than is usually used in clinical intervention studies. Understanding of a broader literature that examines factors beyond what have been traditionally described as socioeconomic status is needed.[180,181] Consideration of socioeconomic status together with factors related to social determinants are important to understanding distress and hardship experienced by patients receiving palliative radiation therapy; however, there was no evidence specific to the populations and comparisons of interest identified for this review.

A range of followup times was reported across studies. Unfortunately, candidates for palliative radiation therapy for MBD have a limited remaining life span. Substantial loss due to death at longer followup times occurred across studies, creating challenges for drawing conclusions across various comparisons due to diminishing sample size.

4.3 Applicability

Patient characteristics, primary tumor histology and treatment regimens represented in included studies are similar to those commonly encountered in clinical situations and therefore, many of our findings are likely applicable to typical clinical practice. Given the range of primary tumors, lesion locations and characteristics represented in included studies, we suspect that the study populations may not differ substantially from those encountered in typical radiation oncology settings. The heterogeneity across these factors is reflected in the proportions of males and females in studies as some primary tumors are specific to men (e.g., prostate) or more common in women (e.g., breast cancer); again, this is likely consistent with typical practice. Race and ethnicity were rarely reported in studies. In the three studies reporting race, most participants were white (76% to 81%); applicability of our finding to other racial or ethnic groups is unclear. In most studies, patients likely used several methods for pain control as well as adjunctive therapies; this, too, is likely consistent with clinical practice. Studies in this review most usually employed 8 Gy for SF EBRT, which is consistent with usual clinical practice. Regimens for MF EBRT varied across studies with the most common being 3 Gy x10 fractions or 4 Gy x5 fractions. This is consistent with usual clinical practice. Of note, older studies did not specify whether EBRT was two-dimensional conformal radiation therapy (2DEBRT) or three-dimensional conformal radiation therapy (3DEBRT), which is now likely most commonly used. In some circumstances, however, 2D is still used clinically.

Criteria for moving forward with re-irradiation were not explicitly described in most studies; this is consistent with usual practice. Unfortunately, evidence comparing dose/fraction approaches is sparse for re-irradiation so applicability of our findings for re-irradiation is unclear.

Clinically, a range of patients including those with complicated MBD and others with uncomplicated MBD is likely. Most included studies were in populations of mixed spine/nonspine lesions with uncomplicated MBD. Four RCTs in patients with spine MBD specifically enrolled patients with MSCC consistent with a definition of complicated MBD. Our findings may be not entirely applicable to patients with complicated MBD as optimal single or multiple fraction regimens for complicated MBD remain unclear.

Given growing evidence for improved oncologic outcomes with metastasis-directed therapy for oligometastatic disease, some SBRT studies included patients with limited numbers of metastatic sites and focused more on local recurrence and overall survival; palliative intent was not always clear. Most SBRT studies were in patients with spine MBD. For the comparison of SBRT versus conventional MF EBRT, we included two studies of SBRT focused on MSCC, one in patients with mixed MBD and one in patients with nonspine MBD.[9] In the latter RCT, the most common primary tumor site was lung (49%); adenocarcinoma was the most common histology (63%). The extent to which the findings from this one trial may be applicable to a broader scope of patients with symptomatic nonspine MBD is unknown.

4.4 Implications for Clinical Practice, Education, Research, or Health Policy

4.4.1 Considerations for Clinical Practice and Health Policy

Our review found that, in patients with uncomplicated MBD, the likelihood of achieving overall pain response for SF EBRT and MF EBRT is probably similar, particularly after 4 weeks, although re-irradiation was more common with SF EBRT than with MF EBRT. There may be no differences in other primary outcomes or in adverse events including pathologic fracture and new spinal cord compression, or serious toxicities between SF and MF EBRT, however many harms were uncommon and evidence for many was insufficient.

Substantial variation in the delivery of palliative radiation therapy for MBD has been noted by many.[15,16,18-20] Guidelines and quality measures have generally discouraged the use of multiple fractions in favor of few fractions or SF EBRT.[21,182,183] Reasons cited for variability in use of SF EBRT over MF EBRT have included lack of consensus regarding optimal dose and fractions for either initial radiotherapy or retreatment[9,15] and lack of clarity regarding which patients may benefit most for various dose/fractionation schemes. Variations in implementing recommendations for SF EBRT may also be due to differences in MBD characteristics as well as patient circumstances, characteristics and prognosis.

Our findings generally support guidelines and initiatives[21,184] encouraging use of single or a limited number of fractions and lower total dose for palliative radiation in patients with uncomplicated MBD based on similarities in likelihoods for achieving overall pain response, noting that there is an association between SF EBRT and re-irradiation. Our findings provide some confirmation that use of lower single fraction doses is less effective for pain improvement in patients with mixed MBD, but evidence related to spine MBD or more complicated pathology was not identified. Our findings comparing lower total dose with higher total dose multiple fraction schemes suggest that the likelihood of overall pain response is probably similar in mixed MBD and in MSCC for the ranges of doses and fractions studied. This supports consideration of fewer fractions and lower total doses when multiple fractions are used. Of note, however, certain studies incorporated estimation of patient prognosis into inclusion criteria or ultimately enrolled patients with poor overall survival, and thus consideration of prognosis likely must be part of clinical decision-making. Although information on harms, particularly radiation-induced spinal cord pathology and serious adverse events was limited across all comparisons, consideration of potential harms is also important for clinical decision making.

There is variability in use of more advanced techniques such as SBRT and lack of consensus regarding such use. Our review provides a synthesis across recently published RCTs of SBRT. We found that SBRT (usually 1 or 2 fractions) was associated with a slightly higher likelihood of

overall pain response versus conventional, multiple fraction EBRT (3 Gy/10 fractions or 4 Gy/5 fractions). Analysis included one small RCT in patients with nonspine MBD (49% from lung cancer) and two small RCTs in patients with spine MBD. Applicability of these findings across a broader range of patients is unclear. The findings may facilitate initial discussion of how SBRT may benefit patients with MBD, although many gaps in evidence remain. In addition, access to treatments is important to consider. Conventional EBRT (2D or 3D) is likely available within 25 miles or less for most patients in the United States, however smaller communities outside of metropolitan areas and rural communities may not have access to newer technologies such as SBRT.[185] Anecdotally, some have questioned the role that reimbursement may play in use of new technologies.

Evidence comparing dose/fraction schemes for re-irradiation is sparse. Low evidence from one large RCT supports decisions for SF versus MF EBRT for re-irradiation; our review found no differences in overall pain response or harms between SF and MF EBRT. Evidence from a retrospective NRSI also suggests no difference between SF versus MF SBRT for pain improvement, however recommendations should be made cautiously due to limited information and confidence on harms. Similarly, evidence for Key Question 3 (EBRT alone or in combination with other therapies), which was primarily comprised of NRSI, was generally insufficient for most comparators and outcomes, making evidence-based decisions and recommendation formulation challenging.

It was not possible to capture the nuances of clinical decision-making related to individual patient circumstances, prognosis, tumor location and features and various clinical factors that might inform the need for a specific dose or number of fractions or need for re-irradiation in a review such as this. While evidence from our report will support decision making and formulation of clinical recommendations, individual patient circumstances and preferences for palliative care must also be considered. As noted in information presented for the contextual questions, while aspects of patient financial distress and burden are important to consider, it is currently unclear how to measure, evaluate or consider these in the context of palliative radiotherapy for MBD for either clinical decision making or policy.

Clinical guidelines are intended to facilitate evidence-based decision making and help decrease practice variability but need to be implemented to be effective. Information from contextual questions in our report suggests that online clinical pathways and education-based interventions, particularly when coupled with use of peer-review or audit, may be most effective in promoting guideline implementation. To the extent that reimbursement may play a role in uptake of clinical guidelines, novel payment care models/incentivized quality metrics provide an intriguing area of research.

4.4.2 Research Recommendations

Gaps in the existing evidence on radiation for palliation in MBD are many. Most RCTs enrolled patients with uncomplicated MBD; thus high-quality comparative studies, preferably RCTs, in patients with complicated MBD would add to the evidence base. Furthermore, evidence for the use of radiation in the prophylactic setting for asymptomatic MBD to reduce risk of skeletal complications is needed. While RCT evidence comparing SBRT with conventional EBRT continues to emerge, studies specifically focused on palliative treatment of MBD are needed for spine and nonspine applications and in populations with complicated and uncomplicated MBD. In addition, rigorous studies directly comparing dose/fraction schemes for SBRT are necessary. Such studies need to be sufficiently powered explicitly to directly evaluate

the impact of dose/fraction schemes on harms, particularly pathologic fractures, to go beyond the information available from studies looking at predictive factors for fracture.[186,187] Additional high-quality evidence comparing dose/fraction schemes for re-irradiation are important to verifying current findings for EBRT and SBRT. There is a need for high-quality studies that evaluate the impact of EBRT and another palliative therapies alone and in combination to better clarify joint benefits and harms. To facilitate comparisons across these studies, standardized definitions for important outcomes such as pain response, pain flare, and others are needed and outlined in the International Consensus on Palliative Radiotherapy Endpoints.[179] Additionally, use of consistent scoring and reporting methods for outcomes related to quality of life is needed. Verification of outcomes such as pathologic fractures and cord compression (e.g., via imaging) may be helpful to assure consistency across studies. Describing criteria or rationale for re-irradiation and documenting patient response to re-irradiation separate from initial radiation may refine understanding regarding the discrepancy in re-irradiation between single and multiple fraction regimens. Many studies, particularly NRSIs, provide information based on the number of treated sites or vertebral segments, but do not appropriately adjust for correlated data. Although some NSRIs used methods to account for competing risks for outcomes like survival, they did not consistently adjust for potential confounding factors using multivariate analysis. Reporting data based on number of patients is preferable. Better understanding of possible differential effectiveness or harms based on specific patient characteristics (e.g., age, sex), MBD characteristics (complicated, uncomplicated, type of lesion, number of lesions), or other factors which may help identify which patients may benefit most from particular treatment regimens are important. RCTs that include a priori plans for subgroup analyses, including tests for interaction, that are sufficiently powered are needed to effectively evaluate this. Understanding of the extent to which social determinants of health may impact the delivery, effectiveness and harms of palliative radiation therapy will require modification of study designs and analyses beyond reporting limited to patient characteristics (e.g., age, sex) in studies comparing treatment options. Incorporation and analysis of elements of socioeconomic status such as education, employment status, income, insurance status, family and social support together with information on race and ethnicity in studies may provide initial insights regarding social determinants of health, patient distress and disease burden.

4.5 Conclusions

SF EBRT and MF EBRT probably provide a similar likelihood of overall pain response for initial palliative radiotherapy for symptomatic, uncomplicated MBD, though SF EBRT was associated with greater likelihood for re-irradiation. The frequency of harms and toxicities, including new pathologic fracture and spinal cord compression, may be similar between SF EBRT and MF EBRT. SF EBRT of 4 Gy may have a slightly lower likelihood of overall pain response (improvement) compared with higher (6 or 8 Gy) single doses, but there are probably no differences in the likelihood of overall pain response between MF EBRT regimens that were compared. SBRT (1 or 2 fractions) may provide a slightly higher likelihood of overall pain response versus conventional, multiple fraction EBRT, but evidence is limited. Limited evidence suggests that the likelihood of overall pain response between SF EBRT and MF EBRT may be similar in patients undergoing re-irradiation. Additional evidence is needed for benefits and harms for initial palliative radiation and for re-irradiation from high-quality, prospective studies that compare dose/fractionation schemes in patients with complicated MBD and that compare SBRT dose/fractionation schemes, particularly in patients with nonspine MBD. Sufficiently

powered RCTs are needed to evaluate differential effectiveness and harms by important patient characteristics, MBD characteristics, and other factors. Additional research evaluating EBRT in combination with other therapies is also needed.

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6. Abbreviations and Acronyms

2DCRT	two-dimensional conformal radiation therapy
3DCRT	three-dimensional conformal radiation therapy
AHRQ	Agency for Healthcare Research and Quality
ANCOVA	analysis of covariance
ARD	absolute risk difference
ASTRO	American Society for Radiation Oncology
BPI	Brief Pain Inventory
BPTWG	Bone Pain Trial Working Group
CI	confidence interval
CPG	Clinical Practice Guideline
EBRT	external beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EORTC-QLQ-BM22	EORTC Quality of Life Group Bone Metastases Module
EORTC QLQ-C15-PAL	EORTC Quality of Life Questionnaire–Core 15 Palliative
EORTC QLQ-C30	EORTC Quality of Life Questionnaire
HBI	hemibody irradiation
HDMF	higher total dose multiple fraction
HDSF	higher total dose single fraction
HR	hazard ratio
IMRT	intensity modulated radiation therapy
IQR	interquartile range
KPS	Karnofsky Performance Scale
KQ	Key Question
LDMF	lower total dose multiple fraction
LDSF	lower total dose single fraction
MBD	metastatic bone disease
MCID	minimal clinically important difference
MCS	Mental Component Score
MD	mean difference
MF	multiple fraction
MFRT	multiple fraction radiation treatment
MPI	multidimensional pain inventory
MQOL	McGill Quality of Life Questionnaire
MSCC	metastatic spinal cord compression
NA	not applicable
NR	not reported

NRS	numerical rating scale
NRSI	nonrandomized study of interventions
NSAID	nonsteroidal anti-inflammatory drug
QOL	quality of life
PL	profile likelihood
OR	odds ratio
RCT	randomized controlled trial
RR	risk ratio
RT	radiation therapy
SCC	spinal cord compression
SBRT	stereotactic body radiation therapy
SD	standard deviation
SF	single fraction
SF-36	Short-Form 36 Questionnaire
SFRT	single fraction radiation treatment
SINS	Spinal Instability in Neoplasia Score
SRE	skeletal-related event
VCF	vertebral compression fracture
VAS	visual analog scale
WHO	World Health Organization

Addendum

A recently published randomized controlled trial (RCT)[1] comparing stereotactic body radiation therapy (SBRT) with conventional external beam radiation therapy (EBRT) was brought to the attention of the Evidence-based Practice Center by the American Society for Radiation Oncology (ASTRO) after submission of the final review to the Agency for Healthcare Research and Quality. This addendum briefly summarizes the findings of this RCT and provides limited data abstraction of it in the related appendix (located at https://effectivehealthcare.ahrq.gov/products/radiation-therapy-bone-metastases/research). We briefly summarize evidence for the primary outcomes considered in the full published review.

Study Description

This large, fair quality, government funded RCT (N=353 randomized)[1] compared a single 16 Gy or 18 Gy SBRT dose with a single 8 Gy EBRT dose for treatment of spine metastases. Patients were predominately white (80%) and male (54%) with a mean age of 63 years andwith a median Numeric Pain Rating Scale (NPRS) score of 7 (0-10 scale) at baseline; most reported pain medication at baseline (87%). Baseline Zubrod performance score was 0 in 25 percent of patients (0 to 4 scale, 0 being fully functional and asymptomatic). Zubord scores differed between treatment groups; a value of 1 was most common in both treatment groups (53.6% in SBRT vs. 63.8% for EBRT); more SBRT recipients that EBRT recipients had a value of 2 (22% vs. 10.0%). Most metastases were single (76%), and not radioresistant (87%); baseline spinal cord compression or impending fracture were not reported. In the full report, four RCTs (6 publications)[2-7]compared SBRT with EBRT; mean ages and proportion of males and white participants were similar to this new RCT. SBRT doses varied (12 to 24 Gy in 1 fraction, 24 Gy total in 2 fractions, 30 Gy total in 3 fractions, 35 Gy in 5 fractions) and the most common EBRT dose was 30 Gy (3 Gy x 10); one trial[3] primarily used single fraction EBRT (8 Gy) and two trials also used 20 Gy (4 Gy x 5).[3,4] One trial[2] was in patients with nonspine metastatic bone disease (MBD) only, two RCTs[4,6] include patients with only spine MBD, and one[3] includes patients with mixed spine and nonspine MBD.

Results

Overall pain response (partial or complete pain relief) was more common with SBRT versus EBRT at 4 weeks (n=246, 64.7% vs. 55.9%, risk ratio [RR] 1.16, 95% confidence interval [CI] 0.93 to 1.43) in patients who had only a single treatment site but was not statistically significant. Overall pain response across all patients was less likely with SBRT versus EBRT at 12 weeks (N=214, 41.3% vs. 60.5%, RR 0.68, 95% CI 0.52 to 0.89). Authors report a risk difference of -19 (95% CI -32.9 to -5.5) favoring EBRT but no difference between techniques using a 1-sided test or for mean change in baseline scores at the index site (-2.98 vs. -3.83, 0-10 scale), suggesting that SBRT was not found to be superior to EBRT. No difference in pain response between SBRT and EBRT was seen at 52 weeks (N=97, 57.7% vs.55.3%, RR 1.04, 95% CI 0.73 to 1.49) across all patients; substantial attrition is noted. In contrast, in the full report, a small likelihood of overall pain improvement with SBRT was seen posttreatment up to 4 weeks (2 RCTs [excluding poor quality], N=325, 60% vs. 48%, RR 1.24, 95% CI 0.98 to 1.57, I^2=0%)[2,4] and at 12 weeks (4 RCTs, N=408, 59% vs. 44%, RR 1.31, 95% CI 1.05 to 1.61, I^2=0%).[2-4,6] Differences in response definitions, techniques, patient populations, and MBD characteristics may partially explain differences in findings for this new RCT and those included in the published review.

Authors of the new RCT[1] report no difference between SBRT and EBRT for any of the **quality-of-life** measures evaluated at any time, including Functional Assessment of Cancer Therapy (FACT-G), the Brief Pain Inventory (BPI), and the EuroQol (EQ-5D). This is consistent with findings in the full review.

Treatment-related harms were similar for SBRT and EBRT in the new RCT, and findings are consistent with those in the full review. There was no difference in the proportion of vertebral compression factures (19.5% vs. 21.6%). Authors report that there were no clinical signs of acute or late spinal cord complications. Late Grade 4 toxicities were reported in two SBRT and one EBRT participant (all attributed to sepsis, lymphopenia). Grade 3 pain frequency with SBRT and EBRT was similar (7.9% vs. 4.3%) and was primarily back pain in both groups.

Regarding **secondary outcomes,** authors report no differences between SBRT and EBRT in the progression of known metastases (34% vs. 42%, p=0.12) or in survival rates at 52 weeks (44.3% vs. 53.1%) or 104 weeks (31.5% for both techniques, hazard ratio 0.91, 95% CI 0.37 to 1.06, timing not reported).

Addendum References

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Appendix A. Methods

Details of Study Selection

Search Strategy

Literature Databases: Multiple databases were searched: Ovid® MEDLINE®, EMBASE®, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. Detailed search strategies are listed below. All searches were conducted by a qualified medical librarian and were peer-reviewed.

Publication Date Range: Searches were conducted by Key Question such that Key Questions 1 and 2 and Key Question 3 had separate search strategies, with study dates reaching back to 1985 up to January 30, 2023. The year 1985 was chosen as a cut-off date after technical expert input and corresponds to publication of the earliest RCTs relevant to this topic. Searches were deduplicated and screened for inclusion.

Supplemental Evidence and Data for Systematic review (SEADS): Various stakeholder were informed about submitting information relevant to this review using a Federal Register notification. A portal about the opportunity to submit information was made available on the Effective Health Care (EHC) Website. No submissions were received for this report.

Hand Searching: Reference lists of included articles, as well as relevant systematic reviews, were reviewed for includable studies.

Search Strategy: The search strategy for Key Questions 1 and 2 does not distinguish between initial and repeat treatment (these are poorly indexed concepts and better sorted by hand especially as many studies may have both) but does specify that the methods/techniques/dosing of the treatment be an element of the study. The search strategy for Key Question 3 can be generalized as being focused on external beam radiation therapy (EBRT) only when combined another therapy (EBRT only can be a trial arm but not the only intervention studied). These searches featured hedges to identify systematic reviews, randomized controlled trials and nonrandomized studies of interventions and underwent peer-review by a Librarian at another Evidence-based Practice Center. A refinement of the wording of the Key Questions required a reevaluation of the original PubMed Strategies by a new Evidence-based Practice Center (EPC) Librarian. No new searching was deemed necessary to capture the concepts contained in the new Key Question 1 and Key Question 3. However, examination of the new Key Question 2 deemed that a re-tooled search focusing specifically on re-irradiation therapies of Bone Metastases was necessary. The new EPC Librarian created a strategy to capture MEDLINE records related to these concepts and ran it against OVID MEDLINE.

Medline Search

Key Questions 1 and 2 Reported Search Strategy
Database: Ovid MEDLINE(R) ALL <1985 to January 23, 2023>

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

Key Question 3 Reported Search Strategy
Database: Ovid MEDLINE(R) ALL <1985 to January 23, 2023>

("bone neoplasms/secondary"[MeSH Terms] OR "bone metastas*"[Title/Abstract] OR "bone neoplasms/radiotherapy"[MeSH Terms] OR ("bone neoplasms"[MeSH Major Topic] AND "Neoplasm Metastasis"[MeSH Terms]) OR (("Bone"[Title] OR "bones"[Title]) AND ("tumor*"[Title] OR "neoplasm"[Title]) AND ("metasta*"[Title] OR "secondary"[Title] OR "spread"[Title] OR "spreads"[Title] OR "invasion"[Title] OR "advanced"[Title] OR "stage 4"[Title] OR "stage iv"[Title] OR "Neoplasm Metastasis"[MeSH Major Topic]))) AND ("external beam radiation therapy"[Title/Abstract] OR "EBRT"[Title/Abstract] OR "Radiotherapy"[MeSH Terms] OR "external beam therapy"[Title/Abstract] OR "external beam irradiation"[Title/Abstract] OR "external beam radiation"[Title/Abstract] OR "external beam rt"[Title/Abstract] OR "Three-dimensional conformal"[Title/Abstract] OR "3D-CRT"[Title/Abstract] OR "3-d conformal"[Title/Abstract] OR "3d conformal"[Title/Abstract] OR "Intensity-modulated radiation"[Title/Abstract] OR "IMRT"[Title/Abstract] OR "Image-guided radiation"[Title/Abstract] OR "IGRT"[Title/Abstract] OR "tomotherapy"[Title/Abstract]) AND ("combined"[Title] OR "additional"[Title] OR "plus"[Title] OR "Combined Modality Therapy"[MeSH Terms] OR "Surgery"[Title/Abstract] OR "surgical"[Title/Abstract] OR "radionuclide"[Title/Abstract] OR "bisphosphonate*"[Title/Abstract] OR "kyphoplasty"[Title/Abstract] OR "vertebroplasty"[Title/Abstract])

SR hedge: systematic[sb]

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

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

Revised Key Question 2 (Re-Radiation) Search Strategy
Database: Ovid MEDLINE(R) ALL <1946 to January 23, 2023>

1 exp Bone Neoplasms/sc [Secondary] (27469)

2 (metasta* adj5 (bone* or bony or osteo* or spine or spinal* or vertebra*)).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (43613)
3 (secondary adj5 ((bone* or bony or osteo* or spine or spinal* or vertebra*) adj3 (cancer* or tumo?r or neoplas* or malig*))).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (401)
4 1 or 2 or 3 (55520)
5 exp Radiotherapy/ (204154)
6 rt.fs. (207196)
7 5 or 6 (306653)
8 4 and 7 (6264)
9 exp Dose Fractionation, Radiation/ (11054)
10 exp Radiotherapy Dosage/ (67103)
11 exp Time/ (1413214)
12 10 and 11 (6522)
13 9 or 12 (16422)
14 ((radiat* or radiother* or irradiat* or reirradiat*) adj5 (dose* or dosag* or total or amount* or administ* or deliver* or give* or giving or calculat* or method* or techni* or protocol* or algorithm*) adj7 (stagger* or fraction* or hypofraction* or increment* or schedul* or periodic* or gradual* or phas* or step or stepped or steps or stepping or sequen* or stag* or divid* or portion* or apportion* or recurr* or partial* or conform* or stereota* or 3d or 3-d or (three adj2 dimension*))).mp. (33506)
15 exp Radiotherapy, Computer-Assisted/ (36131)
16 (stagger* or fraction* or hypofraction* or increment* or schedul* or periodic* or gradual* or phas* or step or stepped or steps or stepping or sequen* or stag* or divid* or portion* or apportion* or partial* or conform* or stereota* or 3d or 3-d or (three adj2 dimension*)).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (7990585)
17 15 and 16 (25680)
18 13 or 14 or 17 (55750)
19 8 and 18 (1070)
20 (reirradiat* or re-irradiat* or reradiat* or re-radiat* or retreat* or re-treat* or repeat* or replicat* or retreat* or re-treat* or redo or re-do or ((additional* or second or 2nd or subsequen*) adj3 (course* or round* or series or set or undergo* or radiother* or rt or radiation* or irradiat* or treat* or therap*))).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1210592)
21 19 and 20 (224)

Cochrane Search

EBM Reviews - Cochrane Central Register of Controlled Trials <January 2023>

1	exp Bone Neoplasms/	1305
2	exp Radiotherapy/	6670
3	bone metastas*.ti.	990
4	radiation therapy.ti.	4180
5	2 or 4	10141
6	1 or 3	2007
7	5 and 6	217
8	limit 7 to medline records	189
9	7 not 8	28

Embase Search

EM_Bone cancer RT KQ1_Embase only_20220627_text_2833hits

(('bone metastasis'/exp OR bone* NEAR/1 metasta* OR 'bone cancer'/exp/dm_rt OR ('bone cancer'/exp/mj AND 'metastasis'/exp) OR ((bone OR bones:ti) AND (tumor* OR neoplasm*:ti) AND (((metasta*:ti OR secondary:ti OR spread:ti OR spreads:ti OR invasion:ti OR advanced:ti OR 'stage 4':ti OR stage:ti) AND iv:ti) OR 'metastasis'/exp/mj))) AND (('external beam radiation therapy':ti,ab OR 'ebrt':ti,ab OR 'external beam therapy':ti,ab OR 'external beam irradiation':ti,ab OR 'external beam radiation':ti,ab OR 'external beam rt':ti,ab OR 'three-dimensional conformal':ti,ab OR '3d-crt':ti,ab OR '3-d conformal':ti,ab OR '3d conformal':ti,ab OR 'intensity-modulated radiation':ti,ab OR 'imrt':ti,ab OR 'image-guided radiation':ti,ab OR 'igrt':ti,ab OR 'tomotherapy':ti,ab) OR 'radiotherapy'/exp) AND (surgery:ab,ti OR surgical:ab,ti OR radionuclide:ab,ti OR bisphosphonate*:ab,ti OR kyphoplasty:ab,ti OR vertebroplasty:ab,ti) AND [embase]/lim) NOT (('bone metastasis'/exp OR bone* NEAR/1 metasta* OR 'bone cancer'/exp/dm_rt OR ('bone cancer'/exp/mj AND 'metastasis'/exp) OR ((bone OR bones:ti) AND (tumor* OR neoplasm*:ti) AND (((metasta*:ti OR secondary:ti OR spread:ti OR spreads:ti OR invasion:ti OR advanced:ti OR 'stage 4':ti OR stage:ti) AND iv:ti) OR 'metastasis'/exp/mj))) AND (('external beam radiation therapy':ti,ab OR 'ebrt':ti,ab OR 'external beam therapy':ti,ab OR 'external beam irradiation':ti,ab OR 'external beam radiation':ti,ab OR 'external beam rt':ti,ab OR 'three-dimensional conformal':ti,ab OR '3d-crt':ti,ab OR '3-d conformal':ti,ab OR '3d conformal':ti,ab OR 'intensity-modulated radiation':ti,ab OR 'imrt':ti,ab OR 'image-guided radiation':ti,ab OR 'igrt':ti,ab OR 'tomotherapy':ti,ab) OR 'radiotherapy'/exp) AND (surgery:ab,ti OR surgical:ab,ti OR radionuclide:ab,ti OR bisphosphonate*:ab,ti OR kyphoplasty:ab,ti OR vertebroplasty:ab,ti) AND [medline]/lim)

EM_Bone cancer RT KQ1_Embase AND MEDLINE_20220627_text_3605hits

(('bone metastasis'/exp OR bone* NEAR/1 metasta* OR 'bone cancer'/exp/dm_rt OR ('bone cancer'/exp/mj AND 'metastasis'/exp) OR ((bone OR bones:ti) AND (tumor* OR neoplasm*:ti) AND (((metasta*:ti OR secondary:ti OR spread:ti OR spreads:ti OR invasion:ti OR advanced:ti OR 'stage 4':ti OR stage:ti) AND iv:ti) OR 'metastasis'/exp/mj))) AND (('external beam radiation

therapy':ti,ab OR 'ebrt':ti,ab OR 'external beam therapy':ti,ab OR 'external beam irradiation':ti,ab OR 'external beam radiation':ti,ab OR 'external beam rt':ti,ab OR 'three-dimensional conformal':ti,ab OR '3d-crt':ti,ab OR '3-d conformal':ti,ab OR '3d conformal':ti,ab OR 'intensity-modulated radiation':ti,ab OR 'imrt':ti,ab OR 'image-guided radiation':ti,ab OR 'igrt':ti,ab OR 'tomotherapy':ti,ab) OR 'radiotherapy'/exp) AND (surgery:ab,ti OR surgical:ab,ti OR radionuclide:ab,ti OR bisphosphonate*:ab,ti OR kyphoplasty:ab,ti OR vertebroplasty:ab,ti) AND [embase]/lim) AND (('bone metastasis'/exp OR bone* NEAR/1 metasta* OR 'bone cancer'/exp/dm_rt OR ('bone cancer'/exp/mj AND 'metastasis'/exp) OR ((bone OR bones:ti) AND (tumor* OR neoplasm*:ti) AND (((metasta*:ti OR secondary:ti OR spread:ti OR spreads:ti OR invasion:ti OR advanced:ti OR 'stage 4':ti OR stage:ti) AND iv:ti) OR 'metastasis'/exp/mj))) AND (('external beam radiation therapy':ti,ab OR 'ebrt':ti,ab OR 'external beam therapy':ti,ab OR 'external beam irradiation':ti,ab OR 'external beam radiation':ti,ab OR 'external beam rt':ti,ab OR 'three-dimensional conformal':ti,ab OR '3d-crt':ti,ab OR '3-d conformal':ti,ab OR '3d conformal':ti,ab OR 'intensity-modulated radiation':ti,ab OR 'imrt':ti,ab OR 'image-guided radiation':ti,ab OR 'igrt':ti,ab OR 'tomotherapy':ti,ab) OR 'radiotherapy'/exp) AND (surgery:ab,ti OR surgical:ab,ti OR radionuclide:ab,ti OR bisphosphonate*:ab,ti OR kyphoplasty:ab,ti OR vertebroplasty:ab,ti) AND [medline]/lim)

EM_Bone cancer RT KQ 2 and 3_Embase only_20220627_text_1529hits

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EM_Bone cancer RT KQ 2 and 3_Embase and MEDLINE_20220627_text_2681hits

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fractionation:ti,ab)) AND ('bone cancer'/exp/dm_rt OR (bone AND metasta*:ti,ab)) AND [medline]/lim)

Inclusion and Exclusion Criteria

Criteria for Inclusion/Exclusion of Studies in the Review

The criteria for inclusion and exclusion of studies for the systematic were based on the Key Questions and on the specific criteria for population, interventions, comparators, outcomes, timing, and settings (PICOTS), listed in Table A-1.

Table A-1. Inclusion and exclusion criteria: population, interventions, comparators, outcomes, timing, and settings

PICOTS	Inclusion	Exclusion
Population	**Key Question 1:** Symptomatic adults with bone metastases who will receive initial palliative radiation **Key Question 2:** Symptomatic adults with bone metastases who will receive re-radiation for palliation **Key Question 3:** Symptomatic adults with cancer that has metastasized to the bone. **For all Key Questions:** Patients with either complicated or uncomplicated bone metastases will be included. Consider patient and clinical characteristics (e.g., age, sex, social determinants of health, primary tumor histology, site of metastases).	• Patients <18 years old • Asymptomatic patients • Patients with primary bone tumors
Intervention	**Key Questions 1 and 2:** Comparisons of dose-fractionation schemes for EBRT, comparisons of EBRT techniques (e.g., conventional RT vs. SBRT, SBRT vs. IMRT) **Key Question 3:** External beam radiation therapy for the palliative management of bone metastasis a) alone, or b) and c) *with co-interventions*, additional therapies (e.g., surgery, radionuclide therapy, bisphosphonate therapy, ablation kyphoplasty /vertebroplasty)	**Key Questions 1, 2, 3:** Proton beam therapy **Key Question 3**: Brachytherapy
Comparator	**Key Questions 1 and 2:** No cointervention (i.e., EBRT alone) **Key Question 3:** a) another single MBD treatment, b) EBRT alone c) the same cointervention/additional therapy alone	

PICOTS	Inclusion	Exclusion
Outcome	**Effectiveness:** Primary outcomes • Pain (level and duration) • Skeletal function • Relief of spinal cord compression • Quality of life Additional (secondary) outcomes • Local recurrence • Fracture prevention • Overall survival • Need for re-radiation • Use of pain medication, need for other interventions for pain relief **Harms and adverse events** • Harms (e.g., rate of radiation/treatment toxicity, radiation-induced fracture rates, reduced mobility, reduced independence), adverse events (pain flare, radiation recall, fatigue, skin changes, etc.)	• Nonvalidated measurement instruments for clinician or patient rated outcomes (e.g., pain, function, HRQOL)
Timing	Any (timing may depend on treatments provided and outcomes assessed)	None
Setting	Any	• None
Study design, publication type	**All Key Questions:** Focus will be on the best evidence available that permits direct comparisons to answer Key Questions RCTs will be initially sought; in the absence of RCTs, prospective comparative studies that control for confounding will be considered; if no comparative prospective studies are available, retrospective comparative studies that control for confounding will be considered. In the absence of comparative studies, single arm (e.g., case series, pre-post studies) may be considered For evaluation of harms, comparative cohort and case-control studies will be included; we will focus on studies specifically designed to evaluate harms. Studies of at least 20 patients per treatment arm	**GENERAL** • Dosimetry modeling studies • Nonhuman studies • NRSI for effectiveness if RCTs are available • Studies with <20 patients per arm • Single arm studies (unless no comparative studies); if used, exclude studies of <20 patients • Case reports **Publication dates**: Prior to 1985 • **Publication types:** Conference abstracts or proceedings, editorials, letters, white papers, citations that have not been peer-reviewed, single site reports of multi-site studies

EBRT = external beam radiotherapy; HRQOL = health-related quality of life; IMRT = intensity modulated radiation therapy; MBD = metastatic bone disease; NRSI = nonrandomized study of intervention; PICOTS = population, intervention, comparator, outcome, timing, setting; RCT = randomized controlled trial; RT = radiation therapy; SBRT = stereotactic radiation therapy.

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

Study Design: We used a best evidence approach[1] and randomized controlled trials (RCTs) were sought initially. Given the paucity of RCTs available to answer some Key Questions, prospective comparative studies that controlled for confounding were considered; where none were identified, retrospective comparative studies that control for confounding were considered. For evaluation of harms, we included comparative cohort and case-control studies with a focus on those specifically designed to evaluate harms.

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

Process for Selecting Studies

In accordance with the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*,[2] we used the pre-established criteria above to screen citations (titles and abstracts) identified through our searches or SEADS submissions to determine eligibility for full-text review. We used DistillerSR® to improve efficiency in screening articles. Given the paucity of RCTs for portions of this review, we included nonrandomized studies of interventions (NSRIs). We followed a "best-evidence" approach[1] and to the extent possible, focused on comparative NRSI which control for confounding in the absence of RCTs. In the absence of NRSIs that controlled for confounding, comparative NRSIs that did not control for confounding were considered. Where multiple RCTs or controlled comparative prospective NRSIs were available (e.g., does-fractionation schemes for Key Question 1), we included other comparative NRSIs only if they evaluated harms. Case series were excluded. We focused on primary studies and reviewed systematic review (SR) references for relevant studies as identified SRs did not fully answer the Key Questions. All excluded abstracts were dual reviewed to assure accuracy for inclusion. All citations deemed appropriate for inclusion by at least one reviewer were retrieved. Each full-text article was independently reviewed for eligibility by two team members, including any articles suggested by Technical Expert Panel (TEP) members, peer reviewers or that arose from the public posting process. Any disagreements were resolved by consensus. A flow diagram of study screening and inclusion is below in Appendix B. A record of studies included in the review and those excluded at the full-text level with reasons for exclusion are listed below in Appendix D and H, respectively.

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

Data Extraction and Data Management

After studies were selected to inclusion, to capture information related to intervention heterogeneity and complexity and heterogeneity across enrolled populations, we created an organization framework and tailored detailed data abstraction tools following principles from the Template for Intervention Description and Replication (TIDieR) checklist.[3] Using standardized templates, data from included studies were abstracted into categories that include but are not limited to: study design, year, setting, country, funding, sample size, eligibility criteria, attrition, radiation therapy delivery (type, dose, frequency/fractions, prior and additional radiation), prior and concurrent treatments, population and clinical characteristics including key subgroups

(gender, age), primary tumor histology, characteristics (e.g., size), location (spine, nonspine and specific location including weight bearing structures) and numbers of metastatic lesions treated, effectiveness-related outcomes (e.g., validated pain, function and quality of life measures), local tumor control and overall survival as well as treatment-related side effects/harms. For this report, EBRT refers to conventional EBRT to distinguish it from SBRT. For the comparison of single versus single fraction and multiple versus multiple fractions, the lower total dose EBRT scheme was chosen as the intervention, which generally had fewer fractions, and the higher total dose EBRT scheme as the control/referent, which generally represented more fractions. Information on confounders (in addition to those already identified for abstraction related to patient and MBD characteristics such as presence of fracture, performance status) and methods of adjustment for them were also abstracted as was data on followup. Information relevant for assessing applicability was abstracted, including the characteristics of the population, interventions and the number of patients enrolled relative to the number assessed for eligibility. We extracted information regarding complicated and uncomplicated bone metastases as reported by the authors of the included studies. Uncomplicated bone metastases are defined as "the presence of painful bone metastases unassociated with impending or existing pathologic fracture or existing spinal cord or cauda equina compression"[4] and complicated bone metastases are those with any of those features (i.e., pathological fracture, cord compression). Few studies defined their populations in terms of complicated and uncomplicated bone metastases, but we extracted information related to pathological fracture and spinal cord compression at baseline or noted if these were exclusion criteria to get a sense of whether the populations fit into either of these categories. Definitions of pain responses (overall, partial, complete response) varied across trials as did pain measures used. Function was extracted as either skeletal function or general function. Skeletal function included measures of spinal stability (e.g., spinal instability neoplastic score [SINS]) or the prevention of fractures or skeletal-related events (SREs). Overall function included measures such as Karnofsky Performance Scale (KPS), Barthel Index or other measures of activities of daily living (ADLs) meant to assess functional independence. In patients with metastatic spinal cord compression (MSCC), relief of spinal cord compression was captured by outcomes related to neurologic function/improvement such as motor function or ambulation and bladder or sphincter control. For safety/harms, we focused on new or worsening spinal cord compression, neurological function and pathological fractures, pain flare, Grades 3 and 4 toxicities, and serious adverse events (e.g., treatment-related death, discontinuation due to treatment-related adverse event, radiation induced myelopathy). All extracted study data was verified for accuracy and completeness by a second team member.

Risk of Bias Assessment of Individual Studies

Methods from the *Methods Guide for Effectiveness and Comparative Effectiveness Review*[2] were used in concordance with the approach recommended in the chapter, Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions.[5] RCTs were assessed based on criteria established in the *Cochrane Handbook for Systematic Reviews of Interventions (Chapter 8.5 Risk of Bias Tool)*[6] and precepts for appraisal developed by the Cochrane Back and Neck Group.[7] Because nonrandomized studies are at increased risk of selection bias and confounding, we assessed risk of bias using instruments tailored to observational studies[8] that consider methods of patient selection (e.g., consecutive patients, use of an inception cohort) and appropriate control for confounding of relevant prognostic factors. Based on the risk of bias

assessment, individual included studies were rated as being "good," "fair," or "poor" quality as described below in Table A-2.

Table A-2. Criteria for grading the quality of individual studies

Rating	Description and Criteria
Good	• Least risk of bias, results generally considered valid • Employ valid methods for selection, inclusion, and allocation of patients to treatment; report similar baseline characteristics in different treatment groups; clearly describe attrition and have low attrition; use appropriate means for preventing bias (e.g., blinding of patients, care providers, and outcomes assessors); and use appropriate analytic methods (e.g., intention-to-treat analysis)
Fair	• Susceptible to some bias but not enough to necessarily invalidate results • May not meet all criteria for good quality, but no flaw is likely to cause major bias; the study may be missing information making it difficult to assess limitations and potential problems • Category is broad; studies with this rating will vary in strengths and weaknesses; some fair-quality studies are likely to be valid, while others may be only possibly valid
Poor	• Significant flaws that imply biases of various kinds that may invalidate results; "fatal flaws" in design, analysis or reporting; large amounts of missing information; discrepancies in reporting; or serious problems with intervention delivery • Studies are at least as likely to reflect flaws in the study design or execution as the true difference between the compared interventions • Considered to be less reliable than higher quality studies when synthesizing the evidence, particularly if discrepancies between studies are present

It was not possible for studies to effectively blind participants (or providers) with regard to EBRT regimen for many comparisons. Studies were downgraded to fair for lack of blinding in these instances as bias from patient expectations of treatment, attentional affects, and performance bias is possible; this is consistent with the approach used in prior Agency for Healthcare Research and Quality (AHRQ) reviews of nonpharmacological treatments for pain

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

Data Synthesis and Analysis

We constructed evidence tables (Appendix E) identifying the study and patient characteristics (as discussed above), results of interest, and quality ratings for all included studies, as well as summary tables when deemed appropriate (Results Appendix B, Tables B2–B17) and/or figures to highlight the main findings (Appendix I). We reviewed and highlighted studies by using a hierarchy-of-evidence approach and focused the synthesis on the highest quality data for each Key Question. We analyzed RCTs and NRSIs separately and reported them separately unless findings were very consistent across study designs and the studies were clinically homogeneous.

Meta-analyses were conducted to obtain more precise effect estimates when at least two trials were amenable to pooling. To determine the appropriateness of meta-analysis, we considered clinical and methodological diversity and assessed statistical heterogeneity. For binary outcomes (e.g., pain response, re-radiation), risk ratio (RR) was used as the effect measure; a risk difference (RD) was only reported or calculated if there was an association found. Definitions of pain responses varied across trials and included achievement of pain reduction by a specific threshold (e.g., ≥2 points decrease in VAS score than baseline) with many trials also including decreased or stable analgesic use in the response definition. Both complete pain response and overall pain response were meta-analyzed. Overall pain response included both complete pain

response and partial pain response or was defined as an improvement in pain after radiation therapy. Some studies[9-14] defined partial pain response that was consistent with overall pain response hence the reported data were treated as overall pain response in the meta-analyses. Results Appendix B, Table B-2 contains the definitions for pain response as reported by the authors. For continuous outcomes (e.g., pain, quality of life), mean difference (MD) was used as the effect measure as the studies reported outcomes using the same scale, or the outcomes could be converted to the same scale (e.g., pain, converted to 0-10 scale). MD was calculated using the followup score if reported and then the change score from baseline. When standard deviation (SD) was not reported, or could not be calculated from the reported data, it was imputed using the average coefficient of variation from the other included studies reporting the same outcome. One study[15] only reported overall 95% confidence interval (CI) of change scores by combining both treatment arms; we calculated SD assuming same standard error (SE) for both treatment arms.

A random effects model based on the profile likelihood method[16] was used to obtain pooled RR and MD. The primary analyses were stratified by the length of followup: post RT to 4 weeks, >4 weeks to 12 weeks, >12 weeks, and not reported (NR) or unclear. When more than one followup times were reported in the followup period above, results from longer followup time was used in meta-analyses, unless the reported data from a shorter followup period were more representative of the study population.[17,18] When a study[17] reported data from both per protocol analysis and an analysis assuming death and drop out as nonresponders, data from the former were used in the primary analysis, and data from the latter were used in sensitivity analysis, to avoid including patients who have already died in the denominator in later timepoints. Additional sensitivity analyses were conducted by excluding studies rated poor.

Statistical heterogeneity among the studies was assessed using Cochran's χ^2 test and the I^2 statistic (reference).[19] For analyses with at least 10 trials, we constructed funnel plots and performed the Egger test to detect small sample effects (a marker for potential publication bias).[20] All meta-analyses were conducted using Stata/SE 16.1 (StataCorp, College Station, TX).

We classified the magnitude of effects for continuous measures of pain and function using the same system as in prior AHRQ reviews on pain[21-25] (Appendix J). Effects below the threshold for small were categorized as no effect. Where possible, we reported on the proportion of patients meeting thresholds for clinically important differences (e.g., >30% pain relief).

To evaluate differential efficacy and safety (heterogeneity of effect, interaction), we focused on RCTs as they have the least potential for bias and confounding thus allowing for causal inference. Few of the included RCTs performed formal tests for interaction between subgroups; data from subgroup analyses was included for completeness. For trials that perform tests for interaction, confidence in such analyses requires consideration of the overall study risk of bias (study quality) as well as whether subgroup variables and analyses were specified a priori, the hypothesized impact of a subgroup on the outcome/effect and sample size as evaluation of interaction requires greater sample size. These considerations are based on recommendations from Oxman and Guyatt and the Instrument to assess the Credibility of Effect Modification (ICEMAN) criteria and others.[26-28]

Grading the Strength of the Body of Evidence

Outcomes to be assessed for strength of evidence (SOE) were prioritized based on input from the Technical Expert Panel (TEP). Based on this prioritized list, the strength of evidence for comparison-outcome pairs within each Key Question was initially assessed by one researcher for

each clinical outcome (see PICOTS, Table A-1) by using the approach described in the *Methods Guide for Effectiveness and Comparative Effectiveness Review*.[2] To ensure consistency and validity of the evaluation, the initial assessment was independently reviewed by at least one other experienced investigator using the following criteria:

- Study limitations (low, medium, or high level of study limitations)
    - Rated as the degree to which studies for a given outcome are likely to reduce bias based on study design and conduct. The aggregate risk of bias across individual studies reporting an outcome is considered.
- Consistency (consistent, inconsistent, or unknown/not applicable)
    - Rated by degree to which studies find similar magnitude of effect (i.e., range sizes are similar) or same direction of effect (i.e., effect sizes have the same sign)
- Directness (direct or indirect)
    - Rated by degree to which the outcome is directly or indirectly related to health outcomes of interest. Patient centered outcomes are considered direct
- Precision (precise or imprecise)
    - Describes the level of certainty of the estimate of effect for a particular outcome with a precise estimate being on that allows a clinically useful conclusion. This may be based on sufficiency of sample size and number of events, and if these are adequate, the interpretation of the confidence interval. When quantitative synthesis is not possible, sample size and assessment of variance within individual studies will be considered.
- Reporting bias (suspected or undetected)
    - Publication bias, selective outcome reporting, and selective analysis reporting are types of reporting bias. Reporting bias is difficult to assess as systematic identification of unpublished evidence is challenging. If enough RCTs (>10) are available, quantitative funnel plot analysis may be done.

The SOE was assigned an overall grade of high, moderate, low, or insufficient (see Table A-3, below) according to a four-level scale by evaluating and weighing the combined results of the above domains.

Table A-3. Description of strength of evidence grades

Grade	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable (i.e., another study would not change the conclusions).
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available, or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

RCT evidence was initially considered high, with possible downgrades for any of the above domains. For NRSIs, the strength started at moderate for harms outcomes, and low for benefit outcomes. While AHRQ guidance[2,5] allows for upgrading NRSI evidence in certain

circumstances (e.g., large magnitude of effect), no upgrading was considered as none of the included studies was considered good (i.e., evidence was downgraded for risk of bias/study quality in all cases; for NRSI evidence to be upgraded, there can be no downgrades in the 5 primary domains). When both RCTs and NRSIs were included for a given outcome, we followed AHRQ guidance on weighting RCTs over observational studies, assessing consistency across the two bodies of evidence, and determining a final rating.[2] We considered NRSI evidence to supplement RCT evidence to arrive at a final rating. We primarily used RCT evidence as that from NRSIs was of lower strength. If only poor-quality trials were available for a given outcome, SOE was considered insufficient.

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

Assessing Applicability

Applicability will be assessed in accordance with the AHRQ Methods Guide,[2] using the PICOTS framework. Applicability refers to the degree to which outcomes associated with the intervention are likely to be similar across patients and settings relevant to the care of patients undergoing palliative radiation therapy for MBD based on the populations, interventions comparisons and outcomes synthesized across included studies. Multiple factors identified a priori that are likely to impact applicability include primary tumor histology, patient prognosis and life expectancy, lesion characteristics (number, location, whether they are osteolytic, osteoblastic, or mixed), characteristics of enrolled patient populations (e.g., sex, age, social determinants of health, health and functional status, comorbidities) and methods of radiation delivery. Review of abstracted information on these factors will be used to assess situations for which the evidence is most relevant and to evaluate applicability to real-world clinical practice in typical U.S. settings. We will provide a qualitative summary of our assessment.

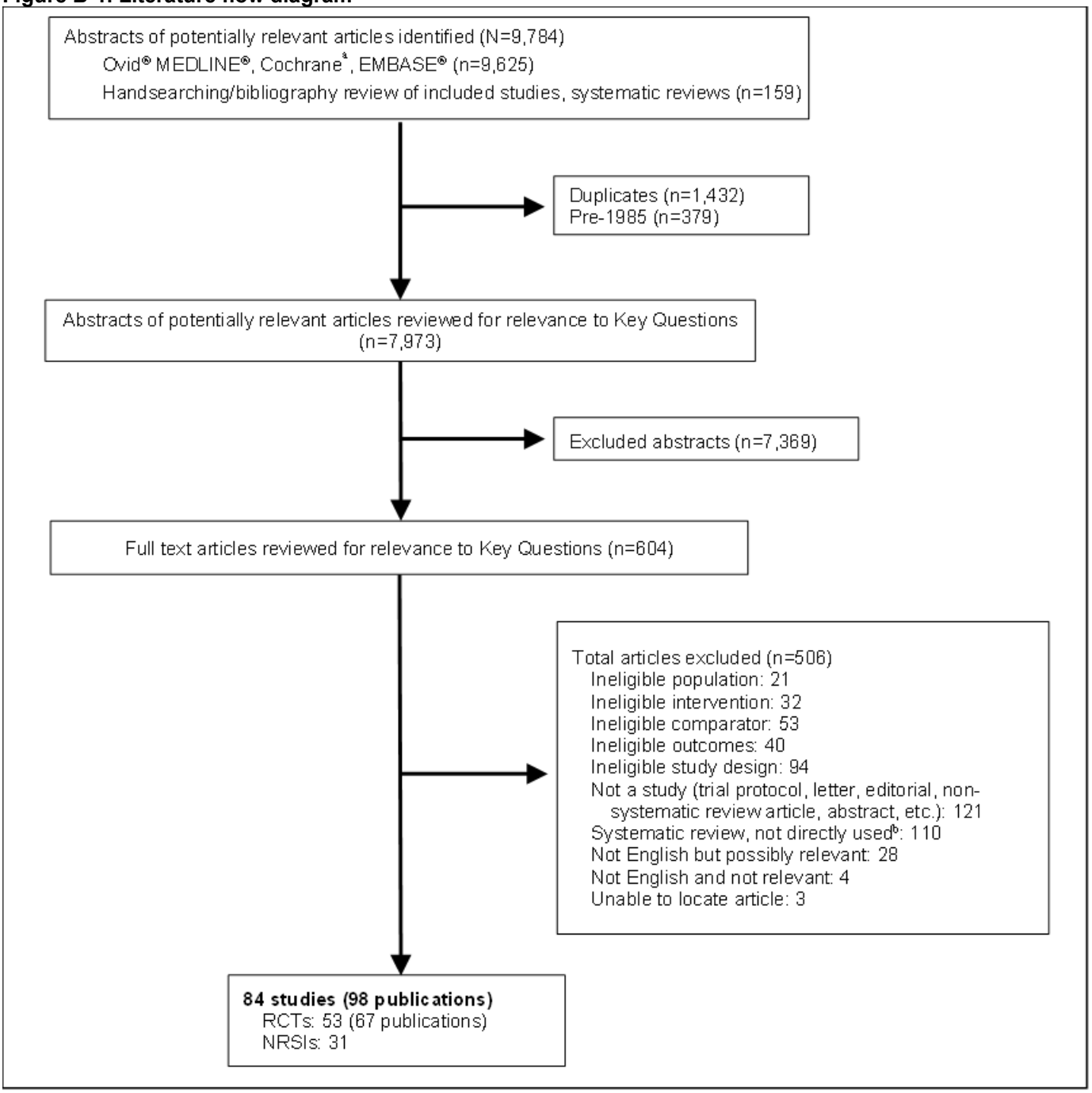
Contextual Questions

We followed the methods of the U.S. Preventive Services Task Force (USPSTF) to evaluate the Contextual Questions.[29] A targeted search was designed by a medical librarian with experience in searching for contextual question evidence for USPSTF reviews, including searching for systematic and narrative reviews. The team also identified any information relevant to this question opportunistically, while reviewing comprehensive literature searches for Key Questions, and incorporated relevant information from TEP calls. The information on the Contextual Questions were summarized in the introduction of the report and presented in the Results section of the report. Appendix C contains additional information related to the Contextual Questions.

Appendix B. Results Overview

Results of Literature Searches

Figure B-1. Literature flow diagram



NRSI = comparative nonrandomized study of interventions; RCT = randomized controlled trial

[a] Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews

[b] Bibliographies/reference lists were reviewed for relevant studies not captured by the systematic search.

A total of 9,784 abstracts were identified, 9,625 from electronic database searches and an additional 159 from handsearching and bibliography review of included studies and systematic reviews. After dual review of titles and abstracts, 604 articles were selected for full-text review, of which 84 studies (in 98 publications) were ultimately included in this review: 53 randomized controlled trials (RCTs) (in 67 publications)[9-15,17,18,30-87] and 31 comparative nonrandomized studies of interventions (NRSIs).[88-122] The most evidence was identified for Key Question 1 (62 studies in 75 publications) and the comparison of dose-fractionation schemes (external beam radiation therapy [EBRT] and stereotactic body radiation therapy [SBRT]) specifically (34 RCTs in 43 publications[9-15,18,30,32-34,38-43,45-55,58,59,61,66,68-71,73,74,83-85,87] and 11 NRSIs);[88,92,94-96,99,101-103,112,116,118-121] for the comparison of techniques for EBRT delivery, six RCTs (in 10 publications)[17,63,65,72,77-82] and seven NRSIs[89,97,105,108,110,113,122] were included. The number of included studies for the remaining Key Questions is as follows: Key Question 2 (2 RCTs,[37,84] 3 NRSIs[98,107,109]; all comparing single versus multiple dose-fractionation schemes), Key Question 3a (3 RCTs,[44,60,67] 2 NRSIs[91,93]), Key Question 3b (9 RCTs in 10 publications,[31,35,36,56,57,62,64,75,76,86] 7 NRSIs[90,93,100,104,106,115,117]), and Key Question 3c (3 NRSIs[93,111,114]). For Key Question 3, a variety of different modalities were compared with and/or used in combination with EBRT the most common being radioisotopes and surgery. Four studies had three arms and contributed data to more than one comparison, three RCTs (Key Question 1)[9,58,61] and one NRSI (Key Questions 3a-c).[93] Most of studies evaluated conventional EBRT; five RCTs (in 7 publications)[17,63,72,77,79,82,87] and 12 NRSIs [88-90,94-98,101,110,113,116] SBRT. Two RCTs were rated good quality (4%),[36,57] 36 fair quality (68%)[9-14,17,31-34,37,38,42-46,48,49,51-53,60,62,64-66,70-72,75,78,79,83,87] and 15 poor quality (28%).[18,30,35,39-41,55,58,59,61,63,67,74,76,86] Twenty-one NRSIs were rated fair quality (68%)[88,89,91-94,97,98,101-106,110-113,116,117,122] and 10 were rated poor quality (32%).[90,95,96,99,100,107-109,114,115] Search results and selection of studies are summarized in the literature flow diagram above (Figure B-1). A list of included studies appears in Appendix D and excluded studies with reason for exclusion in Appendix H.

Table B-1. Number of studies overall and by Key Question

Key Question	Intervention	Comparator	n=Number of RCTs (Number of Publications)	n=Number of NRSIs	**Total:** n=Number of RCTs and NRSIs (Number of Publications)
1: fractionation schemes	SF EBRT	MF EBRT	22 (29)[9,11-15,30,32-34,38-41,45,47,49,50,53,54,58,61,66,71,73,74,83-85]	4[92,99,102,103]	26 (33)[9,11-15,30,32-34,38-41,45,47,49,50,53,54,58,61,66,71,73,74,83-85,92,99,102,103]
	SF EBRT	SF EBRT	4 (4)[43,46,48,51]	0	4 (4)[43,46,48,51]
	MF EBRT	MF EBRT	10 (12)[10,18,30,42,52,55,58,59,61,68-70]	1[112]	11 (13)[10,18,30,42,52,55,58,59,61,68-70,112,118-121]
	SF SBRT	MF SBRT	1 (1)[87]	4[94,95,101,116]	5 (5)[87,94,95,101,116]
	MF SBRT	MF SBRT	0	2[88,96]	2 (2)[88,96]
	Any fractionation scheme[a]	Any fractionation scheme	34 (43)[9-15,18,30,32-34,38-43,45-55,58,59,61,66,68-71,73,74,83-85,87]	11[88,92,94-96,99,101-103,112,116,118-121]	45 (54)[9-15,18,30,32-34,38-43,45-55,58,59,61,66,68-71,73,74,83-85,87,88,92,94-96,99,101-103,112,116,118-121]
1: techniques[b]	IMRT	3DCRT	1 (3)[78,80,81]	2[105,108]	3 (5)[78,80,81,105,108]
	EBRT + HBI	EBRT alone	1 (1)[65]	0	1 (1)[65]
	SBRT	EBRT	4 (6)[17,63,72,77,79,82]	4[89,97,110,113]	8 (10)[17,63,72,77,79,82,89,97,110,113]

Key Question	Intervention	Comparator	n=Number of RCTs (Number of Publications)	n=Number of NRSIs	**Total:** n=Number of RCTs and NRSIs (Number of Publications)
	IMRT, 3DCRT or SBRT[c]	EBRT	0	1[122]	1 (1)[122]
	Any technique	Any technique	6 (10)[17,63,65,72,77-82]	7[89,97,105,108,110,113,122]	13 (17)[17,63,65,72,77-82,89,97,105,108,110,113,122]
1: fractionation schemes or techniques	Any	Any	40 (53)[9-15,17,18,30,32-34,38-43,45-55,58,59,61,63,65,66,68-74,77-85,87]	18[88,89,92,94-97,99,101-103,105,108,110,112,113,116,122]	58 (71)[9-15,17,18,30,32-34,38-43,45-55,58,59,61,63,65,66,68-74,77-85,87-89,92,94-97,99,101-103,105,108,110,112,113,116,122]
2: Reirradiation	SF EBRT	MF EBRT	2 (2)[37,84]	2[107,109]	4 (4)[37,84,107,109]
	SF SBRT	MF SBRT	0	1[98]	1 (1)[98]
	Any fractionation scheme	Any fractionation scheme	2 (2)[37,84]	3[98,107,109]	5 (5)[37,84,98,107,109]
3a: single modalities	EBRT	Radioisotopes	3 (3)[44,60,67]	0	3 (3)[44,60,67]
	EBRT	Cryoablation	0	1[93]	1 (1)[93]
	EBRT	ADT	0	1[91]	1 (1)[91]
	Any EBRT	Any other modality	3 (3)[44,60,67]	2[91,93]	5 (5)[44,60,67,91,93]
3b: Combination treatment vs. EBRT alone	EBRT + radioisotopes	EBRT alone (+placebo)	3 (4)[56,57,64,75]	0	3 (4)[56,57,64,75]
	EBRT + dexamethasone	EBRT alone	2 (2)[36,76]	0	2 (2)[36,76]
	EBRT + bisphosphonates	EBRT alone (+placebo)	1 (1)[86]	2[100,115]	3 (3)[86,100,115]
	EBRT + surgery	EBRT alone	1 (1)[62]	3[104,106,117]	4 (4)[62,104,106,117]
	SBRT + surgery	SBRT alone	0	1[90]	1 (1)[90]
	EBRT + cryoablation	EBRT alone	0	1[93]	1 (1)[93]
	EBRT + hyperthermia	EBRT alone	1 (1)[35]	0	1 (1)[35]
	EBRT + capecitabine	EBRT alone	1 (1)[31]	0	1 (1)[31]
	Any combination treatment	Any EBRT alone	9 (10)[31,35,36,56,57,62,64,75,76,86]	7[90,93,100,104,106,115,117]	16 (17)[31,35,36,56,57,62,64,75,76,86,90,93,100,104,106,115,117]
3c: Combination treatment vs. other single modality alone	EBRT + radioisotopes	Radioisotopes alone	0	1[114]	1 (1)[114]
	EBRT + surgery	Surgery alone	0	1[111]	1 (1)[111]
	EBRT + cryoablation	Cryoablation alone	0	1[93]	1 (1)[93]
	Any combination treatment	Any single modality alone	0	3[93,111,114]	3 (3)[93,111,114]
Total No. Studies Included	Any	Any	53 (67)[9-15,17,18,30-87]	31[88-117,122]	84 (98)[9-15,17,18,30-117,122]

3DCRT = three-dimensional conformal radiation therapy; ADT = androgen deprivation therapy; EBRT = external beam radiation therapy; HBI = hemibody irradiation; IMRT = intensity modulated radiation therapy; LDMF = lower total dose multiple fraction; LDSF = lower total dose single fraction; MF = multiple fraction; NRSI = nonrandomized study of interventions; RCT = randomized controlled trial; RT = radiation therapy; SF = single fraction; SBRT = stereotactic body radiation therapy

[a] 3 trials had 3 arms and contributed data to both the SF vs. MF and the MF vs. MF analyses (Abu-Hegazy, 2011;[30] Nongkynrih, 2018;[58] and Ozsaran, 2011[61]).
[b] In the report, SBRT vs. EBRT and IMRT/3DCRT/SBRT vs. EBRT are collectively referred to as "Advanced Techniques" vs. Conventional EBRT and summarized together under that heading.
[c] Most patients received IMRT (67%), followed by 3DCRT (26%) and SBRT (8%)

Definitions of Pain Response

Table B-2. Definitions of pain response from included RCTs

Pain Response Outcome	Author, Year	Treatment Arms	Pain Response Definition
Complete Pain Response	Amouzegar-Hashemi, 2008[32]	SF vs. MF EBRT	Reduction in pain score of at least 2 points
	Anter, 2015[33]	SF vs. MF EBRT	No pain 3 months post-RT
	Bone Pain Trial Working Group, 1999[9]	SF vs. MF EBRT	No pain
	Foro Arnalot, 2008[38]	SF vs. MF EBRT	Absence of pain without the need for increasing analgesia
	Gaze, 1997[39]	SF vs. MF EBRT	Complete pain response: pain score = 0, regardless of analgesic use Complete pain response combined: pain score = 0 and analgesic score = 0
	Gutierrez Bayard, 2014[40]	SF vs. MF EBRT	Without pain
	Hamouda, 2007[11]	SF vs. MF EBRT	VAS pain score 0
	Hartsell, 2005/ Howell, 2013/ Konski 2006[41,47,50]	SF vs. MF EBRT	No pain at 12 weeks after RT
	Majumder, 2012[12]	SF vs. MF EBRT	VAS of 0 without analgesic increase
	Maranzano, 2009[53]	SF vs. MF EBRT	No pain after RT
	Nielsen, 1998[13]	SF vs. MF EBRT	Complete absence of pain
	Nongkynrih, 2018[58]	SF vs. MF EBRT and LDMF vs. HDMF EBRT	Pain score 0 at any time during followup
	Price, 1986[66]	SF vs. MF EBRT	Complete loss of pain
	Roos, 2005[71]	SF vs. MF EBRT	Change in pain score from severe, moderate, or mild to none with no analgesia or adjuvant analgesia for the index pain.
	Sarkar, 2002[74]	SF vs. MF EBRT	Absence of pain in treatment site.
	Steenland, 1999 / van der Linden 2006 / Meeuse 2010[14,54,84]	SF vs. MF EBRT	Pain severity score 0 or 1 (0-10 scale)

Pain Response Outcome	Author, Year	Treatment Arms	Pain Response Definition
	Hoskin, 2015[43]	LDSF vs. HDSF	Complete pain response, categorical: no pain on the categorical scale (none/mild/moderate/severe) Complete pain response, VAS: score 0 on VAS Complete pain response, combined categorical: no pain on the categorical scale and no analgesics Complete pain response, combined VAS: score 0 on VAS and no analgesics
	Hoskin, 1992[46]	LDSF vs. HDSF	Change in score from severe, moderate or mild to none
	Jeremic, 1998[48]	LDSF vs. HDSF	No pain
	Atahan, 2010[10]	LDMF vs. HDMF	No pain in the irradiated areas without a need for analgesic treatment or reduced need for analgesics
	He, 2019[42]	LDMF vs. HDMF	Pain score 0 at treated site with no increase in analgesic intake
	Maranzano, 2005[52]	LDMF vs. HDMF	No pain after RT
	Niewald, 1996[55]	LDMF vs. HDMF	No pain
	Okawa, 1988[59]	LDMF vs. HDMF	“Excellent” = pain disappeared
	Rades, 2016 / Rades, 2018 / Rades, 2019	LDMF vs. HDMF	VAS score 0 (0-10 scale)
	Rasmusson, 1995[18]	LDMF vs. HDMF	Pain relief rating 4 (complete relief)
	Sprave, 2018[78,80,81]	IMRT vs. 3DCRT	VAS score 0, with no increase in analgesic intake after 12 weeks
	Nguyen, 2019[17]	SBRT vs. EBRT	Pain score of 0 (on 0-10 scale) at the treated site and no increase in oral morphine equivalent dose
	Pielkenrood, 2021[63]	SBRT vs. EBRT	pain score of 0 (on a 0-10 scale), without an increase in pain medication use
	Sahgal, 2021[72]	SBRT vs. EBRT	Worst pain score of 0 on the BPI with no associated increase in daily oral morphine equivalent consumption
	Sprave, 2018[77,79,82]	SBRT vs. EBRT	VAS score 0 at the treated site with no concurrent increase in analgesic intake (stable or reducing analgesics in daily oral morphine equivalent dose.
	Chow, 2015[36]	EBRT + other vs. other	Worst pain score of zero at the bony metastatic site, with no concomitant increase in analgesic intake.
	Porter, 1993[64]	EBRT + other vs. other	100% pain relief
	Hoskin, 2015[44]	EBRT vs. other	Pain score 0 with stable/reduced analgesic use
Partial Pain Response	Abu-Hegazy, 2011[30]	SF vs. MF EBRT and LDMF vs. HDMF EBRT	Decrease of ≥1 point on VAS (0-10 scale)
	Amouzegar-Hashemi, 2008[32]	SF vs. MF EBRT	Reduction in pain score ≥1 but not more than 2 grades

Pain Response Outcome	Author, Year	Treatment Arms	Pain Response Definition
	Anter, 2015[33]	SF vs. MF EBRT	Pain score ≥2 points lower than the baseline score
	Foro Arnalot, 2008[38]	SF vs. MF EBRT	Improvement ≥2 (on 0-10 VAS) with no need for increasing analgesia
	Gutierrez Bayard, 2014[40]	SF vs. MF EBRT	Good: ≥2 level decrease in pain Poor/Slight: Only decreases pain level
	Hartsell, 2005 / Howell, 2013 / Konski 2006[41,47,50]	SF vs. MF EBRT	Pain score ≥2 points lower (on 0-10 scale) vs. baseline
	Maranzano, 2009[53]	SF vs. MF EBRT	(a) Patients using minor narcotics who had stable pain or pain requiring minor analgesics, (b) or patients using minor analgesics who had stable pain
	Nielsen, 1998[13]	SF vs. MF EBRT	categorical pain scale) (improvement of at least one category on the 5-point categorical scale
	Nongkynrih, 2018[58]	SF vs. MF EBRT and LDMF vs. HDMF EBRT	Not defined; appears to be overall pain response minus complete pain response
	Price, 1986[66]	SF vs. MF EBRT	"Improvement in pain corresponding to at least one category"; using pain scoring 1-4
	Roos, 2005[71]	SF vs. MF EBRT	Improvement in pain score by ≥1 grade (severe, moderate, mild or none) with no increase in analgesia for index pain
	Sarkar, 2002[74]	SF vs. MF EBRT	Relief of pain at least by one category e.g., severe to moderate (4 to 3 or moderate to mild (3 to 2) on 1-4 scale.
	Hoskin, 2015[43]	LDSF vs. HDSF	PR, categorical: improvement by at least 1 category of pain (e.g., from moderate to mild) Partial pain response, VAS: reduction in the VAS score of ≥10 mm Partial pain response, combined categorical: improvement by at least 1 category of pain (e.g., from moderate to mild) with either no analgesics or decreased or stable analgesics Partial pain response, combined VAS: reduction in the VAS score of ≥10 mm, with either no analgesics or decreased or stable analgesics
	Jeremic, 1998[48]	LDSF vs. HDSF	Improvement in pain score by at last one category, with pain still existing.
	He, 2019[42]	LDMF vs. HDMF	≥2 point increase in pain score with no decrease in analgesic intake overall pain response ≥25% increase in analgesic intake with no decrease in pain score
	Maranzano, 2005[52]	LDMF vs. HDMF	Using narcotic or minor analgesics before RT who had pain requiring minor analgesics after RT
	Okawa, 1988[59]	LDMF vs. HDMF	“Good” = ≥2 stage or higher improvement “Fair” = 1 stage improvement
	Rasmusson, 1995[18]	LDMF vs. HDMF	1-3 on pain relief scale (1=slight relief, 2=partial relief, 3=good relief)
	Sprave, 2018[78,80,81]	IMRT vs. 3DCRT	Pain reduction of ≥2 points (on 0-10 scale) at the treated site without analgesic increase, overall pain response analgesic reduction of 25% or more from baseline without an increase in pain.
	Nguyen, 2019[17]	SBRT vs. EBRT	Reduction in pain score of ≥2 points above baseline with no increase in morphine equivalent dose
	Pielkenrood, 2021[63]	SBRT vs. EBRT	Decline of ≥2 points or decline of an oral morphine equivalent dose of at least 25%, or both

Pain Response Outcome	Author, Year	Treatment Arms	Pain Response Definition
	Sahgal, 2021[72]	SBRT vs. EBRT	Reduction in the worst pain score of ≥2 points compared with baseline and no increase in daily oral morphine equivalent dose consumption, overall pain response no increase in the worst pain score and a reduction in daily oral morphine equivalent dose consumption of ≥ 25%
	Sprave, 2018[77,79,82]	SBRT vs. EBRT	Pain reduction of ≥2 (0-10 scale) at the treated site without analgesic increase, or analgesic reduction of 25% or more from baseline without an increase in pain.
	Chow, 2015[36]	EBRT + other vs. other	Either a reduction in the worst pain score ≥2 points (0-10 scale) without analgesic increase or an analgesic reduction of 25% or more from baseline, without an increase in the worst pain score
	Porter, 1993[64]	EBRT + other vs. other	>50% relief in pain (further information unclear)
	Hoskin, 2015[44]	EBRT vs. other	2-point pain reduction with stable/reduced analgesic use overall pain response 25% analgesic use reduction with ≤1 point change in pain
Overall Pain Response	Amouzegar-Hashemi, 2008[32]	SF vs. MF EBRT	Complete + partial pain response
	Anter, 2015[33]	SF vs. MF EBRT	Complete + partial pain response
	Bone Pain Trial Working Group, 1999[9]	SF vs. MF EBRT	Lesser degree of pain versus pretreatment level (e.g., change from 3 to 2, 2 to 1)
	Foro Arnalot, 2008[38]	SF vs. MF EBRT	Complete + partial pain response
	Gaze, 1997[39]	SF vs. MF EBRT	Improvement in pain score of at least one increment (on a 0-4 scale). [This includes those in whom a complete response, defined as a pain score at followup of 0 (regardless of analgesic use), was achieved.]
	Gutierrez Bayard, 2014[40]	SF vs. MF EBRT	Complete + partial pain response
	Hamouda, 2007[11]	SF vs. MF EBRT	≥50% reduction in VAS (0-10) pain score compared with baseline
	Hartsell, 2005 / Howell, 2013 / Konski 2006[41,47,50]	SF vs. MF EBRT	Complete + partial pain response
	Majumder, 2012[12]	SF vs. MF EBRT	Reduction of ≥2 points (0-10 scale) within analgesic increase
	Maranzano, 2009[53]	SF vs. MF EBRT	Complete + partial pain response
	Nongkynrih, 2018[58]	SF vs. MF EBRT and LDMF vs. HDMF EBRT	Change in pain score of ≥ 2 points (on a 0-10 scale) vs. baseline
	Roos, 2005[71]	SF vs. MF EBRT	Complete + partial pain response
	Sarkar, 2002[74]	SF vs. MF EBRT	Complete + partial pain response

Pain Response Outcome	Author, Year	Treatment Arms	Pain Response Definition
	Steenland, 1999 / van der Linden 2006 / Meeuse 2010[14,54,84]	SF vs. MF EBRT	Decrease in initial pain score by ≥2 points (0-10 VAS)
	Hoskin, 2015[43]	LDSF vs. HDSF	Overall pain response categorical: complete + partial pain response categorical Overall pain response VAS: complete + partial pain response VAS
	Jeremic, 1998[48]	LDSF vs. HDSF	Complete + partial pain response
	Atahan, 2010[10]	LDMF vs. HDMF	50% decrease in pain score in addition to a decrease or no changed in analgesic score
	He, 2019[42]	LDMF vs. HDMF	Complete + partial pain response
	Maranzano, 2005[52]	LDMF vs. HDMF	Complete + partial pain response
	Okawa, 1988[59]	LDMF vs. HDMF	Excellent + Good + Fair relief (not reported but easy to generate)
	Rades, 2016 / Rades, 2018 / Rades, 2019[68-70]	LDMF vs. HDMF	Reported but not explained
	Rasmusson, 1995[18]	LDMF vs. HDMF	Overall pain response Complete/Good: Complete + good pain relief (not defined); Overall pain response Complete/Good/Partial: (not defined) – use this measure as overall pain response, includes complete and partial (most likely what they are defining as "good" falls within partial [or complete] response as others have defined)
	Sprave, 2018[78,80,81]	IMRT vs. 3DCRT	Complete + partial pain response
	Nguyen, 2019[17]	SBRT vs. EBRT	Complete + partial pain response
	Pielkenrood, 2021[63]	SBRT vs. EBRT	Complete + partial pain response
	Sprave, 2018[77,79,82]	SBRT vs. EBRT	Complete + partial pain response
	Chow, 2015[36]	EBRT + other vs. other	Complete + partial pain response
	Smeland, 2003[75]	EBRT + other vs. other	One or more of the following occurring: (1). Reduction of the pain score by at least one level with no deterioration in performance status; (2). Unchanged pain level and reduction of the prescribed daily dose of analgesics by at least 25% compared with the pretreatment situation, with no deterioration in performance status; (3). Improvement of the WHO performance status by at least one level without either an increase of the daily dose of analgesics by >25% or an increase in the pain level
	Hoskin, 2015[44]	EBRT vs. other	Reported, but not explained (Likely complete+partial pain response)
	Oosterhof, 2003[60]	EBRT vs. other	Reduction of pain level by ≥1 point or analgesic use by ≥25% with no performance status deterioration overall pain response Improvement in performance status with no increase in pain level or >25% increase in analgesic use

3DCRT = three-dimensional conformal radiation therapy; BPI = Brief Pain Inventory; EBRT = external beam radiation therapy; HDMF = higher total dose multiple fraction; HDSF = higher total dose single fraction; IMRT = intensity modulated radiation therapy; LDMF = lower total dose multiple fraction; LDSF = lower total dose single fraction; MF = multiple fraction; SF = single fraction; SBRT = stereotactic body radiation therapy; VAS = visual analog scale; WHO = World Health Organization.

Description of Included NRSIs for Key Question 1

SF EBRT Versus MF EBRT (Conventional EBRT)

Four NRSIs[92,99,102,103] compared SF EBRT versus MF EBRT for the palliative treatment of bone metastases and were included for evaluation of harms only (Appendix E, Tables E-1 and E-2).

Across the NRSIs, sample sizes ranged from 47 to 999 (total N=1,534). The average study mean[99] or median[92,102,103] age of participants was 66.3 years (range 63 to 68 years); the average proportion of males in studies was 50 percent (range 30% to 52%). No studies reported race or ethnicity, comorbidities, or social determinants of health. The primary tumor types included breast (range, 10% to 38%), lung (range, 18.6% to 36%), and prostate (range, 16% to 22%). One study reported complicated MBD in 34.9 percent of participants.[92] Total number of bone metastases and nonbone metastases were not reported in any study. In one study, the metastatic bone lesions were lytic in 53 percent of enrolled patients and sclerotic in 17 percent.[102] The site of bone metastases was mixed (i.e., spine and nonspine) in two NRSIs (spine, 44% to 46% and nonspine, 54% to 56%)[92,99] and one study included patients with bone metastases to the spine only (excluding spinal cord compression).[102] No study included bone metastases to nonspine sites only. Pathological fractures were present at baseline in 0 to 23 percent of patients across two studies that reported this information.[92,99]

The single fraction dose was 8 Gy ilevn all studies.[92,99,102,103] The most common multiple fraction doses were 30 Gy (3 Gy x 10) and 20 Gy (4 Gy x 5) over 1 to 2 weeks;[92,99,102,103] one trial used 37.5 Gy (2.5 Gy x 15) over an undisclosed amount of time.[102] Most trials did not clearly report the specific type of EBRT employed but it was most likely 2D or 3DCRT. Concomitant treatments included analgesics (amount not reported),[99,103] steroids (5%),[103] systemic therapy (12% chemotherapy, 26% hormone therapy),[99] and bisphosphonates (30% to 50%).[99,102] Previous treatments included prior radiation therapy (proportion not reported).[92] Followup periods ranged from 1 to 6 months.

One study was conducted in the United States[102] and three were conducted in Canada,[92,99,103] and two were single-center trials. Government and university were the most common funding sources, though two studies did not disclose funding. Three studies were fair quality[92,102,103] and one was poor quality.[99] The poor-quality study had unclear patient sampling methods, lack of blinding, and differences in baseline characteristics between groups without adjustment for those differences (Appendix F, Table F-2).

MF EBRT: LDMF Versus HDMF (Conventional EBRT)

One retrospective NRSI[112] (N=105, median age 67 years, 50% male) compared 3DCRT 20 Gy (4 Gy in 5 fractions over 1 week; LDMF) with 30 Gy (3 Gy in 10 fractions over 2 weeks; HDMF) in patients with mixed site MBD and was included for evaluation of safety only (Appendix E, Tables E-1 and E-2). Several baseline characteristics were unbalanced between the groups with the LDMF group having more spine metastases (61% vs. 51% in HDMF), single metastases (77% vs. 66%), and lung cancer as the primary tumor type (35% vs. 19%). Breast and prostate cancers were the primary cancers in 30 and 14 percent of the population, respectively. Most patients (93%) were taking analgesics at baseline. Other patient and disease characteristics were not reported. Authors did not receive funding for this NRSI, and quality was fair due to

imbalances in prognostic factors across groups at baseline (though authors attempted to control for these), lack of blinding, and unclear attrition (Appendix F, Table F-2).

Summary Results Tables

Key Question 1: Fractionation Schemes

Table B-3. Relief of spinal cord compression: Sphincter, bladder, or bowel control in patients with MSCC treated with SF EBRT versus MF EBRT

Author, Year	Outcome	Followup	SF EBRT % (n/N)	MF EBRT % (n/N)	RR or (95% CI)[a]
Abu Hegazy, 2011[30]	Sphincter control, improved/ regained from baseline (all patients)	Post-RT (NOS)	7.4% (7/95)	6.3% (12/190)[b]	RR 1.17 (0.47, 2.87)
	Sphincter control, improved/ regained from baseline (patients with abnormal function pre-RT)[c]	Post-RT (NOS)	70.0% (7/10)	70.6% (12/17)[b]	RR 0.99 (0.60, 1.65)
Maranzano, 2009[53]	Sphincter control response (maintained or regained)	Post-RT (NOS)	85% (130/153)	87% (131/150)	RR 0.97 (0.89, 1.06)
	Sphincter control, improved/ regained from baseline (all patients)	Post-RT (NOS)	**5.9% (9/153)**	**1.3% (2/150)**	**RR 4.41 (0.97, 20.1)**
	Sphincter control, improved/ regained from baseline (patients with abnormal function pre-RT)[d]	Post-RT (NOS)	34.6% (9/26)	13.3% (2/15)	RR 2.60 (0.64, 10.5)
Thirion, 2020[83]	Bladder function, improved	5 weeks	3% (1/36)	11% (4/37)	RR 0.26 (0.03, 2.19)
	Bladder function, same (NOS)	5 weeks	**83% (30/36)**	**64% (24/37)**	**RR 1.28 (0.97, 1.70)**
Hoskin, 2019[45]	Bladder function, abnormal	4 weeks	32% (66/209)	24% (53/223)	Adj. OR 1.61 (0.92, 2.82)[e]
	Bladder function, abnormal	8 weeks	31% (47/151)	20% (34/166)	Adj. OR 1.78 (0.93, 3.39)[e]
	Bladder function, abnormal	12 weeks	30% (41/139)	23% (35/154)	Adj. OR 1.64 (0.85, 3.14)[e]
	Bladder function, abnormal	Any time	42% (132/316)	34% (111/322)	Adj. OR 1.31 (0.87, 1.97)[e]
	Bowel function, abnormal	4 weeks	39% (82/209)	35% (79/223)	OR 1.18 (0.80, 1.74)
	Bowel function, abnormal	8 weeks	39% (59/151)	37% (61/166)	OR 1.10 (0.70, 1.74)
	Bowel function, abnormal	12 weeks	38% (53/140)	35% (55/155)	OR 1.11 (0.69, 1.78)
	Bowel function, abnormal	Any time	64% (203/315)	63% (204/322)	OR 1.05 (0.76, 1.45)

Adj. = adjusted. CI = confidence interval; EBRT = external beam radiation therapy; MF = multiple fraction; MSCC = metastatic spinal cord compression; NOS = not otherwise specified; OR = odds ratio; RR = ratio; RT = radiation therapy; SF = single fraction.

[a] RRs were calculated by the EPC; ORs and adjusted ORs were provided by the authors.

[b] The two MF groups in this trial were combined into one MF group. There was no difference between groups when evaluated separately.

[c] Authors state that of 27 patients with sphincter dysfunction, 19 patients (70.4%) regained urinary control and only 2 patients with good bladder function worsened and required an indwelling catheter after RT.

[d] Authors state that of 41 patients with sphincter dysfunction, 11 (27%; 95% CI 15 to 43) regained urinary ability, and only 12 (5%; 95% CI 2.5 to 8) with good bladder function got worse and required an indwelling catheter.

[e] Adjusted for bladder function at baseline, sex, age, baseline ambulatory status, primary tumor, number of spinal canal compression sites, and the of metastases at baseline.

Table B-4. Quality of life outcomes: RCTs comparing SF EBRT versus MF EBRT and LDSF EBRT versus HDSF EBRT

EBRT Scheme	Author, Year MBD Site	QOL Measure	QOL Results, SF Vs. MF or LDSF Vs. HDSF
SF EBRT vs. MF EBRT	Gaze, 1997[39] Mixed spine/nonspine	Spitzer QOL index (5 items of activity, daily living, health, support, and outlook rated on a 0-2 scale)	Spitzer QOL index, median (range) **Overall (NR by group)** • Baseline: 6 (0-10) • Post-RT: 7 (1-10) *p=NS for between-group difference*
	Kaasa, 2006[49] Mixed spine/nonspine	EORTC QLQ-C30 (Scales NR) Q9 (Have you had pain?) Q30 (Did pain interfere with your daily activities?)	EORTC QLQ-C30 subscales related to pain[a] **Baseline, mean (SD NR)** • Q9: 3.2 vs. 3.1 • Q30: 3.0 vs. 3.0 • QLQ-C30 Pain Scale: 69 vs. 67 • Pain Intensity Verbal Rating Scale: 3.3 vs. 3.3 **4 weeks, mean (SD NR)** • Q9: 2.5 vs. 2.6 • Q30: 2.6 vs. 2.5 • QLQ-C30 Pain Scale: 52 vs. 53 • Pain Intensity Verbal Rating Scale: 2.8 vs. 2.8 **8 weeks, mean (SD NR)** • Q9: 2.4 vs. 2.6 • Q30: 2.4 vs. 2.6 • QLQ-C30 Pain Scale: 49 vs. 55 • Pain Intensity Verbal Rating Scale: 2.8 vs. 2.9 **12 weeks, mean (SD NR)** • Q9: 2.3 vs. 2.5 • Q30: 2.3 vs. 2.4 • QLQ-C30 Pain Scale: 48 vs. 51 • Pain Intensity Verbal Rating Scale: 2.7 vs. 3.0 **20 weeks, mean (SD NR)** • Q9: 2.4 vs. 2.7 • Q30: 2.5 vs. 2.5 • QLQ-C30 Pain Scale: 51 vs. 54 • Pain Intensity Verbal Rating Scale: 2.8 vs. 2.9 **28 weeks, mean (SD NR)** • Q9: 2.6 vs. 2.4 • Q30: 2.5 vs. 2.5 • QLQ-C30 Pain Scale: 52 vs. 51 • Pain Intensity Verbal Rating Scale: 2.7 vs. 3.0 *p=NS for all; according to authors "levels over time were very similar in the 2 groups, and the (narrow) confidence intervals support treatment equivalence"*
	Nielsen, 1998[13] Mixed spine/nonspine	Global QOL VAS (0-100)	Global QOL VAS (0-100) **Baseline, median (range)**: 41 (1-98) (n=120) vs. 36 (0-89) (n=119) **4 weeks, % (n/N)** • ≥25% increase on VAS: 37% (44/120) vs. 32% (38/119); RR 1.15 (95% CI 0.81 to 1.63)[b] • ≥50% increase on VAS :20% (24/120) vs. 21% (25/119); RR 0.95 (95% CI 0.58 to 1.57)[b] • ≥75% increase on VAS: 11% (13/120) vs. 12% (14/119); RR 0.92 (95% CI 0.45 to 1.88)[b] • Complete well-being on VAS: 7% (8/120) vs. 7% (8/119); RR 0.99 (95% CI 0.38 to 2.56)[b] *p=NS for all*
	Steenland, 1999[14] Mixed spine/nonspine	The Rotterdam Symptom Checklist	The Rotterdam Symptom Checklist The analysis of repeated measures showed that no significant differences were observed between the two treatment groups in overall quality of life (P=0.22).

EBRT Scheme	Author, Year MBD Site	QOL Measure	QOL Results, SF Vs. MF or LDSF Vs. HDSF
	Hoskin, 2019[45] MSCC	EORTC QLQ-30 (Scales NR)	EORTC QLQ-30 **SMD in domains (SF – MF) adjusted for baseline values, at 8 weeks:** • Global Health: −0.13 (1-sided 97.5% CI, −0.38 to infinity), p-value for noninferiority = 0.12 • Physical functioning: −0.12 (1-sided 97.5% CI, −0.35 to infinity]; p-value for noninferiority = 0.09) • Emotional functioning: −0.18 (1-sided 97.5% CI, −0.41 to infinity]; p-value for noninferiority = 0.19) *Noninferiority was not met using the pre-specified margin of −0.28 for the lower limit.*
	Lee, 2018[15] MSCC	EORTC QLQ-C30 (Scale NR) *Positive values=better QOL*: • Summary score (excluding financial impact and global quality of life) • Physical functioning score *Negative values=lower pain*: • Pain score	EORTC QLQ-C30 **Mean change from baseline to 5 weeks** (baseline scores NR), n=27 vs. 24 • Summary score: 12.4 vs. 10.8; treatment effect 95% CI 6.6 to 16.7; adjusted p-value=0.859 • Physical functioning score: -3.3 vs. 8.1; treatment effect 95% CI -6.5 to 10.6; p=NR • Pain score: -35.8 vs. -25.7; treatment effect 95% CI -43.4 to -18.7; adjusted p-value=0.985 • Global QOL: 9.0 vs. 2.2; treatment effect 95% CI -3.2 to 14.0; p=NR **Mean change from baseline to 12 weeks** (baseline scores NR), n=21 vs. 15 • Summary score: 16.4 vs. 9.1; treatment effect 95% CI 6.8 to 19.9 • Physical functioning score: 3.3 vs. -7.1; treatment effect 95% CI -13.5 to 11.5 • Pain score: -37.3 vs. -31.1; treatment effect 95% CI -47.7 to -21.8 *adjusted p-value = NS for all (adjusted for baseline scores)*
LDSF EBRT vs. HDSF EBRT	Manas, 2008[51] Mixed spine/nonspine	EORTC QLQ C30 (Scale NR), divided into 3 parts: • Part 1: 5 yes/no questions referring to daily activities. • Part 2: 21 questions referring to the patient's daily symptoms with responses ranging from 1 to 4. • Part 3: 2 questions referring to the patient's general health, with responses ranging from 1 to 7.	EORTC QLQ C30 **Mean (SD NR) at Baseline** • Part 1: 7.63 (NR) (n=51) vs. 7.52 (NR) (n=62) • Part 2: 41.78 (NR) (n=50) vs. 42.51 (NR) (n=57) • Part 3: 7.08 (NR) (n=51) vs. 6.74 (NR) (n=65) **Mean (SD NR) at 30 weeks** • Part 1: 6.67 (NR) (n=51) vs. 6.08 (NR) (n=62) • Part 2: 33.15 (NR) (n=50) vs. 30.81 (NR) (n=57) • Part 3: 9.24 (NR) (n=51) vs. 9.62 (NR) (n=65) **Median (SD NR) at Baseline** • Part 1: 8.00 (NR) (n=51) vs. 7.00 (NR) (n=62) • Part 2: 41.00 (NR) (n=50) vs. 42.00 (NR) (n=57) • Part 3: 7.00 (NR) (n=51) vs. 7.00 (NR) (n=65) **Median (IQR NR) at 30 weeks** • Part 1: 6.00 (NR) (n=51) vs. 6.00 (NR) (n=62) • Part 2: 29.50 (NR) (n=50) vs. 27.00 (NR) (n=57) • Part 3: 10.00 (NR) (n=51) vs. 10.00 (NR) (n=65) *p>0.05 for all (ANCOVA model)*

ANCOVA = analysis of covariance; CI = confidence interval; EBRT = external beam radiation therapy; EORTC QLQ C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 ; IQR = interquartile range; HDSF = higher total dose single fraction; LDSF = lower total dose single fraction; MBD = metastatic bone disease; MSCC = metastatic spinal cord compression; NR = not reported; NS = not statistically significant; QOL = quality of life; RCT = randomized controlled trial; RR = risk ratio; SD = standard deviation; VAS = visual analog scale.

[a] Data estimated from graphs, confidence intervals not estimable.

[b] Calculated by Evidence-based Practice Center.

Table B-5. Overall survival: RCTs comparing SF EBRT versus MF EBRT

Author, Year	MBD Site	Overall Survival, SF EBRT Vs. MF EBRT
Hoskins, 2019[45]	MSCC	Overall Survival (95% CI) 12 weeks: 50% (95% CI 45% to 55%) vs. 55% (95% CI 49% to 60%) 52 weeks: 21% (95% CI 16% to 26%) vs. 18% (95% CI 13% to 23%) Stratified HR 1.02 (95% CI 0.74 to 1.41), p=0.91 Overall survival by treatment (median), weeks: 12.4 (IQR 4.6-41.0) vs. 13.6 (IQR 5.9-40.9); 13.1 overall
Thirion, 2020[83]	MSCC	Overall survival, % (n/N) • 5 weeks: 67.9% (38/56) vs. 76.8% (43/56) • 1 year (not reported by treatment arm) o All patients: 18% (20/112) o All evaluable patients: 27% (20/73) • 2 years (not reported by treatment arm) o All patients: 8% (9/112) o All evaluable patients: 12% (9/73) Overall survival, median (95% CI), months • All patients (n=112) o By treatment: 3 (NR) vs. 3 (NR), p=1.0 o Overall: 3 (1.5 to 4.5) • All evaluable patients (n=73): 6.4 (5.4 to 7.4) o By treatment: 6.6 (NR) vs. 6.0 (NR), p=0.39 o Overall: 6.4 (5.4 to 7.4)
Maranzano, 2009[53]	MSCC	Overall survival (median): 17 weeks (same for both groups)
Howell, 2013[47] (Subgroup analysis of Hartsell 2005)[41]	Spine	Overall survival, % (n/N) 12 weeks: 83% (103/124) vs. 85% (94/111) 24 weeks: 62% (77/124) vs. 67% (74/111) 52 weeks: 40% (50/124) vs. 49% (54/111) 104 weeks: 26% (32/124) vs. 26% (29/111) 260 weeks: 5% (5/124) vs. 8% (8/111)
Roos, 2005[71]	Spine	Overall survival, % (n/N) At "close-out date" (median followup 13.5 weeks): 7% (10/137) vs. 9% (12/135) Estimated median overall survival (95% CI) for all 272 patients: 19.2 weeks (16.8–22.8 weeks), with 27% (22–32%) surviving 52 weeks *p=NS by treatment arm (P=0.66) or index site (spine vs. nonspine (P=0.89)*
Gaze, 1997[39]	Mixed	Overall survival (out of 245 patients, N NR by group): 26 weeks: 42.5% vs. 52.7% 52 weeks: 21.6% vs. 32.6% 104 weeks: 5.7% vs. 12.9% 208 weeks: 3.1% vs. 3.2% *p=NS for all*
Hartsell, 2005)[41]	Mixed	Overall survival, % 52 weeks: 41% (n=NR) vs. 42% (n=NR) 104 weeks: 22% (n=NR) vs. 22% (n=NR)
Nielsen, 1998[13]	Mixed	Overall survival, % (n/N) 26 weeks: 68% (82/120) vs. 59% (70/119) 52 weeks: 30% (36/120) vs. 36% (43/119) 78 weeks: 20% (24/120) vs. 27% (32/119) 104 weeks: 18% (22/120) vs. 18% (21/119)
Price, 1986[66]	Mixed	Overall survival, % (n/N) 52 weeks: 35% (49/140) vs. 35% (52/148) 104 weeks: 18% (25/140) vs 18% (27/148)
Bone Trial Working Group[9]	Mixed	Overall survival (median): 44 vs. 42 weeks (survival assessed by estimation from curve); p=NS, assessed by log-rank analysis
Gutierrez Bayard 2014[40]	Mixed	Overall Survival (median): 32 weeks vs. 35 weeks (p=0.50)

Author, Year	MBD Site	Overall Survival, SF EBRT Vs. MF EBRT
Foro Arnalot 2008[38]	Mixed	Mean survival 28 vs. 33 weeks (p=NS); no significant differences between schedules in terms of survival probability (actuarial curve)
Kaasa, 2006[49]	Mixed	Overall survival, median 42 weeks vs. 34 weeks
Steenland, 1999[14]	Mixed	Overall survival, median 33 weeks vs. 28 weeks, p=0.24
Ozsaran, 2001[61]	Mixed	Overall Survival, median 12 weeks (SF) vs. 16 weeks (LDMF) vs. 44 weeks (HDMF) *SF vs. HDMF, p=0.018* *SF vs. LDMF, p=0.635*

CI = confidence interval; EBRT = external beam radiation therapy; HR = hazard ratio; IQR = interquartile range; HDMF = higher total dose multiple fraction; LDMF = lower total dose multiple fraction; MBD = metastatic bone disease; MF = multiple fraction; MSCC = metastatic spinal cord compression; NR = not reported; NS = not statistically significant; RCT = randomized controlled trial; SF = single fraction.

Table B-6. Medication use: RCTs comparing SF EBRT versus MF EBRT

Author MBD Site	No Medication Required: SF Vs. MF	Simple/Moderate Analgesics Required: SF Vs. MF	Narcotics Required: SF Vs. MF	Other: SF Vs. MF
Hoskin, 2019[45] MSCC	NR	NR	NR	Analgesics: 48.0% (146/304) vs. 51.0% (153/300) RD -3.0% (95% CI -10.9% to 5.0%), p=0.47)
Bone Trial Working Group[9] Mixed spine/nonspine	Baseline 9.0% (33/366) vs. 11.6% (42/363) 6 months 32.3% (62/192) vs 28.5% (49/172) 12 months 24.6% (29/118) vs. 36.1% (39/108) *p=NS for all*	**Nonnarcotic/NSAID** Baseline 19.9% (73/366) vs. 19.0% (69/363) 6 months 13.0% (25/192) vs 11.0% (19/172) 12 months 15.3% (18/118) vs. 10.2% (11/108) *p=NS for all*	**Strong narcotic** Baseline 36.9% (135/366) vs. 38.0% (138/363) 6 months 32.8% (63/192) vs 37.8% (65/172) 12 months 35.6% (42/118) vs. 36.1% (39/108) **Mild narcotic** Baseline 34.2% (125/366) vs. 31.4% (114/363) 6 months 21.4% (41/192) vs 19.2% (33/172) 12 months 22.9% (27/118) vs. 14.8% (16/108) *p=NS for all*	NR

Author **MBD Site**	**No Medication Required:** **SF Vs. MF**	**Simple/Moderate Analgesics Required: SF Vs. MF**	**Narcotics Required:** **SF Vs. MF**	**Other:** **SF Vs. MF**
Amouzegar-Hashemi, 2008[32] Mixed spine/nonspine	Baseline 5.7% (4/70) 4 weeks 36.2% (21/58) *p=NS for all comparisons between groups (data NR)*	**Nonnarcotics** Baseline Nonnarcotics: 42.9% (30/70) 4 weeks 32.8% (19/58) *p=NS for all comparisons between groups (data NR)*	**Strong narcotics** Baseline 20% (14/70) 4 weeks 10.3% (6/58) **Weak narcotics** Baseline 31.4% (22/70) 4 weeks 20.7% (12/58) *p=NS for all comparisons between groups (data NR)*	NR
Gaze,1997[39] Mixed spine/nonspine	Baseline 3% vs. 4% Post-RT score 17% vs. 21% *p=NS for all, significant reduction in analgesic use in both arms (N not available)*	**Simple analgesia adequate** Baseline score 5% vs. 6% Post-RT score 13% vs. 12% **Moderate analgesia combination or NSAID needed** Baseline score 40% vs. 35% Post-RT score 32% vs. 24% *p=NS for all, significant reduction in analgesic use in both arms (N not available)*	**Opiate analgesia needed for complete pain relief** Baseline score 40% vs. 42% Post-RT score 33% vs. 39% **High does opiates inadequate** Baseline score 10% vs. 12% Post-RT score 4% vs. 5% *p=NS for all, significant reduction in analgesic use in both arms (N not available)*	NR
Hamouda, 2007[11] Mixed spine/nonspine	Baseline 6% (3/50) vs. 3.8% (2/52) 8 weeks 24% (12/50) vs. 30.8% (16/52) *p=NS for all*	**Nonopioids** Baseline 14% (7/50) vs. 15.4% (8/52) 8 weeks 44% (22/50) vs. 50% (26/52) *p=NS for all*	**Strong opioids** Baseline 34% (17/50) vs. 30.8% (16/52) 8 weeks 10% (5/50) vs. 7.7% (4/52) **Weak opioids** Baseline 46% (23/50) vs. 50% (26/52) 8 weeks 22% (11/50) vs. 11.5% (6/52) *p=NS for all*	NR

Author **MBD Site**	**No Medication Required:** **SF Vs. MF**	**Simple/Moderate Analgesics Required: SF Vs. MF**	**Narcotics Required:** **SF Vs. MF**	**Other:** **SF Vs. MF**
Hartsell, 2005[41] Mixed spine/nonspine	12 weeks 20% (65/318) vs. 22% (69/310); *p=NS*	**Nonnarcotic analgesic** 12 weeks 12.6% (40/318) vs. 9.7% (30/310); *p=NS for all*	**Narcotic** 12 weeks 67% (213/318) vs. 68% (211/310); *p=NS for all*	NR
Kaasa, 2006[49] Mixed spine/nonspine	NR	2 weeks **Paracetamol use**: 115 vs. 105 **NSAID use**: 48 vs. 52 5-6 Weeks **Paracetamol use**: 93 vs. 73 **NSAID use:** 41 vs. 37 *Similar consumption in both groups, p=NS for all (n's only; N not available)*	5-6 Weeks **Mean daily opioid use** (weeks 1-6): 100 mg/day (95% CI 83-118) vs. 115 mg/day (95% CI 66-164) *p=NS between groups over time*	NR
Nongkynrih, 2018[58] Mixed spine/nonspine	NR	**Simple analgesics** Baseline 30% (6/20) vs. 30% (12/40)[a] 4 weeks 45% (9/20) vs. 50% (20/40)[a]	**Narcotics** Baseline 45% (9/20) vs. 55% (22/40)[a] 4 weeks 30% (6/20) vs. 17.5% (7/40)[a]	**Decreased analgesic requirement** 65% (13/20) vs. 65% (26/40)[a]
Ozsaran, 2001[61] Mixed spine/nonspine	Baseline 2.8% (1/36) vs. 13.7% (10/73) Post-treatment (not further specified): 41.7% (15/36) vs. 42.5% (31/73) *p-value between treatment groups NR (compared with baseline, p<0.001 for both*	Baseline **Simple analgesia adequate:** 5.6% (2/36) vs. 9.6% (7/73)[a] **NSAID needed**: 86.1% (31/36) vs. 75.3% (55/73)[a] Post-treatment (not further specified): **Simple analgesia adequate:** 11.1% (4/36) vs. 23.3% (17/73) [a] **NSAID needed:** 44.4% (16/36) vs. 27.4% (20/73)[a] *p-value between treatment groups NR (compared with baseline, p<0.001 for both*	**Narcotic analgesics** Baseline 5.6% (2/36) vs. 1.4% (1/73)[a] Post-treatment (not further specified): 2.8% (1/36) vs. 6.8% (5/73)[a] *p-value between treatment groups NR (compared with baseline, p<0.001 for both*	NR

Author MBD Site	No Medication Required: SF Vs. MF	Simple/Moderate Analgesics Required: SF Vs. MF	Narcotics Required: SF Vs. MF	Other: SF Vs. MF
Gutierrez Bayard, 2014[40] Mixed spine/nonspine	NR	NR	NR	Reduction of analgesia between visits (timing unclear) 1 and 2: (p=0.74) 2 and 3 (p=0.72) 3 and 4 (p=1.00) 4 and 5 (p=0.32) 5 and 6 (p=1.00) 1 and 6 (p=0.79)

CI = confidence interval; EBRT = external beam radiation therapy; MBD = metastatic bone disease; MF = multiple fraction; MSCC = metastatic spinal cord compression; NR = not reported; NS = not statistically significant; NSAID = nonsteroidal anti-inflammatory drug; RCTs = randomized controlled trials; RT = radiation therapy; SF = single fraction.

[a] The two MF groups were combined into one MF group. There was no difference between groups when evaluated separately.

Table B-7. Safety: Toxicity and safety information in trials comparing SF EBRT versus MF EBRT

Scheme	Author, Year Study Design MBD Site	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity	Other Toxicity: Mixed Grades, NR by Group, Data NR, Other	Other AEs/Late AEs
A vs. B SF (8 Gy x 1, n=95) vs. MF (3 Gy x 10, n=100) A vs. C SF (8 Gy x 1, n=95) vs. MF (2 Gy x 20, n=90)	Abu-Hegazy, 2011[30] RCT MSCC	A vs. B Grade 1 Acute Toxicity Esophageal dysphagia: 4.2% (4/95) vs. 3% (3/100) Odynophagia: 2.1% (2/95) vs. 3% (3/100) Vomiting: 2.1% (2/95) vs. 3% (3/100) Diarrhea: 3.2% (3/95) vs. 2% (2/100) A vs. C Grade 1 Acute Toxicity Esophageal dysphagia: 4.2% (4/95) vs. 4.4% (4/90) Odynophagia: 2.1% (2/95) vs. 3.3% (3/90) Vomiting: 2.1% (2/95) vs. 2.2% (2/90) Diarrhea: 3.2% (3/95) vs. 3.3% (3/90)	A vs. B Acute Toxicity Grade 2 Esophageal dysphagia: 0% (0/95) vs. 1% (1/100) Odynophagia: 0% (0/95) vs. 0% (0/100) Vomiting: 0% (0/95) vs. 0% (0/100) Diarrhea: 0% (0/95) vs. 1% (1/100) A vs. C Acute Toxicity Grade 2 Esophageal dysphagia: 0% (0/95) vs. 1.1% (1/90) Odynophagia: 0% (0/95) vs. 0% (0/90) Vomiting: 0% (0/95) vs. 0% (0/90) Diarrhea: 0% (0/95) vs. 2.2% (2/90)	NR	NR	Late toxicity: no instances occurred	NR

Scheme	Author, Year Study Design MBD Site	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity	Other Toxicity: Mixed Grades, NR by Group, Data NR, Other	Other AEs/Late AEs
SF (8 Gy x 1, n=345) vs. MF (4 Gy x 5, n=341)	Hoskin, 2019[45] RCT MSCC	NR	NR	NR	NR	Skin radiation reactions, grade 1 or 2: 11.6% (40/345) vs 19.4% (66/341) Fatigue: 48.7% (168/345) vs 55.4% (189/341) Any AE: Grade 1 and 2: 51.9% (179/345) vs. 56.9% (194/341) Grade 3 and 4: 20.6% (71/345) vs. 20.5% (70/341) Grade 5 (death, unrelated to RT): 0.9% (3/345) vs. 1.5% (5/341)	Impaired bladder function: Any time: 41.8% (132/316) vs. 34.5% (111/322); adjusted OR 1.31 (95% CI 0.87 to 1.97) 1 Week: 32% (93/294) vs. 25% (76/300), adjusted OR, 1.15 (95% CI 0.67 to 1.99) 4 weeks: 32% (66/209) vs. 24% (53/223), adjusted OR, 1.61 (95% CI 0.92 to 2.82) 8 weeks: 31.1% (47/151) vs 20.5% (34/166), adjusted OR, 1.78 [95% CI, 0.93-3.39]; 12 weeks: 30% (41/139) vs. 23% (35/154), adjusted OR, 1.64 (95% CI 0.86 to 3.14)

Scheme	Author, Year Study Design MBD Site	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity	Other Toxicity: Mixed Grades, NR by Group, Data NR, Other	Other AEs/Late AEs
SF (8 Gy x 1, n=345) vs. MF (4 Gy x 5, n=341) (Continued)							Impaired bowel function[a]: Any time: 64.4% (203/315) vs. 63.5% (204/322); unadjusted OR 1.05 (95% CI 0.76 to 1.45) 1 Week: 45% (131/293) vs. 44% (132/300), unadjusted OR, 1.03 (95% CI 0.74 to 1.42) 4 weeks: 39% (82/209) vs. 35% (79/223), unadjusted OR 1.18 (95% CI 0.80 to 1.74) 8 weeks: 39.1% (59/151) vs 36.7% (61/166), RD 2.3% [95% CI, 8.4%-13.0%]; (unadjusted OR, 1.10 [95% CI, 0.70-1.74] 12 weeks: 38% (53/140) vs. 35% (55/155), unadjusted OR 1.11 (95% CI 0.69 to 1.78)

Scheme	Author, Year Study Design MBD Site	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity	Other Toxicity: Mixed Grades, NR by Group, Data NR, Other	Other AEs/Late AEs
SF (8 Gy x 1, n=153) vs. MF (8 Gy x 2, n=150)	Maranzano, 2009[53] RCT MSCC	NR	NR	NR	NR	Whole population only Grade 1/2 oral/esophageal dysphagia: 6.6% (20/303) Grade 3 esophagitis: 0.6% (2/303)	Radiation-induced myelopathy: 0% (0/153) vs. 0% (0/150)
SF (10 Gy x 1, n=58) vs. MF (4 Gy x 5, n=59)	Thirion, 2020[83] RCT MSCC	NR	Acute toxicity (all Grade 2) -lower intestine: 10.9% (6/55) vs. 11.1% (5/45) -upper intestine: 1.8% (1/55) vs. 11.1% (5/45) -fatigue: 1.8% (1/55) vs. 6.7% (3/45) -esophageal: 1.8% (1/55) vs. 4.4% (2/45) -skin: 1.8% (1/55) vs. 2.2% (1/45) -salivary gland: 1.8% (1/55) vs. 0% (0/45) Late toxicity (n=52) Grade 2 -intestinal: 3.7% (1/27) vs. 16% (4/25) -fatigue: 3.7% (1/27) vs. 4% (1/25)	NR	NR	Any Grade 2-3 toxicity at any time: 11.1% (6/54) vs. 26.1% (12/46), p=0.069 Late toxicity (n=52) Grade 3 -pain in upper thigh-hip: 0% (0/27) vs. 4% (1/25)	NR

Scheme	Author, Year Study Design MBD Site	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity	Other Toxicity: Mixed Grades, NR by Group, Data NR, Other	Other AEs/Late AEs
SF (8 Gy x 1, n=31) vs. MF (3 Gy x 10, n=33)	Majumder, 2012[12] RCT Spine	None	GI toxicities Grade 2: 12.5% (4/NR)[b] vs. 12.1% (4/NR)[b]	GI toxicities Grade 3: 0% (0/NR)[b] vs. 6.1% (2/NR)[b]	None	GI toxicities Grade 0: 87.5% (28/NR)[b] vs. 81.8% (21/NR)[b]	Withdrawals due to AEs: 0% in both groups; n's unclear
SF (8 Gy x 1, n=124) vs. MF (3 Gy x 10, n=111)	Howell, 2013[47] RCT Subgroup analysis of Hartsell, 2005 in patients with spine metastases	NR	NR	Grade 3 Acute toxicity: 0.8% (1/124) vs. 2.7% (3/111) Late toxicity: 1.6% (2/124) vs. 0% (0/111)	Grade 4 Acute toxicity: 0% (0/124) vs. 0.9% (1/111) Late toxicity: 0% (0/124) vs. 0.9% (1/111)	NR	NR
SF (8 Gy x 1, n=137) vs. MF (4 Gy x 5, n=135)	Roos,[71] 2005[c] RCT Spine	NR	NR	NR	NR	Grade 3 acute toxicities Whole population only Upper GI: 1.3% (3/233) Lung: 1.3% (3/233) --Toxicities were generally absent or mild	Adverse events, % (n/N) Pain flare (N=233), unclear n by group, used ITT) -Mild: 1.5% (2/137) vs. 1.5% (2/135) -Moderate: 3.6% (5/137) vs. 1.5% (2/135) -Severe: 5.1% (7/137) vs. 1.5% (2/135) p=0.029 across grades Early death (within 32 days): 5.1% (7/137) vs. 4.4% (6/135)

Scheme	Author, Year Study Design MBD Site	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity	Other Toxicity: Mixed Grades, NR by Group, Data NR, Other	Other AEs/Late AEs
SF (8 Gy x 1, n=66) vs. MF (4 Gy x 5 or 3 Gy x 10 or 2.5 Gy x 15, n=233)	Lam, 2015[102] NRSI Spine	NR	NR	NR	NR	NR	New or deteriorated neurological symptoms: 12.3% (8/66) vs. 4.3% (10/233) Hospitalization due to uncontrolled pain at RT site: 21.2% (14/66) vs. 9.4% (22/233) Propensity score matched analysis for SF vs MF, rate of first AE at 3 months, 22.5% vs. 7.7% (5/66), HR=3.2 (95% CI 1.3 to 7.5), p=0.009 Multivariate regression of SF vs MF for first AE, controlling for SINS, BMI, and neuropathic pain, HR=2.78 (95% CI 1.51 to 5.15, p=0.001

Scheme	Author, Year Study Design MBD Site	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity	Other Toxicity: Mixed Grades, NR by Group, Data NR, Other	Other AEs/Late AEs
SF (8 Gy x 1, n=66) vs. MF (4 Gy x 5 or 3 Gy x 10 or 2.5 Gy x 15, n=233) (Continued)							Multivariate regression of SF vs MF for risk of death, controlling for SINS, BMI, and neuropathic pain, HR=1.95 (95% CI 1.42 to 2.68), p<0.001 Cumulative incidence of first AE by 6 months Subgroup SINS<11: 21.2% (12/56) vs. 9.9% (18/203) Subgroup SINS ≥11: ≥40% (≥4/9)[d] vs. 20% (6/30)
SF (8 Gy x 1, n=51) vs. MF (4 Gy x 5, n=49)	Anter, 2015[33] RCT Mixed spine and nonspine	Acute toxicity, No. of patients GI Grade 1: 13.6% (6/44) vs. 20.5% (9/44) Hematologic Grade 1: 6.8% (3/44) vs. 11.4% (5/44) Lung Grade 1: 0% (0/44) vs. 4.5% (2/44) CNS Grade 1: 2.3% (1/44) vs. 2.3% (1/44)	Acute toxicity, No. of patients GI Grade 2: 6.8% (3/44) vs. 9.1% (4/44) Hematologic Grade 2: 2.3% (1/44) vs. 4.5% (2/44) Lung Grade 2: 2.3% (1/44) vs. 4.5% (2/44) CNS Grade 2: 0% (0/44) vs. 2.3% (1/44)	Acute toxicity, No. of patients GI Grade 3: 2.3% (1/44) vs. 2.3% (1/44) Hematologic Grade 3: 0% (0/44) vs. 0% (0/44) Lung Grade 3: 0% (0/44) vs. 0% (0/44) CNS Grade 3: 0% (0/44) vs. 0% (0/44)	Acute toxicity, No. of patients GI Grade 4: 0% (0/44) vs. 0% (0/44) Hematologic Grade 4: 0% (0/44) vs. 0% (0/44) Lung Grade 4: 0% (0/44) vs. 0% (0/44) CNS Grade 4: 0% (0/44) vs. 0% (0/44)	NR	NR

Scheme	Author, Year Study Design MBD Site	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity	Other Toxicity: Mixed Grades, NR by Group, Data NR, Other	Other AEs/Late AEs
SF (8 Gy x 1, n=383) vs. MF (4 Gy x 5 or 3 Gy x 10, n=378)	Bone Trial Working Group, 1999[9] RCT Mixed spine and nonspine	NR	NR	NR	NR	Nausea[e]: 55.7% (34/61) vs. 65.1% (41/63) Vomiting[e]: 29.5% (18/61) vs. 31.7% (20/63) Use of Anti-sickness tablets taken within 2 weeks post-RT[e]: 39.3% (24/61) vs. 41.3% (26/63)	NR
SF (8 Gy x 1, n=78) vs. MF (3 Gy x 10, n=82)	Foro Arnalot, 2008[38] RCT Mixed spine and nonspine	Dermatitis: 7.7% (6/78) vs. 9.8% (8/82) GI Toxicity: 2.6% (2/78) vs. 2.4% (2/82)	Dermatitis: 2.7% (2/78) vs. 4.9% (4/82) GI Toxicity: 0%	Whole population only Dermatitis: 0% GI Toxicity: 0%	Whole population only Dermatitis: 0% GI Toxicity: 0%	Whole population only Grade 1 or 2: 11.5% (9/78) vs. 18.3% (15/82) Grade ≥3: 0% p=NS	NR
SF (10 Gy x 1, n=134[f], 151 sites) vs. MF (4.5 Gy x 5, n=131[f], 144 sites)	Gaze, 1997[39] RCT Mixed spine and nonspine	Acute toxicities Grade 1 -Nausea and vomiting: 18% (20/110) vs. 8% (8/98) -Tiredness and lassitude: 35% (39/110) vs. 30% (29/96)	Acute toxicities Grade 2 -Nausea and vomiting: 10% (11/110) vs. 11% (11/98) -Tiredness and lassitude: 24% (26/110) vs. 29% (11/96)	Acute toxicities Grade 3 -Nausea and vomiting: 11% (12/110) vs. 15% (15/98) -Tiredness and lassitude: 10% (11/110) vs. 14% (13/96)	Acute toxicities Grade 4 -Nausea and vomiting: 1% (1/110) vs. 0% (0/98) -Tiredness and lassitude: 3% (3/110) vs. 2% (2/96)	Acute toxicities Grade 0 -Nausea and vomiting: 60% (66/110) vs. 65% (64/98) -Tiredness and lassitude: 29% (32/110) vs. 25% (24/96)	Late AEs: 0% (0/110) vs. 0% (0/98)

Scheme	Author, Year Study Design MBD Site	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity	Other Toxicity: Mixed Grades, NR by Group, Data NR, Other	Other AEs/Late AEs
SF (8 Gy 1, n=455) vs. MF (3 Gy x 10, n=443)	Hartsell, 2005[41] RCT Mixed spine and nonspine	Acute toxicity 12 weeks Grade 1: 15.7% (68/433) vs. 26.8% (111/414) Late toxicity >12 weeks (max 196 weeks) Grade 1: 7.3% (26/354) vs. 5.6% (19/342)	Acute toxicity 12 weeks Grade 2: 8.3% (36/433) vs. 16.9% (70/414) Late toxicity >12 weeks (max 196 weeks) Grade 2: 3.1% (11/354) vs. 4.4% (15/342)	Acute toxicity 12 weeks Grade 3: 3% (13/433) vs. 4.1% (17/414) Late toxicity >12 weeks (max 196 weeks) Grade 3: 0.6% (2/354) vs. 0.6% (2/342)	Acute toxicity 12 weeks Grade 4: 0% (0/433) vs. 0.5% (2/414) Late toxicity >12 weeks (max 196 weeks) Grade 4: 0% (0/354) vs. 0% (0/342)	NR	NR
SF (8 Gy x 1, n=50) vs. MF (2 Gy x 20, n=52)	Hamouda, 2007[11] RCT Mixed spine and nonspine	NR	NR	NR	NR	Toxicity noted as "very modest", included anorexia, erythema, nausea, vomiting and tiredness	Late AEs: 0%
SF (8 Gy x 1, n=122) vs. MF (5 Gy x 4, n=119)	Nielsen, 1998[13] RCT Mixed spine and nonspine	NR	NR	NR	NR	Whole population only Toxicity: 35.1% (84/239)	NR

Scheme	Author, Year Study Design MBD Site	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity	Other Toxicity: Mixed Grades, NR by Group, Data NR, Other	Other AEs/Late AEs
SF (8 Gy x 1, n=29) vs. MF (4 Gy x 5, n=30) vs. MF (3 Gy x 10, n=28)	Ozsaran, 2001[61] RCT Mixed spine and nonspine	NR	NR	NR	NR	Whole population only Acute toxicity (NOS) -Grade 1 or 2, mostly GI: 16.1% (14/87) -Grade 3 or 4: 0%, p=0.382 for toxicity between groups	NR
SF (8 Gy x 1, n=36) vs. MF (3 Gy x 10, n=30)	Sarkar, 2002[74] RCT Mixed spine and nonspine	Grade I (mild) -nausea/vomiting: 29% (9/31) vs. 34.5% (10/29) -diarrhea: 9.7% (3/31) vs. 6.9% (2/29)	Grade II (moderate) -nausea/vomiting: 3.2% (1/31) vs. 3.4% (1/29) -diarrhea: 0% both groups	NR	NR	AEs Erythema (Grade I): 22.6% (7/31) vs. 20.7% (6/29)	Withdrawals due to AEs: 0% in both groups
SF (8 Gy x 1, n=579) vs. MF (4 Gy x 6, n=578)	Steenland, 1999[14] RCT Mixed spine and nonspine	NR	NR	NR	NR	Nausea, vomiting, tiredness, itching and painful skin at 4 weeks: p=NS	Small bowel ileus: 0% (0/579) vs. 0.2% (1/578) Radiation enteritis: 0.2% (1/579) vs. 0% (0/578)

Scheme	Author, Year Study Design MBD Site	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity	Other Toxicity: Mixed Grades, NR by Group, Data NR, Other	Other AEs/Late AEs
Overall (n=111) SF (8 Gy x 1,n=70) vs. MF (4 Gy x 5,n=28) vs. MF (3 Gy x 10, n=6) vs. fractionation NR (n=8)	Hird, 2009[99] NRSI Mixed spine and nonspine	NR	NR	NR	NR	NR	Whole population only Pain flare overall: 39.6% (44/111) Pain flare 8 Gy x 1: 38.6% (27/70) Pain flare multiple fractions: 39% (16/41) Breast cancer pain flare: 52% (N=NR) (p=0.03) Prostate cancer pain flare: 25% (N=NR) (p=0.03) Lung cancer pain flare: 23% (N=NR) (p=0.03) Median pain flare duration: 1.5 days

Scheme	Author, Year Study Design MBD Site	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity	Other Toxicity: Mixed Grades, NR by Group, Data NR, Other	Other AEs/Late AEs
SF (8 Gy x 1, n=23) vs. MF (4 Gy x 5, n=21)	Loblaw,[103] 2007[g] NRSI Mixed spine and nonspine	NR	NR	NR	NR	NR	Pain flare incidence based on various definitions (Tannock) Incidence: 43.5% (10/23) vs. 23.8% (5/21) (p=0.21) Median duration: 3 days (range 2 to 6) Pain flare (Chow) Incidence: 56.5% (13/23) vs. 23.8% (5/21) (p=0.04) Median duration: 3 days (range 2 to 6) Sub-analysis: Pain flare vs. nonpain flare group (N=29) Pain relief at 13 weeks: 33.3% (3/9) vs. 30% (6/20) (p=0.94)

AE = adverse event; CI = confidence interval; EBRT = external beam radiation therapy; GI = gastrointestinal; HR = hazard ratio; MBD = metastatic bone disease; MF = multi-fraction; MSCC = metastatic spinal cord compression; NOS = not otherwise specified; NR = not reported; NRSI = nonrandomized study of interventions; NS = not significant; OR = odds ratio; RCT = randomized control trial; RT = radiation therapy; SF = single fraction; SINS = spinal instability neoplastic score.

[a] Authors do not report adjusted ORs for this outcome.

[b] Denominators unclear. Authors only report numerators and percentages. However, back calculating for denominators results in Ns bigger than sample size.

[c] 89% of patients had spinal metastases.

[d] Authors report ≥40% (≥4/9).

[e] Nausea/vomiting and antiemetic use were assessed in a parallel observational study, with patients randomized also asked to enroll in separate study and complete record of nausea/vomiting. This included 133 patients (61 vs. 63 evaluable). Detailed results of this separate study are provided though not all patients enrolled in this study.

[f] Numerators are number of randomizations, not unique patients; 20 patients were randomized twice per pragmatic design of trail.

[g] Analysis of 47 out of 104 accrued patients from the Canadian Bone Metastasis Trial who agreed to complete a pain diary using various pain flare definitions. Parent RCT (Kirkbride et al. 2000)[123] appears to only have been published as an abstract, we could not find a full length, peer-reviewed article. This citation was excluded during full-text review.

Table B-8. Safety: Toxicity and safety information in trials comparing LDSF EBRT versus HDSF EBRT

Scheme	Author, Year Study Design MBD Site	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity	Other Toxicity: Mixed Grades, NR by Group, Data NR, Other	Other AEs/Late AEs
LDSF (4 Gy x 1, n=109) vs. HDSF (6 Gy x 1, n=108) vs. HDSF (8 Gy x 1, n=110)	Jeremic, 1998[48] RCT Mixed spine and nonspine	NR	NR	NR	NR	Nausea/vomiting, Grade 1 and 2: 19.3% (21/109) vs. 18.5% (20/108) vs. 21.8% (24/110), p=NS Diarrhea, Grade 1 and 2: 12.8% (14/109) vs. 11.1% (12/108) vs. 14.5% (16/110), p=NS Other acute GI toxicity: 0% (0/109) vs. 0% (0/108) vs. 0% (0/110)	NR
LDSF (6 Gy x 1, n=51) + zoledronic acid vs. HDSF (8 Gy x 1, n=67) + zoledronic acid	Mañas, 2008[51] RCT Mixed spine and nonspine	NR	NR	NR	NR	The most frequency adverse reactions were fever (4.4% overall) and nausea (3.7% overall)	Adverse reaction (not defined): 30 weeks: 14% (8/57)[a] vs. 21.3% (17/80)[a] Adverse event (not defined, (drug related): 30 weeks: 47.4% (27/57)[a] vs. 61.3% (49/80)[a]

AE = adverse event; EBRT = external beam radiation therapy; GI = gastrointestinal; HDSF = higher dose single fraction ("control" arm); LDSF = lower dose single fraction ("intervention" arm); MBD = metastatic bone disease; NR = not reported; NS = not significant; RCT = randomized control trial.

[a] Safety data included additional nonrandomized patients. Authors do not report by only randomized patients.

Table B-9. Safety: Toxicity and safety information in trials comparing LDMF EBRT versus HDMF EBRT

Scheme	Author, Year Study Design MBD Site	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity	Other Toxicity: Mixed Grades, NR by Group, Data NR, Other	Other AEs/Late AEs
LDMF (8 Gy x 2, n=142) vs. HDMF (5 Gy x 3, n=134)	Maranzano, 2005[52] RCT MSCC	No antiemetic prophylaxis Grade 1 nausea: 6% (7/109)	NR	52 weeks Esophagitis: 1.4% (2/142) vs. 0.7% (1/134) Pharyngeal dysphagia: 0% (0/142) vs. 0.7% (1/134) Diarrhea: 1.4% (2/142) vs. 1.5% (2/134) Comparison of Anti-emetic prophylaxis (not of fractions) vs. no antiemetic prophylaxis Grade 3 vomiting: 3% (5/167) vs. 0.9% (1/109) Antiemetic prophylaxis Grade 3 nausea: 3% (5/167)	NR	52 weeks Whole population only Grade 1/2 oral/esophageal dysphagia: 14.1% (39/276) Grade 1/2 diarrhea: 7.2% (20/276) Anti-emetic prophylaxis vs. no antiemetic prophylaxis Grade 1/2 vomiting: 13.2% (22/167) vs. 5.5% (6/109) Anti-emetic prophylaxis Grade 1/2 nausea: 9.6% (16/167)	Late spinal cord morbidity: no instances reported

Scheme	Author, Year Study Design MBD Site	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity	Other Toxicity: Mixed Grades, NR by Group, Data NR, Other	Other AEs/Late AEs
LDMF (3 Gy x 10, n=100) vs. HDMF (2 Gy x 20, n=90)	Abu Hegazy,[30] 2011[a] RCT MSCC	Acute Toxicity Grade 1 Esophageal dysphagia: 3% (3/100) vs. 4.4% (4/90) Odynophagia: 3% (3/100) vs. 3.3% (3/90) Vomiting: 3% (3/100) vs. 2.2% (2/90) Diarrhea: 2% (2/100) vs. 3.3% (3/90) p=NS for all	Acute Toxicity Grade 2 Esophageal dysphagia: 1% (1/100) vs. 1.1% (1/90) Odynophagia: 0% (0/100) vs. 0% (0/90) Vomiting: 0% (0/100) vs. 0% (0/90) Diarrhea: 1% (1/100) vs. 2.2% (2/90) p=NS for all	NR	NR	Late toxicity: no instances occurred	NR
LDMF (4 Gy x 5, n=101) vs. HDMF (3 Gy x 10, n=102)	Rades, 2016[70] RCT MSCC	NR	NR	NR	NR	In both groups, in all patients, acute toxicity such as nausea, diarrhea, and radiation dermatitis did not exceed grade 2. Late radiation toxicity such as myelopathy or vertebral fractures as not observed	NR

Scheme	Author, Year Study Design MBD Site	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity	Other Toxicity: Mixed Grades, NR by Group, Data NR, Other	Other AEs/Late AEs
LDMF (5 Gy x 3, n=100) vs. HDMF (3 Gy x 10, n=100)	Rasmusson, 1995[18] RCT Mixed spine and nonspine	NR	NR	NR	NR	4 weeks -Erythema (slight): 6.1% (5/82) vs. 5.9% (5/85) -Nausea: 19.5% (16/82) vs. 21.2% (18/85) -Diarrhea: 5.9% (5/82) vs. 7.3% (6/85) 12 weeks -Nausea: 6.5% (4/62) vs. 10.1% (7/69) -Diarrhea: 4.8% (3/62) vs. 1.4% (1/69) 26 weeks -Nausea: 4.4% (2/45) vs. 1.9% (1/52) -Diarrhea: 2.2% (1/45) vs. 1.9% (1/52) 52 weeks -Nausea: 0% (0/28) vs. 0% (0/31)	Radiation-induced myelopathy: 0% in both groups at all timepoints (4 weeks: n=82 vs. 85; 12 weeks: n=62 vs. 69; 26 weeks: 45 vs. 52; 52 weeks: 28 vs. 31)
LDMF (3 Gy x 5, n=51) + ZA vs. HDMF (3 Gy x 10, n=49) + ZA	Atahan, 2010[10] RCT Mixed spine and nonspine	NR	NR	NR	NR	Whole population only Nausea: 10% (10/100) Diarrhea: 4% (4/100) Dyspepsia: 1% (1/100)	Whole population only Flu-like symptoms: 5% (5/100) Urinary infection: 1% (1/100)

Scheme	Author, Year Study Design MBD Site	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity	Other Toxicity: Mixed Grades, NR by Group, Data NR, Other	Other AEs/Late AEs
LDMF (4 Gy x 7 or 4 Gy x 10, n=91) vs. HDMF (2 Gy x 20 or 2 Gy x 30, n=92)	He, 2019[42] RCT Mixed spine and nonspine	Gastrointestinal: 11% (10/91) vs. 7.6% (7/92) Hematological: 6.6% (6/91) vs. 5.4% (5/92)	Gastrointestinal: 5.5% (5/91) vs. 3.3% (3/92) Hematological: 2.2% (2/91) vs. 1.1% (1/92)	0%	0%	Grade 1/2 Gastrointestinal: 16.5% (15/91) vs. 10.9% (10/92) (p=0.54) Hematologic: 8.8% (8/91) vs. 6.5% (6/92) (p=0.79)	NR
LDMF (4 Gy x 5, n=30) vs. HDMF (3 Gy x 10, n=28)	Ozsaran, 2001[61] RCT Mixed spine and nonspine	NR	NR	NR	NR	Whole population only Acute toxicity (NOS) -Grade 1 or 2, mostly GI: 16.1% (14/87) -Grade 3 or 4: 0% p=0.382 for toxicity between groups	NR
LDMF (4 Gy x 5, n=58) vs. HDMF (3 Gy x 10, n=47)	Valeriani, 2015[112] NRSI Mixed spine and nonspine	NR	NR	NR	Diarrhea: 0% (0/58) vs. 2% (1/47)	Overall acute toxicity: 2.6% vs. 24% (p=0.001) Mild dysphagia: 0% vs. 4.3% (2/47) Grade 1-2 toxicities were nausea and vomiting, details NR	NR

AE = adverse event; EBRT = external beam radiation therapy; GI = gastrointestinal; HDMF = higher total dose multi-fraction; LDMF = lower total dose multi-fraction; MBD = metastatic bone disease; MSCC = metastatic spinal cord compression; NR = not reported; NRSI = nonrandomized study of interventions; NS = not significant; RCT = randomized control trial; ZA = zoledronic acid.

[a] Study also includes an arm for single fraction radiation therapy; data for that arm is not presented here.

Table B-10. Safety: Spinal cord compression and pathologic fracture in patients receiving SF EBRT versus MF EBRT

EBRT Scheme	Author, Year Study Design MBD Site	Spinal Cord Compression	Pathological Fracture
SF (8 Gy x 1, n=137) vs. MF (4 Gy x 5, n=135)	Roos,[71] 2005[a] RCT Spine	Cord/cauda equina compressions at index site: 6.6% (9/137) vs. 5.9% (8/135), p=NS	New or progressive pathological fractures: 4.4% (6/137) vs. 3.7% (5/135), p=NS
SF (8 Gy x 1n n=66) vs. MF (4 Gy x 5 or 3 Gy x 10 or 2.5 Gy x 15, n=233)	Lam, 2015[102] NRSI Spine	Cord/cauda equina compression: 10.6% (7/66) vs. 1.7% (4/233)	Vertebral fracture: 13.6% (9/66) vs. 3.0% (7/233), OR=3.73 (95% CI 1.61 to 8.63), p=0.003
SF (8 Gy x 1, n=383) vs. MF (4 Gy x 5 or 3 Gy x 10, n=378)	Bone Trial Working Group, 1999[9] RCT Mixed spine and nonspine	Cord compression at index site: n=6 vs. 4 (N=NR)	Pathologic fracture at long-bone index site: n=7 vs. 2 (N=NR)
SF (8 Gy 1, n=45) vs. MF (3 Gy x 10, n=45)	Gutierrez Bayard, 2014[40] RCT Mixed spine and nonspine	NR	Pathological Fracture: 15.6% (7/45) vs. 4.4% (2/45) Skeletal-related event (at least 1 event of reirradiation or pathological fracture following radiation): 28.8% (13/45) vs. 13.3% (6/45)
SF (8 Gy x 1, n=50) vs. MF (2 Gy x 20, n=52)	Hamouda, 2007[11] RCT Mixed spine and nonspine	NR	Pathological fracture of irradiated site: 6% (3/50) vs. 11.5% (6/52)
SF (8 Gy 1, n=455) vs. MF (3 Gy x 10, n=443)	Hartsell, 2005[41] RCT Mixed spine and nonspine	NR	Pathological fractures within treatment field: 5% (n=NR) vs. 4% (n=NR) Pathological fractures adjacent to the treatment site: 3% to 4% (not reported by group)
SF (8 Gy x 1, n=186) vs. MF (3 Gy x 10, n=190)	Kaasa, 2006[49] RCT Mixed spine and nonspine	Spinal cord compression (required treatment; not referrable to treatment site only):10 vs. 5	Pathological Fracture (required treatment; not referrable to treatment site only): 4.3% (8/186) vs. 11.1% (21/190)

EBRT Scheme	Author, Year Study Design MBD Site	Spinal Cord Compression	Pathological Fracture
SF (8 Gy x 1, n=186) vs. MF (3 Gy x 10, n=190)	Sande, 2009[73] (Kaasa 2006[49] is index trial) RCT Mixed spine and nonspine	Spinal cord compression onset: 1% (1/85) vs. 4% (4/95) (p=0.37) Sub-analysis by cancer type Spinal cord compression Breast: 0% (0/18) vs. 0% (0/28) Lung: 0% (0/12) vs. 7.1% (1/14) Prostate: 3.7% (1/27) vs. 11.5% (3/26)	Fracture: 4.7% (4/85) vs. 5.3% (5/95) (p=1.00) Sub-analysis by cancer type Pathological Fracture Breast: 5.6% (1/18) vs. 10.7% (3/28) Lung: 8.3% (1/12) vs. 7.1% (1/14) Prostate: 3.7% (1/27) vs. 0% (0/26) Sub-analysis by metastasis site Pathological fracture Upper limbs: 0% (0/8) vs. 9.1% (1/11) Lower limbs: 0% (0/11) vs. 16.7% (2/12) Column: 2.9% (1/35) vs. 0% (0/36) Thorax: 0% (0/6) vs. 0% (0/12) Pelvis: 12.5% (3/24) vs. 9.1% (2/22)
SF (8 Gy x 1, n=122) vs. MF (5 Gy x 4, n=119)	Nielsen, 1998[13] RCT Mixed spine and nonspine	NR	Pathological fractures: 5% (6/120) vs. 5% (6/119)
SF (8 Gy x 1, n=29) vs. MF (4 Gy x 5, n=30) vs. MF (3 Gy x 10, n=28)	Ozsaran, 2001[61] RCT Mixed spine and nonspine	Whole population only Spinal cord compression: 0% (0/87)	Whole population only Fracture: 2.3% (2/87)
SF (8 Gy x 1, n=140) vs. MF (3 Gy x 10, n=148)	Price, 1986[66] RCT Mixed spine and nonspine	Spinal cord compression: 1.4% (2/140) vs. 0.7% (1/148)	Radiation-induced fracture of the femur: 0% (0/140) vs. 0.7% (1/148)

EBRT Scheme	Author, Year Study Design MBD Site	Spinal Cord Compression	Pathological Fracture
SF (8 Gy x 1, n=579) vs. MF (4 Gy x 6, n=578)	Steenland, 1999[14] RCT Mixed spine and nonspine	Compression: 2.2% (13/579) vs. 1.7% (10/578) The mean time to occurrence was 21 weeks in the SF group and 17 weeks in the MF group.	Fractures: Subgroup analysis by primary tumor type Breast cancer: 3.9% (9/233) vs. 0.9% (2/218) Prostate cancer: 5.4% (7/129) vs. 2.2% (3/138) Lung cancer: 3.6% (5/140) vs. 2% (3/147) Other cancer: 3.9% (3/77) vs. 2.7% (2/75) Subgroup analysis by treatment site Thoracic/lumbar spine: 2.4% (4/165) vs. 0.6% (1/177) Pelvis: 3% (6/199) vs. 1.8% (4/224) Femur: 16.7% (8/48) vs. 6.6% (4/61) Ribs: 0% (0/53) vs. 0% (0/44) Humerus: 2.9% (1/34) vs. 0% (0/27) Other: 6.3% (5/79) vs. 2.2% (1/45)

AE = adverse event; CI = confidence interval; EBRT = external beam radiation therapy; MBD = metastatic bone disease; MF = multi-fraction; MSCC = metastatic spinal cord compression; NR = not reported; NRSI = nonrandomized study of interventions; NS = not significant; RCT = randomized control trial. SF = single fraction.
[a] 89% of patients had spinal metastases.

Table B-11. Safety: Spinal cord compression and pathologic fracture in trials comparing LDSF EBRT versus HDSF EBRT

EBRT Scheme	Author, Year Study Design MBD Site	Spinal Cord Compression	Pathological Fracture
LDSF (4 Gy x 1, n=109) vs. HDSF (6 Gy x 1, n=108) vs. HDSF (8 Gy x 1, n=110)	Jeremic, 1998[48] RCT Mixed spine and nonspine	Spinal cord compression ≤8 weeks: 0% (0/109) vs. 0% (0/108) vs. 0% (0/110) >8 weeks: 6.6% (4/61) vs. 7.9% (5/63) vs. 6.1% (4/66), p=NS	Pathological fracture ≤8 weeks: 0% (0/109) vs. 0% (0/108) vs. 0% (0/110) >8 weeks: 6.3% (3/48) vs. 6.7% (3/45) vs. 6.8% (3/44), p=NS
LDSF (6 Gy x 1, n=51) + ZA vs. HDSF (8 Gy x 1, n=67) + ZA	Manas, 2008[51] RCT Mixed spine and nonspine	Skeletal event (pathological fracture, re-irradiation, or compression): 30 weeks: 23.5% (14/57) vs. 19.4% (15/80), p=0.587	Skeletal event (pathological fracture, re-irradiation, or compression): 30 weeks: 23.5% (14/57) vs. 19.4% (15/80), p=0.587

AE = adverse event; EBRT = external beam radiation therapy; HDSF = higher total dose single fraction ("control" arm); LDSF = lower total dose single fraction ("intervention" arm); MBD = metastatic bone disease; NR = not reported; NS = not significant; RCT = randomized control trial; ZA = zoledronic acid.

Table B-12. Safety: Spinal cord compression and pathologic fracture in studies comparing LDMF EBRT versus HDMF EBRT

EBRT Scheme	Author, Year Study Design MBD Site	Spinal Cord Compression	Pathological Fracture
LDMF (8 Gy x 2, n=142) vs. HDMF (5 Gy x 3, n=134)	Maranzano, 2005[52] RCT MSCC	Whole population only Late spinal cord morbidity: 0%	NR
LDMF (4 Gy x 5, n=101) vs. HDMF (3 Gy x 10, n=102)	Rades, 2016[70] RCT MSCC	NR	Late radiation toxicity - vertebral fractures: 0% (0/101) vs. 0% (0/102)
LDMF (3 Gy x 5, n=51) + ZA vs. HDMF (3 Gy x 10, n=49) + ZA	Atahan, 2010[10] RCT Mixed spine and nonspine	Spinal cord compression: 0% (0/51) vs. 2% (1/49)	Vertebral pathological fracture: 3.9% (2/51) vs. 2% (1/49) Nonvertebral pathological fracture: 2% (1/51) vs. 10.2% (5/49)
LDMF (4 Gy x 5, n=51) vs. HDMF (2 Gy x 15, n=49)	Niewald, 1996[55] RCT Mixed spine and nonspine	NR	Pathological fracture: 7.8% (4/51) vs. 12.2% (6/49), p=NS
LDMF (4 Gy x 5, n=30) vs. HDMF (3 Gy x 10, n=28)	Ozsaran, 2001[61] RCT Mixed spine and nonspine	Whole population only Spinal cord compression: 0% (0/87)	Whole population only Fracture: 2.3% (2/87)
LDMF (4 Gy x 5, n=58) vs. HDMF (3 Gy x 10, n=47)	Valeriani, 2015[112] NRSI Mixed spine and nonspine	NR	Pathological fracture: 0% (0/58) vs. 2.1% (1/47)

AE = adverse event; EBRT = external beam radiation therapy; HDMF = higher dose multi-fraction; LDMF = lower dose multi-fraction; MBD = metastatic bone disease; MSCC = metastatic spinal cord compression; NR = not reported; NRSI = nonrandomized study of interventions; NS = not significant; RCT = randomized control trial; ZA = zoledronic acid.

Table B-13. Safety: Spinal cord compression and pathologic fracture in studies comparing SF SBRT versus MF SBRT

SBRT Scheme	Author, Year Study Design MBD Site	Spinal Cord Compression	Pathological Fracture
SF+MF (24 Gy x 1, n=3; 18-26 Gy x 2,n=32) vs. MF (18-40 Gy x ≥3, n=45)	Al-Omair, 2013[88] NRSI Spine	NR	Whole population only Fracture: 11.3% (9/80) Median time to fracture: 29 weeks
SF (18-24 Gy x 1, n=NR) vs. MF (6 Gy x 5, n=NR)	Ghia, 2016[95] NRSI Spine	NR	Vertebral body fracture: 46.2% (6/13) vs. 9% (1/11) p=0.11
SF (8 Gy x 1, n=66) vs. MF (4 Gy x 5 or 3 Gy x 10 or 2.5 Gy x 15, n=233)	Lam, 2015[102] NRSI Spine	Cord/cauda equina compression: 10.6% (7/66) vs. 1.7% (4/233)	Vertebral fracture: 13.6% (9/66) vs. 3.0% (7/233), OR=3.73 (95% CI 1.61 to 8.63), p=0.003
SF (24 Gy x 1, n=59, 77 lesions) vs. MF (9 Gy x 3, n=58, 77 lesions)	Zelefsky, 2021[87] RCT Mixed spine and nonspine	NR	Grade ≥2 fracture: 2.6% (2/77 lesions) vs 2.6% (2/77 lesions) p=NS for all
SF (18-24 Gy x 1, n=59) vs. MF (20-30 Gy in 3-5 fractions, n=46)	Zelefsky, 2012[116] NRSI Mixed spine and nonspine	NR	Vertebral body fracture: 3.4% (2/59) vs. 4.3% (2/46)
SF (16 Gy x 1 or 18 Gy x 1, n=112) vs. MF (21 Gy x 3 or 25.5 Gy x 3 or 27 Gy x 3 or 30 Gy x 5, n=15)	Kelley, 2019[101] NRSI Mixed spine and nonspine	NR	Whole population only Fracture: 9.1% (26/287 treated vertebrae)

AE = adverse event; CI = confidence interval; MBD = metastatic bone disease; MF = multi-fraction; NR = not reported; NRSI = nonrandomized study of interventions; NS = not significant; OR = odds ratio; RCT = randomized control trial; SBRT = stereotactic body radiation therapy; SF = single fraction.

Table B-14. Toxicity and safety information in studies comparing SF SBRT versus MF SBRT

SBRT Scheme	Author	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity	Other Toxicity: Mixed Grades, NR by Group, Data NR, Other	Other AEs/Late AEs
SF+ MF (24 Gy x 1, n=3; 18-26 Gy x 2, n=32) vs. MF (18-40 Gy x ≥3, n=45)	Al-Omair, 2013[88] NRSI Spine	NR	NR	NR	NR	Whole population only Toxicity Grade 1/2 genitourinary: 3.8% (3/80) Grade 3/4: 0% (0/80)	Whole population only Pain flare: 8.8% (7/80) Local Failure: 26.3% (21/80) Crude median time to local failure: 30 weeks Actuarial median time to failure: 86 weeks
SF (18-24 Gy x 1, n=NR) vs. MF (6 Gy x 5, n=NR)	Ghia, 2016[95] NRSI Spine	NR	NR	Grade 3 late radiculopathy: 4.8% (1/21) vs. 0% (0/26)	NR	NR	Pain flare: 35% (7/20) vs. 30% (6/20), p=1.0
SF (median dose 24 Gy, n=68) vs. MF (median dose 28.5 Gy x 3-6, n=52)	Folkert, 2014[94] NRSI Spine	NR	NR	NR	NR	NR	Tracheoesophageal fistulae: 2.9% (2/68) vs. 0% (0/52); both followed radiation recall esophagitis after Doxorubicin and iatrogenic manipulation (biopsy, dilation or both)
SF (24 Gy x 1, n=59, 77 lesions) vs. MF (9 Gy x 3, n=58, 77 lesions)	Zelefsky, 2021[87] RCT Mixed spine and nonspine	NR	NR	NR	NR	Treatment-related toxicity Grade ≥2: 11.7% (9/77 lesions) vs 6.5% (5/77 lesions), p=0.40 Grade ≥3: 7.8% (6/77 lesions) vs 3.9% (3/77 lesions), p=0.49 Toxicities Grade ≥2 pain: 9.1% (7/77 lesions) vs 3.9% (3/77 lesions) Grade ≥2 neuropathy: 2.6% (2/77 lesions) 0% vs. 0% (0/77 lesions)	NR

SBRT Scheme	Author	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity	Other Toxicity: Mixed Grades, NR by Group, Data NR, Other	Other AEs/Late AEs
SF (18-24 Gy x 1, n=59) vs. MF (20-30 Gy in 3-5 fractions, n=46)	Zelefsky,[116] 2012[a] NRSI Mixed spine and nonspine	NR	Grade 2 radiation induced dermatitis: 3.4% (2/59) vs. 0% (0/46)	NR	Grade 4 erythema: 1.7% (1/59) vs. 0% (0/46)	Grade ≥2 neuropathy: 8.5% (5/59) vs. 2.2% (1/46)	NR
SF (16 Gy x 1 or 18 Gy x 1, n=112) vs. MF (21 Gy x 3 or 25.5 Gy x 3 or 27 Gy x 3 or 30 Gy x 5, n=15)	Kelley, 2019[101] NRSI Mixed spine and nonspine	NR	NR	NR	NR	≥Grade 4 toxicity: 0%	NR

AE = adverse event; MBD = metastatic bone disease; MF = multi-fraction; MSCC = metastatic spinal cord compression; NR = not reported; NRSI = nonrandomized study of interventions; NS = not significant; RCT = randomized control trial; SBRT = stereotactic body radiation therapy; SF = single fraction.

[a] Additional toxicities listed in Table 4 - not attributed to given dose/fraction; n's NR, authors report that denominator only includes treated lesions.

Key Question 1: IMRT Versus 3DCRT

Table B-15. Harms: IMRT versus 3DCRT

Outcome	Author, Year MBD Site	Study Design	Timing	IMRT, % (n/N)	3DCRT, % (n/N)	RR (95% CI)[a]
Pathological fracture	Sprave, 2018[81] Spine	RCT	0 weeks	3% (1/30)[b]	13% (4/30)[b]	NR
	Sprave, 2018[81] Spine	RCT	12 weeks	15% (3/20)	11% (2/19)	NR
	Sprave, 2018[81] Spine	RCT	26 weeks	17% (3/18)	17% (2/12)	NR
	Rades, 2020[105] MSCC	NRSI	"Late"	0% (0/40)	NR	NR
Other serious AEs	Sprave, 2018[78] Spine	RCT	12 weeks	Treatment-related deaths: 0% (0/18)	Treatment-related deaths: 0% (0/14)	NR
	Rades, 2020[105] MSCC	NRSI	"Late"	Myelopathy: 0% (0/40)	NR	NR
	Romano 2017[108] Mixed spine/nonspine	NRSI	During RT and post-RT	Hospital/ED admission: 4% (6/142)	Hospital/ED admission: 4% (4/112)	NR
Toxicity, Grade 3 or 4	Romano 2017[108] Mixed spine/nonspine	NRSI	Acute (during RT and <60 days)	Dysphagia: 1% (1/142) Vomiting: 1% (2/112) Diarrhea: 0% (0/142)	Dysphagia: 1% (1/112) Vomiting: 1% (1/112) Diarrhea: 0% (0/112)	NR
Toxicity, Grade 3	Sprave, 2018[78] Spine	RCT	Post RT[c]	Nausea: 0% (0/27) Diarrhea: 3.7% (1/27)[d] Myalgia: 3.7% (1/27)[d] All others (as below for grade 1/2 toxicity): 0% (0/27)	Nausea: 3.6% (1/28) Diarrhea: 0% (0/28) Myalgia: 0% (0/28) All others (as below for grade 1/2 toxicity): 0% (0/28)	NR
	Range, post RT	1 RCT		0%–3.7%	0%–3.6%	NA
	Sprave, 2018[78] Spine	RCT	12 weeks	Paresthesia: 0% (0/18) Radiculitis: 0% (0/18) Peripheral motoric neuropathy: 5.6% (1/18) Dermatitis: 0% (0/18) Myalgia: 0% (0/18) Myositis: 0% (0/18) All others (as below for grade 1/2 toxicity): 0% (0/18)	Paresthesia: 7.1% (1/14)[e] Radiculitis: 7.1% (1/14)[e] Peripheral motoric neuropathy: 7.1% (1/14)[e] Myalgia: 7.1% (1/14)[e] Dermatitis: 7.1% (1/14) Myositis: 7.1% (1/14) All others (as below for grade 1/2 toxicity): 0% (0/14)	NR
	Range, 12 weeks	1 RCT		0%–5.6%	0%–7.1%	NA
	Sprave, 2018[80] Spine	RCT	26 weeks	Radiculitis: 6% (1/18) All others (as below for grade 1/2 toxicity): 0% (0/18)	Radiculitis: 0% (0/12) All others (as below for grade 1/2 toxicity): 0% (0/12)	NR
	Range, 26 weeks	1 RCT		0%–6%	0%	NA

Outcome	Author, Year MBD Site	Study Design	Timing	IMRT, % (n/N)	3DCRT, % (n/N)	RR (95% CI)[a]
	Rades, 2020[105] MSCC	NRSI	Acute	Nausea/vomiting: 2.5% (1/40)	NR	NR
	Romano 2017[108] Mixed spine/nonspine	NRSI	Acute (during RT and <60 days)	Oral pain: 1% (1/142) Dry mouth: 0% (0/142) Esophagitis: 2% (3/142) Nausea: 2% (3/142)	Oral pain: 1% (1/112) Dry mouth: 0% (0/112) Esophagitis: 1% (1/112) Nausea: 1% (1/112)	NR
Toxicity, Grade 1 or 2	Sprave, 2018[78] Spine	RCT	Post RT	Xerostomia: 29.6% (8/27) Dysphagia: 11.1% (3/27) **Esophagitis: 7.4% (2/27)** Vomiting: 7.4% (2/27) Nausea: 29.6% (8/27) Diarrhea: 7.4% (2/27) Dyspnea: 25.9% (7/27) Pneumonitis: 7.4% (2/27) Myelitis: 0% (0/27) Paresthesia: 29.6% (8/27) **Brachial plexopathy: 0% (0/27)** Radiculitis: 11.1% (3/27) Peripheral motoric neuropathy: 14.8% (4/27) Dermatitis: 7.4% (2/27) Myalgia: 22.2% (6/27) Myositis: 7.4% (2/27)	Xerostomia: 35.7% (10/28) Dysphagia: 25.0% (7/28) **Esophagitis: 35.8% (10/28)** Vomiting: 14.3% (4/28) Nausea: 39.3% (11/28) Diarrhea: 7.1% (2/28) Dyspnea: 35.8% (10/28) Pneumonitis: 7.1% (2/28) Myelitis: 3.6% (1/28) Paresthesia: 28.6% (8/28) **Brachial plexopathy: 17.9% (5/28)** Radiculitis: 17.8% (5/28) Peripheral motoric neuropathy: 3.6% (1/28) Dermatitis: 3.6% (1/28) Myalgia: 25.0% (7/28) Myositis: 3.6% (1/28)	**Esophagitis: RR 0.21 (0.05 to 0.86)** **Brachial plexopathy: RR NC, p=0.023**
	Range, post RT	1 RCT		0%–29.6%	3.6%–35.8%	NA
	Sprave, 2018[78] Spine	RCT	12 weeks	Xerostomia: 11.1% (2/18) Dysphagia: 11.1% (2/18) Esophagitis: 0% (0/18) Vomiting: 0% (0/18) Nausea: 0% (0/18) Diarrhea: 5.6% (1/18) Dyspnea: 11.1% (2/18) Pneumonitis: 0% (0/18) Myelitis: 5.6% (1/18) Paresthesia: 16.7% (3/18) Brachial plexopathy: 5.6% (1/18) Radiculitis: 11.1% (2/18) Peripheral motoric neuropathy: 0% (0/18) Dermatitis: 0% (0/18) Myalgia: 5.6% (1/18) Myositis: 0% (0/18)	Xerostomia: 14.3% (2/14) Dysphagia: 0% (0/14) Esophagitis: 0% (0/14) Vomiting: 7.1% (1/14) Nausea: 14.3% (2/14) Diarrhea: 7.1% (1/14) Dyspnea: 35.7% (5/14) Pneumonitis: 7.1% (1/14) Myelitis: 0% (0/14) Paresthesia: 0% (0/14) Brachial plexopathy: 7.1% (1/14) Radiculitis: 7.1% (1/14) Peripheral motoric neuropathy: 14.3% (2/14) Dermatitis: 0% (0/14) Myalgia: 14.3% (2/14) Myositis: 14.3% (2/14)	NR
	Range, 12 weeks	1 RCT		0%–16.7%	0%–35.7%	NA

Outcome	Author, Year MBD Site	Study Design	Timing	IMRT, % (n/N)	3DCRT, % (n/N)	RR (95% CI)[a]
	Sprave, 2018[80] Spine	RCT	26 weeks	Xerostomia: 0% (0/18) Dysphagia: 0% (0/18) Esophagitis: 0% (0/18) Nausea: 0% (0/18) Diarrhea: 0% (0/18) Dyspnea: 17% (3/18) Myelitis: 0% (0/18) Paresthesia: 11% (2/18) Brachial plexopathy: 6% (1/18) Radiculitis: 6% (1/18) Peripheral motoric neuropathy: 6% (1/18) Dermatitis: 0% (0/18) Myalgia: 6% (1/18) Myositis: 6% (1/18) All others (as above for grade 1/2 toxicity): 0% (0/18)	Xerostomia: 8% (1/12) Dysphagia: 8% (1/12) Esophagitis: 17% (2/12) Nausea: 7% (2/12) Diarrhea: 17% (2/12) Dyspnea: 8% (1/12) Myelitis: 8% (1/12) Paresthesia: 0% (0/12) Brachial plexopathy: 17% (2/12) Radiculitis: 17% (2/12) Peripheral motoric neuropathy: 0% (0/12) Dermatitis: 8% (1/12) Myalgia: 17% (2/12) Myositis: 17% (2/12) All others (as above for grade 1/2 toxicity): 0% (0/12)	NR
	Range, 26 weeks	1 RCT		0%–16.7%	0%–16.7%	NA
	Rades, 2020[105] MSCC	NRSI	Acute	<u>All Grade 2</u> Any: 7.5% (3/40) Diarrhea: 5.0% (2/40) Nausea/fatigue/decreased appetite: 2.5% (1/40)	NR	NR
	Romano 2017[108] Mixed spine/nonspine	NRSI	Acute (during RT and <60 days)	Dysphagia: 6% (9/142) Oral pain: 6% (9/142) Dry mouth: 0% (0/142) Esophagitis: 11% (16/142) Nausea: 24% (34/142) Vomiting: 11% (15/142) Diarrhea: 5% (7/142)	Dysphagia: 7% (8/112) Oral pain: 7% (8/112) Dry mouth: 0% (0/112) Esophagitis: 9% (10/112) Nausea: 29% (32/112) Vomiting: 11% (12/112) Diarrhea: 6% (7/112)	NR

3DCRT = three-dimensional conformal radiation therapy; CI = confidence interval; IMRT = intensity modulated radiation therapy; MSCC = metastatic spinal cord compression; NA = not applicable; NR = not reported; NRSI = nonrandomized study of interventions; RCT = randomized controlled trial; RR = risk ratio; RT = radiation therapy; VCF = vertebral compression fractures.

[a] Calculated by EPC. RR only calculated if differences were significant or close to significant.

[b] No fracture required salvage surgery.

[c] Authors state that no grade 4 or 5 toxicities occurred in either group.

[d] The same patient had both outcomes.

[e] The same patient suffered all four adverse events..

Key Question 1: EBRT Plus HBI Versus EBRT

Table B-16. Harms: EBRT plus HBI versus EBRT alone

Outcome	Outcome	EBRT + HBI %, n/N	EBRT %, n/N	RR (95% CI)[a]
Toxicity, Grade 4	Thrombocytopenia	<1% (1/221)	0% (0/207)	NR
Toxicity, Grade 3	Any (1 event per patient)	5.3% (12/226)	1.4% (3/218)	3.86 (1.10 to 13.49)
	Leukopenia	4% (10/221)	<1% (1/206)	9.65 (1.25 to 74.72)
	Thrombocytopenia	1% (3/221)	0% (0/207)	NR
	Anemia	1% (2/221)	0% (0/208)	NR
	Nausea/vomiting	1% (2/226)	0% (0/218)	NR
	Diarrhea	1% (2/226)	<1% (1/218)	NR
	Skin	0% (0/226)	<1% (1/217)	NR
	Other (details NR)	<1% (1/223)	<0% (0/217)	NR
Toxicity, Grade 2	Any (1 event per patient)	16.8% (38/226)	9.6% (21/218)	1.75 (1.06 to 2.88)
	Leukopenia	3% (7/221)	1% (2/206)	NR
	Thrombocytopenia	2% (5/221)	1% (2/207)	NR
	Anemia	2% (4/221)	1% (3/208)	NR
	Genito-urinary	0% (0/226)	<1% (1/218)	NR
	Nausea/vomiting	10% (22/226)	2% (5/218)	4.24 (1.64 to 11.0)
	Diarrhea	8% (18/226)	4% (8/218)	2.17 (0.96 to 4.89)
	Skin	<1% (1/226)	1% (2/217)	NR
	Mucosa	<1% (1/226)	1% (2/218)	NR
	Other (details NR)	<1% (1/223)	0% (0/217)	NR
Toxicity, Grade 1	Any (1 event per patient)	17.3% (39/226)	9.6% (21/218)	1.79 (1.09 to 2.94)
	Leukopenia	5% (12/221)	1% (3/206)	3.86 (1.10 to 13.49)
	Thrombocytopenia	5% (11/221)	1% (2/207)	5.31 (1.19 to 23.66)
	Anemia	5% (12/221)	3% (7/208)	NR
	Hemorrhage	<1% (1/226)	0% (0/218)	NR
	Genito-urinary	1% (2/226)	<1% (1/218)	NR
	Hypotension	<1% (1/225)	0% (0/217)	NR
	Nausea/vomiting	9% (21/226)	3% (6/218)	3.38 (1.39 to 8.21)
	Diarrhea	7% (15/226)	3% (6/218)	2.41 (0.95 to 6.10)
	Pulmonary	1% (2/226)	0% (0/216)	NR
	Skin	3% (7/226)	2% (5/217)	NR
	Mucosa	1% (2/226)	<1% (1/218)	NR
	Fever	<1% (1/226)	<1% (1/218)	NR
	Other (details NR)	1% (3/223)	1% (2/217)	NR
Other serious AEs	Treatment-related deaths	0% (0/229)	0% (0/221)	NR
	Radiation pneumonitis	0% (0/223)	NR	NR

AEs = adverse events; CI = confidence interval; EBRT = external beam radiation therapy; HBI = hemibody irradiation; NR = not reported; RR = risk ratio.

[a] Calculated by EPC. RR only calculated if differences were significant or close to sig.

Key Question 1: SBRT Versus Conventional EBRT

Table B-17. Harms outcomes for the comparison of SBRT versus conventional EBRT

Outcome	Author, Year MBD Site	Study Design	Timing	SBRT %, n/N,	EBRT %, n/N,
Pathological fracture	Nguyen, 2019[17] Nonspine	RCT	Acute	Radiation induced fracture: 1% (1/81)	Radiation induced fracture: 0% (0/79)
	Sprave, 2018[82] Spine	RCT	12-26 weeks	New pathological fracture, 12 wks: 9% (2/23) New pathological fracture, 26 wks: 28% (5/18) [2 de novo, 3 progression of existing VCF]	New pathological fracture, 12 wks: 4% (1/23) New pathological fracture, 26 wks: 5% (1/20)
	Sahgal, 2021[72] Spine	RCT	26 weeks	Any vertebral compression fracture:11% (12/110) -Grade 1: 11% (11/110) -Grade 3 fracture: 1% (1/110) -Grade 4 fracture: 0% (0/110)	Any vertebral compression fracture: 17% (20/115) -Grade 1: 17% (19/115) -Grade 3 fracture: 0% (0/115) -Grade 4 fracture: 1% (1/115)
	Amini, 2015[89] Mixed spine/nonspine	NRSI	NR	Fracture secondary to tumor progression post RT: 4% (2/50); 1 pelvic, 1 spine	Fracture secondary to tumor progression post RT: 9% (4/45); 2 pelvic, 2 spine
	Sohn, 2016[110] Spine (HCC)	NRSI	NR	Compression fracture (no tumor progression) Grade 1: 11% (3/28) Grade 2: 7% (2/28)	Compression fracture (no tumor progression) Grade 1: 0% (0/28) Grade 2: 4% (1/28)
Spinal cord compression	Sahgal, 2021[72] Spine	RCT	26 weeks	Progression to symptomatic SCC: 0% (0/110)	Progression to symptomatic SCC: 2% (2/115)
Pain flare	Sahgal, 2021[72] Spine	RCT	26 weeks	Pain flare[a]: 43% (45/110)	Pain flare[a]: 34% (35/115)
	Sprave, 2018[79] Spine	RCT	2 days	In-field pain flare: 7.4% (2/27)	In-field pain flare: 7.4% (2/27)
Other serious AEs	Sprave, 2018[79] Spine	RCT	NR	Radiation-related myelopathy: 0% (0/27) Cauda equina injury: 0% (0/27) Late toxicities: 0% (0/27)	Radiation-related myelopathy: 0% (0/28) Cauda equina injury: 0% (0/28) Late toxicities: 0% (0/28)
	Sahgal, 2021[72] Spine	RCT	26 weeks	Discontinuation due to treatment-related toxicity: 0% (0/110) Treatment-related mortality: 0% (0/110)	Discontinuation due to treatment-related toxicity: 0% (0/115) Treatment-related mortality: 0% (0/115)
	Haley, 2011[97] Spine	NRSI	>12 weeks	Late toxicities or other complications: 0% (0/NR)[b]	Late toxicities or other complications: 0% (0/NR)[b]
Toxicity, Grade 4	Pielkenrood, 2021[63] Mixed spine/nonspine	RCT	12 weeks	Any: 0% (0/26)	Any: 0% (0/44)
	Sahgal, 2021[72] Spine	RCT	Acute	Dysphasia: 0% (0/110) Esophagitis[c]: 0% (0/110) Nausea: 0% (0/110) Pain[d]: 0% (0/110)	Dysphasia: 0% (0/115) Esophagitis[c]: 0% (0/115) Nausea: 0% (0/115) Pain[d]: 0% (0/115)
	Sprave, 2018[79] Spine	RCT	Acute	Any: 0% (0/27)	Any: 0% (0/28)
	Range, 3 RCTs			0%	0%

Outcome	Author, Year MBD Site	Study Design	Timing	SBRT %, n/N,	EBRT %, n/N,
	Amini, 2015[89] Mixed spine/nonspine	NRSI	Acute	Pain: 0% (0/50 lesions) Edema: 0% (0/50 lesions) Nausea: 0% (0/50 lesions) Esophagitis: 0% (0/50 lesions) Fatigue: 0% (0/50 lesions) Diarrhea: 0% (0/50 lesions) Dermatitis: 0% (0/50 lesions)	Pain: 0% (0/45 lesions) Edema: 0% (0/45 lesions) Nausea: 0% (0/45 lesions) Esophagitis: 0% (0/45 lesions) Fatigue: 0% (0/45 lesions) Diarrhea: 0% (0/45 lesions) Dermatitis: 0% (0/45 lesions)
	Range, 1 NRSI			0%	0%
Toxicity, Grade 3	Nguyen, 2019[17] Nonspine	RCT	Acute	Nausea: 1% (1/81) Vomiting: 0% (0/81) Fatigue: 11% (9/81)	Nausea: 5% (4/79) Vomiting: 3% (2/79) Fatigue: 5% (4/79)
	Pielkenrood, 2021[63] Mixed spine/nonspine	RCT	12 weeks	Any: 0% (0/26)	Any: 0% (0/44)
	Sahgal, 2021[72] Spine	RCT	Acute	Dysphasia: 1% (1/110) Esophagitis[c]: 0% (0/110) Nausea: 0% (0/110) Pain[d]: 5% (5/110)	Dysphasia: 0% (0/115) Esophagitis[c]: 0% (0/115) Nausea: 1% (1/115) Pain[d]: 4% (5/115)
	Sprave, 2018[79] Spine	RCT	Acute	Any: 0% (0/27)	Any: 0% (0/28)
	Range, 4 RCTs			0%–10%	0%–5%
	Amini, 2015[89] Mixed spine/nonspine	NRSI	Acute	Pain: 0% (0/50 lesions) Edema: 0% (0/50 lesions) Nausea: 0% (0/50 lesions) Esophagitis: 0% (0/50 lesions) Fatigue: 0% (0/50 lesions) Diarrhea: 0% (0/50 lesions) Dermatitis: 2% (1/50 lesions)	Pain: 0% (0/45 lesions) Edema: 0% (0/45 lesions) Nausea: 0% (0/45 lesions) Esophagitis: 0% (0/45 lesions) Fatigue: 0% (0/45 lesions) Diarrhea: 0% (0/45 lesions) Dermatitis: 0% (0/45 lesions)
	Range, 1 NRSI			0%–2%	0%
Toxicity, Grade 2	Nguyen, 2019[17] Nonspine	RCT	Acute	Nausea: 25% (20/81) Vomiting: 9% (7/81)	Nausea: 13% (10/79) Vomiting: 14% (11/79)
	Sahgal, 2021[72] Spine	RCT	Acute	Dysphasia: 1% (1/110) Esophagitis[c]: 2% (2/110) Nausea: 1% (1/110) Pain[d]: 2% (2/110)	Dysphasia: 0% (0/115) Esophagitis[c]: 2% (2/115) Nausea: 2% (2/115) Pain[d]: 3% (4/115)
	Sprave, 2018[79] Spine	RCT	Acute	Dysphagia: 0% (0/27) Emesis: 0% (0/27) Fatigue: 7.4% (2/27) Radiation dermatitis: 0% (0/27)	Dysphagia: 3.6% (1/28) Emesis: 3.6% (1/28) Fatigue: 7.1% (2/28) Radiation dermatitis: 0% (0/28)
	Range, 3 RCTs			0%–25%	0%–14%
	Amini, 2015[89] Mixed spine/nonspine	NRSI	Acute	Pain: 2% (1/50 lesions) Edema: 0% (0/50 lesions) Nausea: 2% (1/50 lesions) Esophagitis: 0% (0/50 lesions) Fatigue: 2% (1/50 lesions) Diarrhea: 0% (0/50 lesions) Dermatitis: 2% (1/50 lesions)	Pain: 2% (1/45 lesions) Edema: 0% (0/45 lesions) Nausea: 2% (1/45 lesions) Esophagitis: 0% (0/45 lesions) Fatigue: 2% (1/45 lesions) Diarrhea: 0% (0/45 lesions) Dermatitis: 4% (2/45 lesions)

Outcome	Author, Year MBD Site	Study Design	Timing	SBRT %, n/N,	EBRT %, n/N,
	Sohn, 2016[110] Spine (HCC)	NRSI	Acute	Dysphagia: 0% (0/28) Sore throat: 0% (0/28) Nausea: 4% (1/28) Diarrhea: 4% (1/28) Skin problems: 0% (0/28) Dry mouth: 0% (0/28)	Dysphagia: 11% (3/28) Sore throat: 0% (0/28) Nausea: 4% (1/28) Diarrhea: 0% (0/28) Skin problems: 4% (1/28) Dry mouth: 4% (1/28)
	Haley, 2011[97] Spine	NRSI	Acute	Nausea and vomiting: 5% (0/22)	Nausea and vomiting: 0% (0/22)
	Range, 3 NRSIs			0%–5%	0%–11%
Toxicity, Grade 1	Sprave, 2018[79] Spine	RCT	Acute	Dysphagia: 3.7% (1/27) Emesis: 0% (0/27) Fatigue: 11.1% (3/27) Radiation dermatitis: 3.7% (1/27)	Dysphagia: 7.1% (2/28) Emesis: 0% (0/28) Fatigue: 17.9% (5/28) Radiation dermatitis:17.9% (5/28)
	Range, 1 RCT			0%–11%	0%–18%
	Amini, 2015[89] Mixed spine/nonspine	NRSI	Acute	Pain: 4% (2/50 lesions) Edema: 2% (1/50 lesions) Nausea: 6% (3/50 lesions) Esophagitis: 4% (2/50 lesions) Fatigue: 6% (3/50 lesions) Diarrhea: 2% (1/50 lesions) Dermatitis: 6% (3/50 lesions)	Pain: 2% (1/45 lesions) Edema: 2% (1/45 lesions) Nausea: 7% (3/45 lesions) Esophagitis: 2% (1/45 lesions) Fatigue: 9% (4/45 lesions) Diarrhea: 0% (0/45 lesions) Dermatitis: 4% (2/45 lesions)
	Sohn, 2016[110] Spine (HCC)	NRSI	Acute	Dysphagia: 4% (1/28) Sore throat: 0% (0/28) Nausea: 11% (3/28) Diarrhea: 0% (1/28) Skin problems: 0% (0/28) Dry mouth: 0% (0/28)	Dysphagia: 18% (5/28) Sore throat: 4% (1/28) Nausea: 7% (2/28) Diarrhea: 4% (1/28) Skin problems: 0% (0/28) Dry mouth: 7% (2/28)
	Haley, 2011[97] Spine	NRSI	Acute	Nausea and vomiting: 0% (0/22) Fatigue: 0% (0/22) Thrombocytopenia: 0% (0/22)	Nausea and vomiting: 5% (1/22) Fatigue: 5% (1/22) Thrombocytopenia: 5% (1/22)
	Range, 3 NRSIs			0%–11%	0%–18%
Toxicity, Grade 1 or 2	Haley, 2011[97] Spine	NRSI	Acute	Esophagitis: 0% (0/22)	Esophagitis: 14% (3/22)
Toxicity, Grade NR	Nguyen, 2019[17] Nonspine	RCT	Acute	Radiation dermatitis: 1% (1/81)	Radiation dermatitis: 3% (2/79)
Total with any toxicity	Sohn, 2016[110] Spine (HCC)	NRSI	Acute	32.1% (9/28)	63% (17/28)
	Haley, 2011[97] Spine	NRSI	Acute	5% (1/22)[e]	27% (6/22)[e]

AE = adverse event; EBRT = external beam radiation therapy; HCC = hepatocellular cancer is primary tumor type; MBD = metabolic bone disease; NR = not reported; NRSI = nonrandomized study of interventions; RCT = randomized controlled trial; SBRT = stereotactic body radiation therapy; VCF = vertebral compression fracture.

[a] Defined as a patient-reported subjective assessment of a worsening of pain at the radiation treatment spinal segment volume.

[b] Authors state that 38 patients completed longer-term followup, >90 days.

[c] Esophagitis events are presented as an aggregate of esophageal pain, esophagitis, and pharyngeal mucositis.

[d] Pain events are presented as an aggregate of general disorders pain, neoplasm-related tumor pain, and musculoskeletal and connective tissue disorders.

[e] All self-limiting and resolved in <8 weeks post-RT.

Secondary Outcomes Results

Key Question 1. Effectiveness and Harms of Dose-Fractionation Schemes and Techniques for Delivery: Initial Radiation

Single Versus Multiple Dose-Fractionation Schemes: Conventional EBRT

Local Control

Across two RCTs in patients with metastatic spinal cord compression (MSCC),[30,53,61] local in-field recurrence was slightly higher after single fraction (SF)- external beam radiation therapy (EBRT) (8 Gy) versus multiple fraction (MF)-EBRT (8 Gy x 2, 3 Gy x 10 or 2 Gy x 20) but there was no difference between groups in either trial: 5.9 versus 2.5 percent (N=303, relative risk [RR] 2.21, 95% confidence interval [CI] 0.69 to 7.01; timing not reported)[53] and 22.2 versus 14.8 percent (N=162, RR 1.50, 95% CI 0.76 to 2.94).[30]

Overall Survival

Fourteen trials (in 15 publications)[9,13,14,38-41,45,47,49,53,61,66,71,83] reported no differences between fractionation schemes in overall survival (Appendix Table B-5 above). Three RCTs were in patients with MSCC.[45,53,83] Across two of these trials,[45,83] survival at 5 to 12 weeks ranged from 50 to 67.9 percent after SF EBRT versus 55 to 76.8 percent after MF EBRT; by 52 weeks, overall survival was around 20 percent of patients in both trials. Median overall survival across all three trials ranged from 12 to 17 weeks in both treatment groups. Two RCTs included patients with only spine metastases (no compression);[47,71] one was a subanalysis[47] of another included trial.[41] At 52 weeks, survival was 40 percent (SF EBRT) vs. 49 percent (MF EBRT) in one trial[47] and 27 percent (22% to 32%) overall in the second trial (p=0.66 by treatment arm; data not provided).[71] At longest followup in both trials, overall survival ranged from 5 to 7 percent (SF EBRT) versus 8 to 9 percent (MF EBRT). Ten RCTs[9,13,14,38-41,49,61,66] were in patients with mixed spine and nonspine MBD. Across four trials, overall survival at 52 weeks in the SF- and MF EBRT groups, respectively, ranged from 21.6 to 41 percent versus 32.6 to 42 percent; at 104 weeks, ranges were 5.7 to 22 percent versus 12.9 to 22 percent.[13,39,41,66] The other six RCTs reported overall survival in terms of median length of survival which ranged from 28 to 44 weeks (SF EBRT) versus 28 to 42 weeks (MF EBRT) in five RCTs;[9,14,38,40,49] the sixth trial reported a significant difference in overall survival between SF EBRT (8 Gy) compared with MF EBRT given as 3 Gy in 10 fractions (12 weeks vs. 44 weeks, p=0.018) but there was no difference when compared with MF EBRT given as 4 Gy in 5 fractions (12 weeks vs. 16 weeks, p=0.635).[61]

Medication Use

Ten trials[9,11,32,39-41,45,49,58,61] reported medication requirements in their patients over the course of followup and found no differences in use between fractionation schemes (Appendix Table B-6 above). In general, roughly a third to a half of patients in both treatment groups were taking simple or moderate nonopioid analgesic after treatment. In the one trial evaluating patients with MSCC, analgesic use was 48 percent after SF-ERBT versus 51 percent after MF EBRT (RD -3.0%, 95% CI -10.9% to 5.0%).[45] The remaining nine trials were all in patients with mixed spine

and nonspine MBD. Across five trials,[9,11,39,41,61] the proportion of patients not requiring any medication for pain ranged from 17 to 41.7 percent (SF EBRT) versus 21 to 42.5 percent (MF EBRT) across followups ranging from post RT (not further specified) to 52 weeks. The proportion of patients in the SF- versus MF EBRT groups, respectively, who required strong narcotics for pain was reported by two RCTs (10% to 35.6% vs. 7.7% to 37.8%)[9,11] over 8 to 52 weeks of followup; the proportion of patients who required mild narcotic for pain was reported by three RCTs (22% to 33% vs. 11.5% vs. 39%)[9,11,39] over followups ranging from post RT (not further specified) to 52 weeks; and the proportion of patients who required any narcotics (strength not specified) was reported by three RCTs (2.8% to 67% vs. 6.8% to 68%)[41,58,61] over followups ranging from post RT (not further specified) to 12 weeks. One trial only stated that there was a reduction in the use of analgesia overall but did not provide data.[40]

Need for Additional Interventions

Two trials reported the need for additional intervention following treatment with EBRT and found no differences between SF EBRT versus the MF EBRT groups. One trial was in patients with MSCC, and reported any additional treatment (N=686; 30.1% vs. 32.3%, respectively; RR 0.93, 95% CI 0.75 to 1.67), to include chemotherapy (11.9% vs. 13.8%), hormone therapy (12.8% vs, 13.2%), radiotherapy (12.5% vs. 10.0%), surgery (2.0% vs. 1.2%), and any supportive care therapy (69.1% vs. 75%; RR 0.92, 95% CI 0.83 to 1.02), to include analgesics (48.0% vs. 51.0%), antiemetics (17.1% vs. 16.3%), corticosteroids (36.2% vs. 38.7%), physiotherapy (25% vs. 32.3%), and bisphosphonates (4.6% vs. 3.7%), through 52 weeks.[45] The second trial (N=288) was in patients with mixed spine and nonspine metastatic bone disease (MBD) and noted the following additional treatments by 4 weeks: changes in hormone therapy or chemotherapy (20% vs. 14%) and hemibody radiation therapy (RT) (1% vs. 0%).

In addition, one NRSI[102] reported that salvage surgery was more common with SF EBRT versus MF EBRT in a propensity score matched cohort (3 vs. 0 patients, p=0.04) but there was no difference between these schemes for use of interventional procedures.

Single Fraction EBRT: LDSF Versus HDSF EBRT

Overall Survival

Two trials reported similar median survivals for lower total dose single fraction (LDSF) (30 to 32 weeks) versus higher total dose single fraction (HDSF) (29 to 36 weeks).[46,48] One of these trials reported no differences in survival rates for three single doses (4 Gy, 6 Gy, 8 Gy) at 52 weeks (32% vs. 40% vs. 32%), 104 weeks (12 % vs. 17% vs. 11%) or 156 weeks (7.3% vs. 8.3% vs. 10%).[48]

Multiple Fraction EBRT: LDMF Versus HDMF

Local Control

Two trials in patients with MSCC reported higher rates of local, in-field recurrence with lower total dose multiple fraction (LDMF) versus higher total dose multiple fraction (HDMF). The difference was only significant in the larger (N=276), fair-quality trial (4% vs. 0% at 52 weeks, p=0.02);[52] rates in the poor-quality trial (N=108) were 16.1% versus 13.5%, respectively, at 104 weeks.[30] There was no difference in risk of local recurrence between MF schemes over 52 weeks of followup in a third, poor-quality trial (N=104)[18] of mixed MBD in patients with breast

cancer. A fourth, fair-quality RCT (N=183)[42] in patients with HCC (site of MBD not reported) reported that time to treatment failure was significantly shorter in the LDMF group (p=0.03), but definition of treatment failure and relevance to local control was unclear in this trial.

Overall Survival

There were no differences in overall survival across seven RCTs (2 MSCC,[52,70] 4 mixed MBD,[10,18,55,61] and 1 MBD site unclear[42]) with one exception: a small, poor-quality trial (N=58) reported significantly worse overall survival with LDMF (median 16 vs. 44 weeks with HDMF).[61] One of the trials specifically evaluated patients receiving concomitant zoledronic acid and reported survival in terms of overall survival without a skeletal-related event.[10] Across the other five RCTs, overall survival with LDMF versus HDMF, respectively, was as follows: 26 weeks (42% vs. 38%, 1 RCT of MSCC[70]; 54% vs. 63%, 1 RCT of mixed MBD in breast cancer[18]) and 52 weeks (10% vs. 18%, 1 RCT of MSCC[52]; range 28% to 39% vs. 35% to 41% across 3 RCTs in mixed/unknown site MBD).[18,42,55] Of the three latter trials, one was in patients with hepatocellular cancer[42] and the other in patients with breast cancer only.[18]

Medication Use

There was no difference in the proportion of patients treated with LDMF and HDMF who used narcotics immediately post-RT or at 4 weeks across three poor-quality RCTs in mixed site MBD (LDMF: range 11% to 25%; HDMF: range 10% to 33%).[18,58,61] In one trial, there remained no difference at later timepoints (up to 52 weeks).[18]

Need for Other Interventions

There was no difference between LDMF and HDMF in the need for subsequent surgical intervention (6% vs. 6%) or chemotherapy (22% vs. 35%) in one poor-quality trial (N=100) in mixed site MBD.[55]

Single Versus Multiple Dose-Fractionation Schemes: SBRT

Local Control

Local recurrence was reported in all five included studies (1 RCT and 4 NRSIs). The RCT found that SF-SBRT was associated with lower cumulative incidence of local recurrence compared with MF-SBRT at 1 year (0%, 95% CI not calculable, vs. 6.5%, 95% CI 1% to 12%), 2 years (2.7%, 95% CI 0% to 6.5% vs. 9.1%, 95% 2.6% to 15.6%), and 3 years (5.8%, 95% CI 0.2% to 11.5% vs. 22%, 95% CI 11.9% to 32.1%).[87] Determination of control was based on imaging evidence of lack of local recurrence or progression following initial complete response in the irradiated field and the Response Evaluation Criteria In Solid Tumors (RECIST) guideline criteria.

Fair-quality NRSIs from the same institution also found that SF-SBRT was associated with better local relapse-free survival (adjusted HR 0.28, 95% CI NR, p=0.008) in patients with MBD from renal cell carcinoma[116] and better local control in patients with high-grade sarcoma spine metastases (adjusted HR 0.35, 95% CI 0.13 to 0.90).[94] Two poor-quality studies in patients with spinal MBD reported similar findings. One NRSI in patients with MBD from renal cell carcinoma found MF-SBRT associated with worse local control (adjusted HR 5.26, 95% CI 1.14 to 24.14) compared with SF-SBRT, however the estimate is imprecise.[95] One other poor-quality

NRSI found that MF-SBRT was associated with worse local radiologic control compared with SF-SBRT in multivariate analyses but doesn't provide adjusted effect size estimates.[101]

Overall Survival

Two NRSIs found that SF-SBRT versus MF-SBRT was not a significant predictor of overall survival. The fair-quality NRSI reported higher overall survival with SF-SBRT versus MF-SBRT at 52 weeks (70.7% vs. 46.2%), 78 weeks (58.9% vs. 36.5%), and at 104 weeks (43.5% vs. 32.6%) in patients with spinal MBD due to high-grade sarcoma; however, there was no association in multivariate analyses (HR and 95% CI not reported, p=0.573).[94] The poor-quality NRSI in patients with renal cell carcinoma spinal metastases also reported that SF-SBRT was not a prognostic factor for overall survival.[95]

Multiple Versus Multiple Dose-Fractionation Schemes: SBRT

Local Control and Overall Survival

The NRSI of post-operative SBRT (N=80) in patients with spinal metastases reported that 18 to 26 Gy delivered in 1 or 2 fractions was associated with better local control (i.e., imaging-based disease progression compared with preoperative MRI) compared with 18 to 40 Gy delivered in 3 to 5 fractions (adjusted HR 0.32, 95% CI 0.12 to 0.85).[88] There was no difference between MF schemes in overall survival (proportions not reported by group).

A second NRSI in patients with spinal metastases,[96] which did not adjust for confounding (N=57), reported estimates for local control (i.e., no radiological sign of tumor progression at treated site) based on numbers of lesions and suggested less control with fewer fractions (78% vs. 93%); similarly, overall survival estimates were lower with fewer fractions (40.6% vs. 76%). Unadjusted estimates should be interpreted cautiously.

IMRT Versus 3DCRT

Local Control, Overall Survival, Medication Use, and Additional Treatments

There were no significant differences in the overall survival probability between intensity modulated radiation therapy (IMRT) and three-dimensional conformal radiation therapy (3DCRT) at 26 weeks (80.0% [standard error 7.3%] vs. 75.8% [8.0%]) or 52 weeks (72.4% [8.4%] vs. 48.5% [9.7%]; p=0.128) in one RCT.[78] Within the first 12 weeks, 33.3 percent (10/30) of patients in the IMRT group and 36.7 percent (11/30) in the 3DCRT group had died; by 26 weeks, the rates were 40.0 percent (12/30) and 60.0 percent (18/30), respectively (RD -20.0%, 95% CI -44.8% to 4.8%; RR 0.67, 95% CI 0.39 to 1.13).[81] None of the deaths in either group were considered related to radiation therapy. There was also no significant difference between IMRT and 3DCRT in medication use (i.e., oral equivalent morphine dose) through 26 weeks (data not reported) in this trial.[81]

One poor-quality NRSI found that IMRT (n=40) resulted in better local control rates versus 3DCRT (n=664, historical control group) in propensity score-matched analysis: across four of the quintiles there were no cases of local failure with IMRT compared with a range of 15 to 24 percent with 3DCRT (local failure in the remaining quintile was 25% vs. 21%, respectively).[105] Consistent with the RCT, there were no difference between groups in overall survival. A second NRSI reported no difference between IMRT versus 3DCRT (N=254) in the need for additional outpatient care for symptom management either during or up to 8 weeks post RT; however,

fewer patients treated with IMRT were admitted to a nursing home or hospice within 8 weeks (13% vs. 24%; RR 0.53, 95% CI 0.31 to 0.90).[108]

EBRT Plus HBI Versus EBRT Alone

Local Control and Overall Survival

EBRT plus hemibody irradiation (HBI) resulted in lower overall rates of disease progression (i.e., better local control) within the targeted hemibody field (18.8% vs. 26.2%, RR 0.72, 95% CI 0.51 to 1.01) over 52 weeks and delayed time-to-occurrence of disease progression compared with EBRT alone (Appendix E, Table E-1).[65] Overall survival did not differ between groups at any timepoint evaluated (11.8% vs. 12.2%, respectively, at approximately 2 years).

SBRT Versus EBRT

Local Control

Stereotactic body radiation therapy (SBRT) was associated with a large decrease in the likelihood of local failure/progression at 26 weeks compared with EBRT in one RCT (N=229) evaluating spinal metastases (2.6% vs. 10.4%, RR 0.25, 95% CI 0.07 to 0.87).[72] In a second RCT of nonspine metastases, though the difference was not statistically significant, SBRT resulted in a lower likelihood of local failure compared with EBRT in intent-to-treat (ITT) analysis (HR 0.18, 95% CI 0.02 to 1.47); however, clinical significance is unknown.[17]

In one NRSI (N=47) of spinal metastases from hepatocellular carcinoma there was no difference between SBRT and EBRT in local control rates, respectively, at 8 (91.6% vs. 87.0%), 12 (79.2% vs. 78.3%), 26 (58.3% vs. 65.2%) and 52 (25.0% vs. 30.4%) weeks.[110]

Narcotic Use

There was no difference between SBRT and conventional EBRT in medication use reported as mean daily oral morphine-equivalent dose consumption in pooled analyses across three RCTs (2 spine metastases and 1 mixed spine/nonspine sites) at longest followup time (3 RCTs, N=322, mean difference (MD) -5.48 mg, 95% CI -24.07 mg to 14.41 mg, I^2=0%)[63,72,79] or when stratified by various timepoints (post RT to 4 weeks, 12 weeks and 26 weeks) (Appendix I, Figures I-27 and I-28). The fourth RCT in patients with nonspine metastases reported a lower likelihood of an increase in narcotic use (≥50%) from baseline to 12 weeks following SBRT compared with EBRT in ITT analysis (HR 0.26, 95% CI 0.07 to 0.95; no other data provided).[17]

Additional Treatments

None of the RCTs reported additional treatments. In one NRSI (N=56) of spinal metastases from hepatocellular carcinoma, additional treatment (other than radiation) at the index site was required in three (10.7%) SBRT patients and five (17.9%) EBRT patients.[110] In the SBRT arm, two kyphoplasties were performed due to compression fracture (no tumor progression) and one vertebroplasty due to tumor progression. In the EBRT arm, one vertebroplasty was performed due compression fracture while the remaining treatments (two surgeries and two vertebroplasties) were due to tumor progression. In a second, small NRSI (N=44) in patients with spinal metastases no patient in the SBRT group compared with four patients (18.2%) in the EBRT arm underwent additional treatment at the index site by 26 weeks (2 surgeries, 2 kyphoplasties [in 1 patient], and 1 samarium injection).[97]

Overall Survival

There were no differences between SBRT and conventional EBRT in overall survival across all four RCTs.[17,63,72,79] Overall survival at 12 weeks ranged from 84 to 93 percent in the SBRT arms and 82 to 89 percent in the EBRT arms across three trials in patients with spine or mixed spine and nonspine sites.[63,72,79] Overall survival at 26 weeks ranged from 70 to 77 percent and 71 to 73 percent, respectively, across two trials in spine metastases.[72,79] In one of these trials, the median survival time was 7.9 months for both groups (p=0.659).[79] In the trial of patients with nonspine bone metastases, overall survival at 26 weeks was 40 percent after SBRT and 49 percent after EBRT and median survival time was the same for both groups (6.7 months, 95% CI 4.6 to 10.9 months); however, the authors state that after applying a QOL-adjusted survival analysis using the Q-TWiST method, SBRT was associated with significantly higher overall survival compared with the EBRT group (no data provided).[17]

Key Question 2. Effectiveness and Harms of Dose-Fractionation Schemes and Techniques for Delivery: Re-Irradiation

Single Versus Multiple Dose-Fraction Schemes: Conventional EBRT

Medication Use

At baseline, 11 percent of participants who received SF EBRT (8 Gy) and 13 percent of patients who received MF EBRT (4 Gy x 5) did not require opioids for pain management, which corresponded to 32 and 19 percent 2 months after treatment in one NRSI (N=60, RR 1.71, 95% CI 0.70 to 4.22).[109] In the same study, strong opioid use substantially decreased from 43 and 37 percent at baseline to 4 and 3 percent, respectively at 2 months (N=60, RR 1.14, 95% CI 0.075 to 17.44).

Overall Survival

One RCT reported no treatment-related deaths; after a median of 12.2 months, 53 percent of patients who received 8 Gy SF EBRT versus 52 percent of patients who received 20 Gy MF EBRT (4 Gy x 5) MF EBRT had died with median survivals of 9.3 months (95% CI 7.8 to 10.5) compared with 9.7 months (95% CI 8.5 to 10.8), HR 0.96, 95% CI 0.8 to 1.2.[37]

Single Versus Multiple Dose-Fraction Schemes: Conventional EBRT Overall Survival

In one retrospective NRSI (N=228; 348 lesions), median survival was 13 months (11 months vs. 18 months, p-value NR) with a 1-year survival of 46 percent with SF-SBRT compared with 63 percent with MF-SBRT (RR 0.72, 95% CI 0.57 to 0.92);[98] the estimate was below the threshold for a small effect.

Key Question 3a. Effectiveness and Harms of EBRT Versus Another Single Treatment Modality

EBRT Versus Radioisotopes

Medication Use

In one poor-quality RCT (N=148), the proportion of patients who reported a 50 percent or more reduction in analgesic intake with local EBRT compared with strontium at 12 weeks or prior to crossover was about 34 versus 26 percent, RR 1.31, 95% CI 0.73 to 2.35 (data from graph).[67]

Overall Survival

In one RCT (N=203), overall survival was a median of 11 months in patients treated with palliative EBRT (usual radiotherapy regimen at study center) compared with 7.2 months in patients treated with strontium (HR 1.34, 95% CI 1.01 to 1.75).[60]

EBRT Versus Cryoablation

Medication Use

There was a substantially smaller proportion of patients who no longer needed narcotic analgesics after EBRT compared with cryoablation (13.6% vs. 36%, RR 0.37, 95% CI 0.19 to 0.75), whereas all received narcotics prior to study entry in one moderate-quality NRSI (N=150).[93]

EBRT Versus Bisphosphonates

Overall Survival

There was no difference in overall survival (median of 12.2 vs. 12.9 months; HR 1.12, 95% CI 0.92 to 1.37) or pathological fracture rates (N=470, 2% vs. 3%, RR 0.71, 95% CI 0.23 to 2.22) between patients treated with EBRT versus ibandronate, respectively, in one moderate-quality RCT.[44]

EBRT Versus Androgen Deprivation Therapy

One NSRI compared EBRT with androgen deprivation therapy (ADT) in patients with oligometastatic prostate cancer (Appendix E, Table E-2); only patients with bone metastases are included here.[91] Sample size was 162, median age at primary treatment was 62 years, all were male. This NRSI did not report race/ethnicity, comorbidities, or social determinants of health. Location of metastatic lesions was not reported. Tumor classification was T2 (40%), T3a (27%), greater than or equal to T3b (33%). Median number of lesions on positive 11C-choline PET/CT scan was one in patients treated with EBRT and two in patients treated with ADT. All patients had previously received radical prostatectomy, radiotherapy, or both. In this study, patients received fractionated radiation therapy or SBRT in 1 to 5 fractions for a dose of at least 80 Gy as determined by their radiation oncologist. The dose and drug used for ADT was not reported. Median followup was 48.6 months in patients treated with EBRT and 50.7 months in patients treated with ADT (mean 50 months in all patients with bone metastases). This study was rated fair quality (Appendix F, Table F-2).

Local Recurrence and Need for Additional Treatment

There was no difference in rate of radiologic recurrence (defined as a positive positron emission tomography scan, no further details provided) after treatment with EBRT versus ADT (72.2% vs. 61.7, adjusted HR 0.76, 95% CI 0.87 to 2.15) or in the need for second-line systemic therapies (40.9% vs. 57.4%, adjusted HR 0.79, 95% CI 0.40 to 1.43) in one fair-quality NRSI.[91] It was unclear which variables were controlled for in the multivariate analysis.

Overall Survival

There was no difference in the incidence of cancer-specific death between groups in the same NRSI: there were 19 deaths in patients followed for a median of 48.6 months after EBRT compared with nine deaths in patients followed for a median of 50.7 months after ADT (16.5% vs. 14.9%, RR 1.11, 95% CI 0.50 to 2.46).[91] The 5-years cancer-specific mortality-free survival rates were 83.7% and 80.8% for EBRT and ADT patients, respectively (HR 1.1, 95% CI 0.4 to 2.4).

Key Question 3b. Effectiveness and Harms of EBRT Combined With Another Treatment Modality Versus EBRT alone

EBRT Plus Surgery Versus EBRT Alone

Local Control

One NRSI (N=201)[106] showed no difference in local control rates at 26 weeks (93% for surgery plus EBRT vs. 93% for EBRT alone, RR 0.99, 95% CI 0.91 to 1.08) or 52 weeks (85% vs. 89%, RR 0.96, 95% CI 0.85 to 1.08).

Medication Use

Adding surgery to EBRT was associated with less use of corticosteroids (daily dexamethasone equivalent 1.6 vs. 4.2 mg, p=0.0093) and opioids (daily morphine equivalent 0.4 vs. 4.8 mg, p=0.002) than EBRT alone in one RCT (N=101).[62]

Overall Survival

Results for overall survival were mixed. Two NRSIs (N=488)[104,106] showed no difference in 26-week survival between patients treated with surgery and EBRT and those given EBRT alone (59% vs. 52%, pooled RR 1.06, 95% CI 0.87 to 1.29, $I^2 = 0\%$). One of these studies (N=287)[104] also showed no difference in survival at latest followup (mean 27 weeks, 25% vs. 21%, RR 1.18, 95% CI 0.74 to 188); however, the other study (N=201)[106] suggested a moderate 52-week survival benefit associated with surgery, though statistical significance was borderline (38% vs. 24%, RR 1.56, 95% CI 1.01 to 2.41). A third, smaller NRSI (N=46)[117] suggested an improvement in overall survival time associated with surgery, but the difference was not statistically significant (45.9 vs. 36.8 weeks, p=0.24).

SBRT Plus Surgery Versus SBRT Alone

Local Control

One poor-quality NRSI of SBRT and surgery (N=57 patients, 69 lesions) reported no difference in local recurrence rates between patients undergoing surgery and those treated with SBRT alone (14% vs. 6.3%, RR 2.29, 95% CI 0.50 to 10.41).[90]

EBRT Plus Dexamethasone Versus EBRT

Medication Use and Overall Survival

There was no difference in the use of pain medication within 1.4 weeks of radiation therapy between patients treated with dexamethasone and EBRT (228 mg median cumulative oral morphine equivalence) compared with those given EBRT alone (224 mg) in one good-quality RCT (N=298).[36] Mortality rates were also similar between treatment arms in this trial (7% vs. 10%, RR 0.74, 95% CI 0.35 to 1.56). Median survival was 26 weeks with or without dexamethasone in the smaller, poor-quality trial (N=57).[76]

EBRT Plus Bisphosphonates Versus EBRT

Local Control

In one poor-quality NRSI (N=72)[115] few patients had local progression within 6 weeks; rates did not differ with and without zoledronate, and the estimate of effect was imprecise (6.5% vs. 9.4%, RR 0.69, 95% CI 0.12 to 3.84).

Need for Additional Treatment

Across both NRSIs (N=134),[100,115] few patients required surgery after radiation therapy, and there was no difference in rates between patients given zoledronate with EBRT compared to EBRT alone (3.0% vs. 3.4%, pooled RR 0.99, 95% CI 0.05 to 11.50, $I^2 = 6.2\%$).

Overall Survival

In one poor-quality RCT (N=40),[86] there was a large survival benefit: 36 percent of those given zoledronate and EBRT survived for one year, compared with 0 percent of patients given EBRT plus placebo (p=0.004). One poor-quality NRSI (N=62)[100] found a potential survival benefit associated with zoledronate: 2-year overall survival was 54 percent with zoledronate and EBRT compared to 33 percent with EBRT alone (RR 1.63, 95% CI 0.88 to 3.01), though the difference was not statistically significant.

EBRT Plus Radioisotopes Versus EBRT Alone

Local Control

Recurrence of bone metastases and need for re-irradiation was reported in one trial (Appendix E, Table E-1).[64] Patients treated with EBRT plus strontium-89 had a moderate reduction in risk of new painful lesions compared with those treated with EBRT plus placebo at 12-week followup (42% vs. 68%; RR 0.63, 95% CI 0.45 to 0.88; ARD -0.25, 95% CI -0.42 to -0.08). Similarly, the proportion of patients in the EBRT plus strontium-89 group were less likely to require re-irradiation compared to the control group; risk estimates consistently favored the

combined group from 26 to 74 weeks, and absolute risk difference between groups ranged from 0.19 to 0.40 percent.

Overall Survival

Overall survival was reported in all three RCTs;[56,57,64,75] reporting methods varied, and data could not be pooled (Appendix E, Table E-1). In one trial, patients treated with EBRT plus radium-223 were more likely to survive versus those treated with EBRT alone at timepoints ranging from 20 weeks to 2 years.[56,57] The difference between treatment and control groups increased over time, but never reached statistical significance, potentially due to small sample sizes in each group. For example, at 20 weeks the proportion of surviving patients was 94 percent in the treatment group and 87 percent in the control group (RR 1.08, 95% CI 0.92 to 1.27). At 1 year, 58 percent of the treatment group and 45 percent of the control group were still living (RR 1.27, 95% CI 0.78 to 2.07), while at 2 years, corresponding overall survival rates were 30 percent and 13 percent (RR 2.35, 95% CI 0.82 to 6.72). In this trial, the median overall survival was 65.3 weeks in the treatment group and 46.4 weeks in the control group (adjusted HR 2.12, 95% CI 1.13 to 3.98). There was no difference between treatment and control groups in overall survival in the other two trials.[64,75]

EBRT Plus Cryoablation Versus EBRT Alone

Medication Use

EBRT plus cryotherapy was associated with a reduction in need for pain medication at 12 weeks versus EBRT alone (24% vs. 86%; RR 0.28, 95% CI 0.14 to 0.56) in one fair-quality NRSI.[93] Among those patients in both groups that required additional medication for pain control, the median morphine equivalent dose was lower in the EBRT plus cryotherapy group (20 mg, 95% CI 2.2 to 50) than in the EBRT alone group (70 mg, 95% CI 60 to 80), p=0.004.

EBRT Plus Capecitabine Versus EBRT Alone

Medication Use

One fair-quality RCT assessed analgesic use using the WHO scale; scoring is from 0 to 5 and higher scores represent more pain medication needed. At all timepoints up to 12 weeks, there was a one-point difference between EBRT plus capecitabine and EBRT alone in WHO score (Appendix E, Table E-1).[31] Although these differences were generally statistically significant, their clinical significance is unclear.

Key Question 3c. Effectiveness and Harms of EBRT Combined With Another Treatment Modality Versus the Same Treatment Modality Alone

EBRT Plus Cryoablation Versus Cryoablation Alone

Medication Use

EBRT plus cryoablation was associated with a reduction in need for pain medication at 12 weeks versus cryoablation alone (N=50, 24% vs. 64%; RR 0.38, 95% CI 0.18 to 0.80) in one

fair-quality NRSI.[93] Among those patients in both groups that required additional medication for pain control, the median morphine equivalent dose, though lower in the EBRT plus cryotherapy group (20 mg, 95% CI 2.2 to 50), was not statistically different compared with the cryoablation group (50 mg, 95% CI 2.9 to 60), p=0.71.

EBRT Plus Strontium-89 Versus Strontium-89 Alone

Local Control

According to the authors of one poor-quality NRSI, combined EBRT and strontium-89 was associated with better local control (bone metastasis lesions reduced "obviously or partly") at 12 to 26 weeks post treatment ($p<0.05$); however, the difference between groups did not reach statistical significance according to our calculations: 86.8 percent (46/53) vs. 75.5 percent (40/53), RR 1.15, 95% CI 0.95 to 1.39.[114]

EBRT Plus Surgery Versus Surgery Alone

Need for Additional Treatment and Overall Survival

Fewer patients in the EBRT plus surgery group required secondary procedures to the index site compared with surgery alone (2.9% [1/34] vs. 15.4% [4/26], p=0.035) in one fair-quality NRSI.[93] Revision surgeries were performed primarily due to pain associated with radiographic loosening of the prosthesis.

The median overall survival was significantly longer after combined EBRT plus surgery, 12.4 months (mean 19 months; range, 1 week to 48.6 months), versus surgery alone, 3.3 months (mean 12 months; range, 3 days to 43.5 months) (p=0.02, Kaplan Meier analysis) in the same NRSI; the difference remained significant on multivariate analysis (p=0.025).[93]

Differential Effectiveness and Safety

Key Question 1: Fractionation Schemes

Table B-18. Subgroup analyses for KQ 1, SF EBRT vs. MF EBRT: Age

Comparison	Age Category	Outcome	Time Point	Findings SF Vs. MF	Percentage (Events/Patients) SF Vs. MF	Study Design SF Vs. MF Dose/Scheme
SF EBRT vs. MF EBRT	Age <65 years	Ambulatory response rate[a]	8 weeks	RD 0.3% (99% CI -23.5% to 24.0%)	NR (n=102)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Age 65-75 years	Ambulatory response rate[a]	8 weeks	RD 6.6% (99% CI -14.4% to 27.5%)	NR (n=128)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Age >75 years	Ambulatory response rate[a]	8 weeks	RD -18.7% (99% CI -39.5% to 2.0%)	NR (n=112)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Age <65 years	Overall survival	12 weeks	HR 0.9 (99% CI 0.59 to 1.38)	51% (46/91) vs. 51% (58/113) Median,13 vs. 12 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Age 65-75 years	Overall survival	12 weeks	HR 1.08 (99% CI 0.75 to 1.56)	47% (70/148) vs. 56% (61/109) Median,11 vs. 14 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)

Comparison	Age Category	Outcome	Time Point	Findings SF Vs. MF	Percentage (Events/Patients) SF Vs. MF	Study Design SF Vs. MF Dose/Scheme
	Age >75 years	Overall survival	12 weeks	HR 1.08 (99% CI 0.73 to 1.61)	54% (57/106) vs. 56% (67/119) Median,15 vs. 17 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)

CI = confidence interval; EBRT = external beam radiation therapy; HR = hazard ratio; KQ = Key Question; MF = multiple fraction; NR = not reported; RCT = randomized controlled trial; RD = risk difference; SF = single fraction.
[a] Positive ambulatory response rate: ambulatory status grade 1 or 2 at 8 weeks (which could be a result of an improvement from a grade 3 or 4 or maintenance of grade 1 or 2 from baseline) using a window of 49 to 62 days.

Table B-19. Subgroup analyses for KQ 1, SF EBRT vs. MF EBRT: Sex

Comparison	Sex Category	Outcome	Time Point	Findings SF Vs. MF	Percentage (Events/Patients) SF Vs. MF	Study Design SF Vs. MF Dose/Scheme
SF EBRT vs. MF EBRT	Male	Ambulatory response rate[a]	8 weeks	RD -2.0% (99% CI -16.5% to 12.5%)	NR (n=248)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Female	Ambulatory response rate[a]	8 weeks	RD -8.8% (99% CI -34.3% to 16.6%)	NR (n=94)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Male	Overall survival	12 weeks	HR 1.02 (99% CI 0.78 to 1.32)	53% (135/255) vs. 52% (129/248) Median, 14 vs. 13 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Female	Overall survival	12 weeks	HR 1.08 (99% CI 0.69 to 1.68)	43% (39/90) vs. 61% (57/93) Median, 11 vs. 17 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)

CI = confidence interval; EBRT = external beam radiation therapy; HR = hazard ratio; KQ = Key Question; MF = multiple fraction; NR = not reported; RCT = randomized controlled trial; RD = risk difference; SF = single fraction.
[a] Positive ambulatory response rate: ambulatory status grade 1 or 2 at 8 weeks (which could be a result of an improvement from a grade 3 or 4 or maintenance of grade 1 or 2 from baseline) using a window of 49 to 62 days

Table B-20. Subgroup analyses for KQ 1, SF EBRT vs. MF EBRT: Sex and partner status

Comparison	Subgroup Category	Outcome	Time Point	Findings SF Vs. MF	Percentage (Events/Patients) SF Vs. MF	Study Design SF Vs. MF Dose/Scheme
SF EBRT vs. MF EBRT	Females with partner	Reirradiation	144 weeks	RR 2.43 (95% CI 1.06 to 5.59)	16% (18/112) vs. 7% (7/106)	1 RCT [50] 8 Gy vs. 30 Gy (3 Gy x 10)
	Females without partner	Reirradiation	144 weeks	RR 14.85 (95% CI 2.00 to 110.26)	15% (15/99) vs. 1% (1/98)	1 RCT [50] 8 Gy vs. 30 Gy (3 Gy x 10)
	Males with partner	Reirradiation	144 weeks	RR 2.23 (95% CI 1.18 to 4.21)	18% (28/154) vs. 8% (12/147)	1 RCT [50] 8 Gy vs. 30 Gy (3 Gy x 10)
	Males without partner	Reirradiation	144 weeks	RR 0.68 (95% CI 0.17 to 2.70)	6% (3/54) vs. 9% (5/61)	1 RCT [50] 8 Gy vs. 30 Gy (3 Gy x 10)

CI = confidence interval; EBRT = external beam radiation therapy; KQ = Key Question; MF = multiple fraction; RCT = randomized controlled trial; RR = risk ratio; SF = single fraction.

Table B-21. Subgroup analyses for KQ 1, SF EBRT vs. MF EBRT: Primary tumor type

Comparison	Primary Tumor Type	Outcome	Time Point	Findings SF Vs. MF	Percentage (Events/Patients) SF Vs. MF	Study Design SF Vs. MF Dose/Scheme
SF EBRT vs. MF EBRT	Breast	Overall pain response	8 weeks	RR 0.92 (95% CI 0.78 to 1.09)	88% (22/25) vs. 96% (23/24)	1 RCT[11] 8 Gy vs. 40 Gy (2 Gy x 20)
	Lung	Overall pain response	8 weeks	RR 0.94 (95% CI 0.48 to 1.85)	60% (6/10) vs. 64% (7/11)	1 RCT[11] 8 Gy vs. 40 Gy (2 Gy x 20)
	Prostate	Overall pain response	8 weeks	RR 1.00 (95% CI NC)	100% (8/8) vs. 100% (10/10)	1 RCT[11] 8 Gy vs. 40 Gy (2 Gy x 20)
	Other	Overall pain response	8 weeks	RR 1.0 (95% CI 0.65 to 1.53)	86% (6/7) vs. 86% (6/7)	1 RCT[11] 8 Gy vs. 40 Gy (2 Gy x 20)
	Breast	Overall pain response	12 weeks	RR 1.04 (95% CI 0.93 to 1.15)	78% (169/218) vs. 75% (152/203)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Lung	Overall pain response	12 weeks	RR 1.08 (95% CI 0.89 to 1.32)	62% (83/133) vs. 58% (72/125)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Prostate	Overall pain response	12 weeks	RR 1.01 (95% CI 0.89 to 1.16)	78% (95/121) vs. 77% (96/124)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Other	Overall pain response	12 weeks	RR 1.07 (95% CI 0.82 to 1.38)	64% (45/70) vs. 60% (41/68)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Favorable group[a]	Overall pain response	12 weeks	RR 0.98 (95% CI 0.78 to 1.22)	77% (34/44) vs. 79% (34/43)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Breast	Overall pain response	12 weeks	HR 0.9 (95% CI 0.7 to 1.2) for MF vs. SF	90% (92/102) vs. 89% (84/94) [planned subgroup from Steenland 1999 above, patients with observed favorable prognosis, i.e., surviving >12 mos.]	1 RCT[85] 8 Gy vs. 24 Gy (4 Gy x 6)
	Lung	Overall pain response	12 weeks	HR 0.6 (95% CI 0.2 to 2.1) for MF vs. SF	77% (13/17) vs. 43% (3/7) [planned subgroup from Steenland 1999 above, patients with observed favorable prognosis, i.e., surviving >12 mos.]	1 RCT[85] 8 Gy vs. 24 Gy (4 Gy x 6)

Comparison	Primary Tumor Type	Outcome	Time Point	Findings SF Vs. MF	Percentage (Events/Patients) SF Vs. MF	Study Design SF Vs. MF Dose/Scheme
	Prostate	Overall pain response	12 weeks	HR 1.5 (95% CI to 2.5) for MF vs. SF	85% (29/34) vs. 90% (36/40) [planned subgroup from Steenland 1999 above, patients with observed favorable prognosis, i.e., surviving >12 mos.]	1 RCT[85] 8 Gy vs. 24 Gy (4 Gy x 6)
	Other	Overall pain response	12 weeks	HR 0.7 (95% CI 0.2 to 2.7) for MF vs. SF	71% (5/7) vs. 50% (4/8) [planned subgroup from Steenland 1999 above, patients with observed favorable prognosis, i.e., surviving >12 mos.]	1 RCT[85] 8 Gy vs. 24 Gy (4 Gy x 6)
	Breast	Complete pain response	12 weeks	RR 1.25 (95% CI 1.01 to 1.56)	49% (108/219) vs. 39% (81/206)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Lung	Complete pain response	12 weeks	RR 1.47 (95% CI 0.94 to 2.31)	28% (37/133) vs. 19% (24/127)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Prostate	Complete pain response	12 weeks	RR 0.86 (95% CI 0.63 to 1.16)	38% (46/122) vs. 44% (55/125)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Other	Complete pain response	12 weeks	RR 0.53 (95% CI 0.24 to 1.16)	11% (8/71) vs. 21% (15/70)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Favorable group[a]	Complete pain response	12 weeks	RR 0.94 (95% CI 0.63 to 1.40)	50% (22/44) vs. 53% (24/45)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Breast	Ambulatory response rate[b]	8 weeks	RD 11.0% (99% CI -21.0% to 42.9%)	NR (n=46)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Lung	MeAmbulatory response rate[b]	8 weeks	RD -17.3% (99% CI -58.7% to 24.0%)	NR (n=40)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Prostate	Ambulatory response rate[b]	8 weeks	RD 3.3% (99% CI -12.6% to 19.2%)	NR (n=182)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	GI	Ambulatory response rate[b]	8 weeks	RD -10.0% (99% CI -57.4% to 37.4%)	NR (n=29)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Other	Ambulatory response rate[b]	8 weeks	RD -35.1% (99% CI -69.4% to -0.9%)	NR (n=45)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Breast	Overall survival	12 weeks	HR 0.84 (99% CI 0.41 to 1.75)	72% (28/39) vs. 69% (28/40) Median, 24 vs. 22 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)

Comparison	Primary Tumor Type	Outcome	Time Point	Findings SF Vs. MF	Percentage (Events/Patients) SF Vs. MF	Study Design SF Vs. MF Dose/Scheme
	Lung	Overall survival	12 weeks	**HR 1.64 (99% CI 1.00 to 2.68)**	15% (10/66) vs. 45% (30/66) Median, 5 vs. 8 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Prostate	Overall survival	12 weeks	HR 0.96 (99% CI 0.67 to 1.36)	69% (105/152) vs. 63% (96/152) Median, 31 vs. 22 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	GI	Overall survival	12 weeks	HR 1.1 (99% CI 0.57 to 2.09)	29% (10/35) vs. 32% (12/38) Median, 7 vs. 7 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Other	Overall survival	12 weeks	HR 1.01 (99% CI 0.57 to 1.79)	38% (20/53) vs. 47% (21/45) Median, 10 vs. 10 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Breast	Re-irradiation	NR[c]	RR 2.07 (95% CI 0.52 to 8.20)	22% (4/18) vs. 11% (3/28)	1 RCT[73] 8 Gy vs. 30 Gy (3 Gy x 10)
	Lung	Re-irradiation	NR[c]	RR 2.92 (95% CI 0.69 to 12.40)	42% (5/12) vs. 15% (2/14)	1 RCT[73] 8 Gy vs. 30 Gy (3 Gy x 10)
	Prostate	Re-irradiation	NR[c]	RR 2.89 (95% CI 0.88 to 9.50)	33% (9/27) vs. 12% (3/26)	1 RCT[73] 8 Gy vs. 30 Gy (3 Gy x 10)
	Breast	Re-irradiation	12 weeks	RR 3.98 (95% CI 2.18 to 7.25)	22% (51/233) vs. 6% (12/218)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Lung	Re-irradiation	12 weeks	RR 6.75 (95% CI 3.15 to 14.46)	32% (45/140) vs. 5% (7/147)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Prostate	Re-irradiation	12 weeks	RR 2.07 (95% CI 1.16 to 3.68)	22% (29/129) vs. 11% (15/138)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Other	Re-irradiation	12 weeks	RR 3.06 (95% CI 1.39 to 6.74)	29% (22/77) vs. 9% (7/75)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Breast	Pathological fracture	NR	RR 0.52 (95% CI 0.06 to 4.61)	6% (1/18) vs. 11% (3/28)	1 RCT[73] 8 Gy vs. 30 Gy (3 Gy x 10)
	Lung	Pathological fracture	NR	RR 1.17 (95% CI 0.08 to 16.72)	8% (1/12) vs. 7% (1/14)	1 RCT[73] 8 Gy vs. 30 Gy (3 Gy x 10)
	Prostate	Pathological fracture	NR	RR NC; p=0.326	4% (1/27) vs. 0% (0/26)	1 RCT[73] 8 Gy vs. 30 Gy (3 Gy x 10)
	Breast	Pathological fracture	12 weeks	RR 4.21 (95% CI 0.92 to 19.27)	4% (9/233) vs. 1% (2/218)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Lung	Pathological fracture	12 weeks	RR 1.75 (95% CI 0.43 to 7.19)	4% (5/140) vs. 2% (3/147)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Prostate	Pathological fracture	12 weeks	RR 2.50 (95% CI 0.66 to 2.31)	5% (7/129) vs. 2% (3/138)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Other	Pathological fracture	12 weeks	RR 1.46 (95% CI 0.25 to 8.50)	4% (3/77) vs. 3% (2/75)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)

Comparison	Primary Tumor Type	Outcome	Time Point	Findings SF Vs. MF	Percentage (Events/Patients) SF Vs. MF	Study Design SF Vs. MF Dose/Scheme
	Breast	SCC	NR	NA	0% (0/18) vs. 0% (0/28)	1 RCT[73] 8 Gy vs. 30 Gy (3 Gy x 10)
	Lung	SCC	NR	RR NC; p=0.355	0% (0/12) vs. 7% (1/14)	1 RCT[73] 8 Gy vs. 30 Gy (3 Gy x 10)
	Prostate	SCC	NR	RR 0.32 (95% CI 0.04 to 2.89)	4% (1/27) vs. 12% (3/26)	1 RCT[73] 8 Gy vs. 30 Gy (3 Gy x 10)

CI = confidence interval; EBRT = external beam radiation therapy; GI = gastrointestinal; HR = hazard ratio; KQ = Key Question; MF = multiple fraction; NA = not applicable; NC = not calculable; NR = not reported; RCT = randomized controlled trial; RD = risk difference; RR = risk ratio; SF = single fraction.

[a] Patients with favorable prognosis, that is patients with breast cancer with no visceral metastases in a long term complete remission (more than 1 year) due to first line systemic treatment and patients with a diagnosis of prostate cancer, a Karnofsky index of 60% or more, who had not been treated by hormonal treatment yet.

[b] Positive ambulatory response rate: ambulatory status grade 1 or 2 at 8 weeks (which could be a result of an improvement from a grade 3 or 4 or maintenance of grade 1 or 2 from baseline) using a window of 49 to 62 days.

[c] Most re-irradiations occurred within the first 9 months

Table B-22. Subgroup analyses for KQ 1, SF EBRT vs. MF EBRT: Metastases site

Comparison	Site of Metastases	Outcome	Time Point	Findings SF Vs. MF	Percentage (Events/Patients) SF Vs. MF	Study Design SF Vs. MF Dose/Scheme
SF EBRT vs. MF EBRT	Spine	Overall pain response	8 weeks	RR 0.99 (95% CI 0.82 to 1.21)	90% (19/21) vs. 91% (20/22)	1 RCT[11] 8 Gy vs. 40 Gy (2 Gy x 20)
	Pelvis	Overall pain response	8 weeks	RR 1.0 (95% CI 0.83 to 1.21)	93% (14/15) vs. 93% (14/15)	1 RCT[11] 8 Gy vs. 40 Gy (2 Gy x 20)
	Limbs	Overall pain response	8 weeks	RR 0.93 (95% CI 0.55to 1.57)	70% (7/10) vs. 75% (9/12)	1 RCT[11] 8 Gy vs. 40 Gy (2 Gy x2 0)
	Other	Overall pain response	8 weeks	RR 0.50 (95% CI 0.19 to 1.33)	50% (2/4) vs. 100% (3/3)	1 RCT[11] 8 Gy vs. 40 Gy (2 Gy x 20)
	Weight-bearing	Overall pain response	12 weeks	RR 0.93 (95% CI 0.79 to 1.09)	63% (102/161) vs. 68% (108/158)	1 RCT[41] 8 Gy vs. 30 Gy (3 Gy x 10)
	Nonweight-bearing	Overall pain response	12 weeks	RR 1.05 (95% CI 0.88 to 1.26)	66% (84/127) vs. 63% (80/127)	1 RCT[41] 8 Gy vs. 30 Gy (3 Gy x 10)
	Cervical spine	Overall pain response	12 weeks	RR 3.0 (95% CI 0.48 to 18.6)	60% (6/10) vs. 20% (1/5) [subgroup from Hartsell 2005 above, patients with spine metastases only]	1 RCT[47] 8 Gy vs. 30 Gy (3 Gy x 10)
	Thoracic spine	Overall pain response	12 weeks	RR 1.07 (95% CI 0.77 to 1.48)	77% (20/26) vs. 72% (18/25) [subgroup from Hartsell 2005 above, patients with spine metastases only]	1 RCT[47] 8 Gy vs. 30 Gy (3 Gy x 10)

Comparison	Site of Metastases	Outcome	Time Point	Findings SF Vs. MF	Percentage (Events/Patients) SF Vs. MF	Study Design SF Vs. MF Dose/Scheme
	Lumbar spine	Overall pain response	12 weeks	RR 1.12 (95% CI 0.81 to 1.53)	68% (26/38) vs. 61% (27/44) subgroup from Hartsell 2005 above, patients with spine metastases only]	1 RCT[47] 8 Gy vs. 30 Gy (3 Gy x 10)
	Multiple spine sites	Overall pain response	12 weeks	RR 1.33 (95% CI 0.27 to 6.61)	67% (2/3) vs. 50% (1/2) [subgroup from Hartsell 2005 above, patients with spine metastases only]	1 RCT[47] 8 Gy vs. 30 Gy (3 Gy x 10)
	Cervical MSCC – Yes	Ambulatory response rate[a]	8 weeks	RD -14.3% (99% CI -48.3% to 19.8%)[b]	NR (n=18)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Cervical MSCC – No	Ambulatory response rate[a]	8 weeks	RD -2.0% (99% CI -15.2% to 11.2%)[b]	NR (n=322)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Thoracic MSCC – Yes	Ambulatory response rate[a]	8 weeks	RD -0.9% (99% CI -16.6% to 14.9%)[b]	NR (n=240)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Thoracic MSCC – No	Ambulatory response rate[a]	8 weeks	RD -10.6% (99% CI -30.0% to 8.9%)[b]	NR (n=100)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Lumbar MSCC – Yes	Ambulatory response rate[a]	8 weeks	RD -8.3% (99% CI -30.4% to 13.8%)[b]	NR (n=98)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Lumbar MSCC – No	Ambulatory response rate[a]	8 weeks	RD -1.6% (99% CI -17.0% to 13.7%)[b]	NR (n=242)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Sacrum MSCC – Yes	Ambulatory response rate[a]	8 weeks	RD -16.7% (99% CI -55.9% to 22.5%)[b]	NR (n=13)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Sacrum MSCC – No	Ambulatory response rate[a]	8 weeks	RD -2.5% (99% CI -15.6% to 10.6%)[b]	NR (n=327)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	MSCC, Spinal cord only (C1-T12)	Ambulatory response rate[a]	8 weeks	RR 0.98 (95% CI 0.82 to 1.17); RD -1.3% (90% CI -11.4% to 8.9%)[a]	67.6% (73/108) vs. 68.9% (84/122)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	MSCC, Cauda equina only (L1-S2)	Ambulatory response rate[a]	8 weeks	RR 0.89 (95% CI 0.74 to 1.08); RD -9.2% (95% CI -22.4% to 4.0%)[b]	78.3% (36/46) vs. 87.5% (35/40)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	MSCC, both spinal cord and cauda equina (T6-L5)	Ambulatory response rate[a]	8 weeks	RR 0.75 (95% CI 0.35 to 1.62); RD -16.7% (90% CI -53.3% to 20.0%)[b]	50.0% (5/10) vs. 66.7% (6/9)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	MSCC, Spinal cord only (C1-T12)	Abnormal bladder function	8 weeks	OR 1.29 (95% CI 0.70 to 2.37)[b]	30% (29/97) vs. 25% (29/117)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	MSCC, Cauda equina only (L1-S2)	Abnormal bladder function	8 weeks	OR 4.53 (95% CI 1.35 to 15.14)[b]	34% (15/44) vs. 10% (4/39)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)

Comparison	Site of Metastases	Outcome	Time Point	Findings SF Vs. MF	Percentage (Events/Patients) SF Vs. MF	Study Design SF Vs. MF Dose/Scheme
	MSCC, both spinal cord and cauda equina (T6-L5)	Abnormal bladder function	8 weeks	OR 3.00 (95% CI 0.25 to 36.32)[b]	30% (3/10) vs. 13% (1/8)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	MSCC, Spinal cord only (C1-T12)	Abnormal bladder function	Any time	OR 1.29 (95% CI 0.88 to 1.88)[b]	42% (92/219) vs. 36% (85/236)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	MSCC, Cauda equina only (L1-S2)	Abnormal bladder function	Any time	OR 1.69 (95% CI 0.86 to 3.32)[b]	42% (34/81) vs. 30% (21/70)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	MSCC, both spinal cord and cauda equina (T6-L5)	Abnormal bladder function	Any time	OR 1.08 (95% CI 0.24 to 4.79)[b]	38% (6/16) vs. 36% (5/14)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	MSCC, Spinal cord only (C1-T12)	Abnormal bowel function	8 weeks	OR 1.13 (95% CI 0.65 to 1.95)[b]	42% (41/97) vs. 39% (46/117)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	MSCC, Cauda equina only (L1-S2)	Abnormal bowel function	8 weeks	OR 1.19 (95% CI 0.46 to 3.05)[b]	32% (14/44) vs. 28% (11/39)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	MSCC, both spinal cord and cauda equina (T6-L5)	Abnormal bowel function	8 weeks	OR 1.11 (95% CI 0.16 to 7.51)[b]	40% (4/10) vs. 38% (3/8)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	MSCC, Spinal cord only (C1-T12)	Abnormal bowel function	Any time	OR 1.12 (95% CI 0.76 to 1.64)[b]	65% (145/219) vs. 63% (148/236)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	MSCC, Cauda equina only (L1-S2)	Abnormal bowel function	Any time	OR 0.86 (95% CI 0.44 to 1.69)[a]	64% (51/80) vs. 67% (47/70)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	MSCC, both spinal cord and cauda equina (T6-L5)	Abnormal bowel function	Any time	OR 1.29 (95% CI 0.30 to 5.43)[b]	56% (9/16) vs. 50% (7/14)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Upper limbs	Reirradiation	NR	RR 2.75 (95% CI 0.30 to 25.35)	25% (2/8) vs. 9% (1/11)	1 RCT[73] 8 Gy vs. 30 Gy (3 Gy x 10)
	Lower limbs	Re-irradiation	NR	RR 1.64 (95% CI 0.33 to 8.03)	27% (3/11) vs. 17% (2/12)	1 RCT[73] 8 Gy vs. 30 Gy (3 Gy x 10)
	Column	Re-irradiation	NR	RR 3.43 (95% CI 1.03 to 11.42)	29% (10/35) vs. 8% (3/36)	1 RCT[73] 8 Gy vs. 30 Gy (3 Gy x 10)
	Thorax	Re-irradiation	NR	RR 2.00 (95% CI 0.15 to 26.74)	17% (1/6) vs. 8%(1/12)	1 RCT[73] 8 Gy vs. 30 Gy (3 Gy x 10)
	Pelvis	Re-irradiation	NR	RR 3.21 (95% CI 0.74 to 13.33)	29% (7/24) vs. 9% (2/22)	1 RCT[73] 8 Gy vs. 30 Gy (3 Gy x 10)

Comparison	Site of Metastases	Outcome	Time Point	Findings SF Vs. MF	Percentage (Events/Patients) SF Vs. MF	Study Design SF Vs. MF Dose/Scheme
	Thoracic/lumbar spine	Re-irradiation	12 weeks	RR 4.75 (95% CI 2.15 to 10.49)	18% (31/165) vs. 4% (7/177)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Pelvis	Re-irradiation	12 weeks	RR 2.98 (95% CI 1.85 to 4.81)	27% (53/199) vs. 9% (20/224)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Femur	Re-irradiation	12 weeks	RR 3.05 (95% CI 1.15 to 8.06)	25% (12/48) vs. 8% (5/61)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Ribs	Re-irradiation	12 weeks	RR 1.99 (95% CI 0.76 to 5.22)	23% (12/53) vs. 11% (5/44)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Humerus	Re-irradiation	12 weeks	RR 2.91 (95% CI 0.90 to 9.40)	32% (11/34) vs. 11% (3/27)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Other (not defined)	Re-irradiation	12 weeks	RR 15.95 (95% CI 2.24 to 113.32)	35% (28/79) vs. 2% (1/45)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Upper limbs	Pathological fracture	NR	RR NC, p=0.394	0% (0/8) vs. 9% (1/11)	1 RCT[73] 8 Gy vs. 30 Gy (3 Gy x 10)
	Lower limbs	Pathological fracture	NR	RR NC, p=0.166	0% (0/11) vs. 17% (2/12)	1 RCT[73] 8 Gy vs. 30 Gy (3 Gy x 10)
	Column	Pathological fracture	NR	RR NC, p=0.311	3% (1/35) vs. 0% (0/36)	1 RCT[73] 8 Gy vs. 30 Gy (3 Gy x 10)
	Thorax	Pathological fracture	NR	NA	0% (0/6) vs. 0% (0/12)	1 RCT[73] 8 Gy vs. 30 Gy (3 Gy x 10)
	Pelvis	Pathological fracture	NR	RR 1.38 (95% CI 0.25 to 7.48)	13% (3/24) vs. 9% (2/22)	1 RCT[73] 8 Gy vs. 30 Gy (3 Gy x 10)
	Thoracic/lumbar spine	Pathological fracture	12 weeks	RR 4.29 (95% CI 0.48 to 37.99)	2% (4/165) vs. 1% (1/177)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Pelvis	Pathological fracture	12 weeks	RR 1.69 (95% CI 0.48 to 5.90)	3% (6/199) vs. 2% (4/224)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Femur	Pathological fracture	12 weeks	RR 2.54 (95% CI 0.81 to 7.94)	17% (8/48) vs. 7% (4/61)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Ribs	Pathological fracture	12 weeks	NA	0% (0/53) vs. 0% (0/44)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Humerus	Pathological fracture	12 weeks	NC, p=0.373	3% (1/34) vs. 0% (0/27)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Other (not defined)	Pathological fracture	12 weeks	RR 2.85 (95% CI 0.34 to 23.62)	6% (5/79) vs. 2% (1/45)	1 RCT[14] 8 Gy vs. 24 Gy (4 Gy x 6)
	Cervical MSCC – Yes	Overall survival	12 weeks	HR 1.83 (99% CI 0.57 to 5.82) for MF vs. SF	42% (5/12) vs. 66% (12/18) Median, 9 vs. 28 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)

Comparison	Site of Metastases	Outcome	Time Point	Findings SF Vs. MF	Percentage (Events/Patients) SF Vs. MF	Study Design SF Vs. MF Dose/Scheme
	Cervical MSCC – No	Overall survival	12 weeks	HR 0.99 (99% CI 0.79 to 1.25) for MF vs. SF	50% (167/333) vs. 54% (173/321) Median, 13 vs. 13 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Thoracic MSCC – Yes	Overall survival	12 weeks	HR 1.05 (99% CI 0.81 to 1.35) for MF vs. SF	49% (124/254) vs. 52% (132/254) Median, 12 vs. 13 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Thoracic MSCC – No	Overall survival	12 weeks	HR 0.98 (99% CI 0.62 to 1.56) for MF vs. SF	53% (48/91) vs. 63% (54/85) Median, 14 vs. 17 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Lumbar MSCC – Yes	Overall survival	12 weeks	HR 0.92 (99% CI 0.59 to 1.44) for MF vs. SF	55% (51/92) vs. 55% (47/85) Median, 14 vs. 15 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Lumbar MSCC – No	Overall survival	12 weeks	HR 1.07 (99% CI 0.83 to 1.39) for MF vs. SF	48% (121/253) vs. 54% (137/254) Median, 11 vs. 13 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Sacrum MSCC – Yes	Overall survival	12 weeks	HR 0.93 (99% CI 0.22 to 3.82)	58% (7/12) vs. 80% (8/10) Median, 13 vs. 14 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Sacrum MSCC – No	Overall survival	12 weeks	HR 1.02 (99% CI 0.82 to 1.29)	50% (167/333) vs. 54% (178/329) Median, 12 vs. 13 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)

CI = confidence interval; EBRT = external beam radiation therapy; HR = hazard ratio; KQ = Key Question; MF = multiple fraction; MSCC = metastatic spinal cord compression; NA = not applicable; NC = not calculable; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; RD = risk difference; RR = risk ratio; SF = single fraction.

[a] Positive ambulatory response rate: ambulatory status grade 1 or 2 at 8 weeks (which could be a result of an improvement from a grade 3 or 4 or maintenance of grade 1 or 2 from baseline) using a window of 49 to 62 days

[b] RDs or ORs as reported by authors.

Table B-23. Subgroup analyses for KQ 1, SF EBRT vs. MF EBRT: Number of painful sites

Comparison	Number of Painful Sites	Outcome	Time Point	Findings SF Vs. MF	Percentage (Events/Patients) SF Vs. MF	Study Design SF Vs. MF Dose/ Scheme
SF EBRT vs. MF EBRT	Single	Overall pain response	12 weeks	RR 0.97 (95% CI 0.84 to 1.12)	69% (114/165) vs. 71% (111/156)	1 RCT[41] 8 Gy vs. 30 Gy (3 Gy x 10)
	Multiple	Overall pain response	12 weeks	RR 0.99 (95% CI 0.81 to 1.22)	59% (73/123) vs. 60% (77/129)	1 RCT[41] 8 Gy vs. 30 Gy (3 Gy x 10)
	Single (SCC)	Ambulatory response rate[a]	8 weeks	RD -3.1% (99% CI -16.2% to 9.9%)	NR (n=316)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Multiple (SCC)	Ambulatory response rate[a]	8 weeks	RD -3.6% (99% -53.2% to 45.9%)	NR (n=26)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Single (SCC)	Overall survival	12 weeks	HR 0.97 (99% CI 0.77 to 1.23)	52% (158/303) vs. 54% (168/311) Median 13 vs. 14 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Multiple (SCC)	Overall survival	12 weeks	HR 1.61 (99% CI 0.77 to 3.36)	37% (16/42) vs. 63% (19/30) Median 9 vs. 16 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)

CI = confidence interval; EBRT = external beam radiation therapy; HR = hazard ratio; KQ = Key Question; MF = multiple fraction; NR = not reported; RCT = randomized controlled trial; RD = risk difference; RR = risk ratio; SCC = spinal cord compression; SF = single fraction.

[a]Defined as the percentage of patients who achieved ambulatory status grade 1 (ambulatory without the use of walking aids and grade 5 of 5 muscle power in all muscle groups) or 2 (ambulatory with assistance of walking aids or grade 4 of 5 muscle power in any muscle group), which could be a result of an improvement from a grade 3 or 4 or maintenance of grade 1 or 2 from baseline.

Table B-24. Subgroup analyses for KQ 1, SF EBRT vs. MF EBRT: Extent of metastases

Comparison	Extent of Metastases	Outcome	Time Point	Findings SF Vs. MF	Percentage (Events/Patients) SF Vs. MF	Study Design
SF EBRT vs. MF EBRT	Absent	Ambulatory response rate[a]	8 weeks	RD -2.8% (99% CI -19.0% to 13.3%)	NR (n=202)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Present	Ambulatory response rate[a]	8 weeks	RD -3.5% (99% CI -23.8% to 16.8%)	NR (n=140)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Absent	Overall survival	12 weeks	HR 1.11 (99% CI 0.81 to 1.51)	57% (106/186) vs. 67% (124/185) Median,15 vs. 23 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Present	Overall survival	12 weeks	HR 0.92 (99% CI 0.67 to 1.27)	43% (68/159) vs. 40% (62/156) Median,10 vs. 9 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)

CI = confidence interval; EBRT = external beam radiation therapy; HR = hazard ratio; KQ = Key Question; MF = multiple fraction; NR = not reported; RCT = randomized controlled trial; RD = risk difference; SF = single fraction.

[a] Positive ambulatory response rate: ambulatory status grade 1 or 2 at 8 weeks (which could be a result of an improvement from a grade 3 or 4 or maintenance of grade 1 or 2 from baseline) using a window of 49 to 62 days

Table B-25. Subgroup analyses for KQ 1, SF EBRT vs. MF EBRT: Baseline performance status

Comparison	Performance Status	Outcome	Time Point	Findings SF Vs. MF	Percentage (Events/Patients) SF Vs. MF	Study Design SF Vs. MF Dose/Scheme
SF EBRT vs. MF EBRT	ECOG grades 0–2[a]	Overall pain response	8 weeks	RR 0.96 (95% CI 0.82 to 1.12)	87% (34/39) vs. 91% (39/43)	1 RCT[11] 8 Gy vs. 40 Gy (2 Gy x 20)
	ECOG grade 3[a]	Overall pain response	8 weeks	RR 0.94 (95% CI 0.57 to 1.55)	73% (8/11) vs. 78% (7/9)	1 RCT[11] 8 Gy vs. 40 Gy (2 Gy x 20)
	WHO grades 0/1[b]	Ambulatory response rate[c]	8 weeks	RD 3.1% (99% CI -13.2% to 19.4%)	NR (n=130)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	WHO grade 2[b]	Ambulatory response rate[c]	8 weeks	RD -8.1% (99% CI -30.0 to 13.7)	NR (n=93)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	WHO grade 3[b]	Ambulatory response rate[c]	8 weeks	RD -10.8% (99% -37.7% to 16.1%)	NR (n=91)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	WHO grade 4[b]	Ambulatory response rate[c]	8 weeks	RD -10.3% (99% -56.5% to 36.0%)	NR (n=25)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	WHO grades 0/1[b]	Overall survival	12 weeks	HR 0.87 (99% CI 0.55 to 1.38)	71% (69/97) vs. 74% (70/94) Median, 28 vs. 28 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	WHO grade 2[b]	Overall survival	12 weeks	HR 1.12 (99% CI 0.7 to 1.78) f	56% (49/88) vs. 57% (46/81) Median, 14 vs. 16 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	WHO grade 3[b]	Overall survival	12 weeks	HR 1.11 (99% CI 0.76 to 1.61)	36% (41/114) vs. 45% (54/121) Median, 9 vs. 10 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	WHO grade 4[b]	Overall survival	12 weeks	HR 1.28 (99% CI 0.7 to 2.34)	26% (11/44) vs. 35% (14/41) Median, 5 vs. 7 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)

CI = confidence interval; EBRT = external beam radiation therapy; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; KQ = Key Question; MF = multiple fraction; NR = not reported; RCT = randomized controlled trial; RD = risk difference; RR = risk ratio; SF = single fraction; WHO = World Health Organization.

[a] ECOG Grades 0-2: fully active, able to carry on all pre-disease performance without restriction; or restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work; or ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours. ECOG Grade 3: capable of only limited self-care, confined to bed or chair more than 50% of waking hours

[b] WHO grades 0-1: fully active, able to carry on all pre-disease performance without restriction; or restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work; WHO grade 2: ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours; WHO grade 3: capable of only limited self-care, confined to bed or chair more than 50% of waking hours; WHO grade 4: completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

[c] Positive ambulatory response rate: ambulatory status grade 1 or 2 at 8 weeks (which could be a result of an improvement from a grade 3 or 4 or maintenance of grade 1 or 2 from baseline) using a window of 49 to 62 days

Table B-26. Subgroup analyses for KQ 1, SF EBRT vs. MF EBRT: Baseline ambulatory status

Comparison	Ambulatory Status	Outcome	Time Point	Findings SF Vs. MF	Percentage (Events/Patients) SF Vs. MF	Study Design SF Vs. MF Dose/Scheme
SF EBRT vs. MF EBRT	Grades 1/2[a]	Ambulatory response rate[b]	8 weeks	RD -5.3% (99% CI -17.8% to 7.2%)	NR (n=264)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Grades 3/4 [a]	Ambulatory response rate[b]	8 weeks	RD -5.6% (99% CI -34.1% to 22.9%)	NR (n=78)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Grades 1/2[a]	Overall survival	12 weeks	HR 0.96 (99% CI 0.72 to 1.28)	60% (137/228) vs. 61% (136/223) Median, 19 vs. 17 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Grades 3/4 [a]	Overall survival	12 weeks	HR 1.18 (99% CI 0.81 to 1.71)	30% (35/117) vs. 43% (51/118) Median, 7 vs. 8 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)

CI = confidence interval; EBRT = external beam radiation therapy; HR = hazard ratio; KQ = Key Question; MF = multiple fraction; NR = not reported; RCT = randomized controlled trial; RD = risk difference; SF = single fraction.

[a] Grades 1/2 = ambulatory with or without the use of walking aids; Grades 3/4 = unable to walk or absence or flicker of motor power in any muscle group

[b] Positive ambulatory response rate: ambulatory status grade 1 or 2 at 8 weeks (which could be a result of an improvement from a grade 3 or 4 or maintenance of grade 1 or 2 from baseline) using a window of 49 to 62 days

Table B-27. Subgroup analyses for KQ 1, SF EBRT vs. MF EBRT: Baseline worst pain score

Comparison	Baseline Worst Pain Score	Outcome	Time Point	Findings SF Vs. MF	Percentage (Events/Patients) SF Vs. MF	Study Design SF Vs. MF Dose/Scheme
SF EBRT vs. MF EBRT	5–6	Overall pain response	12 weeks	RR 0.97 (95% CI 0.73 to 1.28)	54% (45/83) vs. 56% (41/73)	1 RCT[41] 8 Gy vs. 30 Gy (3 Gy x 10)
	7–10	Overall pain response	12 weeks	RR 0.97 (95% CI 0.85 to 1.10)	69% (136/197) vs. 71% (145/204)	1 RCT[41] 8 Gy vs. 30 Gy (3 Gy x 10)
	<5 with ≥60 mg/day morphine	Overall pain response	12 weeks	RR 2.50 (95% CI 0.67 to 9.31)	63% (5/8) vs. 25% (2/8)	1 RCT[41] 8 Gy vs. 30 Gy (3 Gy x 10)

CI = confidence interval; EBRT = external beam radiation therapy; KQ = Key Question; MF = multiple fraction; RCT = randomized controlled trial; RR = risk ratio; SF = single fraction.

Table B-28. Subgroup analyses for KQ 1, SF EBRT vs. MF EBRT: Baseline treatment

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings SF Vs. MF	Percentage (Events/Patients) SF Vs. MF	Study Design SF Vs. MF Dose/Scheme
SF EBRT vs. MF EBRT	Bisphosphonate use	Yes	Overall pain response	12 weeks	RR 0.99 (95% CI 0.80 to 1.23)	67% (57/85) vs. 68% (50/74)	1 RCT[41] 8 Gy vs. 30 Gy (3 Gy x 10)
	Bisphosphonate use	No	Overall pain response	12 weeks	RR 0.97 (95% CI 0.84 to 1.12)	64% (129/203) vs. 58% (138/211)	1 RCT[41] 8 Gy vs. 30 Gy (3 Gy x 10)
	Any baseline treatment	Yes	Ambulatory response rate[a]	8 weeks	RD 0.8% (99% CI -15.1% to 16.6%)	NR (n=197)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Any baseline treatment	No	Ambulatory response rate[a]	8 weeks	RD -9.3% (99% CI -29.7% to 11.1%) Interaction p-value for any baseline treatment: 0.35	NR (n=144)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Chemotherapy	Yes	Ambulatory response rate[a]	8 weeks	RD -4.2% (99% CI -48.8% to 40.5%)	NR (n=36)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Chemotherapy	No	Ambulatory response rate[a]	8 weeks	RD -4.2% (99% CI -17.4% to 9.0%) Interaction p-value for chemotherapy: 0.96	NR (n=306)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Hormone treatment	Yes	Ambulatory response rate[a]	8 weeks	RD 6.5% (99% CI -10.8% to 23.8%)	NR (n=141)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Hormone treatment	No	Ambulatory response rate[a]	8 weeks	RD -11.6% (99% CI -28.9% to 5.8%) Interaction p-value for hormone treatment: 0.08	NR (n=201)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	RT	Yes	Ambulatory response rate[a]	8 weeks	RD -8.3% (99% CI -39.4% to 22.7%)	NR (n=57)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	RT	No	Ambulatory response rate[a]	8 weeks	RD -2.4% (99% CI -16.3% to 11.4%) Interaction p-value for RT: 0.66	NR (n=285)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Any baseline treatment	Yes	Overall survival	12 weeks	HR 1.01 (99% CI 0.74 to 1.36)	57% (107/188) vs. 57% (114/200) Median, 17 vs. 15	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Any baseline treatment	No	Overall survival	12 weeks	HR 1.03 (99% CI 0.74 to 1.44)	42% (66/156) vs. 52% (73/141) Median, 10 vs. 13	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings SF Vs. MF	Percentage (Events/Patients) SF Vs. MF	Study Design SF Vs. MF Dose/Scheme
	Chemotherapy	Yes	Overall survival	12 weeks	HR 1.13 (99% CI 0.6 to 2.14)	45% (14/31) vs. 46% (21/46) Median, 10 vs. 10	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Chemotherapy	No	Overall survival	12 weeks	HR 1.03 (99% CI 0.81 to 1.31)	51% (160/314) vs. 56% (165/295) Median, 13 vs. 14	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Hormone treatment	Yes	Overall survival	12 weeks	HR 0.95 (99% CI 0.64 to 1.42)	68% (85/125) vs. 40% (27/68) Median, 33 vs. 27	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Hormone treatment	No	Overall survival	12 weeks	HR 1.09 (99% CI 0.83 to 1.43)	40% (88/220) vs. 48% (107/222) Median, 9 vs. 11	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	RT	Yes	Overall survival	12 weeks	HR 0.79 (99% CI 0.48 to 1.29)	51% (35/69) vs. 40% (27/68) Median, 13 vs. 8	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	RT	No	Overall survival	12 weeks	HR 1.08 (99% CI 0.84 to 1.39)	50% (138/276) vs. 58% (158/273) Median, 12 vs. 16	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)

CI = confidence interval; EBRT = external beam radiation therapy; HR = hazard ratio; KQ = Key Question; MF = multiple fraction; NR = not reported; RCT = randomized controlled trial; RD = risk difference; RR = risk ratio; RT = radiotherapy; SF EBRT = single fraction conventional external beam radiation therapy.

[a] Positive ambulatory response rate: ambulatory status grade 1 or 2 at 8 weeks (which could be a result of an improvement from a grade 3 or 4 or maintenance of grade 1 or 2 from baseline) using a window of 49 to 62 days

Table B-29. Subgroup analyses for KQ 1, SF EBRT vs. MF EBRT: Baseline bladder and bowel function

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings SF Vs. MF	Percentage (Events/Patients) SF Vs. MF	Study Design
SF EBRT vs. MF EBRT	Bladder function	Normal	Ambulatory response rate[a]	8 weeks	RD -2.3% (99% CI -15.2% to 10.6%)	NR (n=269)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Bladder function	Abnormal	Ambulatory response rate[a]	8 weeks	RD 1.9% (99% CI -28.2% to 32.0%) Interaction p-value for bladder function: 0.71	NR (n=72)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Bowel function	Normal	Ambulatory response rate[a]	8 weeks	RD 1.0% (99% CI -14.6% to 16.7%)	NR (n=184)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Bowel function	Abnormal	Ambulatory response rate[a]	8 weeks	RD -7.5% (99% CI -27.3% to 12.4%) Interaction p-value for bowel function: 0.43	NR (n=157)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Bladder function	Normal	Overall survival	12 weeks	HR 0.96 (99% CI 0.74 to 1.25)	55% (135/246) vs. 57% (148/259) Median, 15 vs. 14 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Bladder function	Abnormal	Overall survival	12 weeks	HR 1.17 (99% CI 0.75 to 1.81)	37% (36/96) vs. 46% (38/82)	1 RCT[45]

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings SF Vs. MF	Percentage (Events/Patients) SF Vs. MF	Study Design
						Median, 8 vs. 11 weeks	8 Gy vs. 20 Gy (4 Gy x 5)
	Bowel function	Normal	Overall survival	12 weeks	HR 0.87 (99% CI 0.62 to 1.2)	58% (96/165) vs. 60% (105/175) Median, 20 vs. 17 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Bowel function	Abnormal	Overall survival	12 weeks	HR 1.17 (99% CI 0.85 to 1.6)	42% (74/177) vs. 49% (81/166) Median, 9 vs. 12 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)

CI = confidence interval; EBRT = external beam radiation therapy; HR = hazard ratio; KQ = Key Question; MF = multiple fraction; NR = not reported; RCT = randomized controlled trial; RD = risk difference; SF EBRT = single fraction conventional external beam radiation therapy.

[a] Positive ambulatory response rate: ambulatory status grade 1 or 2 at 8 weeks (which could be a result of an improvement from a grade 3 or 4 or maintenance of grade 1 or 2 from baseline) using a window of 49 to 62 days

Table B-30. Subgroup analyses for KQ 1, SF EBRT vs. MF EBRT: Duration of symptoms

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings SF Vs. MF	Percentage (Events/Patients) SF Vs. MF	Study Design
SF EBRT vs. MF EBRT	Duration of symptoms	<1 week	Ambulatory response rate[a]	8 weeks	RD -0.9% (99% CI -23.0% to 21.2%)	NR (n=126)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Duration of symptoms	≥1 week to <4 weeks	Ambulatory response rate[a]	8 weeks	RD -0.2% (99% CI -22.8% to 22.4%)	NR (n=92)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Duration of symptoms	≥4 weeks	Ambulatory response rate[a]	8 weeks	RD -10.0% (99% CI -36.1% to 16.1%) Interaction p-value for duration of symptoms: 0.72	NR (n=75)	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Duration of symptoms	<1 week	Overall survival	12 weeks	HR 1.11 (99% CI 0.78 to 1.56)	42% (62/147) vs. 54% (72/133) Median, 20 vs. 13 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Duration of symptoms	≥1 week to <4 weeks	Overall survival	12 weeks	HR 0.87 (99% CI 0.58 to 1.31)	55% (56/102) vs. 49% (51/104) Median, 17 vs. 12 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)
	Duration of symptoms	≥4 weeks	Overall survival	12 weeks	HR 0.84 (99% CI 0.47 to 1.49)	67% (37/55) vs. 57% (36/63) Median, 9 vs. 12 weeks	1 RCT[45] 8 Gy vs. 20 Gy (4 Gy x 5)

CI = confidence interval; EBRT = external beam radiation therapy; HR = hazard ratio; KQ = Key Question; MF = multiple fraction; NR = not reported; RCT = randomized controlled trial; RD = risk difference; SF EBRT = single fraction conventional external beam radiation therapy.

[a] Positive ambulatory response rate: ambulatory status grade 1 or 2 at 8 weeks (which could be a result of an improvement from a grade 3 or 4 or maintenance of grade 1 or 2 from baseline) using a window of 49 to 62 days

Table B-31. Subgroup analyses for KQ 1, MF EBRT vs. MF EBRT: Primary tumor type

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients) MF Vs. MF	Study Design
MF EBRT vs. MF EBRT	Primary Tumor Type	Breast	Overall pain response	NR	NA	83% (5/6 sites) vs. 100% (8/8 sites) vs. 89% (8/9 sites)	1 RCT [59] 20 Gy (2 Gy x 10) vs. 22.5 Gy (4.5 Gy x 5) vs. 30 Gy (2 Gy x 15)
	Primary Tumor Type	Lung	Overall pain response	NR	NA	66% (4/6 sites) vs. 58% (7/12 sites) vs. 80% (8/10 sites)	1 RCT [59] 20 Gy (2 Gy x 10) vs. 22.5 Gy (4.5 Gy x 5) vs. 30 Gy (2 Gy x 15)
	Primary Tumor Type	Epipharynx	Overall pain response	NR	NA	100% (3/3 sites) vs. 88% (7/8 sites) vs. 100% (5/5 sites)	1 RCT [59] 20 Gy (2 Gy x 10) vs. 22.5 Gy (4.5 Gy x 5) vs. 30 Gy (2 Gy x 15)
	Primary Tumor Type	Uterus	Overall pain response	NR	NA	100% (4/4 sites) vs. 100% (2/2 sites) vs. 0% (0/1 sites)	1 RCT [59] 20 Gy (2 Gy x 10) vs. 22.5 Gy (4.5 Gy x 5) vs. 30 Gy (2 Gy x 15)
	Primary Tumor Type	Esophagus	Overall pain response	NR	NA	33% (1/3 sites) vs. 0% (0/1 sites) vs. NA	1 RCT [59] 20 Gy (2 Gy x 10) vs. 22.5 Gy (4.5 Gy x 5) vs. 30 Gy (2 Gy x 15)
	Primary Tumor Type	Stomach	Overall pain response	NR	NA	NA vs. 0% (0/1 sites) vs. 50% (1/2 sites)	1 RCT [59] 20 Gy (2 Gy x 10) vs. 22.5 Gy (4.5 Gy x 5) vs. 30 Gy (2 Gy x 15)

EBRT = external beam radiation therapy; KQ = Key Question; MF = multiple fraction; NA = not applicable; NR = not reported; RCT = randomized controlled trial.

Table B-32. Subgroup analyses for KQ 1, MF EBRT vs. MF EBRT: Tumor histology

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients) MF Vs. MF	Study Design
MF EBRT vs. MF EBRT	Tumor histology	Adenocarcinoma	Overall pain response	NR	NA	73% (11/15 sites) vs. 75% (12/16 sites) vs. 77% (14/18 sites)	1 RCT [59] 20 Gy (2 Gy x 10) vs. 22.5 Gy (4.5 Gy x 5) vs. 30 Gy (2 Gy x 15)
	Tumor histology	Squamous cell carcinoma	Overall pain response	NR	NA	77% (7/9 sites) vs. 73% (11/15 sites) vs. 71% (5/7 sites)	1 RCT [59] 20 Gy (2 Gy x 10) vs. 22.5 Gy (4.5 Gy x 5) vs. 30 Gy (2 Gy x 15)
	Tumor histology	Anaplastic carcinoma	Overall pain response	NR	NA	100% (1/1 sites) vs. 75% (3/4 sites) vs. 67% (2/3 sites)	1 RCT [59] 20 Gy (2 Gy x 10) vs. 22.5 Gy (4.5 Gy x 5) vs. 30 Gy (2 Gy x 15)
	Tumor histology	Unknown	Overall pain response	NR	NA	100% (2/2 sites) vs. 100% (1/1 sites) vs. 100% (1/1 sites)	1 RCT [59] 20 Gy (2 Gy x 10) vs. 22.5 Gy (4.5 Gy x 5) vs. 30 Gy (2 Gy x 15)

EBRT = external beam radiation therapy; KQ = Key Question; MF = multiple fraction; NR = not reported; NA = not applicable; RCT = randomized controlled trial.

Table B-33. Subgroup analyses for KQ 1, MF EBRT vs. MF EBRT: Metastases site

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients) MF Vs. MF	Study Design
MF EBRT vs. MF EBRT	Metastases site	Vertebral column	Overall pain response	NR	NA	75% (12/16 sites) vs. 79% (15/19 sites) vs. 76% (13/17 sites)	1 RCT [59] 20 Gy (2 Gy x 10) vs. 22.5 Gy (4.5 Gy x 5) vs. 30 Gy (2 Gy x 15)
	Metastases site	Pelvis	Overall pain response	NR	NA	80% (4/5 sites) vs. 72% (5/7 sites) vs. 83% (5/6 sites)	1 RCT [59] 20 Gy (2 Gy x 10) vs. 22.5 Gy (4.5 Gy x 5) vs. 30 Gy (2 Gy x 15)
	Metastases site	Extremities	Overall pain response	NR	NA	66% (2/3 sites) vs. 57% (4/7 sites) vs. 50% (2/4 sites)	1 RCT [59] 20 Gy (2 Gy x 10) vs. 22.5 Gy (4.5 Gy x 5) vs. 30 Gy (2 Gy x 15)
	Metastases site	Rib	Overall pain response	NR	NA	100% (2/2 sites) vs. 100% (3/3 sites) vs. 100% (1/1 sites)	1 RCT [59] 20 Gy (2 Gy x 10) vs. 22.5 Gy (4.5 Gy x 5) vs. 30 Gy (2 Gy x 15)

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients) MF Vs. MF	Study Design
	Metastases site	Sternum	Overall pain response	NR	NA	100% (1/1 sites) vs. NA vs. 100% (1/1 sites)	1 RCT [59] 20 Gy (2 Gy x 10) vs. 22.5 Gy (4.5 Gy x 5) vs. 30 Gy (2 Gy x 15)

EBRT = external beam radiation therapy; KQ = Key Question; MF = multiple fraction; NA = not applicable; NR = not reported; RCT = randomized controlled trial.

Table B-34. Subgroup analyses for KQ 1, MF EBRT vs. MF EBRT: Survival prognosis

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings MF Vs. MF	Percentage (Events/Patients) MF Vs. MF	Study Design
MF EBRT vs. MF EBRT	Survival prognosis	Poor prognosis	Overall Response[a]	4 weeks	RR 1.00 (95% CI 0.82 to 1.22)	85% (34/40) vs. 85% (28/33)	1 RCT [68] 20 Gy (4 Gy x5) vs. 30 Gy (3 Gy x 10)
	Survival prognosis	Intermediate prognosis	Overall Response[a]	4 weeks	RR 0.96 (95% CI 0.84 to 1.10)	89% (34/38) vs. 93% (41/44)	1 RCT [68] 20 Gy (4 Gy x5) vs. 30 Gy (3 Gy x 10)
	Survival prognosis	Poor prognosis	Overall Response[a]	12 weeks	RR 1.14 (95% CI 0.95 to 1.38)	100% (18/18) vs. 87% (14/16)	1 RCT [68] 20 Gy (4 Gy x5) vs. 30 Gy (3 Gy x 10)
	Survival prognosis	Intermediate prognosis	Overall Response[a]	12 weeks	RR 1.00 (95% CI 0.91 to 1.10)	97% (28/29) vs. 97% (28/29)	1 RCT [68] 20 Gy (4 Gy x5) vs. 30 Gy (3 Gy x 10)
	Survival prognosis	Poor prognosis	Overall Response[a]	26 weeks	RR 1.13 (95% CI 0.89 to 1.42)	100% (12/12) vs. 89% (8/9)	1 RCT [68] 20 Gy (4 Gy x5) vs. 30 Gy (3 Gy x 10)
	Survival prognosis	Intermediate prognosis	Overall Response[a]	26 weeks	RR 0.95 (95% CI 0.87 to 1.05)	95% (20/21) vs. 100% (21/21)	1 RCT [68] 20 Gy (4 Gy x5) vs. 30 Gy (3 Gy x 10)
	Survival prognosis	Poor prognosis	Motor function improvement[b]	4 weeks	RR 0.88 (95% CI 0.50 to 1.55)	38% (15/40) vs. 42% (14/33)	1 RCT [68] 20 Gy (4 Gy x5) vs. 30 Gy (3 Gy x 10)
	Survival prognosis	Intermediate prognosis	Motor function improvement[b]	4 weeks	RR 0.87 (95% CI 0.52 to 1.45)	39% (15/38) vs. 45% (20/44)	1 RCT [68] 20 Gy (4 Gy x5) vs. 30 Gy (3 Gy x 10)
	Survival prognosis	Poor prognosis	Motor function improvement[b]	12 weeks	RR 0.89 (95% CI 0.40 to 1.98)	39% (7/18) vs. 44% (7/16)	1 RCT [68] 20 Gy (4 Gy x5) vs. 30 Gy (3 Gy x 10)
	Survival prognosis	Intermediate prognosis	Motor function improvement[b]	12 weeks	RR 0.87 (95% CI 0.51 to 1.48)	45% (13/29) vs. 52% (15/29)	1 RCT [68] 20 Gy (4 Gy x5) vs. 30 Gy (3 Gy x 10)
	Survival prognosis	Poor prognosis	Motor function improvement[b]	26 weeks	RR 0.86 (95% CI 0.50 to 1.46)	67% (8/12) vs. 78% (7/9)	1 RCT [68] 20 Gy (4 Gy x5) vs. 30 Gy (3 Gy x 10)

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings MF Vs. MF	Percentage (Events/Patients) MF Vs. MF	Study Design
	Survival prognosis	Intermediate prognosis	Motor function improvement[b]	26 weeks	RR 1.00 (95% CI 0.56 to 1.78)	52% (11/21) vs. 52% (11/21)	1 RCT [68] 20 Gy (4 Gy x5) vs. 30 Gy (3 Gy x 10)
	Survival prognosis	Poor prognosis	Ambulatory rates (w/w/o aid)	4 weeks	RR 0.94 (95% CI 0.66 to 1.35)	60% (24/40) vs. 64% (21/33)	1 RCT [68] 20 Gy (4 Gy x5) vs. 30 Gy (3 Gy x 10)
	Survival prognosis	Intermediate prognosis	Ambulatory rates (w/w/o aid)	4 weeks	RR 1.03 (95% CI 0.85 to 1.25)	84% (32/38) vs. 82% (36/44)	1 RCT [68] 20 Gy (4 Gy x5) vs. 30 Gy (3 Gy x 10)
	Survival prognosis	Poor prognosis	Ambulatory rates (w/w/o aid)	12 weeks	RR 1.28 (95% CI 0.76 to 2.16)	72% (13/18) vs. 56% (9/16)	1 RCT [68] 20 Gy (4 Gy x5) vs. 30 Gy (3 Gy x 10)
	Survival prognosis	Intermediate prognosis	Ambulatory rates (w/w/o aid)	12 weeks	RR 1.04 (95% CI 0.84 to 1.30)	86% (25/29) vs. 83% (24/29)	1 RCT [68] 20 Gy (4 Gy x5) vs. 30 Gy (3 Gy x 10)
	Survival prognosis	Poor prognosis	Ambulatory rates (w/w/o aid)	26 weeks	RR 0.96 (95% CI 0.60 to 1.56)	75% (9/12) vs. 78% (7/9)	1 RCT [68] 20 Gy (4 Gy x5) vs. 30 Gy (3 Gy x 10)
	Survival prognosis	Intermediate prognosis	Ambulatory rates (w/w/o aid)	26 weeks	RR 1.00 (95% CI 0.78 to 1.28)	86% (18/21) vs. 86% (18/21)	1 RCT [68] 20 Gy (4 Gy x5) vs. 30 Gy (3 Gy x 10)
	Survival prognosis	Poor prognosis	Overall Survival	4 weeks	RR 1.07 (95% CI 0.78 to 1.46)	60% (35/58) vs. 58% (30/53)	1 RCT [68] 20 Gy (4 Gy x5) vs. 30 Gy (3 Gy x 10)
	Survival prognosis	Intermediate prognosis	Overall Survival	4 weeks	RR 0.95 (95% CI 0.82 to 1.12)	85% (37/43) vs. 90% (44/49)	1 RCT [68] 20 Gy (4 Gy x5) vs. 30 Gy (3 Gy x 10)
	Survival prognosis	Poor prognosis	Overall Survival	12 weeks	RR 1.03 (95% CI 0.59 to 1.80)	31% (18/58) vs. 30% (16/53)	1 RCT [68] 20 Gy (4 Gy x5) vs. 30 Gy (3 Gy x 10)
	Survival prognosis	Intermediate prognosis	Overall Survival	12 weeks	RR 0.95 (95% CI 0.76 to 1.21)	74% (32/43) vs 77% (38/49)	1 RCT [68] 20 Gy (4 Gy x5) vs. 30 Gy (3 Gy x 10)
	Survival prognosis	Poor prognosis	Overall Survival	26 weeks	RR 1.25 (95% CI 0.63 to 2.47)	26% (15/58) vs. 19% (11/53)	1 RCT [68] 20 Gy (4 Gy x5) vs. 30 Gy (3 Gy x 10)
	Survival prognosis	Intermediate prognosis	Overall Survival	26 weeks	RR 1.14 (95% CI 0.82 to 1.58)	65% (28/43) vs. 58% (28/49)	1 RCT [68] 20 Gy (4 Gy x5) vs. 30 Gy (3 Gy x 10)

CI = confidence interval; EBRT = external beam radiation therapy; KQ = Key Question; MF = multiple fraction; RCT = randomized controlled trial; RR =; risk ratio; RT = radiation therapy; w/w/o = with or without.

[a] Defined as improvement or no further progression of motor deficits.

[b] Defined as a change of ≥2 points on a 0-14 scale.

Table B-35. Subgroup analyses for KQ 1, SF EBRT vs. SF EBRT: Primary tumor type

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings SF Vs. SF	Percentage (Events/Patients) SF Vs. SF	Study Design
SF EBRT vs. SF EBRT	Primary tumor type	Breast	Overall pain response	8 weeks	**4 Gy vs. 6 or 8 Gy, RR 0.75 (95% CI 0.58 to 0.97)**	60% (28/47) vs. 79% (33/42) vs. 80% (39/49)	1 RCT [48] 4 Gy vs. 6 Gy vs. 8 Gy
	Primary tumor type	Lung	Overall pain response	8 weeks	4 Gy vs. 6 or 8 Gy, RR 0.76 (95% CI 0.46 to 1.26)	50% (9/18) vs. 65% (15/23) vs. 67% (14/21)	1 RCT [48] 4 Gy vs. 6 Gy vs. 8 Gy
	Primary tumor type	Prostate	Overall pain response	8 weeks	4 Gy vs. 6 or 8 Gy, RR 0.76 (95% CI 0.51 to 1.13)	61% (11/18) vs. 75% (15/20) vs. 88% (14/16)	1 RCT [48] 4 Gy vs. 6 Gy vs. 8 Gy
	Primary tumor type	Myeloma	Overall pain response	8 weeks	4 Gy vs. 6 or 8 Gy, RR 1.07 (95% CI 0.62 to 1.84)	80% (4/5) vs. 67% (4/6) vs. 83% (5/6)	1 RCT [48] 4 Gy vs. 6 Gy vs. 8 Gy
	Primary tumor type	Kidney	Overall pain response	8 weeks	4 Gy vs. 8 Gy, RR 0.57 (95% CI 0.22 to 1.47)	43% (3/7) vs. NA vs. 75% (6/8)	1 RCT [48] 4 Gy vs. 6 Gy vs. 8 Gy
	Primary tumor type	Rectum	Overall pain response	8 weeks	4 Gy vs. 6 or 8 Gy, RR 0.44 (95% CI 0.13 to 1.50)	29% (2/7) vs. 56% (5/9) vs. 75% (6/8)	1 RCT [48] 4 Gy vs. 6 Gy vs. 8 Gy
	Primary tumor type	Other	Overall pain response	8 weeks	4 Gy vs. 6 or 8 Gy, RR 1.11 (95% CI 0.90 to 1.37)	100% (7/7) vs. 88% (7/8) vs. 100% (2/2)	1 RCT [48] 4 Gy vs. 6 Gy vs. 8 Gy

CI = confidence interval; EBRT = external beam radiation therapy; KQ = Key Question; NA = not applicable; RCT = randomized controlled trial; RR = risk ratio; SF = single fraction.

Table B-36. Subgroup analyses for KQ 1, SF EBRT vs. SF EBRT: Metastases site

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings SF Vs. SF	Percentage (Events/Patients) SF Vs. SF	Study Design
SF EBRT vs. SF EBRT	Metastases site	Cervical spine	Overall pain response	8 weeks	4 Gy vs. 6 or 8 Gy, RR 0.96 (95% CI 0.50 to 1.87)	75% (3/4) vs. 80% (4/5) vs. 75% (3/4)	1 RCT [48] 4 Gy vs. 6 Gy vs. 8 Gy
	Metastases site	Thoracic spine	Overall pain response	8 weeks	4 Gy vs. 6 or 8 Gy, RR 1.10 (95% CI 0.86 to 1.40)	81% (22/27) vs. 72% (18/25) vs. 76% (19/25)	1 RCT [48] 4 Gy vs. 6 Gy vs. 8 Gy
	Metastases site	Lumbosacral spine	Overall pain response	8 weeks	4 Gy vs. 6 or 8 Gy, RR 1.22 (95% CI 0.97 to 1.52)	83% (25/30) vs. 67% (22/33) vs. 70% (26/37)	1 RCT [48] 4 Gy vs. 6 Gy vs. 8 Gy
	Metastases site	Pelvis/hip	Overall pain response	8 weeks	4 Gy vs. 6 or 8 Gy, RR 1.06 (95% CI 0.84 to 1.34)	73% (32/44) vs. 78% (31/40) vs. 59% (22/37)	1 RCT [48] 4 Gy vs. 6 Gy vs. 8 Gy
	Metastases site	Femur	Overall pain response	8 weeks	4 Gy vs. 6 or 8 Gy, RR 1.29 (95% CI 0.91 to 1.82)	100% (3/3) vs. 75% (3/4) vs. 80% (4/5)	1 RCT [48] 4 Gy vs. 6 Gy vs. 8 Gy

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings SF Vs. SF	Percentage (Events/Patients) SF Vs. SF	Study Design
	Metastases site	Humerus	Overall pain response	8 weeks	4 Gy vs. 6 or 8 Gy, RR 1.50 (95% CI 0.67 to 3.34)	100% (1/1) vs. 100% (1/1) vs. 50% (1/2)	1 RCT [48] 4 Gy vs. 6 Gy vs. 8 Gy

CI = confidence interval; EBRT = external beam radiation therapy; KQ = Key Question; RCT = randomized controlled trial; RR = risk ratio; SF = single fraction.

Key Question 1: Delivery Techniques

Table B-37. Subgroup analyses for KQ 1, SBRT vs. 3DCRT: Primary mechanism of interference with bone remodeling

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings SBRT Vs. 3DCRT	Percentage (Events/Patients) SBRT Vs. 3DCRT	Study Design
SBRT (24 Gy x 1) vs. 3DCRT (30 Gy, 3 Gy x 10)	Mechanism interfering with bone remodeling	Osteolytic	New pathological fracture	12 weeks	RR 1.33 (95% CI 0.17 to 10.25)	33.3% (2/6) vs. 25.0% (1/4)	1 RCT [82]
	Mechanism interfering with bone remodeling	Osteoblastic	New pathological fracture	12 weeks	NA	0% (0/2) vs. 0% (0/4)	1 RCT [82]
	Mechanism interfering with bone remodeling	Mixed	New pathological fracture	12 weeks	NA	0% (0/15) vs. 0% (0/14)	1 RCT [82]
	Mechanism interfering with bone remodeling	Osteolytic	New pathological fracture	26 weeks	NA	0% (0/6) vs. 0% (0/3)	1 RCT [82]
	Mechanism interfering with bone remodeling	Osteoblastic	New pathological fracture	26 weeks	NA	0% (0/1) vs. 0% (0/4)	1 RCT [82]
	Mechanism interfering with bone remodeling	Mixed	New pathological fracture	26 weeks	RR 5.45 (95% CI 0.75 to 39.71)	45.5% (5/11) vs. 8.3% (1/12)	1 RCT [82]

3D-CRT = three-dimensional conformal radiation therapy; CI = confidence interval; KQ = Key Question; NA = not applicable; RCT = randomized controlled trial; RD = relative risk; RR = risk ratio; SBRT = stereotactic body radiation therapy.

Key Question 3a: EBRT Versus Another Single Therapy

Table B-38. Subgroup analyses for KQ 3a, SF EBRT vs. bisphosphates: Primary tumor type

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
SF EBRT (8 Gy) vs. Ibandronate (6 mg)	Primary tumor type	Breast	Overall pain response	4 weeks	RR 1.29 (95% CI 0.70 to 2.35)	64% (9/14) vs. 50% (9/18)	1 RCT[44]
	Primary tumor type	Lung	Overall pain response	4 weeks	RR 0.88 (95% CI 0.32 to 2.41)	31% (5/16) vs. 36% (5/14)	1 RCT[44]
	Primary tumor type	Breast	Overall pain response	12 weeks	RR 1.64 (95% CI 0.79 to 3.40)	64% (7/11) vs. 39% (7/18)	1 RCT[44]
	Primary tumor type	Lung	Overall pain response	12 weeks	RR 1.50 (95% CI 0.41 to 5.45)	50% (5/10) vs. 33% (2/6)	1 RCT[44]

CI = confidence interval; EBRT = external beam radiation therapy; KQ = Key Question; RCT = randomized controlled trial; RR = risk ratio; SF = single fraction.

Key Question 3b: EBRT Plus Another Therapy Versus EBRT Alone

Table B-39. Subgroup analyses for KQ 3b, MF EBRT plus dexamethasone vs. MF EBRT alone: Primary tumor type

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
MF EBRT (28 Gy, 4 Gy x 7) plus dexamethasone 96 mg vs. MF EBRT (28 Gy, 4 Gy x 7) alone	Primary tumor type	Breast	Ambulatory	26 weeks	RR 1.37 (95% CI 0.97 to 1.95)	94% (17/18) vs. 69% (11/16)	1 RCT[76]
	Primary tumor type	Breast + thoracic metastases	Ambulatory	26 weeks	RR 1.85 (95% CI 0.91 to 3.76)	92% (12/13) vs. 50% (4/8)	1 RCT[76]

CI = confidence interval; EBRT = external beam radiation therapy; KQ = Key Question; MF = multiple fraction; RCT = randomized controlled trial; RR = risk ratio.

Appendix C. Contextual Questions

Table C-1. Contextual Question 2: Summary of studies evaluating strategies for guideline promotion and implementation

Strategy	Author, Year (Country)	Strategy Characteristics	Evaluation/Study Characteristics	Authors Findings, Conclusions
Online clinical pathway with/without peer review	Beriwal, 2012[124] United States	• Online care pathway • Online tool to enter pathway choices (1 to 5 fractions, with option of 10-14 fractions for specific clinical scenarios) • With or without peer review (online pathway monitoring)	• Evaluation • 13 clinical sites; 3 academic, 10 community • 7905 met sites treated; 64% in community • Date from 2003-2010	Findings: • Academic sites more likely to use 1-5 fractions vs. community sites. • 1-5 fractions more common after implementation online pathway monitoring for both community and academic sites • Mean number of fractions deceased after online peer review Conclusion: Clinical pathway implementation appears to be effective in changing patterns of care, particularly with online clinical peer review as a valuable aid to encourage adherence to evidence-based practice.
	Rotenstein, 2018[125] United States	• Web-based clinical pathway with 20 endpoints, validated prognostic scoring systems • Compliance with SFRT recommendations • Reasons for noncompliance	• Academic center • Pathway based on guidelines, expert input, literature • Pathway used in 38% of 723 radiation therapy prescriptions for MBD	Findings: • Use of SFRT increased 30% after launch • Increase physician confidence with compliance • Reasons for noncompliance: patient convenience; disagreement on patient live expectancy • Limitations: workflow disruption, inability to handle nuanced situations Conclusion: Demonstrates utility of clinical pathway decision support in complex academic settings

Strategy	Author, Year (Country)	Strategy Characteristics	Evaluation/Study Characteristics	Authors Findings, Conclusions
	Gebhardt, 2015[126] United States	• Online entry of management decisions that subjected off-pathway choices to be peer reviewed • Initial tool 2003, peer review began 2009 • Tool modified 2014 to encourage SFRT, >10 fractions considered off pathway	• Compared SFRT use between 2003 and 2008 to use between 2009 and 2013 and use in 2014 • 16 sites (4 academic, 12 community) • Multivariate evaluation of factors associated with SFRT and >10 fractions. • 12,678 courses delivered	Findings: • SFRT increased from 7.6% (2003-3008) to 10.9% (2009-2013) to 15.8% (2014) • >10 fraction use decreased: 18.6% (2003-2008), 15.2% (2009 to 2013), 9.7% (2014) • Academic physicians more likely to use SFRT Conclusion: While SFRT use was previously in line with national average, adoption rate increased to >15%. The use of >10-fraction regimens decreased significantly, predominantly among community practices. By 2014, >90% of courses were delivered with <10 fractions. This study demonstrates that provider-driven clinical pathways are able to standardize practice patterns and promote change consistent with evidence-based guidelines
	Alcorn, 2022[127] United States	• Development of web-based provider decision platform	• Use of Ottawa Decision Support Framework to develop Bone Metastases Ensemble Trees for Survival-Decision Support Platform (BMETS-DSP) • Assessment of decision quality • Use of stakeholder input and evidence-based publications	Findings: • BMETS-DSP platform developed to collect patient specific data, display individualized survival prediction curve, provide case-specific, evidence-based recommendations • International Patient Decision Aids Standards (IPDAS) met • Pilot data suggests the platform may increase confidence in and likelihood sharing estimated prognosis as well as selection of prognosis-appropriate RT regimens Conclusion: Successful development of a provider-facing decision support platform to aid in the provision of palliative RT in better alignment with patient and disease features. Impact of the BMETS-DSP on decision outcomes will be further assessed in a randomized, controlled study.

Strategy	Author, Year (Country)	Strategy Characteristics	Evaluation/Study Characteristics	Authors Findings, Conclusions
EMR Alert	Grant, 2021[128] United States	• Multi-phase custom electronic health record alert system embedded in EHR in March 2018 based on National Quality Forum measure 1822 • Prior to XRT course, alert system notified use of the National Quality Forum recommendations; following completion either affirmed compliance or advised change in treatment schedule	• Compliance rates before and after intervention • 2399 treatment courses	Findings: • No change in rates of compliance following implementation of a custom EHR alert system • 86% before, 86.9% after EHR intervention Conclusion: To be of most benefit, future palliative bone metastasis decision aids should leverage peer review, target a clear practice deficiency, center upon high-quality practice guidelines, and allow flexibility to reflect the diversity of clinical scenarios. Lack of improvement may suggest alert fatigue, prior saturation of the measure, or disagreement with the quality recommendations.
Education-based intervention and/or Audit	Booth, 1993[129] United Kingdom	• Department-wide audit of use of number of fractions used in department to treat symptomatic bone metastases • Presented along with literature review and establishment of department guidelines recommending use of SFRT	• Three audits conducted to determine number of fractions used from June 1990-August 1990, June 1991-August 1991, and November 1991-Janaury 1992	Findings: • At first audit, 34% patients treated with SFRT; second audit after guidelines were established showed increase to 45%; final audit after re-assertion of guidelines increased to 68% • A decrease in mean number of reactions was also seen Conclusion: Audit was seen to reduce the number of fractions used to treat bone metastases in the department.
	Olson, 2016[130] Canada	• Audit and education-based intervention • Anonymous audit of radiation therapy prescriptions for bone metastases done in 2012 and presented to radiation oncologists with guidelines, meta-analyses, practice leader recommendations (dissemination of programmatic quality indicators) • All regional centers in British Columbia Canada	• Population-based intervention to increase the consistency and use of SFRT for MBD • SFRT use for MBD from 2007 through 2011 compared with use of SFRT in 2013, to assess the impact of the audit and educational intervention • 16,898 RT courses delivered 2007-2011 • 3200 courses delivered in 2013	Findings: • Rates of SFRT use per year from 2007-2011 were 50.5%, 50.9%, 48.3%, 48.5%, 48.0% and for year after the audit, 59.7% for 2013 • SFRT increased in each of 5 regional centers and was more consistent Conclusion: An audit-based intervention increased utilization of SFRT for bone metastases. The intervention reversed a trend to decreasing SFRT use, reduced costs, and improved patient convenience. This suggests that dissemination of programmatic quality indicators in oncology can lead to increased utilization of evidence-based practice.

Strategy	Author, Year (Country)	Strategy Characteristics	Evaluation/Study Characteristics	Authors Findings, Conclusions
	Olson, 2018[131] Canada	• Audit and education-based intervention • Anonymous audit of radiation therapy prescriptions for bone metastases done in 2012 and presented to radiation oncologists with guidelines, meta-analyses, practice leader recommendations • All regional centers in British Columbia Canada	• Followup to Olson 2016 to evaluate persistence of impact of intervention • Compared pre-intervention (2007-2011) SFRT use to post-intervention (2013 to 2016)	Findings: • Pre-intervention years: 2007-2011 were 50.5%, 50.9%, 48.3%, 48.5%, 48.0% versus post-intervention: 2013 to 2016 were 60%, 62%, 59%, and 56% • SFRT across variation centers: highest users at 35% and 81%; lowest-using center still showed a significant increase (26% to 35%) Conclusion: The audit and education-based intervention resulted in a lasting and meaningful 10% change in practice; data suggest that programmatic comparison and dissemination of SFRT prescribing practices can achieve a population-based SFRT utilization rate near 60%.
	Walker 2018[132] United States	• Mandated, prospective peer-review of total dose and fraction schedules during weekly chart rounds	• In 2016, instituted peer review of total dose and fractionation of all palliative treatment plans at weekly chart rounds • Total 242 treatment courses for uncomplicated MBD from July 2015 to December 2016; 105 before peer review intervention, 137 after	Findings: • Increased adoption of 8 Gy SFRT from 2.8% to post-intervention 13.9% and use of 20 Gy 5 fraction from 25.7% to 32.8% • Decrease in in 30 GY/10 fractions from 55.2% to 47.4% and us of ≥11 fractions from 16.2% to 5.8% Conclusion: Prospective peer review of palliative regimens for bone metastases can lead to greater adoption of shorter palliative fractionation schedules in daily practice, in accordance with national guidelines.
	Shahhat, 2021[133] Canada	• Coordinated knowledge translation campaign education • Included educational outreach visits, local consensus meetings, audit and feedback interventions to encourage greater SFRT use	• Intervention – early 2017 • Manitoba provincial radiation therapy database. • Compared 2016 (pre-intervention) vs. 2017 (post-intervention) • 927 patients treated in 2017	Findings: • Absolute increase in 21.1% in SFRT (from 38% in 2016 to 59.1% in 2017) • Factors associated with MRFT use: complicated MBD, soft-tissue extension, primary hematological malignancy, treatment at subsidiary center Conclusion: The comprehensive knowledge translation campaign carried out in Manitoba resulted in a significant increase in SFRT use for bone metastases. Continued audit/feedback strategies are recommended to further reinforce knowledge translation efforts supporting SFRT use in the future.

Strategy	Author, Year (Country)	Strategy Characteristics	Evaluation/Study Characteristics	Authors Findings, Conclusions
	Donati, 2021[134] Italy	• Intensive education intervention in January 2015 • Single center • Two meetings: First presentation of audit data on SRFT rates, second presentation of evidence for SFRT for uncomplicated MBD • Opportunity to use SFRT was systematically recalled during weekly discussion of clinical cases	• Pre-post intervention evaluation over 5 years • 627 patients with uncomplicated MBD • Retrospective analysis, compared all patients having RT 2014 (reference year) vs. 2015-2019 (post-intervention)	Findings: • Increase in SFRT from 4.0% (2014) to 63.5% (2019) • Delivery of SFRT correlated with older age, lung cancer primary, prescription for palliative treatment and treatment date. Conclusion: A simple but intensive and prolonged departmental education strategy can increase the rate of patients treated with SFRT by nearly 16 times
Clinical algorithm	Dennstädt, 2021[135] Switzerland	• Describes principles for development of clinical algorithms in medicine to assist in decision making, using dose selection for palliative RT for bone metastases as an example	• Utilizing relevant criteria for decision making (complicated vs. uncomplicated, tumor load, life expectancy), devise a possible clinical algorithm • Proposes methods for validation and evaluation of performance	Findings: • Provides possible algorithm and describes challenges and limitations for implementation Conclusion: Algorithm development may provide a structured approach to decision making in medical decision making in oncology
Peer incentivization alone	Yu, 2020[136] United States	• Using a cohort of Medicare Beneficiaries with breast cancer, constructed physician peer groups based on patient-sharing relationships	• Examined rate of short course EBRT for palliative RT for bone metastases within peer groups from 2011-2012 to 2013-2014 • 2748 patients treated by 1505 radiation oncologists belonging to 560 peer groups	Findings: • 59.0% of patients received short course treatment • No significant relationship between peer group use of short course RT in 2011-2012 vs. 2013-2014 Conclusion: Physician peer groups did not influence use of short course RT for palliation; may be influenced by social context and saturation of use of short course RT for palliation during the studied time period

Strategy	Author, Year (Country)	Strategy Characteristics	Evaluation/Study Characteristics	Authors Findings, Conclusions
Guideline dissemination alone	Ashworth, 2016[137] Canada	• Cancer care Ontario released practice guideline on SFRT use for uncomplicated MBD in 2004	• Retrospective evaluation of use prior to guideline release 1999-2003) vs. immediately after (2004-2007) and later (2009-2012) • Evaluation of temporal trends using retrospective data from Ontario's population-based cancer registry Compared spinal vs other skeletal site, evaluated variability across cancer centers • Adjusted for potential confounders	Findings: • Use of SFRT increased from 42.3% to 52.6% immediately post guideline release but decreased to 44.0% at later followup • Large variation in use of SRFT across centers (range, 26.0%-67.8%) which persisted after guideline publication • Less use of SFRT in spinal fields vs. other skeletal sites (31.5% vs 57.1%) • Greater us of SFRT in older patients, those with shorter life expectancy, residing farther from cancer center • Temporal trends significant after controlling for patient factors Conclusion: The publication of an Ontario practice guideline endorsing the use of SFRT was associated with only a transient increase in the use of SFRT in Ontario and did little to reduce inter-center variations in fractionation
	Kim, 2020[138] Canada	• Electronic dissemination of guidelines • Choosing Wisely Canada guidelines disseminated via email every 4 weeks to radiation oncologists for final quarter 2015; pertinent guideline portions included in email body	• Evaluation of 807 patients having palliative XRT in 2016 • Evaluated increase in use of SFRT vs. previous year (38.1%) • Review of individual treatment plans • Factors associated with use of SFRT and MFRT; Multivariate analysis	Findings: • Use of MFRT remained stable from 2015 to 2016 (62% vs. 62%) • Use of SFRT found to vary widely by individual provider (as high as 77% for all cases to 0%) Conclusion: Dissemination of Choosing Wisely Canada recommendations alone did not increase SFRT use by radiation oncologists in 2016. A comprehensive knowledge translation and change management campaign is underway.

Strategy	Author, Year (Country)	Strategy Characteristics	Evaluation/Study Characteristics	Authors Findings, Conclusions
Payment care model/Incentivized quality metrics	Jawaorksi, 2021[139] United States	• 28 facilities within Michigan Radiation Oncology consortium subjected to quality measure "% of patients who do not receive >10 fractions for treatment of bone metastases" • Measure was a component of facility-level pay-for-performance program, prior authorization exemption program, and physician-level value-based reimbursement	• 1445 consecutive patients with 1934 plans • Baseline established by convenience survey at 14.8% extended fractionation use • Compared this baseline to post-intervention	Findings: • Use of extended fractionation after intervention was 3.4%, lower than expected; remained low and declined over time • Factors predicting for extended fractionation use were complicated metastases, lack of CNS or visceral disease, nonteaching vs. teaching facilities, and physicians with more years in practice Conclusion: Resource intensive interventions including extended fractionation persist, though use was low after the intervention.
	Kapadia, 2022[140] United States	• OCM, an alternate payment model that incentivizes participating practices to improve quality and value of care	• Assessed CMS data to evaluate whether OCM alternative payment model for practices providing chemotherapy to patients with cancer affected the overall use and value of radiation therapy in terms of Choosing Wisely recommendations • Patients (19,366 MBD episodes); MBD from breast or prostate cancer including OCM episodes and non-OCM comparator group	Findings: • OCM had no effect on fractionation patterns for palliative RT (84.0% used ≤10 fractions in baseline period, compared with 87.5% in intervention period); comparison group (81.6% at baseline v. 86.2% during intervention); no difference for use of single-fraction treatment as well • Results similar for practice with and without a radiation oncologist Conclusion: OCM had no effect on fractionation patterns for MBD; future payment models focused on radiation oncology providers may be better poised to improve the value of radiation oncology care

Strategy	Author, Year (Country)	Strategy Characteristics	Evaluation/Study Characteristics	Authors Findings, Conclusions
Dedicated palliative radiation oncology service lines	Skamene, 2018[141] United States	• Implementation of a dedicated palliative radiation oncology service line at a single institution • Dedicated team includes specialized providers, daily rounds of palliative patients, and rapid access	• Retrospectively collected data from all patients treated with palliative intent at the center as well as three nonparticipating satellites • Included all patients' treatment before and after introduction of the service line	Findings: • Use of SFRT and hypofractionated RT (≤5) increased from 6.4% and 27.6% respectively to 22.3% and 53.5% • Compared with sites without a dedicated palliative radiation oncology service, patients treated in the service line more likely to receive SFRT or hypofractionated RT Conclusion: Implementation of a dedicated palliative radiation oncology service was associated with increased use of SFRT and hypofractionated RT

BMETS-DSP = Bone Metastases Ensemble Trees for Survival-Decision Support Platform; CNS = central nervous system; EHR = electronic health record; IPDAS = International Patient Decision Aids Standards; MBD = metastatic bone disease; MFRT = multiple fraction radiation therapy; OCM = Oncology Care Model; RT = radiation therapy; SFRT = single fraction radiation therapy; XRT: radiation therapy prescription.

Table C-2. Contextual Question 3. Summary of primary findings for studies describing financial burden

Author (Year)	Patient and Study Characteristics, Funding	Data and Primary Findings
Sahgal 2021[72] Canada	• RCT comparing conventional EBRT (20 Gy/5 fractions) vs. SBRT (24 Gy/2 fractions) • N= 229 patients with MRI confirmed spinal MBD without neurologic deficit; 52% male; median ages 65 vs. 63 years • >75% with occasional pain, 77% had VAS pain score 2-7; ECOG status score of 1 in 78% • Various primary tumors; 74% radiosensitive • Multicenter: Canada (90%), Australia (10%) • EORTC-QLQ-30 question: "Has your physical condition or medical treatment caused you financial difficulties?"; measured at baseline, 1-, 3- and 6-months posttreatment. • Funding: Canadian Cancer Society, Australian National Health and Medical Research Council	Financial question (scale 0-100 [worse])[a] Mean change score, SD; A (EBRT) vs. B (SBRT) • Baseline: n= 106 vs.106 28.30 (31.80) vs. 30.50 (33.21) • 1 month: n= 89 vs. 90 1.5 (24.1) vs. -5.9 (24.1); p=0.03 • 3 months: n= 81 vs. 82 0.4 (27.1) -7.3 (27.1); p=0.11 • 6 months: n=63 vs. 63 -1.1 (24.7) vs. -3.7 (24.7); p= 0.45 • Overall change, baseline to 6 months: n (%),[b] A vs. B; Improved: 22 (23) vs. 34 (35) Stable: 45 (48) vs.48 (50) Worsened: 27 (29) vs. 14 (15) Chi-square p=0.035 Mantel-Haenszel p=0.011 Findings: At one month, SBRT was associated with improved perception of financial strain compared with cEBRT based on mean change scores; however, the difference was no longer statistically significant at 3 or 6 months. Substantial variation is noted (large standard deviations). From baseline to 6 months, a higher proportion of SBRT recipients' perception of financial strain improved or stable compared with cEBRT recipients Author conclusion: SBRT was associated with improved perception of financial strain versus cEBRT. This finding could reflect the financial burden faced by patients with a terminal illness, and the differential effect of 2 days of treatment as opposed to 5 days.
Fischer-Valuck 2018[142] United States	• National Cancer Data Base (NCDB) data; retrospective study • N= 2641 patients with prostate cancer analyzed. • 84% received long-course-RT (30 Gy/10 fractions and 37.5 Gy/15 fractions, 14.6% received short-course-RT (8 Gy/1 fraction and 20Gy/5 fraction) • Median followup 19.2 months • Funding: NR	Findings: • Each increase in mile from the treatment center, there was an increased likelihood of receiving SC-RT (OR: 1.01, (95% CI 1.00-1.02); P = .040). • Multivariate analysis: Distance of >15 miles associated with increased odds of SC-RT compared with 0-5 miles, OR 1.38, 95%CI 1.05 to 1.83, p=0.23 Author conclusion: Increasing age, treatment at an academic/research center, treatment to the rib, increasing distance to treatment facility, and diagnosis in 2014 were associated with increased likelihood of receiving short-course RT.
Nongkynrih 2018[58] India	• RCT comparing 8 Gy/1 fraction (A), 20 Gy/5 fractions (B), 30 Gy/10 fractions (C) primarily to spine and pelvis • >70% male • >70% from rural, Karnofksy performance status of ≥60,>60% • Various primary sites • N=60 (20 per group) • Limited assessment of economic impact: average distance from home to treatment and related total expenditures • Funding: NR	Average distance and average cost (rupees) of travel for complete treatment • A: 101 km, Rs 1010/patient • B: 512 km, Rs 5120/patient • C: 970 km, Rs 9700/patient Author interpretation: Group A appears to be most economical, however, because of added advantage of most effective palliation in group B, it appears to be economically more feasible and favorable, because total expenditure on travel during radiation treatment is almost double in group C as compared to group B per patient.

Author (Year)	Patient and Study Characteristics, Funding	Data and Primary Findings
van den Hout 2003[143] Netherlands	• Cost-utility analysis of SFRT (8 Gy/1 fraction) vs. MFRT (4 Gy/6 fractions) from societal perspective • Data from 1996 Dutch Bone Metastasis Study (RCT, fair quality), N=1157 • N=166 patient subset who completed cost questionnaires: various tumors • Mean age, 65 years, >50% male, average Karnofsky score 72 (30-100); • Limited patient-specific economic data; costs per patient during first 12 weeks after randomization reported for radiotherapy, medical costs and other nonmedical costs • Retreatment ≤12 weeks, 18% vs. 5% (based on RCT) • Cost in 2002 USD • Funding: NR	A vs. B Costs (95% CI) Presumed patient cost for radiotherapy • Time, travel, out-of-pocket: $134 ($87 to $181) vs. $704 ($396 to $1012) Presumed patient nonmedical costs (other than radiotherapy)[c] • Overall $190 (-$89 to $464) vs. 28 (-$289 to $345) • Time, travel $94 ($41 to $147) vs. $130 ($74 to $186) • Out of pocket $127 ($42 to $212) vs. $64 ($22 to $106) • Domestic help $438 ($302 to $597) vs. $482 ($339 to $625) • Unpaid and paid labor -$468 ($656 to -$280) vs. -$647 (-$903 to -$391) Societal costs: $4700 ($3721 to $5679) vs. $6453 ($4869 to $8037) Author interpretation: The total nonmedical costs other than for radiotherapy were small because the additional costs were compensated by the value of the provided labor. From the patient perspective, SFRT is less burdensome versus MFRT. Although there is a considerable difference in retreatment probability (7% vs. 25%), an extra SFRT may still be less burdensome for most patients. Authors believe that difference in re-treatment may related to doctor's opinion on expected effectiveness and tolerance more than inadequacy of SFRT. Patients in SFRT group were retreated at lower pain scores vs. MFRT (6.8 vs. 7.5)

cEBRT= conventional external beam radiation therapy; CI = confidence interval; EORTC-QLQ-30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; ECOG=Eastern Cooperative Oncology Group; MBD = metastatic bone disease, MFRT = multiple fraction radiation therapy; NR = not reported; RCT = radiation therapy; Rs = rupee; SBRT = stereotactic body radiation therapy; SD = standard deviation; SFRT = single fraction radiation therapy; USD = United States dollars.

[a] EORTC-QLQ-30 scoring for items on 0-100 scale; higher scores indicate higher level for symptoms and single item scales indicate worse state for patient; authors considered change of 10 clinically relevant.

[b] Authors are not clear about what is reported in the parentheses in Table 2 of supplemental material; we assume n (%) are reported; Mantel-Haenszel used to verify direction of difference.

[c] Negative costs represent profits.

Appendix D. Included Studies List

1. 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up. Bone Pain Trial Working Party. Radiother Oncol. 1999 Aug;52(2):111-21. PMID: 10577696.
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Appendix E. Evidence Tables

Shown in associated Excel file at https://effectivehealthcare.ahrq.gov/products/radiation-therapy-bone-metastases/research.

Appendix F. Quality Assessments

Shown in associated Excel file at https://effectivehealthcare.ahrq.gov/products/radiation-therapy-bone-metastases/research.

Appendix G. Strength of Evidence

All outcomes were considered direct; therefore, the Directness domain is not shown on the strength of evidence tables.
See Appendix D, Included Studies List, for references.

Key Question 1

Table G-1. Key Question 1: Conventional EBRT, SF versus MF for initial radiation strength of evidence

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
Single (SF) vs. Multiple fractionation (MF) schemes for conventional EBRT	Pain, Overall Response *Post-RT to 4 weeks*	9 RCTs (N=1,280) Maranzano, 2009 MSCC Majumder, 2012 Spine Amouzegar-Hashemi, 2008 Foro Arnalot, 2008 Gaze, 1997 Hamouda, 2007 Nielsen, 1998 Price, 1986 Sarkar, 2002 Mixed spine and nonspine	12 to 52 weeks	Moderate	Consistent	Precise	Undetected	Moderate	**All Trials** SF: 67.5% (439/650) vs. MF: 71.9% (453/630) Pooled RR 0.93, 95% CI 0.88 to 0.99, I^2=0% Small decrease in likelihood of pain response with SF vs. MF **Mixed spine, nonspine (7 RCTs, N=924)** SF: 71.9% (338/470) vs. MF: 77.3% 251/454 Pooled RR 0.93, 95% CI 0.87 to 0.99 I^2=0% Small decrease in likelihood of pain response with SF vs. MF **MSCC/spine (2 RCTs, N=356**) SF: 56.1% (101/180) vs. MF: 58.0% (102/176) Pooled RR 0.96, 95% CI 0.78 to 1.16, I^2=0% No difference

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Pain, Overall Response *>4 to 12 weeks*	7 RCTs (N=2,173) Nielsen 1998, Anter 2015, Steenland 1999, Sarkar 2002, Hartsell 2005, Foro Arnalot 2008, Hamouda 2007 Mixed spine and nonspine	8 to 104 weeks	Moderate	Consistent	Precise	Undetected	Moderate	SF: 69.4% (756/1089) vs. MF: 68.3% (740/1084) Pooled RR 1.01, 95% CI 0.95 to 1.07, I^2=0 No difference
	Pain, Overall Response *>12 weeks*	2 RCTs (N=214) Nielsen 1998, Hamouda 2007 Mixed spine and nonspine	20 to 24 weeks	Moderate	Consistent	Precise	Undetected	Moderate	SF:58.3% (60/103) vs. MF: 66.7% (74/111) Pooled RR 0.87, 95% CI 0.68 to 1.12, I^2=0 No difference
	Pain, Overall Response *Timing NR or unclear*	2 RCTs (N=953) BPTWG, 1999 Mixed spine and nonspine Roos, 2005 Spine	52 to 260 weeks	Moderate	Consistent	Precise	Undetected	Moderate	**All trials** SF: 71.1% (347/488) vs. MF: 73.1% (340/465) Pooled RR 0.98, 95% CI 0.82 to 1.09, I^2=40 **Mixed (1 RCT)** SF: 78.1% (274/351) vs. MF: 77.9% (257/330), RR 1.0, 95% CI 0.93 to 1.09 **Spine (1 RCT)** SF: 53.3% (73/137) vs. MF: 61.5% (83/135) RR 0.87, 95% CI 0.71 to 1.06 No difference for all

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Pain, VAS/NRS/EOTRC scores[a] *Post-RT to 4 weeks*	4 RCTs (N=1,854) Hoskin 2019 MSCC Majumder 2012 Spine Kaasa 2006 Steenland 1999 Mixed spine and nonspine	4 to 52 weeks	Moderate	Consistent	Precise	Undetected	Moderate	SF: n=932; MF: n=922 Pooled mean difference 0.29, 95% CI -0.03 to 0.65, I^2=53.9% on a 0 to 10 scale No difference (estimate is below threshold for small effect)
	Pain, VAS/NRS scores *>4 to 12 weeks*	5 RCTs (N=1,837) Hoskin, 2019 Lee, 2018 MSCC Steenland, 1999 Nongkynrih, 2018 Kaasa, 2006 Mixed spine and nonspine	12 to 52 weeks	Moderate	Consistent	Imprecise	Undetected	Low	SF: n=920; MF: n=917 Pooled mean difference 0.03, 95% CI -0.42 to 0.41, I^2=65.6% No difference
	Pain, VAS/NRS scores *>12 weeks*	3 RCTs (N=1,395) Steenland, 1999 Nongkynrih, 2018 Kaasa, 2006 Mixed spine and nonspine	26 to 52 weeks	Moderate	Consistent	Imprecise	Undetected	Low	SF: n=693; MF: n=702 Pooled mean difference -0.07, 95% CI -0.46 to 0.29, I^2=0% No difference

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Function	2 (N=150) Gutierrez Bayard, 2014 Nongkynrih, 2018 Mixed spine and nonspine	26 to 260 weeks	High	Consistent	Imprecise	Undetected	Insufficient	<u>Improvement in performance status, measure (KPS or EORTC performance scale) and timing unclear:</u> **1 RCT** SF: 10% (2/20) vs. MF: 15% (6/40); RR 0.67, 95% CI, 0.45 to 3.01 <u>Barthel Index</u> **1 RCT (N=90**) *Time to improvement of one grade of functionality* SF: mean 4.8 months (95% CI 3.3 to 6.4 months) vs. MF: 5.4 months (95% CI 3.9 to 6.9 months), p=0.339 *Time to performance of ADLs independently and without pain* SF: mean 7 months (95% CI 5 to 9 months) vs. MF: mean 5 months (95% CI 4 to 7 months], respectively, p=0.549 No difference
	Relief of SCC *Post-RT to 4 weeks*	3 RCTs (N=1,027) Abu Hegazy, 2011[b] Maranzano, 2009 Hoskin, 2019 All MSCC	52 to 156 weeks[c] (across 2 RCTs)	Moderate	Consistent	Precise	Undetected	Moderate	**Ambulation: Maintenance or improvement from baseline** SF: 86.3% (82/95) vs. MF: 86.8% (165/190), RR 0.99, 95% CI 0.90 to 1.10 SF: 62.1% (95/153) vs. MF: 69.3% (104/150), RR 0.90 (95% CI 0.76 to 1.05) SF: 66.8% (143/214) vs. MF: 67.6% (152/225), RR 0.99 (95% CI 0.87 to 1.13) No difference

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Relief of SCC *>4-12 weeks*	2 RCTs (N=373) Hoskin, 2019 Thirion, 2020 Both MSCC	12 to 52 weeks	Moderate	Consistent	Imprecise	Undetected	Low	**Ambulation: Maintenance or improvement from baseline** SF: 61.1% (22/36) vs. MF: 54.1% (20/37), RR 1.13, 95% CI 0.76 to 1.68 SF 71.8% (102/142) vs. MF: 67.7% (107/158), RR 1.06, 95% CI 0.91 to 1.23 No difference
	Quality of Life *Various timepoints*	6 RCTs (N=2,338) Gaze, 1997 Kaasa, 2006 Nielsen, 1998 Steenland, 1999 Mixed spine and nonspine Hoskin, 2019 Lee, 2018 MSCC	12 to 156 weeks	Moderate	Consistent	Imprecise	Undetected	Low	No differences across 5 RCTs (timepoints ranged from 4 to 28 weeks): 3 used the EORTC QLQ-C30 but reported it differently; 1 use the VAS (0-100) QOL scale; 1 used the Spitzer QOL index; and 1 used the Rotterdam Symptom Check List (but provided no data).

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Pathological fracture	**9 RCTs** (N=4,069) BPTWG, 1999 Gutierrez Bayard, 2014 Hamouda, 2007 Hartsell, 2005 Kaasa, 2006 Nielsen, 1998 Price, 1986 Steenland, 1999 Mixed spine and nonspine Roos, 2005 Spine **1 NRSI** (N=299, full cohort; N=132, propensity-matched cohort) Lam 2015 Spine	Median 13.5 weeks to 104 weeks	Moderate	Consistent (RCTs) Unknown (NRSI) Inconsistent across study designs	Imprecise	Undetected	Low	**All RCTs** SF: 4.1% (84/2057) vs. MF: 3.4% (70/2029) Pooled RR 1.18, 95% CI 0.68 to 2.08, I^2=53.1% **RCTs, Mixed** (8 RCTs) SF: 4.1% (781920) vs. MF: 3.3% (65/1984) Pooled RR 1.18, 95% CI 0.62 to 2.26 **RCTs, Spine** (1 RCT) SF: 4.4% (6/137) vs. MF: 3.7% (5/135) RR 1.18, 95% CI 0.37 to 3.78 RCTs: No difference **NRSI** Symptomatic vertebral fractures: 13.6% (9/66) vs. 3.0% (7/233) in full cohort, OR 3.73 (95% CI 1.61 to 8.63) (unclear if adjusted estimate) Greater odds of fracture with SF EBRT Risk of fracture, 13.6% (9/66) vs. 1.5% (1/66), in propensity score matched cohort.

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	New spinal cord compression	5 RCTs (N=2,774) BPTWG 1999 Kaasa 2006 Price 1986 Steenland 1999 Mixed spine and nonspine Roos 2005 Spine	Median 13.5 weeks to 104 weeks	Moderate	Consistent	Imprecise	Undetected	Low	**All RCTs** SF: 2.9% (40/1393) vs. MF: 2.0% (28/1381) Pooled RR 1.41, 95% CI 0.87 to 2.30, I^2=0% **Spine** (1 RCT; N=272) SF: 6.6% (9/137) vs. MF: 5.9% (8/135), RR 1.1, 95% CI 0.44 to 2.79 No difference
	Cord or cauda equina compression, deterioration of neural symptoms	1 NRSI (N=299, full cohort; N=132, propensity-matched cohort) Lam 2015 Spine	26 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	Full cohort SF: 10.5% (7/66) vs. MF: 1.7% (4/233), p=0.003 Propensity score-matched cohort SF: 10.6% (7/66) vs. MF: 0% (0/66), p=0.002 Higher risk with SF EBRT
	Skeletal related event (reradiation or pathologic fracture)	1 RCT (N=90) Gutierrez Bayard 2014 Mixed spine and nonspine	260 weeks	High	Unknown	Imprecise	Undetected	Insufficient	SF: 28.8% (13/45) vs. MF: 13.3% (6/45) RR 2.17, 95% CI 0.90 to 5.19 No difference

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Spinal adverse event (SAE)	1 NRSI (N=299, full cohort; N=132, propensity-matched cohort) Lam 2015 Spine	26 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	Any SAE[d]: SF: 27.3% (18/66) vs. MF: 14.2% (33/233), adjusted HR 2.78, 95% CI 1.51 to 5.15 3-month cumulative incidence: SF: 16.9% (11/66) vs. MF: 6.4% (15/233) Propensity score-matched analysis, rate of first AE at 3 months: SF: 22.5% (15/66) vs. MF 7.7% (5/66), HR 3.2, 95% CI 1.3 to 7.5 SF EBRT associated with higher likelihood of SAEs
	Pain Flare[e]	1 RCT (N=233) Roos 2005 Spine	Median 13.5 weeks	Moderate	Unknown	Imprecise	Undetected	Low	**Any** SF: 10.2% (14/137) vs. MF: 4.4% (6/135), RR 2.0, 95% CI 0.91 to 5.81 **Mild** SF: 1.5% (2/137) vs. MF: 1.5% (2/135) **Moderate** SF: 3.6% (5/137) vs. MF: 1.5% (2/135) **Severe** SF: 5.1% (7/137) vs. MF: 1.5% (2/135) No difference

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Pain Flare (various definitions)[f] *1.4 to 2 weeks*	2 NRSI (N=155) Hird 2009 (N=111) Mixed spine and nonspine Loblaw 2007 (N=44) MBD sites not reported	6 to 12 weeks	High	Unknown	Imprecise	Undetected	Insufficient	Mixed spine and nonspine (1 RCT) SF: 38.6% (27/70) vs. MF: 39% (16/41), crude RR 1.35, 95% CI 0.87 to 2.11 MBD sites not reported (1 RCT) Tannock definition: SF: 43.5% (10/23) vs. MF: 23.8% (5/21), RR 1.83, 95% CI 0.75 to 4.47 Chow Definition: SF: 56.5% (13/23) vs. MF: 23.8% (5/21); RR 2.37, 95% CI 1.02 to 5.53 No difference
	Radiation myelopathy	1 RCT (N=303) Maranzano, 2009 MSCC	Median 135 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	SF: 0% (0/153) vs. MF: 0% (150) No difference: events may be rare; study may be insufficiently powered
	Toxicity Acute; Grade 4	3 RCT (N=1,141)[g] Anter ,2015 Gaze, 1997 Hartsell, 2005 Mixed spine and nonspine 1 RCT (N=235) Howell, 2013 (subanalysis of Hartsell 2005) Spine	12 to 260 weeks	Moderate	Consistent	Imprecise	Undetected	Insufficient	Mixed (3 RCTs): SF: 0% to 3% (N range, 44 to 433) vs. MF: 0% to 2% (N range, 44 to 414) Spine (RCT subanalysis): SF: 0% (0/124) vs. MF: 1% (1/111) No difference: events may be rare; individual studies may be insufficiently powered

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Toxicity Acute Any Grade 3	1 RCT (N=847) Hartsell, 2005 Mixed spine and nonspine	104 weeks	High	Unknown	Imprecise	Undetected	Insufficient	SF: 3.0% (13/433) vs. MF: 4.1% (17/414) RR 0.73, 95% CI 0.36 to 1.49 No difference
	Toxicity (various) Acute Any Grade 3	2 RCT (N=296) Anter, 2015 Gaze, 1997 Mixed spine and nonspine	12 weeks and NR (reports up to 156 weeks)	High	Unknown	Imprecise	Undetected	Insufficient	1 RCT: GI toxicity, 2.3% (1/44) in SF and MF group; no other toxicities (hematological, lung, CNS) occurred 1 RCT: Nausea and vomiting: SF: 10.9% (12/110) vs. MF: 15.3% (15/98); RR 0.71, 95% CI 0.35 to 1.45 Tiredness and lassitude: SF: 10% (11/110) vs. MF: 13.5% (13/96); RR 0.67, 95% CI 0.31 to 1.46 No difference
	Toxicity (various) Any Grade 3	3 RCTs (N=287 across 2 RCTs) Thirion, 2020 (N=52) MSCC Majumder, 2012 (N=NR) Howell, 2013 (n=235, subanalysis of Hartsell, 2005) Spine	4 to 240 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	Late upper thigh pain (1 RCT, MSCC): SF: 0% (0/27) vs. MF: 4% (1/25) GI toxicities (1 RCT, spine): 0% vs. 6.1% (denominators unclear) Any acute (RCT subanalysis, spine): <1% (1/124) vs. 2.7% (3/111); RR 0.30, 95% CI 0.03 to 2.83 No difference

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Toxicity, Late (>12 weeks) Any Grade 3 and 4	1 RCT (N=696) Hartsell, 2015 Mixed spine and nonspine Howell, 2013 (n=235), subanalysis of Hartsell, 2005 Spine only	104 to 240 weeks	High	Unknown	Imprecise	Undetected	Insufficient	**Mixed** Grade 3 SF: <1% (2/354) vs. MF: <1% (2/342), RR 0.97, 95% CI 0.14 to 6.82 Grade 4 SF: 0% (0/354) vs. MF: 0% (0/342) **Spine** Grade 3 SF: 1.6% (2/124) vs. MF: 0% (0/111) Grade 4 SF: 0% (0/124) vs. MF: <1% (1/111) No difference
	Acute Toxicity: Nausea, vomiting quite a bit or very much	1 RCT (N=124) BPTWG, 1999 Mixed spine and nonspine	52 weeks	Moderate	Unknown	Imprecise	Undetected	Low	Nausea SF: 39.3% (24/61) vs. MF: 39.7% (25/63); RR 0.99, 95% CI 0.64 to 1.53 Vomiting SF: 19.7% (12/61) vs. MF: 20.6% (13/63); RR 0.95, 95% CI 0.47 to 1.92 No difference
	Impaired bladder function *Any time and 8 weeks*	1 RCT (N=638) Hoskin, 2019 MSCC	52 weeks	Moderate	Unknown	Imprecise	Undetected	Low	**Any time** SF: 43.7% (132/316) vs. MF: 34.5% (111/322); cumulative RD 7.3%, 95 CI -14.8% to 0.2%; adjusted OR 1.31, 95% CI 0.87 to 1.97 **8 weeks** SF: 31.1% (47/151) vs. MF: 20.5% (34/166); RD 10.6%, 95% CI 1.0% to 20.2%; adjusted OR, 1.78, 95% CI 0.93 to 3.39 No difference

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Impaired bowel function *Any time and 8 weeks*	1 RCT (N=638) Hoskin, 2019 MSCC	52 weeks	Moderate	Unknown	Imprecise	Undetected	Low	**Any time** SF: 64.4% (203/315) vs. MF: 63.4% (204/322); unadjusted OR 1.05, 95% CI 0.76 to 1.45 **8 weeks** SF: 39.1% (59/151) vs. MF: 36.7% (61/166); RD 2.3%, 95% CI 8.4% to 13.0%; unadjusted OR 1.10, 95% CI 0.70 to 1.74 No difference
	Various Adverse Events	1 RCT (N=1,157) Steenland, 1999 Mixed spine and nonspine	52 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	1 Small bowel ileus in MF group; 1 radiation enteritis in SF group due to retreatment
	Withdrawals due to AEs	2 RCTs (N=119) Majumder, 2012 Spine Sarkar, 2002 Mixed spine and nonspine	4 to 8 weeks	Moderate	Consistent	Imprecise	Undetected	Low	SF: 0% vs. MF: 0% (N's unclear) No difference

ADLs = activities of daily living; AE = adverse event; BPTWG = Bone Pain Trial Working Group; CI = confidence interval; EBRT = external beam radiation therapy; EORTC = European Organization for Research and Treatment of Cancer; GI = gastrointestinal; KPS = Karnofsky performance scale; MBD = metastatic bone disease; MF = multiple fraction; MSCC = metastatic spinal cord compression; NR = not reported; NRS = numerical rating scale; NRSI = nonrandomized study of interventions; OR = odd ratio; QOL = quality of life; RCT= Randomized controlled trial; RD = risk difference; RR = risk ratio; RT = Radiation therapy; SAE = serious adverse event; SCC = spinal cord compression; SF = single fraction; VAS = visual analog scale.

[a] Use of VAS for Lee 2018, NRS for Kaasa 2006.

[b] Multi-fraction arms were combined.

[c] Abu-Hegazy did not specify followup period.

[d] SAEs: included hospitalization for uncontrolled pain, symptomatic vertebral fracture, interventional procedure salvage surgery, new or deteriorated neurologic symptoms, cord or cauda equina compression.

[e] Defined as a temporary increase in pain at the index site within a week of commencing RT.

[f] Definitions of pain flare: Hird - 2-point increase in the worst pain score (0–10) compared to baseline with no decrease in analgesic intake, or a 25% increase in analgesic intake with no decrease in worst pain score. Loblaw - used 2 definitions (Tannock = Pain flare was defined as the converse of a pain response) (Chow = Pain flare was defined as a two-point increase in the PPI with no decrease in analgesic score or a 25% increase in analgesic score with no decrease in PPI on at least two consecutive days).

[g] Only the poor quality trial (Gaze 1997) specified type: nausea/vomiting, tiredness/lassitude.

Table G-2. Key Question 1: Conventional EBRT, LDSF versus HDSF for initial radiation strength of evidence

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
Single fractionation schemes for conventional EBRT: lower total dose (LDSF) vs. higher total dose single fraction (HDSF)[a]	Pain, Overall Response *Post-RT to 4 weeks*	2 RCTs (N=861) Jeremic, 1998 Hoskin, 2015 Mixed spine and nonspine	52 to 156 weeks	Moderate	Inconsistent	Precise	Undetected	Low	LDSF: 64.2% (237/369) vs. HDSF: 76.8% (378/492) Pooled RR 0.80, 95% CI 0.58 to 1.02, I^2=75.5% LDSF was associated with slightly lower likelihood of overall response
	Pain, Overall Response *>4 to 12 weeks*	2 RCTs (N=743) Jeremic, 1998 Hoskin, 2015 Mixed spine and nonspine	52 to 156 weeks	Moderate	Inconsistent	Precise	Undetected	Low	LDSF: 74.3% (228/307) vs. HDSF: 83.3% (363/436) Pooled RR 0.89, 95% CI 0.72 to 1.0, I^2=63.9% LDSF was associated with slightly lower likelihood of overall response
	Pain, Overall Response *>12 weeks*	1 RCT (N=180) Hoskin, 2015 Mixed spine and nonspine	52 weeks	Moderate	Unknown	Precise	Undetected	Low	LDSF: 82.3% (65/79) vs. HDSF: 93.1% (94/101) RR 0.88, 95% CI 0.79 to 0.99 LDSF was associated with slightly lower likelihood of overall response

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Pain, VAS scores *30 weeks*	1 RCT (N=115) Mañas, 2008[b] Mixed spine and nonspine	30 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	VAS pain (0-10), mean (SDs NR) Supine: LDSF: 1.79 vs. HDSF: 1.04, p=0.067 Seated: LDSF:1.67 vs. HDSF: 0.96, p=0.123 Standing: LDSF: 2.34 vs. HDSF: 1.27, p=0.006 May be a small improvement in pain in supine and standing positions with HDSF compared with LDSF (Inadequate data to calculate effect sizes, confidence intervals)
	Function KPS score *30 weeks*	1 RCT (N=117) Mañas, 2008[b] Mixed spine and nonspine	30 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	KPS (0 to 100 scale)[c] mean (SDs NR) LDSF: 77.27 vs. HDSF: 84.62, p=0.1635 (ANCOVA model) No difference (Inadequate data to calculate effect sizes, confidence intervals)

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Quality of Life EORTC QLQ C-*30*[d] *weeks*	1 RCT (N=113) Mañas, 2008[b] Mixed spine and nonspine	30 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	Means (SDs NR) Part 1 LDSF: 6.67 vs. HDSF: 6.08, p=0.8464 Part 2 LDSF: 33.15 vs. HDSF: 30.81, p=0.8146 Part 3 LDSF: 9.24 vs. HDSF: 9.62, p=0.9967 (ANCOVA model) No difference (Inadequate data to calculate effect sizes, confidence intervals)
	Pathological fracture *≤8 weeks*	1 RCT (N=327) Jeremic, 1998 Mixed spine and nonspine	Mean, 42 to 50 weeks	Moderate	Unknown	Imprecise	Undetected	Low	LDSF: 0% (0/109) vs. HDSF: 0% (0/218) No difference
	Pathological fracture *>8 weeks*	1 RCT (N=137) Jeremic, 1998 Mixed spine and nonspine	Mean, 42 to 50 weeks	Moderate	Unknown	Imprecise	Undetected	Low	LDSF: 6.3% (3/48) vs. HDSF: 9.7% (6/89) RR 0.92, 95% CI 0.24 to 3.54 No difference
	New spinal cord compression *≤8 weeks*	1 RCT (N=327) Jeremic, 1998 Mixed spine and nonspine	Mean, 42 to 50 weeks	Moderate	Unknown	Imprecise	Undetected	Low	LDSF: 0% vs. HDSF: 0% No difference
	New spinal cord compression *>8 weeks*	1 RCT (N=190) Jeremic, 1998 Mixed spine and nonspine	Mean, 42 to 50 weeks	Moderate	Unknown	Imprecise	Undetected	Low	LDSF: 6.6% (4/61) vs. HDSF: 7.0% (9/129) RR 0.94, 95% CI 0.30 to 2.93 No difference

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Skeletal events (pathological fracture, re-irradiation, or spinal cord compression)	1 RCT (N=137) Mañas, 2009[b] Mixed spine and nonspine	30 weeks	Moderate	Unknown	Imprecise	Undetected	Low	LDSF: 23.5% (14/57) vs. HDSF: 19.4% (15/80) RR 1.31, 95% CI 0.68 to 2.49 No difference
	Adverse events (not specified)	1 RCT (N=137) Mañas, 2009[b] Mixed spine and nonspine	30 weeks	Moderate	Unknown	Imprecise	Undetected	Low	LDSF: 47.4% (27/57) vs. HDSF: 61.3% (49/80) RR 0.77, 95% CI 0.56 to 1.07 No difference
	Adverse reactions (not specified)	1 RCT (N=137) Mañas, 2009[b] Mixed spine and nonspine	30 weeks	Moderate	Unknown	Imprecise	Undetected	Low	LDSF: 14.0% (8/57) vs. HDSF: 21.3% (17/80) RR 0.66, 95% CI 0.31 to 1.42 No difference

CI = confidence interval; EBRT = external beam radiation therapy; EORTC QLQ C-30 = The European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (version 3); HDSF = higher dose single fraction; KPS = Karnofsky Performance Status Scale; LDSF = lower dose single fraction; MBD = metastatic bone disease; MSCC = metastatic spinal cord compression; NR = not reported; NRS = numerical rating scale; RCT = randomized control trial; RR = risk ratio; SD = standard deviation; VAS = visual analog scale.

[a] Higher dose single fraction was considered the control.

[b] All patients received zoledronic acid plus calcium and vitamin D supplements.

[c] Higher scores indicate better function.

[d] Manas divides into 3 parts: Part 1 with five yes/no questions on daily activities; Part 2 with 21 questions on daily symptoms (1-4 scale for each question); and Part 3 consisting of two questions (1-7 scale).

Table G-3. Key Question 1: Conventional EBRT, LDMF versus HDMF for initial radiation strength of evidence

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
Multiple fractionation schemes for conventional EBRT: lower total dose (LDMF) vs. higher total dose multiple fractions (HDMF)	Pain, Overall Response *Post-RT to 4 weeks*	6 RCTs (N=788) Maranzano, 2005 Rades, 2019 MSCC Atahan, 2010 Niewald, 1996 Nongkynrih, 2018 Rasmusson, 1995 Mixed spine and nonspine	26 to 156 weeks	Moderate	Consistent	Precise	Undetected	Moderate	LDMF: 64.1% (252/393) vs. HDMF: 67.0% (258/385) Pooled RR 0.96, 95%CI 0.87 to 1.06, I^2=0% No difference
	Pain, Overall Response *>4 to 12 weeks*	3 RCTs (N=275) Rades, 2019 MSCC Atahan, 2010 Rasmusson, 1995 Mixed spine and nonspine	26 to 52 weeks	Moderate	Consistent	Precise	Undetected	Moderate	LDMF: 79.6% (109/137) vs. HDMF: 80.4% (111/138) Pooled RR 1.02, 95% CI 0.89 to 1.12, I^2=0% No difference
	Pain, Overall Response *>12 weeks*	2 RCTs (N=114) Rades, 2019 MSCC Rasmusson, 1995 Mixed spine and nonspine	26 to 52 weeks	High	Consistent	Precise	Undetected	Low	LDMF: 78.6% (44/56) vs. HDMF: 72.4% (42/58) Pooled RR 1.10, 95% CI 0.86 to 1.38, I^2=0% No difference
	Pain, Overall Response *Timing not reported or unclear*	3 RCTs (N=372) Niewald, 1996 Okawa, 1988 Mixed spine and nonspine He, 2019 MBD sites NR	65 weeks in 1 RCT (2 RCTs unclear)	High	Consistent	Precise	Undetected	Low	LDMF: 70.4% (119/169) vs. HDMF: 74.4% (151/203) Pooled RR 0.95, 95% CI 0.87 to 1.08. I^2=0% No difference

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Function, general/overall: Improvement in mobility	1 RCT (N=100) Niewald, 1996 Mixed spine and nonspine	Median 52 weeks	High	Unknown	Imprecise	Undetected	Insufficient	Immediately posttreatment LDMF: 70.6% (36/51) vs. HDMF: 71.4% (35/49) RR 0.99, 95% CI 0.77 to 1.27 Last followup (time NR) LDMF: 25.5% (13/51) vs. HDMF: 24.5% (12/49) RR 1.04, 95% CI 0.53 to 2.05 No difference
	Function, general/overall: Moderate or severe limitations in activity *Various timepoints*	1 RCT (N=166 at baseline) Rasmusson, 1995 Mixed spine and nonspine	52 weeks	High	Unknown	Imprecise	Undetected	Insufficient	**4 weeks** LDMF: 41.7% (25/60) vs. HDMF: 42.4% (28/66); RR 0.98, 95% CI 0.65 to 1.48 **12 weeks** LDMF: 32.6% (14/43) vs. HDMF: 34.7% (17/49); RR 0.92, 95% CI 0.52 to 1.67 **26 weeks** LDMF: 25.0% (7/28) vs. HDMF: 22.6% (7/31); RR 1.11, 95% CI 0.44 to 2.76 **52 weeks** LDMF: 23.1% (3/13) vs. HDMF: 35.7% (5/14); RR 0.65, 95% CI 0.19 to 2.18 No difference
	Function general/overall: Performance status improvement *Timing unclear*	1 RCT (N=40) Nongkynrih, 2018 Mixed spine and nonspine	26 weeks	High	Unknown	Precise	Undetected	Insufficient	LDMF: 65% (13/20) vs. HDMF: 65% (13/20); RR 1.00, 95% CI 0.63 to 1.58 No difference

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Relief of spinal cord compression (ambulatory) *Various timepoints*	2 RCTs (N=382) Rades, 2016 Abu-Hegazy, 2011 MSCC	Post-RT to 26 weeks	Moderate	Consistent	Precise	Undetected	Moderate	1 RCT (Rades) **Post-RT (time NR)** LDMF: 63.5% (61/96) vs. HDMF: 64.6% (62/96); RR 0.98, 95% CI 0.80 to 1.22 **4 weeks** LDMF: 71.8% (56/78) vs. HDMF: 74.0% (57/77), RR 0.97, 95% CI 0.80 to 1.17 **12 weeks** LDMF: 80.9% (38/47) vs. HDMF: 73.3% (33/45); RR 1.10, 95% CI 0.88 to 1.38 **26 weeks** LDMF: 81.8% (27/33) vs. HDMF: 83.3% (25/30); RR 0.98 95% CI 0.78 to1.23 1 RCT (Abu-Hegazy) **Post-RT (time NR)** LDMF: 87% (87/100) vs. HDMF: 86.7% (78/90); RR 1.00, 95% CI 0.90 to 1.12 No differences at any time

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Relief of spinal cord compression (motor function based on regain of walking capacity) *Post-RT*	1 RCT (N=276) Marzano, 2005 MSCC		Moderate	Unknown	Imprecise	Undetected	Low	**Pre-RT, not walking** LDMF: 34.5% (49/142) vs. HDMF: 32.1% (43/134) **Post-RT, regained walking** LDMF: 28.6% (14/49) vs. HDMF: 27.9% (12/43) RR 1.02, 95% CI 0.53 to 1.97 No difference
	Relief of spinal cord compression (motor function) *Various timepoints*	1 RCT (N=203 at baseline) Rades, 2016 MSCC	26 weeks	Moderate	Unknown	Imprecise	Undetected	Low	**Post-RT (time NR)** LDMF: 24.0% (23/96) vs. HDMF: 28.1% (27/96); RR 0.85, 95% CI 0.53 to 1.38 **4 weeks** LDMF: 38.5% (30/78) vs. HDMF: 44.2% (34/77); RR 0.87, 95%CI 0.60 to 1.27 **12 weeks** LDMF: 42.6% (20/47) vs. HDMF: 48.9% (22/45), RR 0.87, 95% CI 0.56 to 1.36 **26 weeks** LDMF: 57.6% (19/33) vs. HDMF: 60.0% (18/30), RR 0.96, 95% CI 0.63 to 1.45 No difference

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Relief of spinal cord compression (Regain sphincter control) *Post-RT*	2 RCTs (N=466) Maranzano, 2005 Abu-Hegazy, 2011 MSCC	Post-RT to 52 weeks	Moderate	Consistent	Imprecise	Undetected	Low	**1 RCT** Abnormal pre-RT: LDMF: 11.3% (16/142) vs. HDMF: 9.7% (13/134) Sphincter control regained: LDMF: 12.5% (2/16) vs. HDMF: 15.4% (2/13); RR 0.81, 95% CI 0.13 to 5.00 **1 RCT** Abnormal pre-RT LDMF: 10% (10/100) vs. HDMF: 7.8% (7/90) Return to normal sphincter control: LDMF: 70% (7/10) vs. HDMF: 71.4% (5/7); RR 0.98, 95% CI 0.53 to 1.82 No difference
	Relief of spinal cord compression (Neurological Deficit) *Post-RT*	1 RCT (N=190) Abu-Hegazy, 2011 MSCC	Post-RT	High	Unknown	Imprecise	Undetected	Insufficient	Deficit pretreatment LDMF: 19% (19/100) vs. HDMF: 22.2% (20/90) Post-RT recovery LDMF: 31.6% (6/19) vs. HDMF: 30% (6/20); RR 1.05, 95% CI 0.41 to 2.70 No difference

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Pathological fracture	2 RCTs (N=197) Niewald 1996, Atahan, 2010 1 NRSI (N=105) Valeriani Mixed spine and nonspine 1 RCT (N=203) Rades 2016 MSCC	26 to 52 weeks 4 weeks 26 weeks	Moderate	Consistent	Imprecise	Undetected	Low	**Mixed spine and nonspine** 2 RCTs LDMF: 6.9% (7/102) vs. HDMF: 12.6% 12/95); Pooled RR 0.54, 95% CI 0.19 to 1.51, I^2=0% 1 NRSI LDMF: 0% (0/58) vs. HDMF: 2.1% (1/47) **MSCC (1 RCT)** LDMF: 0% (0/101) vs. HDMF: 0% (0/102) No difference: studies may have been underpowered
	Spinal cord compression	2 RCTs (N=187) Atahan, 2010 MBD sites NR Ozsaran, 2001 Mixed spine and nonspine	26 weeks	Moderate	Consistent	Imprecise	Undetected	Insufficient	1 RCT (Atahan) LDMF: 0% (0/51) vs. HDMF: 2.0% (1/49); RR 0.32, 95%CI 0.01 to 7.68 1 RCT (Ozsaran) LDMF: 0% (0/38) vs. HDMF: 0% (0/35) No difference: studies may have been underpowered

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Grade 3 Toxicity	1 RCT (N=276) Maranzano, 2005 MSCC	52 weeks	Moderate	Unknown	Imprecise	Undetected	Low	Esophagitis LDMF: 1.4% (2/142) vs. HDMF: <1% (1/134); RR 1.89, 95% CI 0.17 to 20.57 Pharyngeal dysphagia LDMF: 0% (0/142) vs. HDMF: <1% (1/134) Diarrhea LDMF: 1.4% (1/142) vs. HDMF: 1.5% (2/134); RR 0.47, 95% CI 0.04 to 5.14 No difference
	Grade 3 or 4 Toxicity	1 NRSI (N=105) Valeriani, 2015 Mixed spine and nonspine	Up to 18 months	High	Unknown	Imprecise	Undetected	Insufficient	LDMF: 0% (0/58) vs. HDMF: 2.1% (1/47) No difference
	Radiation-induced myelopathy or cord morbidity	3 RCTs (N=679 as baseline)[a] Maranzano, 2005 Rades, 2016 Rasmusson, 1995 MSCC	Range	Moderate	Unknown	Imprecise	Undetected	Insufficient	All studies in patients with MSCC. Authors only provide statements that this did not occur.

CI= confidence interval; EBRT = external beam radiation therapy; HDMF = higher total dose multiple fraction; LDMF = lower total dose multiple fraction; MBD = metastatic bone disease; MSCC = metastatic spinal cord compression; NRSI = nonrandomized controlled studies of interventions; RCT = randomized controlled trial; RR = risk ratio; RT = radiation therapy; VAS = visual analog scale.
[a] N at study start reported; authors do not provide number of patients at followup for this outcome.

Table G-4. Key Question 1: SBRT, SF versus MF and MF versus MF fractionation schemes for initial radiation strength of evidence

Comparison	Outcome Timing	Number of RCTs (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
Single (SF) vs. Multiple fractionation (MF) schemes for SBRT	Pathological fracture	1 RCT (N=117) Zelefsky, 2021 1 NRSI (N=105) Zelefsky, 2012 Mixed spine and nonspine	Median 226 weeks Median 52 weeks	Moderate Moderate	Consistent	Imprecise	Undetected	Low	RCT Grade ≥2 fracture: SF: 2.6% (2/77 lesions) vs. MF: 2.6% (2/77 lesions) No difference Highest quality NRSI[a] Vertebral body fracture SF: 3.4% (2/59) vs. MF: 4.3% (2/46); RR 0.78, 95% CI 0.11 to 5.33 No difference
	Pain Flare	1 NRSI (N=43) Ghia, 2016 Spine	Median 23 months	High	Unknown	Imprecise	Undetected	Insufficient	SF: 35% (7/20 sites) vs. MF: 30% (6/20 sites) No difference
	Grade 4 Toxicity	1 NRSI (N=105) Zelefsky, 2012 Mixed spine and nonspine 1 NRSI (N= 127) Kelley, 2019 Spine	Median 52 weeks Median 23.6 weeks	Moderate (mixed) High (spine)	Unknown	Imprecise	Undetected	Low (mixed) Insufficient (spine)	**Mixed spine and nonspine** Grade 4 erythema SF: 1.7% (1/59) vs. MF: 0% (0/46) No difference **Spine** Grade ≥4 toxicity SF: 0% (0/112) vs. MF: 0% (0/15) No difference

Comparison	Outcome Timing	Number of RCTs (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Grade ≥ 3 or Grade ≥ 2 Toxicity	1 RCT (N= 117) Zelefsky, 2021 1 NRSI (N=105) Zelefsky, 2012 Mixed spine and nonspine	Median 226 weeks Median 52 weeks	Moderate Moderate	Consistent	Imprecise	Undetected	Low	**RCT** Any toxicity: Grade ≥3 SF: 7.8% (6/77 lesions) vs. MF: 3.9% (3/77 lesions), p=0.49 Grade ≥2 SF: 11.7% (9/77 lesions) vs. MF: 6.5% (5/77 lesions), p=0.39 Specific Grade ≥2: Pain SF: 9.1% (7/77 lesions) vs. MF: 3.9% (3/77 lesions), p=NR Neuropathy SF: 2.6% (2/77 lesions) vs. MF: 0% (0/77 lesions), p=NR **NRSI** Grade ≥2 neuropathy SF: 8.5% (5/59) vs. MF: 2.2% (1/46); RR 3.89, 95% CI 0.47 to 32.22 No difference for any outcome
	Adverse events, Other	1 NRSI (N= 105) Zelefsky, 2012 Mixed spine and nonspine	Median 52 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	Tracheoesophageal fistulae: SF: 2.9% (2/68)[b] vs. MF: 0% (0/52) No difference
Multiple fractionation schemes for SBRT: lower total dose (LDMF) vs. higher total dose multiple fraction (HDMF)	Pain *12 weeks*	1 NRSI (N=57) Guckenberger, 2018 Spine	12 weeks	High	Unknown	Imprecise	Unknown	Insufficient	Overall pain response LDMF: 91% of lesions vs. HDMF: 85% of lesions VAS pain, mean (SD) LDMF: 1.2 (1.8) vs. HDMF: 2.0 (2.3) (number of patients NR) No difference

Comparison	Outcome Timing	Number of RCTs (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	New vertebral compression fracture	1 NRSI (N=57) Guckenberger, 2018 Spine	12 weeks	High	Unknown	Imprecise	Unknown	Insufficient	LDMF: 9% of lesions vs. HDMF: 17% of lesions (number of patients NR) No difference
	Acute Toxicity Grade 4; Radiation induced myelopathy	1 NRSI (N=57) Guckenberger, 2018 Spine	12 weeks	High	Unknown	Imprecise	Unknown	Insufficient	Grade 4 toxicity LDMF: 0% of lesions vs. HDMF: 0% of lesions Radiation induced myelopathy LDMF: 0% of lesions vs. HDMF: 0% of lesions (number of patients NR) No difference

CI = confidence interval; HDMF = higher total dose multiple fraction; LDMF = lower total dose multiple fraction; MF = multiple fraction; NR = not reported; NRS = numerical rating scale; NRSI = nonrandomized studies of intervention; RCT = randomized control trial; RR = risk ratio; SBRT = stereotactic body radiotherapy; SD = standard deviation; SF = single fraction; VAS = visual analog scale.

[a] An additional poor quality NRSI (Ghai 2016) reported vertebral body fractures based on a small number of assessable sites with SF 46.2% (6/13) vs. 9.1% (1/11), p = 0.11.

[b] Both instances followed radiation recall esophagitis after the administration of doxorubicin and iatrogenic manipulation in the form of biopsy, dilation, or both.

Table G-5. Key Question 1: IMRT versus 3DCRT for initial radiation strength of evidence

Comparison	Outcome Timing	Number of RCTs (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
IMRT vs. 3DCRT	Pain, Overall Response *8-12 weeks*	1 RCT (N=39) Sprave, 2018 Spine	Median 17.2 weeks	Moderate	Unknown	Imprecise	Undetected	Low	IMRT: 70% (14/20) vs. 3DCRT: 47.4% (9/19) RR 1.48 (95% CI 0.85 to 2.57) No difference
	Pain, Overall Response *26 weeks*	1 RCT (N=29) Sprave, 2018 Spine	Median 17.2 weeks	Moderate	Unknown	Imprecise	Undetected	Low	IMRT: 70.6% (12/17) vs. 3DCRT: 58.3% (7/12) RR 1.21 (95% CI 0.69 to 2.14) No difference
	Pain, VAS scores *Post-RT*	1 RCT (N=56) Sprave, 2018 Spine	Median 17.2 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	No difference in VAS pain scores between IMRT vs. 3DCRT, p=0.08 (data not provided)
	Pain, VAS scores and neuropathic pain *12 weeks*	1 RCT (N=39) Sprave, 2018 Spine	Median 17.2 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	Greater improvement in pain (VAS) with IMRT vs. 3DCRT, p=0.04 No difference in neuropathic pain with IMRT vs. 3DCRT, p=0.95 (data not provided)
	Pain, VAS scores and neuropathic pain *26 weeks*	1 RCT (N=29) Sprave, 2018 Spine	Median 17.2 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	No difference in VAS pain scores with IMRT vs. 3DCRT, p=0.43 No difference in neuropathic pain with IMRT vs. 3DCRT, p=0.43 (data not provided)

Comparison	Outcome Timing	Number of RCTs (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Relief of spinal cord compression, motor deficits *26 weeks*	1 NRSI (N=716) Rades, 2020 MSCC	NR	High	Unknown	Imprecise	Undetected	Insufficient	IMRT vs. 3DCRT **Improvement in motor deficits** *Quintile 1* IMRT: 37.5% (3/8) vs. 3DCRT: 31.6% (66/209); RR 1.19 (95% CI 0.47 to 2.97) *Quintile 2* IMRT: 75% (6/8) vs. 3DCRT: 24.2% (65/269); RR 3.10 (95% CI 1.97 to 4.88) *Quintile 3* IMRT: 66.7% (6/9) vs. 3DCRT: 27.2% (40/147); RR 2.45 (95% CI 1.44 to 4.17) *Quintile 4* IMRT: 57.1% (4/7) vs. 3DCRT: 15.8% (3/19); RR 3.62 (95% CI 1.07 to 12.27) *Quintile 5* IMRT: 62.5% (5/8) vs. 3DCRT 45% (9/20); RR 1.39 (95% CI 0.67 to 2.86)

Comparison	Outcome Timing	Number of RCTs (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Quality of Life	1 RCT (N=60) Sprave, 2018 Spine	Median 17.2 weeks	Moderate	Unknown	Imprecise	Undetected	Low	**EORTC-QLQ-BM 22 (0-100)[a], mean difference (95% CI), IMRT vs. 3DCRT** <u>Painful sites</u> Post RT: -6.4 (-18.1 to 5.3) (N=56) 12 weeks: -8.3 (-23.6 to 7.0) (N=39) 26 weeks: -2.5 (-20.9 to 15.9) (N=29) <u>Pain characteristics</u> Post RT: -2.8 (-18.7 to 13.1) (N=56) 12 weeks: 0.10 (-22.5 to 22.7) (N=39) 26 weeks: 5.70 (-19.9 to 31.3) (N=29) <u>Functional Interference</u> Post RT: -6.0 (-20.6 to 8.6) (N=56) 12 weeks: -0.20 (-19.1 to 18.7) (N=39) 26 weeks: 0.30 (-21.1 to 21.6) (N=29) <u>Psychosocial effects</u> Post RT: -12.9 (-26.0 to 0.2) (N=55) 12 weeks: -12.9 (-30.2 to 4.4) (N=38) 26 weeks: -13.6 (-32.7 to 5.5) (N=29) No difference on any QOL domain

Comparison	Outcome Timing	Number of RCTs (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Adverse events, Pathological fracture	1 RCT (N=39) Sprave, 2018 Spine 1 NRSI (N=716) Rades, 2020 MSCC	Median 17.2 weeks NR	Moderate High	Unknown	Imprecise	Undetected	Insufficient	**1 RCT** 12 weeks IMRT: 15% (3/20) vs. 3DCRT: 10.5% (2/19); RR 1.43, 95% CI 0.27 to 7.61 26 weeks IMRT: 16.7% (3/18) vs. 3DCRT: 16.7% (2/12); RR 1.00, 95% CI 0.19 to 5.12 No difference **1 NRSI** IMRT only (n=40): no cases of vertebral fracture
	Adverse Events, Toxicity	1 RCT (N=55) Sprave, 2018 Spine 1 NRSI (N=716) Rades, 2020 MSCC	Median 17.2 weeks NR	Moderate High	Unknown	Imprecise	Undetected	Insufficient	**1 RCT** IMRT: 0% (0/27)[b] vs. 3DCRT: 0% (0/28)[b] *post RT* IMRT: 3.7% (1/27)[c] vs. 3DCRT: 3.6% (1/28)[d] (nausea); RR 1.04, 95% CI 0.07 to 15.76 *12 weeks* IMRT: 5.6% (1/18)[e] vs. 3DCRT 21.4% (3/14)[f]; RR 0.36, 95% CI 0.03 to 2.23 *26 weeks* IMRT: 5.6% (1/18)[g] vs. 3DCRT: 0% (0/12) **1 NRSI:** IMRT only: 2.5% (1/40)[h]

Comparison	Outcome Timing	Number of RCTs (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Adverse events; Death, myelopathy	1 RCT (N=55) Sprave, 2018 Spine 1 NRSI (N=716) Rades, 2020 MSCC	Median 17.2 weeks NR	Moderate High	Unknown	Imprecise	Undetected	Insufficient	RCT: No treatment related deaths NRSI: No cases of late myelopathy in the IMRT arm (n=40) (not reported in the 3DCRT arm)

3DCRT = 3-dimensional conformal radiation therapy; CI = confidence interval; EORTC-QLQ-BM 22 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Bone Metastases 22; IMRT = intensity-modulated radiation therapy; MSCC = metastatic spinal cord compression; NR = not reported; NRS = numerical rating scale; NRSI = nonrandomized study of interventions; RCT = randomized controlled trial; RR = risk ratio; RT = radiation therapy; VAS = visual analog scale.

[a] For pain domains, lower score = better quality of life; for function and psychosocial domains, higher score = better quality of life.

[b] Grade 4.

[c] Grade 3 diarrhea and myalgia.

[d] Grade 3 nausea.

[e] Grade 3 peripheral motor neuropathy.

f Grade 3, 1 case dermatitis, 1 case myositis, and 1 case paresthesia, radiculitis, peripheral motor neuropathy and myalgia.

[g] Grade 3 radiculitis.

[h] Grade 3 nausea and vomiting.

Table G-6. Key Question 1: EBRT with HBI versus EBRT alone for initial radiation strength of evidence

Comparison	Outcome Timing	Number of RCTs (Patients) Author. Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
EBRT + HBI vs. EBRT alone	Pain, Function, QOL	----	----	----	----	----	----	----	No primary efficacy outcomes reported.
	Adverse events, Toxicity, Grade 3 or 4	1 RCT (N=428) Poulter, 1992 MBD sites NR	NR	Moderate	Unknown	Imprecise	Undetected	Insufficient	**Any Grade 4** EBRT + HBI: 0.4% (1/226) vs. EBRT: 0% (0/218); RR NC, p=0.33 **Any Grade 3** EBRT + HBI: 5.3% (12/226) vs. EBRT: 1.4% (3/218); RR 3.86, 95% CI 1.10 to 13.49 Increased risk of Grade 3 toxicities with the EBRT + HBI vs. EBRT alone, specifically: hematological toxicities (i.e., leukopenia, thrombocytopenia, and anemia), especially grade 3 nausea/vomiting were more common. All events were transitory.
	Adverse events, Other serious AEs	1 RCT (N=428) Poulter, 1992 MBD sites NR	NR	Moderate	Unknown	Imprecise	Undetected	Insufficient	Radiation pneumonitis: ERBT + HBI (0%; 0/221) (not reported for EBRT alone) Comparative safety not reported.

---- = not applicable because there is no evidence.
AE = adverse events; CI = confidence interval; EBRT = external mean radiation therapy; HBI = hemibody irradiation; MBD = metastatic bone disease; MF = multiple fraction; NC = not calculable; NR = not reported; NRS = numerical rating scale; QOL = quality of life; RCT = randomized controlled trial; RR = risk ratio; SF = single fraction; VAS = visual analog scale.

Table G-7. Key Question 1: SBRT versus conventional EBRT for initial radiation strength of evidence

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
SBRT vs. EBRT	Pain, Overall Response *4 weeks*	3 RCTs (N=394) Sahgal, 2021 Spine Nguyen, 2019 Nonspine Pielkenrood, 2021 Mixed spine and nonspine	12 to 104 weeks	Moderate	Consistent[a]	Imprecise	Undetected	Low	2 RCTs (spine and nonspine) SBRT: 60.2% (100/166) vs. EBRT: 48.4% (77/159) RR 1.24, 95% CI 0.98 to 1.57, I^2=0% Small increase in likelihood of pain response with SBRT (excluding a poor-quality, outlier trial)[a]
	Pain, Overall Response *12 weeks*	4 RCTs (N=408) Sahgal, 2021 Sprave, 2018 Spine Nguyen, 2019 Nonspine Pielkenrood, 2021 Mixed spine and nonspine	12 to 104 weeks	Moderate	Consistent	Precise	Undetected	Moderate	SBRT: 59.4% (126/212) vs. EBRT: 44.4% (87/196) RR 1.31, 95% CI 1.05 to 1.61, I^2=0% Small increase in likelihood of pain response with SBRT
	Pain, Overall Response *26 weeks*	3 RCTs (N=324) Sahgal, 2021 Sprave, 2018 Spine Nguyen, 2019 Nonspine	median 26.8 to 104 weeks	Moderate	Consistent	Imprecise	Undetected	Low	SBRT: 49.7% (80/161) vs. EBRT: 36.8% (60/163) RR 1.32, 95% CI 1.01 to 1.92, I^2=24.3% Small increase in likelihood of pain response with SBRT
	Pain, Overall Response *36 weeks*	1 RCT (N=48) Nguyen, 2019 Nonspine	104 weeks	Moderate	Unknown	Imprecise	Undetected	Low	SBRT: 77.3% (17/22) vs. EBRT: 46.2% (12/26) RR 1.67, 95% CI 1.04 to 2.69 Moderate increase in likelihood of pain response with SBRT

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Pain, Overall Response *>36 weeks*	1 NRSI (N=95 lesions) Amini, 2015 Mixed spine and nonspine	Median 43.5 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	**40 weeks** SBRT: 74.9% vs. EBRT: 44.1% **52 weeks** SBRT: 74.9% vs. EBRT: 39.9% **104 weeks** SBRT: 74.9% vs. EBRT: 35.7% p=0.020 (n's/lesions NR) Greater likelihood of pain response with SBRT
	Pain, VAS/NRS scores *Post-RT to 4 weeks*	**2 RCTs** (N=143) Sprave, 2018 Spine Pielkenrood, 2021 Mixed spine and nonspine **1 NRSI** (N=56) Sohn, 2016 Spine	Range, 12 to mean 32.4 weeks Mean 49 weeks	High	Consistent Unknown	Imprecise	Undetected	Insufficient	**RCTs** SBRT: n=72; EBRT: n=71 Pooled difference 0.84, 95% CI -0.45 to 2.31, I^2=0%, on a 0 to 10 scale No difference **NRSI** Mean (SD) change from baseline to 4 weeks, 0-10 scale SBRT: -3.7 (2.7) (n=28) vs. EBRT: -2.8 (2.4) (n=28); p=0.13 No difference
	Pain, VAS/NRS scores *>4 to 12 weeks*	2 RCTs (N=135) Sprave, 2018 Spine Pielkenrood, 2021 Mixed spine and nonspine	12 to mean 32.4 weeks	High	Consistent	Imprecise	Undetected	Insufficient	SBRT: n=68; EBRT: n=67 Pooled difference -0.90, 95% CI -2.34 to 0.76, I^2=0%, on a 0 to 10 scale No difference

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Pain, VAS/NRS scores *>12 weeks*	1 RCT (N=39) Sprave, 2018 Spine	mean 32.4 weeks	Moderate	Unknown	Imprecise	Undetected	Low	SBRT: n=19; EBRT: n=20 Difference -2.13, 95% CI -3.59 to -0.67, I^2=0%, on a 0 to 10 scale Large improvement in pain with SBRT
	Skeletal function *≥12 weeks*	1 RCT (N=229) Sahgal, 2021 Spine	median 26.8 weeks	Moderate	Unknown	Imprecise	Undetected	Low	**SINS score** (0-18 scale), mean (SD) change from baseline **12 weeks** SBRT: -0.94 (1.69) (n=114) vs. EBRT: -0.49 (1.61) (n=115); difference in change scores -0.45, 95% CI -0.88 to -0.02 Improved SINS score (i.e., increased stability) with SBRT **26 weeks** SBRT: -0.74 (1.99) (n=114) vs. EBRT: -0.73 (1.86) (n=115); difference in change scores -0.01, 95% CI -0.51 to 0.49 No difference

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Quality of Life *Post RT to 4 weeks*	**EORTC QLQ-BM22** **2 RCTs** (N=varies) Sahgal, 2021 Sprave, 2018 Spine **1 NRSI** (N=varies) van de Ven, 2020 Mixed spine and nonspine **EORTC-QLQ-Core 15-PAL** **1 RCT** (N=NR) Pilkenrood, 2021 Mixed spine and nonspine **1 NRSI** (N=56) van de Ven, 2020 Mixed spine and nonspine **MD Anderson Symptom Inventory** **1 RCT** (N=NR) Nguyen, 2019 Nonspine	Median 26.8 to mean 32.4 weeks Median 156 weeks[b] NR Median 156 weeks[b]	Moderate	Consistent	Imprecise	Undetected	Low	**QLQ-BM22 (0-100)** 2 RCTs, pooled mean difference, SBRT vs. EBRT Painful sites[c]: -4.18, 95% CI -10.80 to 2.47, I^2=0% (N=233) Painful characteristics[c]: -7.73, 95% CI -17.64 to 1.19, I^2=0% (N=232) Functional interference[d]: 1.97, 95% CI -8.51 to 9.41, I^2=0% (N=234) Psychosocial aspects[d]: 3.26, 95% CI -3.24 to 9.08, I^2=0% (N=233) No difference on any QOL domain 1 NRSI, mean (SD NR) Functional interference[d] SBRT: 78 (n=39) vs. EBRT: 69 (n=35) Psychosocial aspects[d] SBRT: 60 (n=31) vs. EBRT: 54 (n=34) No difference on either QOL domain

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Quality of Life *Post RT to 4 weeks* *(Continued)*								**QLQ-Core 15-PAL Global QOL (0-100)**[c] 1 RCT, median (IQR) SBRT: 50 (50 to 67) vs. EBRT: 67 (50 to 83), p=NS No difference 1 NRSI[e], mean (SD NR) SBRT: 56 (n=29) vs. EBRT: 52 (n=27) No difference **MD Anderson Symptom Inventory** Proportion of patients without severe symptoms SBRT: 60% vs. EBRT: 63%, p=NS (n's unclear) No difference

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Quality of Life *12 weeks*	**EORTC QLQ-BM22** **2 RCTs** (N=varies) Sahgal, 2021 Sprave, 2018 Spine **1 NRSI** (N=varies) van de Ven, 2020 Mixed spine and nonspine **EORTC-QLQ-Core 15-PAL** **1 RCT (**N=NR) Pilkenrood, 2021 Mixed spine and nonspine **1 NRSI** (N=59) van de Ven, 2020 Mixed spine and nonspine **MD Anderson Symptom Inventory** **1 RCT** (N=NR) Nguyen, 2019 Nonspine	Median 26.8 to mean 32.4 weeks Median 156 weeks[b] NR Median 156 weeks[b] NR	Moderate	Consistent	Imprecise	Undetected	Low	**QLQ-BM22 (0-100)** 2 RCTs, pooled mean difference, SBRT vs. EBRT Painful sites[c]: -1.58, 95% CI -8.44 to 4.98, I^2=0% (N=208) Painful characteristics[c]: -3.48, 95% CI -12.77 to 7.46, I^2=0% (N=208) Functional interference[d]: 2.86, 95% CI -5.77 to 10.19, I^2=0% (N=211) Psychosocial aspects[d]: 2.50, 95% CI -6.96 to 9.32, I^2=0% (N=211) No difference on any QOL domain 1 NRSI, mean (SD NR) Functional interference[d]: SBRT: 79 (n=35) vs. EBRT: 75 (n=24) Psychosocial aspects[d]: EBRT: 60 (n=37) vs. EBRT: 57 (n=24) No difference on either QOL domain

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Quality of Life *12 weeks* *(Continued)*								**QLQ-Core 15-PAL Global QOL (0-100)**[c] 1 RCT, median (IQR) SBRT: 67 (50 to 83) vs. EBRT: 67 (67 to 83), p=NS No difference 1 NRSI[e], mean (SD NR) SBRT: 75 (n=36) vs. EBRT: 67 (n=23) No difference **MD Anderson Symptom Inventory** Proportion of patients without severe symptoms SBRT: 70% vs. EBRT: 75%, p=NS (n's unclear) No difference

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Quality of Life *26 weeks*	**EORTC QLQ-BM22** **2 RCTs** (N=varies) Sahgal, 2021 Sprave, 2018 Spine **1 NRSI** (N=varies) van de Ven, 2020 Mixed spine and nonspine **EORTC-QLQ-Core 15-PAL** **1 NRSI** (N=73) van de Ven, 2020 Mixed spine and nonspine **MD Anderson Symptom Inventory** **1 RCT** (N=NR) Nguyen, 2019 Nonspine	Median 26.8 to mean 32.4 weeks Median 156 weeks[b] Median 156 weeks[b] NR	Moderate	Consistent	Imprecise	Undetected	Low	**QLQ-BM22 (0-100)** 2 RCTs, pooled mean difference, SBRT vs. EBRT Painful sites[c]: 1.81, 95% CI -10.59 to 10.94, I^2=41.0% (N=162) Painful characteristics[c]: 2.85, 95% CI -7.39 to 13.33, I^2=0% (N=162) Functional interference[d]: 2.04, 95% CI -6.07 to 10.58, I^2=0% (N=165) Psychosocial aspects[d]: -2.20, 95% CI -10.18 to 5.99, I^2=0% (N=164) No difference on any QOL domain 1 NRSI , mean (SD NR) Functional interference[d], SBRT: 85 (n=39) vs. EBRT: 73 (n=33) Psychosocial aspects[d]: SBRT: 69 (n=39) vs. EBRT: 53 (n=33) No difference on either QOL domain

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Quality of Life *26 weeks* *(Continued)*								**QLQ-Core 15-PAL Global QOL (0-100)**[c] 1 NRSI[e], mean (SD NR): SBRT: 77 (n=40) vs. EBRT: 66 (n=33) No difference **MD Anderson Symptom Inventory** Proportion of patients without severe symptoms SBRT: 88% vs. EBRT: 86%, p=NS (n's unclear) No difference

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Quality of Life *52 weeks*	**MD Anderson Symptom Inventory** 1 RCT (N=NR) Nguyen, 2019 Nonspine **EORTC QLQ-BM22 and Core 15-PAL** 1 NRSI (N=varies) van de Ven, 2020 Mixed spine and nonspine	NR Median 156 weeks[b]	Moderate	Unknown	Imprecise	Undetected	Insufficient	**MD Anderson Symptom Inventory** Proportion of patients without severe symptoms SBRT: 89% vs. EBRT: 90%, p=NS No difference **QLQ-BM22 (0-100)** 1 NRSI, mean (SD NR) Functional interference[d]: SBRT: 90 (n=14) vs. EBRT: 77 (n=19) Psychosocial aspects[d]: SBRT: 71 (n=15) vs. EBRT: 58 (n=19) No difference on either QOL domain **QLQ-Core 15-PAL Global QOL (0-100)**[c] 1 NRSI[e], mean (SD NR) SBRT: 83 (n=14) vs. EBRT: 66 (n=18) No difference
	Adverse events, Spinal cord compression *26 weeks*	1 RCT (N=225) Sahgal, 2021 Spine	median 26.8 weeks	Moderate	Unknown	Imprecise	Undetected	Low	SBRT: 0% (0/110) vs. EBRT: 1.7% (2/115) (both SCCs were after VCFs) No difference

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Adverse events, Pathological fracture	3 RCTs (N=440) Sahgal, 2021 Sprave, 2018 Spine Nguyen, 2019 Nonspine	Median 26.8 to 104 weeks	Moderate	Consistent (12 weeks) Inconsistent (26 weeks)	Imprecise	Undetected	Low (12 weeks) Insufficient (26 weeks)	<u>Mixed spine/nonspine MBD</u> **≤12 weeks** 2 RCTs SBRT: 2.9% (3/104) vs. EBRT: 1.0% (1/102), RR 2.28, 95% CI 0.26 to 21.47, I^2=0% No difference <u>Spine</u> **26 weeks** 2 RCTs SBRT: 13.3% (17/128) vs. EBRT: 15.6% (21/135) RR 0.77, 95% CI 0.18 to 16.75, I^2=74.6% No difference
	Adverse events, Pain flare	2 RCTs (N=279) Sahgal, 2021 Sprave, 2018 Spine	Median 26.8 to mean 32.4 weeks	Moderate	Consistent	Imprecise	Undetected	Low	**1-2 days post RT** 1 RCT (N=54) [Sprave] SBRT: 7.4% (2/27) vs. EBRT: 7.4% (2/27) RR 1.00 (95% CI 0.15 to 6.59) No difference **26 weeks post RT** 1 RCT (N=225) [Sahgal] SBRT: 43% (45/110) vs. EBRT: 34% (35/115) RR 1.34, 95% CI 0.94 to 1.92 No difference

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Adverse events, other serious AEs	**2 RCTs** (N=280) Sahgal, 2021 Sprave, 2018 Spine **1 NRSI** (N=38) Haley, 2011 Spine	Median 26.8 to mean 32.4 weeks 4 weeks	Moderate Moderate	Unknown	Imprecise	Undetected	Insufficient	**RCTs** No cases (SBRT or EBRT) of radiation-related myelopathy, cauda equina injury or late toxicities (1 RCT, N=55, mean 32.4 weeks), or discontinuation due to treatment-related toxicity or treatment-related mortality (1 RCT, N=225, mean 28.6 weeks) **NRSI** No late toxicities (NOS) occurred in either group at followup >12 weeks.
	Adverse Events[f], Toxicity	**4 RCTs** (N=529) Sahgal, 2021 Sprave, 2018 Spine Nguyen, 2019 Nonspine Pielkenrood, 2021 Mixed spine/nonspine **1 NRSI** (N=95 lesions) Amini, 2015 Mixed spine/nonspine	12 to 104 weeks	Moderate Moderate	Consistent	Imprecision	Undetected	Insufficient	<u>Grade 4</u> **3 RCTs** SBRT: 0% (0/182) vs. EBRT: 0% (0/187) **1 NRSI** SBRT: 0% (0/50 lesions) vs. EBRT: 0% (0/45 lesions) No difference/no occurrences <u>Grade 3[g]</u> **4 RCTs** SBRT: range, 0%–10% (n=263) vs. EBRT: range, 0%–5% (n=266) **1 NRSI** SBRT: 2% (1/50 lesions) vs. EBRT: 0% (0/45 lesions) No difference Events may be rare; individual studies may not have been powered to detect rare events.

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration (Range)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Any acute toxicity	**2 NRSIs** (N=100) Haley, 2011 Sohn, 2016 Spine	4 weeks to mean 49.1 weeks	Moderate	Consistent	Imprecise	Undetected	Insufficient	SBRT: 20% (10/50) vs. EBRT: 46% (23/50); RR 0.43, 95% CI 0.23 to 0.82; all self-limiting and resolved in <8 weeks Fewer acute toxicities with SBRT

AE = adverse events; CI = confidence interval; EBRT = conventional external beam radiation therapy; EORTC QLQ BM22 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Bone Metastases 22; EORTC QLQ-Core 15-PAL Global QOL = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative; IQR = interquartile range; MBD = metastatic bone disease; MD Anderson = Monroe Dunaway Anderson; NOS = not otherwise specified; NRS = numerical rating scale; NRSI = nonrandomized study of interventions; NS = not statistically significant; QOL = quality of life; RCT = randomized controlled trial; RR = risk ratio; RT = radiation therapy; SBRT = stereotactic body radiation therapy; SD = standard deviation; SINS = spinal instability in neoplasm score; SCC = spinal cord compression; VAS = visual analog scale; VCFs = vertebral compression fractures.

[a] After exclusion of poor quality trial.

[b] Median duration of followup differed between groups: SBRT was 25 months (range, 5-52 months) and 3DCRT was 46 months (range, 9-55 months) , p= 0.044.

[c] Lower score = better quality of life.

[d] Higher score = better quality of life.

[e] Also reports physical functioning (which was marginally significant according to authors) and emotional functioning.

f It is unclear/possible that patients had more than one grade event.

[g] The most common Grade 3 toxicities in both treatment arms were fatigue and pain.

Key Question 2

Table G-8. Key Question 2: Conventional EBRT and SBRT, SF vs. MF schemes for re-irradiation strength of evidence

Comparison	Outcome Timing	Number of RCTs (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
Single (SF) vs. Multiple fractionation (MF) schemes for ***conventional EBRT*** *for re-irradiation*	Pain, Overall Response *8 weeks*	1 RCT (N=850) Chow, 2014 1 NRSI (N=60) Sayed, 2013 Both mixed spine and nonspine	Median 53 weeks	Moderate High	Consistent	Imprecise Imprecise	Undetected Undetected	Low	RCT: SF: 28% (118/425) vs. MF: 32% (135/425) RR 0.87, 95% CI 0.71 to 1.08 NRSI: SF: 93% (27/28) vs. MF: 88% (28/32) RR 1.10, 95% CI 0.95 to 1.28 No difference
	Pain, Response to treatment *Timing post re-irradiation NR*	1 RCT (N=145) Van der Linden, 2004 Mixed spine and nonspine	No specific followup duration	High	Unknown	Imprecise	Undetected	Insufficient	SF: 66% (79/119) vs. MF: 46% (12/26) RR 1.44, 95% CI 0.63 to 2.22
	Function improvement (walking) on Brief Pain Inventory *8 weeks*	1 RCT (N=850) Chow, 2014 Mixed spine and nonspine	Median 53 weeks	Moderate	Unknown	Imprecise	Undetected	Low	SF: 28% (102/358) vs. MF: 33% (121/362) RR 0.85, 95% CI 0.69 to 1.06 No difference
	Motor Function improvement (Grade I-IV) in patients with SCC *4 weeks*	1 NRSI (N=62) Rades, 2005 MSCC	Median 52 weeks	High	Unknown	Imprecise	Undetected	Insufficient	SF: 38% (13/34) vs. MF (3 Gy x 5) 33% (5/15) vs. MF (4 Gy x 5) 54% (7/13), p=0.69 No difference

Comparison	Outcome Timing	Number of RCTs (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Motor Function improvement (Grade I-IV) *12 weeks*	1 NRSI (N=62) Rades, 2005 MSCC	Median 52 weeks	High	Unknown	Imprecise	Undetected	Insufficient	SF: 43% (13/30) vs. MF (3 Gy x 5) 36% (5/14) vs. MF (4 Gy x 5) 54% (7/13), p=0.78 No difference
	Motor Function improvement (Grade I-IV) *26 weeks*	1 NRSI (N=62) Rades, 2005 MSCC	Median 52 weeks	High	Unknown	Imprecise	Undetected	Insufficient	SF: 48% (11/23) vs. MF (3 Gy x 5) 57% (4/7) vs. MF (4 Gy x 5) 75% (6/8), p=0.67 No difference
	Quality of Life improvement on EORTC QLQ-C30 (0-100 scale) *8 weeks*	1 (N=850) Chow, 2014 Mixed spine and nonspine	Median 53 weeks	Moderate	Unknown	Imprecise	Undetected	Low	SF: 34% (79/230) vs. MF: 35% (83/234) RR 0.97, 95% CI 0.78 to 1.24 No difference
	Adverse events, SCC or cauda equina	1 (N=850) Chow, 2014 Mixed spine and nonspine	Median 53 weeks	Moderate	Unknown	Imprecise	Undetected	Low	SF: 2% (7/425) vs. MF: <1% (2/425) OR 3.54, 95% CI 0.73 to 17.15 No difference
	Adverse events, Pathological fracture	1 (N=850) Chow, 2014 Mixed spine and nonspine	Median 53 weeks	Moderate	Unknown	Imprecise	Undetected	Low	SF: 7% (30/425) vs. MF: 5% (20/425) OR 1.54, 95% CI 0.85 to 2.75 No difference
	Adverse Events, Toxicity	1 (N=850) Chow, 2014 Mixed spine and nonspine	Median 53 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	Grade 4: SF: 0.2% (1/425, cardiac ischemia or infarction) vs. MF: 0% (0/450) No difference

Comparison	Outcome Timing	Number of RCTs (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
*Single (SF) vs. Multiple fractionation (MF) schemes for **SBRT** for re-irradiation*	Pain improvement 4-6 months	1 NRSI (N=228) Heron, 2012 Spine[a]	Median 51 weeks	Moderate	Unknown	Precise	Undetected	Low	SF: 71% (88/124) vs. MF: 73% (76/104) RR 0.97, 95% CI 0.83 to 1.14 No difference
	Adverse Events, Toxicity	1 NRSI (N=228) Heron, 2012 Spine[a]	Median 51 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	Grade 3: SF: 0.8% (1/124) vs. MF: 0% (0/104) RR 2.52, 95% CI 0.10 to 61.21 No difference

CI = confidence interval; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; MF = multiple fraction; MSCC = metastatic spinal cord compression; NRS = numerical rating scale; NRSI = nonrandomized study of interventions; OR = odds ratio; RR = risk ratio; SCC = spinal cord compression; SF = single fraction; SBRT = stereotactic body radiation therapy.

[a] 4% vs. 18% had SCC at baseline.

Key Question 3a

Table G-9. Key Question 3a: EBRT versus other single therapy strength of evidence

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
EBRT vs. strontium (Sr)-89	Pain, Subjective Response[a] or dramatic improvement	2 RCTs (N=314) Oosterhof, 2003 Quilty, 1994 MBD site(s) NR	12 weeks to NR (until death, <12 months for most)	Moderate	Consistent	Imprecise	Undetected	Insufficient	Subjective response (1 RCT, Oosterhof): *Timing NR* EBRT: 33.3% vs. Sr-89: 34.7%, p=NR (n/Ns not determinable) Dramatic improvement (1 RCT, Quilty): *12 weeks or prior to crossover* EBRT: 33% (16/48) vs. Sr-89: 29% (18/63) RR 1.17, 95% CI 0.67 to 2.04 No difference
	Adverse events, Pain flare	1 RCT (N=203) Oosterhof, 2003 MBD site(s) NR	Until death (<12 months for most)	Moderate	Unknown	Imprecise	Undetected	Low	EBRT: 8.2% (8/102) vs. Sr-89: 18.4% (19/101) RR 0.43, 95% CI 0.86 to 18.17 No difference

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Adverse Events, Grade 3/4 toxicities	2 RCT (N=314) Oosterhof, 2003 Quilty, 1994 MBD site(s) NR	12 weeks to NR (until death, <12 months for most)	Moderate	Consistent	Imprecise	Undetected	Low (based on higher quality RCT[b])	1 RCT (Quilty) Nausea/vomiting: EBRT: 1% (1/102) vs. Sr-89: 4% (4/101) RR 0.25, 95% CI 0.03 to 2.17 Diarrhea: EBRT: 8.3% (8/102) vs. Sr-89: 2% (2/101) RR 3.60, 95% CI 0.86 to 18.17 Hematologic: EBRT: 2% (2/102) vs. Sr-89: 0% (0/101) 1 RCT (Oosterhof) Platelet toxicity: ERBT: 3.4% vs. Sr-89: 6.9% (some EBRT patients may have received hemibody radiotherapy rather than local radiotherapy) No difference
EBRT vs. Cryoablation	Complete pain response *12 weeks*	1 NRSI (N=150) Di Staso, 2015 Mixed spine and nonspine	12 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	EBRT: 11.2% (14/125) vs. Cryoablation: 32% (8/25) RR 0.35, 95% CI 0.16 to 0.75 Large improvement in pain favoring cryoablation

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Quality of Life, 1-item McGill Quality of Life Questionnaire *12 weeks*	1 NRSI (N=150) Di Staso, 2015 Mixed spine and nonspine	12 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	EBRT: mean difference 5, 95% CI 4 to 5 vs. Cryoablation: mean difference 6, 95% CI 5 to 8, on a 0-10 scale No difference
EBRT vs. Bisphosphonates	WHO response rate (based on decrease, stable, or increase pain medication) plus average pain score (no pain, pain reduced by ≥ 2/10 points, pain stable, or increased ≥ 2/10 points) *4 to 12 weeks*	1 RCT (N=470) Hoskin, 2015 Mixed spine and nonspine	Median 50.8 weeks	Moderate	Unknown	Precise	Undetected	Low	**4 weeks**: EBRT: 53.1% (93/175) vs. ibandronate: 49.5% (90/182) RR 1.08, 95% CI 0.88 to 1.32 **12 weeks (after some may have crossed over to other treatment[c]):** EBRT: 49.4% (77/156) vs. Ibandronate: 56.1% (88/157) RR 0.88, 95% CI 0.71 to 1.09 No difference
	Quality of Life (FACIT-G v4.0) *4 to 12 weeks*	1 RCT (N=470) Hoskin, 2015 Mixed spine and nonspine	Median 50.8 weeks	Moderate	Unknown	Imprecise	Undetected	Low	**4 weeks** Mean difference, EBRT vs. Ibandronate: -1.0, 95% CI -4.0 to 2.0, on a 0-108 scale **12 weeks (after some may have crossed over to other treatment[c]):** Mean difference, EBRT vs. Ibandronate: -0.3, 95% CI -3.8 to 3.3, on a 0-108 scale No difference

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Adverse events, pathological fracture *12 weeks*	1 RCT (N=470) Hoskin, 2015 Mixed spine and nonspine	Median 50.8 weeks	Moderate	Unknown	Imprecise	Undetected	Low	EBRT: 72.2% (5/235) vs. Ibandronate: 3% (7/235) RR 0.71, 95% CI 0.23 to 2.22 No difference
	Adverse events, spinal cord compression *12 weeks*	1 RCT (N=431) Hoskin, 2015 Mixed spine and nonspine	Median 50.8 weeks	Moderate	Unknown	Imprecise	Undetected	Low	Patients with chest or abdominal pain: EBRT: 3.3% (7/216) vs. Ibandronate: 5.6% (12/215) RR 0.58, 95% CI 0.23 to 1.45 No difference
	Adverse events, Grade 3/4 toxicities *12 weeks*	1 RCT (N=470) Hoskin, 2015 Mixed spine and nonspine	Median 50.8 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	EBRT: 0.4% (1/235) vs. Ibandronate: 0% (0/235) No difference

CI = confidence interval; EBRT = external beam radiation therapy; FACIT-G = Functional Assessment of Cancer Therapy – General; EBRT = external beam radiation therapy; MBD = metastatic disease; MD = mean difference; NR = not reported; NRSI = nonrandomized study of interventions; RCT = randomized controlled trial; RR = risk ratio; Sr-89 = strontium-89.

[a] If at least one of the following conditions were fulfilled: (1) reduction of the pain score by at least one level and performance status not deteriorated; (2) unchanged pain level and reduction of the prescribed daily analgesics dose by at least 25% compared with the pre-treatment situation, with no performance status; and (3) improvement of the performance status by at least one level without either an increase of the daily.

[b] Oosterhof.

[c] 27% of patients crossed over, most due to lack of sufficient pain relief.

Key Question 3b

Table G-10. Key Question 3b: EBRT plus surgery vs. EBRT alone strength of evidence

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
EBRT + surgery vs. EBRT alone	Pain, VAS/NRS scores *4 weeks*	1 NRSI (N=46) Zhang, 2016 MSCC	Mean 38 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	EBRT + surgery: mean 2.6 vs. EBRT: mean 3.6; difference -1.0, 95% CI -1.4 to -0.6, on a 0-10 scale Small improvement in pain with EBRT + surgery
	Pain, VAS/NRS scores *12 weeks*	1 NRSI (N=46) Zhang, 2016 MSCC	Mean 38 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	EBRT + surgery: mean 3.0 vs. EBRT: mean 4.3; difference -1.3, 95% CI -2.0 to -0.6, on a 0-10 scale Moderate improvement in pain with EBRT + surgery
	Overall function	1 NRSI (N=46) Zhang, 2016 MSCC	Mean 38 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	KPS 80 to 100 after treatment: 85.7% (18/21) vs. 60.0% (16/25), RR 1.34, 95% CI 0.95 to 1.89 Small potential benefit

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Relief of spinal cord compression *Various timepoints*	1 RCT (N=101) Patchell, 2005 3 NRSIs (N=534) Ma, 2017 Zhang, 2016 Rades, 2011 All MSCC	Median 15 vs. 13 weeks 22 to 38 weeks (mean or median)	Moderate Moderate	Consistent	Imprecise	Undetected	Low	**RCT** EBRT vs. EBRT + surgery[a]: **Ambulatory posttreatment:** 57% (29/51) vs. 84% (42/50), adjusted RR 0.68, 95% CI 0.52 to 0.88 Moderate increase in the likelihood of achieving SCC relief with EBRT + surgery **ASIA same/better at 4.3 weeks:** 60% (NR) vs. 86% (NR), adjusted RR 0.30, 95% CI 0.14 to 0.62 Large increase in the likelihood of achieving SCC relief with EBRT + surgery **Frankel same/better at 4.3 weeks:** 61% (NR) vs. 91% (NR), adjusted RR 0.26, 95% CI 0.12 to 0.54 Large increase in the likelihood of achieving SCC relief with EBRT + surgery **Continence maintained:** adjusted RR 0.51, 95% CI 0.29 to 0.90 (rates NR) Large increase in the likelihood of achieving SCC relief with EBRT + surgery

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Relief of spinal cord compression *Various timepoints* *(Continued)*								**NRSIs** **Frankel improved at 8 weeks:** EBRT + surgery: 53.4% (102/191) vs. EBRT: 33.3% (32/96) RR 1.60, 95% CI 1.17 to 2.19 Moderate increase in the likelihood of achieving SCC improvement with EBRT + surgery **Frankel D/E posttreatment:** EBRT + surgery: 85.7% (18/21) vs. EBRT: 72.0% (18/25) RR 1.19, 95% CI 0.88 to 1.61 No difference **Motor function improved at 26 weeks:** EBRT + surgery: 22% (15/67) vs. EBRT: 16% (22/134) RR 1.36, 95% CI 0.76 to 2.45 No difference **Ambulatory posttreatment:** EBRT + surgery: 67% (45/67) vs. EBRT: 61% (82/134) RR 1.10, 95% CI 0.89 to 1.36 No difference

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Quality of Life	2 NRSIs (N=333) Ma, 2017 Zhang, 2016 MSCC	Mean 29 weeks	Moderate	Consistent	Imprecise	Undetected	Insufficient	EBRT + surgery: mean 46.5 vs. EBRT: mean 34.8; pooled MD 10.96, 95% CI 9.00 to 13.79, I^2 = 0.0%, on a 0-100 scale, higher = better[b] Moderate improvement in quality of life with EBRT + surgery
	Adverse events, nerve damage *Post treatment*	1 NRSI (N=287) Ma, 2017 MSCC	Mean 27 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	"Nerve damage", from surgery vs. EBRT (no cases of complete paralysis): 4.7% (9/191) vs. 12.5% (11/88), RR 0.38, 95% CI 0.16 to 0.88[c] No difference
Surgery + SBRT vs. SBRT alone	Relief of spinal cord compression *Timing NR*	1 NRSI (N=57) Bate, 2015 MSCC	Median 43 weeks	High	Unknown	Imprecise	Undetected	Insufficient	Frankel improved SBRT + surgery: 14.3% (3/21) vs. SBRT: 10.4% (5/48) RR 1.37, 95% CI 0.36 to 5.22 No difference

ASIA = American Spinal Injury Association; CI = confidence interval; EBRT = external beam radiation therapy; KPS = Karnofsky Performance Scale; MD = mean difference; MSCC = metastatic spinal cord compression; NR = not reported; NRS = numerical rating scale; NRSI = nonrandomized study of interventions; RCT = randomized controlled trial; RR = risk ratio; RT = radiation therapy; SF = single fraction; VAS = visual analog scale.

[a] Study reported adjusted RRs comparing EBRT alone to surgery with EBRT, so for these outcomes we also reported results for EBRT alone first, surgery with EBRT second.

[b] FACT-G rescaled from range 0 to 108 to range 0 to 100; EORTC reversed so that higher is better. Time point 4 weeks after hospital discharge for Ma 2017, "after treatment" for Zhang 2016.

[c] Nerve damage associated with EBRT in the surgery + EBRT arm not reported.

Table G-11. Key Question 3b: EBRT plus dexamethasone vs. EBRT alone strength of evidence

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
EBRT + dexamethasone vs. EBRT alone	Pain, Overall Response *6 weeks*	1 RCT (N=298) Chow, 2015 Mixed spine and nonspine	Median 6 weeks	Low	Unknown	Imprecise	Undetected	Low	EBRT + DXM: 43% (64/148) vs. EBRT: 35% (52/150) RR 1.25, 95% CI 0.94 to 1.66 Small potential increase in the likelihood of achieving pain response with EBRT + DXM

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Pain, VAS/NRS scores *1.4 weeks*	1 RCT (N=298) Chow, 2015 Mixed spine and nonspine	Median 6 weeks	Low	Unknown	Imprecise	Undetected	Low	Mean reduction EBRT + DXM: -2.37 vs. EBRT: -1.85, on a 0-10 scale difference -0.52, p=0.09 Small potential improvement in pain with EBRT + DXM
	Relief of spinal cord compression (Ambulatory) *Timing unclear*	1 RCT (N=57) Sorensen, 1994 MSCC	NR (≤104 weeks)	High	Unknown	Imprecise	Undetected	Insufficient	EBRT + DXM: 81% (22/27) vs. EBRT: 63% (19/30) RR 1.29, 95% CI 0.93 to 1.78 Small potential increase in the likelihood of being ambulatory posttreatment with EBRT + DM
	Quality of Life *1.4 weeks*	1 RCT (N=298) Chow, 2015 Mixed spine and nonspine	Median 6 weeks	Low	Unknown	Imprecise	Undetected	Low	**EORTC QLQ-C15-PAL (palliative)** Mean change scores for EBRT + DXM vs. EBRT, on a 0-100 scale Nausea: -0.6 vs. 8.0, difference in change scores -8.60, 95% CI -15.37 to -1.83 Appetite: -2.7 vs. 4.5, difference in change scores -7.20, 95% CI -14.71 to 0.32 **EORTC QLQ-BM22 (bone metastases)** Mean change scores for EBRT + DXM vs. EBRT, on a 0-100 scale Functional interference: -10.5 vs. -3.8, difference -6.70, 95% CI -11.75 to -1.65 Small improvement in quality of life with EBRT + DXM

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Pain flare *1.4 weeks*	1 RCT (N=298) Chow, 2015 Mixed spine and nonspine	Median 6 weeks	Low	Unknown	Imprecise	Undetected	Low	EBRT + DXM: 26% (39/148) vs. EBRT: 35% (53/150) RR 0.75, 95% CI 0.53 to 1.05 Small potential decrease in the likelihood of experiencing pain flare with EBRT + DXM
	Adverse events: Grade ≥3 *Post-RT to 4 weeks*	1 RCT (N=298) Chow, 2015 Mixed spine and nonspine	Median 6 weeks	Low	Unknown	Imprecise	Undetected	Low	**Grade ≥3 bone pain** EBRT + DXM: 7.5% (11/147) vs. EBRT: 14% (20/143) RR 0.54, 95% CI 0.27 to 1.08 Small potential decrease in the likelihood of experiencing Grade ≥3 bone pain with EBRT + DXM **Other toxicities** Grade 3 nausea: EBRT + DXM: 0% (0/147) vs. EBRT: 0% (0/143); Grade 3 or 4 fatigue, anorexia, hyperglycemia, constipation, and bloating infrequent (0% to 2%), no difference between treatment arms. No difference in other Grade 3 or 4 toxicities

AE = adverse event; ; EORTC QLQ BM22 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Bone Metastases 22; EORTC QLQ-Core 15-PAL Global QOL = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative; DXM = dexamethasone; MD = mean difference; MSCC = metastatic spinal cord compression; NR = not reported; NRS = numerical rating scale; RCT = randomized controlled trial; RR = risk ratio; RT = radiation therapy; VAS = visual analog scale.

Table G-12. Key Question 3b: EBRT plus bisphosphonates versus EBRT alone strength of evidence

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
EBRT + bisphosphonate vs. EBRT alone	Pain, VAS/NRS scores *52 weeks*	1 RCT (N=40) Zaghloul, 2010 Mixed spine and nonspine	Median 24 weeks	High	Unknown	Imprecise	Undetected	Insufficient	EBRT + ZA: mean 2.95 vs. EBRT: mean 4.37 Difference -1.42, 95% CI -1.76 to -1.08, on a 0-10 scale Moderate improvement in pain with EBRT + ZA
	Adverse events: SRE *>12 weeks*	1 RCT (N=40) Zaghloul, 2010 2 NRSIs (N=134) Hosaka, 2018 Wolanczyk, 2016 All mixed spine and nonspine	Median 24 weeks Median 87 weeks Median 39 weeks	High High	Unknown Consistent (2nd surgery) Unknown (SRE-free rate)	Imprecise Imprecise	Undetected Unclear (SREs in Wolanczyk)	Insufficient	SRE risk: HR 0.413, p=0.008 Proportion of patients with ≥1 SRE, timing unclear: EBRT + ZA vs. EBRT: 60.0% (12/20) vs. 90.0% (18/20); RR 0.67, 95% CI 0.45 to 0.98 Moderate decrease in the risk of SRE with EBRT + ZA SRE-free rate at 104 weeks: 73% (NR/35) vs. 44% (12/27), RR 1.67, 95% CI 1.05 to 2.66 Moderate decrease in the risk of SRE with EBRT + ZA
	Adverse events: Pain flare *Timing NR*	1 NRSI (N=72)[a] Wolanczyk, 2016 Mixed spine and nonspine	Median 39 weeks	High	Unknown	Imprecise	Undetected	Insufficient	EBRT + ZA: 16.1% (5/31) vs. 18.8% (6/32), RR 0.86, 95% CI 0.29 to 2.53 No difference

CI = confidence interval; EBRT = external beam radiation therapy; HR = hazard ratio; MBD = metastatic bone disease; MD = mean difference; MSCC = metastatic spinal cord compression; NR = not reported; NRS = numerical rating scale; NRSI = nonrandomized study of interventions; RCT = randomized controlled trial; RR = risk ratio; SRE = skeletal-related events; VAS = visual analog scale; ZA = zoledronate/zoledronic acid

[a] Including nine given zoledronate alone, not assessed for this review.

Table G-13. Key Question 3b: EBRT plus a radioisotope versus EBRT plus placebo strength of evidence

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
EBRT + radioisotope vs. EBRT + placebo	Pain, Overall Response *12 weeks*	1 RCT (N=93) Smeland, 2003 MBD site(s) NR	12 weeks	Moderate	Unknown	Imprecise	Undetected	Low	EBRT + Sr-89: 30% (13/44) vs. EBRT + placebo: 20% (9/45) RR 1.48 (95% CI 0.70 to 3.10) No difference
	Pain, Overall Response *26 weeks*	1 RCT (N=93) Smeland, 2003 MBD site(s) NR	26 weeks	Moderate	Unknown	Imprecise	Undetected	Low	EBRT + Sr-89: 15% (3/20) vs. EBRT + placebo: 17% (3/18) RR 0.90 (95% CI 0.21 to 3.91) No difference
	Quality of Life *12 and 26 weeks*	2 RCTs (N=219) Porter, 1993 Smeland, 2003 MBD site(s) NR	26 weeks	Moderate	Inconsistent	Unclear (narrative report; no data)	Undetected	Insufficient	EBRT + Sr-89 vs. EBRT + placebo: Narrative report of no difference between groups in EORTC QLC C-30 score in one study (12-week followup) and "superior" quality of life outcomes with EBRT + Sr-89 in one study (p=0.006) (26-week followup) Direction, magnitude of effect unclear

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Adverse Events, Grade 3 or 4 Toxicity	2 RCTs (N=188) Nilsson, 2007 Porter, 1993 MBD site(s) NR	26 and 78 weeks	Moderate	Inconsistent	Imprecise	Undetected	Insufficient	**Thrombocytopenia**: 1 RCT (Porter) EBRT + Sr-89: 34% (23/67) vs. EBRT + placebo: 4% (2/57); RR 9.78, 95% CI 2.41 to 39.72 1 RCT (Nilsson) EBRT + radium-223: 0% (0/33) vs. EBRT + placebo: 3% (1/30); RR 0.31, 95% CI 0.01 to 7.42 **Leukopenia**: 1 RCT (Porter) EBRT + Sr-89: 12% (8/67) vs. EBRT + placebo: 0% (0/57); RR 14.50, 95% CI 0.86 to 245 1 RCT (Nilsson) EBRT + radium-223: 3% (1/33) vs. EBRT + placebo: 0% (0/30); RR 2.82, 95% CI 0.12 to 66.82 1 RCT (Nilsson) **Neutropenia**: EBRT + radium-223: 3% (1/33) vs. EBRT + placebo: 0% (0/30); RR 2.82, 95% CI 0.12 to 66.82 **Anemia**: EBRT + radium-223: 3% (1/33) vs. EBRT + placebo: 3% (1/30); RR 0.94, 95% CI 0.06 to 14.38 No difference
	Serious Adverse Events	1 RCT (N=64) Nilsson, 2007 MBD site(s) NR	78 weeks	Low	Unknown	Imprecise	Undetected	Low	EBRT + radium-223: 24% (8/33) vs. EBRT + placebo: 45% (14/31) RR 0.54, 95% CI 0.26 to 1.10 No difference

CI = confidence interval; EBRT: external beam radiation therapy; EORTC QLQ C-30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; MBD = metastatic bone disease; NR = not reported; RCT = randomized controlled trial; RR = risk ratio; Sr-89: strontium-89.

Table G-14. Key Question 3b: EBRT plus cryoablation vs. EBRT alone strength of evidence

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
EBRT + cryoablation vs. EBRT alone	Pain, Overall Response *12 weeks*	1 NRSI (N=150) Di Staso, 2015 Mixed spine and nonspine	12 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	EBRT + cryoablation: 84.0% (21/25) vs. EBRT: 53.6% (67/125) RR 1.57, 95% CI 1.24 to 1.99 Moderate increase in the likelihood of achieving pain response with EBRT + cryoablation
	Quality of Life *12 weeks*	1 NRSI (N=150) Di Staso, 2015 Mixed spine and nonspine	12 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	McGill Quality of Life meaningful existence subscale score EBRT + cryoablation: mean 7 (95% CI 5.4 to 9) vs. EBRT: mean 5 (95% CI 4 to 5), p=0.003 Direction, magnitude of effect unclear
	Harms related to cryoablation	1 NRSI[a] (N=50) Di Staso, 2015 Mixed spine and nonspine	12 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	Any complication: 20% (10/50) Sacral plexus injury: 14% (7/50) Peripheral nerve injury, transient: 4% (2/50) Humerus fracture: 2% (1/50) Comparative safety unknown (safety not reported for EBRT)

CI = confidence interval; EBRT: external beam radiation therapy; MBD = metastatic bone disease; NRSI = nonrandomized study of interventions; RR = risk ratio

[a] Harms associated with cryoablation were reported in pooled analysis that included the patients in the EBRT plus cryoablation arm (n=25) and in a cryoablation alone arm (n=25).

Table G-15. Key Question 3b: EBRT plus hyperthermia and plus capecitabine vs. EBRT alone strength of evidence

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
EBRT + hyperthermia vs. EBRT alone	Quality of Life	1 RCT (N=57) Chi, 2018 Mixed spine and nonspine	12 weeks	High	Unknown	Imprecise	Undetected	Insufficient	Global health status mean score EBRT + hyperthermia: mean 62.1 (SD 14.8) vs. EBRT: mean 44.5 (SD 15.8), p=0.131 No difference
EBRT + capecitabine vs. EBRT alone	Pain, Overall Response *>4 to 12 weeks*	1 RCT (N=84) Ahmed 2021 MBD site(s) NR	12 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	EBRT + capecitabine: 81.0% (34/42) vs. EBRT: 42.8% (18/42) RR 1.89, 95% CI 1.29 to 2.76 Moderate increase in the likelihood of achieving pain response with EBRT + capecitabine

CI = confidence interval; EBRT = external beam radiation therapy; MBD = metastatic bone disease; NR = not reported; RCT = randomized controlled trial; RR = risk ratio; SD = standard deviation.

Key Question 3c

Table G-16. Key Question 3c: EBRT plus cryoablation vs. cryoablation alone strength of evidence

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
EBRT + cryoablation vs. cryoablation alone	Pain, Overall Response *12 weeks*	1 NRSI (N=50) Di Staso, 2015 Mixed spine and nonspine	12 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	EBRT + cryoablation: 84.0% (21/25) vs. Cryoablation: 68.0% (17/25) RR 1.24, 95% CI 0.90 to 1.70 No difference
	Quality of Life *12 weeks*	1 NRSI (N=50) Di Staso, 2015 Mixed spine and nonspine	12 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	McGill Quality of Life meaningful existence subscale score EBRT + cryoablation: 7 (95% CI 5.4 to 9) vs. Cryoablation: 6 (95% CI 5 to 8) p=0.290 No difference
	Harms related to cryoablation	1 NRSI[a] (N=50) Di Staso, 2015 Mixed spine and nonspine	12 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	Any complication: 20% (10/50) Sacral plexus injury: 14% (7/50) Peripheral nerve injury, transient: 4% (2/50) Humerus fracture: 2% (1/50) (safety not reported for EBRT)

CI = confidence interval; EBRT: external beam radiation therapy; MBD = metastatic bone disease; NRSI = nonrandomized study of interventions; RR = risk ratio.

[a] Harms associated with cryoablation were reported in pooled analysis that included the patients in the EBRT plus cryoablation arm (n=25) and in a cryoablation alone arm (n=25).

Table G-17. Key Question 3c: EBRT plus strontium-89 vs. strontium-89 alone strength of evidence

Comparison	Outcome Timing	Number of Studies (Patients) Author Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
EBRT + strontium-89 vs. strontium-89 alone	Pain, Overall Response[a] *Timing NR*	1 NRSI (N=106) Wang, 2010 MBD site(s) NR	26 weeks	High	Unknown	Imprecise	Undetected	Insufficient	EBRT + Sr-89: 90.6% (48/53) vs. Sr-89: 83.0% (44/53) RR 1.09, 95% CI 0.94 to 1.27 No difference
	Harms related to strontium *4 to 6 weeks*	1 NRSI (N=106) Wang, 2010 MBD site(s) NR	26 weeks	High	Unknown	Imprecise	Undetected	Insufficient	Authors state no difference between groups in Sr-89-related side effects post injection or at 4 to 6 weeks; EBRT-related harms were not reported. Comparative safety unknown

CI = confidence interval; EBRT = external beam radiation therapy; MBD = metastatic bone disease; NR = not reported; NRSI = nonrandomized study of interventions; RR = risk ratio; Sr-89 = strontium-89.

[a] Defined as no or improved pain and normal or improved sleep and activities of daily living (ADLs).

Table G-18. Key Question 3c: EBRT plus surgical stabilization vs. surgical stabilization alone strength of evidence

Comparison	Outcome Timing	Number of Studies (Patients) Author, Year	Study Followup Duration	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
EBRT + surgery vs. surgery alone	Function *12 months*	1 NRSI (N=60) Townsend, 1994 MBD site(s) NR (at baseline, 60% had pathological fracture and 40% had impending fracture[a])	52 weeks	Moderate	Unknown	Imprecise	Undetected	Insufficient	Grade 1 or 2 functional status (normal use of extremity with or without pain) at any timepoint EBRT + surgery: 53% (18/34) vs. surgery: 11.5% (3/26) RR 4.59, 95% CI 1.51 to 13.93 Large increase in likelihood of achieving functional status Grade 1 or 2 with combined EBRT plus surgery
	Harms	None	----	----	----	----	----	----	Harms were not reported.

---- = not applicable because there is no evidence.

CI = confidence interval; EBRT = external beam radiation therapy; MBD = metastatic bone disease; NR = not reported; NRSI = nonrandomized study of interventions; RR = risk ratio.

[a] The proportions differed at baseline between groups: 51% vs. 72% and 49% vs. 28% respectively.

Appendix H. Excluded Studies List

Table H-1. Key to exclusion codes

Exclusion Code	Exclusion Reason
E3	Ineligible population
E4	Ineligible intervention
E5	Ineligible comparator
E6	Ineligible outcomes
E7	Ineligible study design for Key Question
E8	Ineligible publication type/not a study (trial protocol, letter, editorial, nonsystematic review article, abstract)
E9	Systematic review, not directly used, but studies checked for inclusion
E10	Foreign language/not English but possibly relevant
E11	Foreign language/not English and not relevant
E12	Unable to locate article after exhausting all options

Excluded from systematic literature search and hand searching/bibliography review:

1. [No authors listed]. Second-line treatment of metastatic prostate cancer. Prednisone and radiotherapy for symptom relief. Prescrire Int. 2013 Mar;22(136):74-8. PMID: 23593699. Exclusion: E9
2. Abbouchie H, Chao M, Tacey M, et al. Vertebral fractures following stereotactic body radiotherapy for spine metastases. J Med Imaging Radiat Oncol. 2020 Apr;64(2):293-302. doi: 10.1111/1754-9485.13010. PMID: 32174019. Exclusion: E9
3. Adli M, Sevinc A, Kalender ME. Re: Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. J Natl Cancer Inst. 2006 Mar 1;98(5):364-5; author reply 5. doi: 10.1093/jnci/djj077. PMID: 16507835. Exclusion: E8
4. Ahmed KABS, Stauder MCMD, Miller RCMD, et al. Stereotactic Body Radiation Therapy in Spinal Metastases. International journal of radiation oncology, biology, physics. 2012;82(5):e803-e9. doi: 10.1016/j.ijrobp.2011.11.036. Exclusion: E5
5. Ai CL. Efficacy of radiotherapy for bone metastasis tumor. Chinese Journal of Cancer Prevention and Treatment. 2008;15(9):711-2. Exclusion: E10
6. Akça Z, Tunali C. Efficacy of different doses palliative radiotherapy on painful bone metastases. Duzce Medical Journal. 2010;12(2):48-53. Exclusion: E10
7. Akita N, Sekimizu M, Hattori H, et al. Bioabsorbable spacer for proton beam therapy in ewing sarcoma: Two cases report. Pediatric Blood and Cancer. 2020;67(SUPPL 5)doi: 10.1002/pbc.28797. Exclusion: E4
8. Al-Omair A, Da Cunha M, Atenafu E, et al. The risk of vertebral compression fracture (VCF) postspine stereotactic body radiation therapy (SBRT) and evaluation of the spinal instability neoplastic score (SINS). International Journal of Radiation Oncology Biology Physics. 2012;84(3):S39-S40. doi: 10.1016/j.ijrobp.2012.07.108. Exclusion: E8
9. Alcorn SR, Fiksel J, Hu C, et al. Pilot Assessment of the BMET Decision Support Platform: A Tool to Improve Provider Survival Estimates and Selection of Prognosis-Appropriate Treatment for Patients with Symptomatic Bone Metastases. International Journal of Radiation Oncology Biology Physics. 2019;105(1):S47. doi: 10.1016/j.ijrobp.2019.06.474. Exclusion: E8
10. Altundağ MB, Üçer AR, Çalikoğlu T, et al. Single (500 cGy, 800 cGy) and multifraction (300x10 cGy) radiotherapy schedules in the treatment of painful bone metastases. THOD - Turk Hematoloji-Onkoloji Dergisi. 2002;12(1):16-21. Exclusion: E8

11. Ampil F, Sangster G, Caldito G, et al. Palliative Radiotherapy as a Treatment for Carcinoma Invasion of the Sacrum: An Observational Case Series Study. Anticancer Res. 2018 Dec;38(12):6797-800. doi: 10.21873/anticanres.13051. PMID: 30504392. Exclusion: E7

12. Anand AK, Venkadamanickam G, Punnakal AU, et al. Hypofractionated stereotactic body radiotherapy in spinal metastasis - with or without epidural extension. Clin Oncol (R Coll Radiol). 2015 Jun;27(6):345-52. doi: 10.1016/j.clon.2015.01.035. PMID: 25726363. Exclusion: E5

13. Andronis L, Goranitis I, Bayliss S, et al. Cost-Effectiveness of Treatments for the Management of Bone Metastases: A Systematic Literature Review. Pharmacoeconomics. 2018 Mar;36(3):301-22. doi: 10.1007/s40273-017-0595-0. PMID: 29224174. Exclusion: E9

14. Angelakis P, Papavasiliou C, Elias C. Twice per week treatment versus five times per week. A radiotherapeutic clinical trial. Br J Radiol. 1973 May;46(545):350-3. doi: 10.1259/0007-1285-46-545-350. PMID: 4715158. Exclusion: E7

15. Ansari J, Farrag A, Ali A, et al. Concurrent use of nivolumab and radiotherapy for patients with metastatic non-small cell lung cancer and renal cell carcinoma with oligometastatic disease progression on nivolumab. Molecular and Clinical Oncology. 2021;15(4)doi: 10.3892/mco.2021.2376. Exclusion: E7

16. Antonela V, Jure M, Marijana J, et al. PALLIATIVE RADIOTHERAPY (PR) FOR BONE METASTASES - PATTERNS OF CARE AND OUTCOMES ANALYSIS FROM A LARGE TERTIARY CENTER. Libri Oncologici. 2022;50(SUPPL 1):131-2. Exclusion: E8

17. Anzidei M, Napoli A, Brachetti G, et al. Palliative treatment of bone metastases: analysis of biological effects of MR guided Focused Ultrasound (MRgFUS) versus External Beam Radiation Therapy (EBRT). A randomized comparative trial using Functional Diffusion Maps as molecular activity indicator. Journal of therapeutic ultrasound. 2013;2:2013-10. PMID: CN-01295465. Exclusion: E7

18. Arcangeli G, Giovinazzo G, Saracino B, et al. Radiation therapy in the management of symptomatic bone metastases: the effect of total dose and histology on pain relief and response duration. Int J Radiat Oncol Biol Phys. 1998 Dec 1;42(5):1119-26. doi: 10.1016/s0360-3016(98)00264-8. PMID: 9869238. Exclusion: E6

19. Argenone A, Ferraioli P, De Palma G, et al. Cost-benefits of 8Gy therapy for bone metastases: The born of the hospital without pain. Radiotherapy and Oncology. 2014;111:S133. Exclusion: E8

20. Athanassiou E, Kyrgias G, Panoussaki E, et al. Response of patients with bone metastasis of breast, lung and prostate cancer to radiation therapy (RT) alone, versus radiation therapy and diphosphonate (pamidronate). Annals of oncology. 1994;Vol.5(Suppl 8):200p. PMID: CN-00524396. Exclusion: E12

21. Ausili-Cefaro G, Capirci C, Crivellari D, et al. Radiation therapy vs radiation therapy + pamidronate (Aredia) in elderly patients with breast cancer and lytic bone metastases: a GROG-GIOGer randomized clinical trial. Rays - international journal of radiological sciences. 1999 Italy Il Pensiero Scientifico Editore s;Vol.24(2 SUPPL.):49-52p. PMID: CN-00414559. Exclusion: E8

22. Avilés A, Cleto S, Castañeda C, et al. CMED in the treatment of nasal natural killer cell lymphoma with distant metastases. Hematology. 2007 Jun;12(3):241-4. doi: 10.1080/10245330701214327. PMID: 17558700. Exclusion: E3

23. Badrising SK, Louhanepessy RD, van der Noort V, et al. A prospective observational registry evaluating clinical outcomes of Radium-223 treatment in a nonstudy population. Int J Cancer. 2020 Aug 15;147(4):1143-51. doi: 10.1002/ijc.32851. PMID: 31875956. Exclusion: E4

24. Baka I, Argyrou M, Michalitsi M, et al. Value of dosimetric calculations of SM-153 beta particleemitter, in treatment of metastatic bone disease. Physica Medica. 2014;30:e29. Exclusion: E4

25. Balagamwala EH, Jung DL, Angelov L, et al. Incidence and Risk Factors for Vertebral Compression Fractures From Spine Stereotactic Body Radiation Therapy: Results of a Large Institutional Series. International Journal of Radiation Oncology*Biology*Physics. 2013 October 1;87(2):S89. doi: https://doi.org/10.1016/j.ijrobp.2013.06.230. Exclusion: E8

26. Barak F, Werner A, Walach N, et al. The palliative efficacy of a single high dose of radiation in treatment of symptomatic osseous metastases. Int J Radiat Oncol Biol Phys. 1987 Aug;13(8):1233-5. doi: 10.1016/0360-3016(87)90199-4. PMID: 2440837. Exclusion: E4

27. Barrington C, Carr M. 140 Survival outcomes for NSCLC patients following palliative radiotherapy in Velindre Cancer Centre. Lung Cancer. 2021;156:S58. doi: 10.1016/S0169-5002(21)00339-1. Exclusion: E6

28. Barroso-Sousa R, Krop IE, Trippa L, et al. A phase II study of pembrolizumab in combination with palliative radiotherapy (RT) for hormone receptor-positive (HR+) metastatic breast cancer (MBC). Journal of Clinical Oncology. 2019;37doi: 10.1200/JCO.2019.37.15-suppl.1047. Exclusion: E7

29. Barzilai O, Versteeg AL, Sahgal A, et al. Survival, local control, and health-related quality of life in patients with oligometastatic and polymetastatic spinal tumors: A multicenter, international study. Cancer. 2019 Mar 1;125(5):770-8. doi: 10.1002/cncr.31870. PMID: 30489634. Exclusion: E7

30. Batra JS, Karir BS, Vallabhajosula S, et al. Fractionated dose radiolabeled antiprostate specific membrane antigen (PSMA) radioimmunotherapy (177Lu-J591) with or without docetaxel for metastatic castration-resistant prostate cancer (mCRPC). Journal of Clinical Oncology. 2015;33(7). Exclusion: E4

31. Bedard G, Hoskin P, Chow E. Overall response rates to radiation therapy for patients with painful uncomplicated bone metastases undergoing initial treatment and retreatment. Radiother Oncol. 2014 Jul;112(1):125-7. doi: 10.1016/j.radonc.2014.06.015. PMID: 25023043. Exclusion: E9

32. Bekelman JE, Epstein AJ, Emanuel EJ. Single- vs multiple-fraction radiotherapy for bone metastases from prostate cancer. JAMA. 2013 Oct 9;310(14):1501-2. doi: 10.1001/jama.2013.277081. PMID: 24104375. Exclusion: E8

33. Berenson J, Pflugmacher R, Jarzem P, et al. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. Lancet Oncol. 2011 Mar;12(3):225-35. doi: 10.1016/s1470-2045(11)70008-0. PMID: 21333599. Exclusion: E3

34. Berwouts D, De Wolf K, De Neve W, et al. Variations in target volume definition and dose to normal tissue using anatomic versus biological imaging ((18) F-FDG-PET) in the treatment of bone metastases: results from a 3-arm randomized phase II trial. J Med Imaging Radiat Oncol. 2017 Feb;61(1):124-32. doi: 10.1111/1754-9485.12507. PMID: 27527354. Exclusion: E6

35. Bhattacharya IS, Hoskin PJ. Stereotactic body radiotherapy for spinal and bone metastases. Clin Oncol (R Coll Radiol). 2015 May;27(5):298-306. doi: 10.1016/j.clon.2015.01.030. PMID: 25687175. Exclusion: E9

36. Bijlani A, Aguzzi G, Schaal DW, et al. Stereotactic radiosurgery and stereotactic body radiation therapy cost-effectiveness results. Frontiers in Oncology. 2013;3 APRdoi: 10.3389/fonc.2013.00077. Exclusion: E9

37. Bilsky MH, Laufer I, Burch S. Shifting paradigms in the treatment of metastatic spine disease. Spine (Phila Pa 1976). 2009 Oct 15;34(22 Suppl):S101-7. doi: 10.1097/BRS.0b013e3181bac4b2. PMID: 19829269. Exclusion: E9

38. Bilsky MH, Shannon FJ, Sheppard S, et al. Diagnosis and management of a metastatic tumor in the atlantoaxial spine. Spine (Phila Pa 1976). 2002 May 15;27(10):1062-9. doi: 10.1097/00007632-200205150-00011. PMID: 12004173. Exclusion: E7

39. Blitzer PH. Reanalysis of the RTOG study of the palliation of symptomatic osseous metastasis. Cancer. 1985 Apr 1;55(7):1468-72. doi: 10.1002/1097-0142(19850401)55:7<1468::aid-cncr2820550708>3.0.co;2-m. PMID: 2579716. Exclusion: E7

40. Bludau F. Kypho-IORT: Results of phase II-dose escalation study and clinical results of 61 cases. Spine Journal. 2015;15(10):114S-5S. doi: 10.1016/j.spinee.2015.07.082. Exclusion: E8

41. Boevé L, Hulshof M, Verhagen P, et al. Patient-reported Quality of Life in Patients with Primary Metastatic Prostate Cancer Treated with Androgen Deprivation Therapy with and Without Concurrent Radiation Therapy to the Prostate in a Prospective Randomised Clinical Trial; Data from the HORRAD Trial. Eur Urol. 2021 Feb;79(2):188-97. doi: 10.1016/j.eururo.2020.08.023. PMID: 32978014. Exclusion: E4

42. Boevé LMS, Hulshof M, Vis AN, et al. Effect on Survival of Androgen Deprivation Therapy Alone Compared to Androgen Deprivation Therapy Combined with Concurrent Radiation Therapy to the Prostate in Patients with Primary Bone Metastatic Prostate Cancer in a Prospective Randomised Clinical Trial: Data from the HORRAD Trial. Eur Urol. 2019 Mar;75(3):410-8. doi: 10.1016/j.eururo.2018.09.008. PMID: 30266309. Exclusion: E3

43. Bokhari A, Leichter J, Jalaeian H, et al. Abstract No. 165 Radiofrequency ablation in combination with kyphoplasty for the treatment of painful spine metastases: evaluation of VAS pain scale. Journal of Vascular and Interventional Radiology. 2021;32(5):S73. doi: 10.1016/j.jvir.2021.03.171. Exclusion: E8

44. Bollen L, Dijkstra SPD, Bartels R, et al. Clinical management of spinal metastases-The Dutch national guideline. Eur J Cancer. 2018 Nov;104:81-90. doi: 10.1016/j.ejca.2018.08.028. PMID: 30336360. Exclusion: E9

45. Booth M, Summers J, Williams MV. Audit reduces the reluctance to use single fractions for painful bone metastases. Clin Oncol (R Coll Radiol). 1993;5(1):15-8. doi: 10.1016/s0936-6555(05)80687-9. PMID: 7678748. Exclusion: E9

46. Borget I, Decroisette C, David P, et al. Treatment costs of bone metastases in patients with lung cancer: Results from a french prospective, observational, multicenter study (GFPC 0601). Value in Health. 2011;14(7):A441. doi: 10.1016/j.jval.2011.08.1143. Exclusion: E8

47. Borojevic N, Golubicic I, Jelic-Radosevic L. Bone metastases in breast cancer patients: Efficacy of radiotherapy with different fractionation schedules. Journal of B.U.ON. 1999;4(2):167-72. Exclusion: E12

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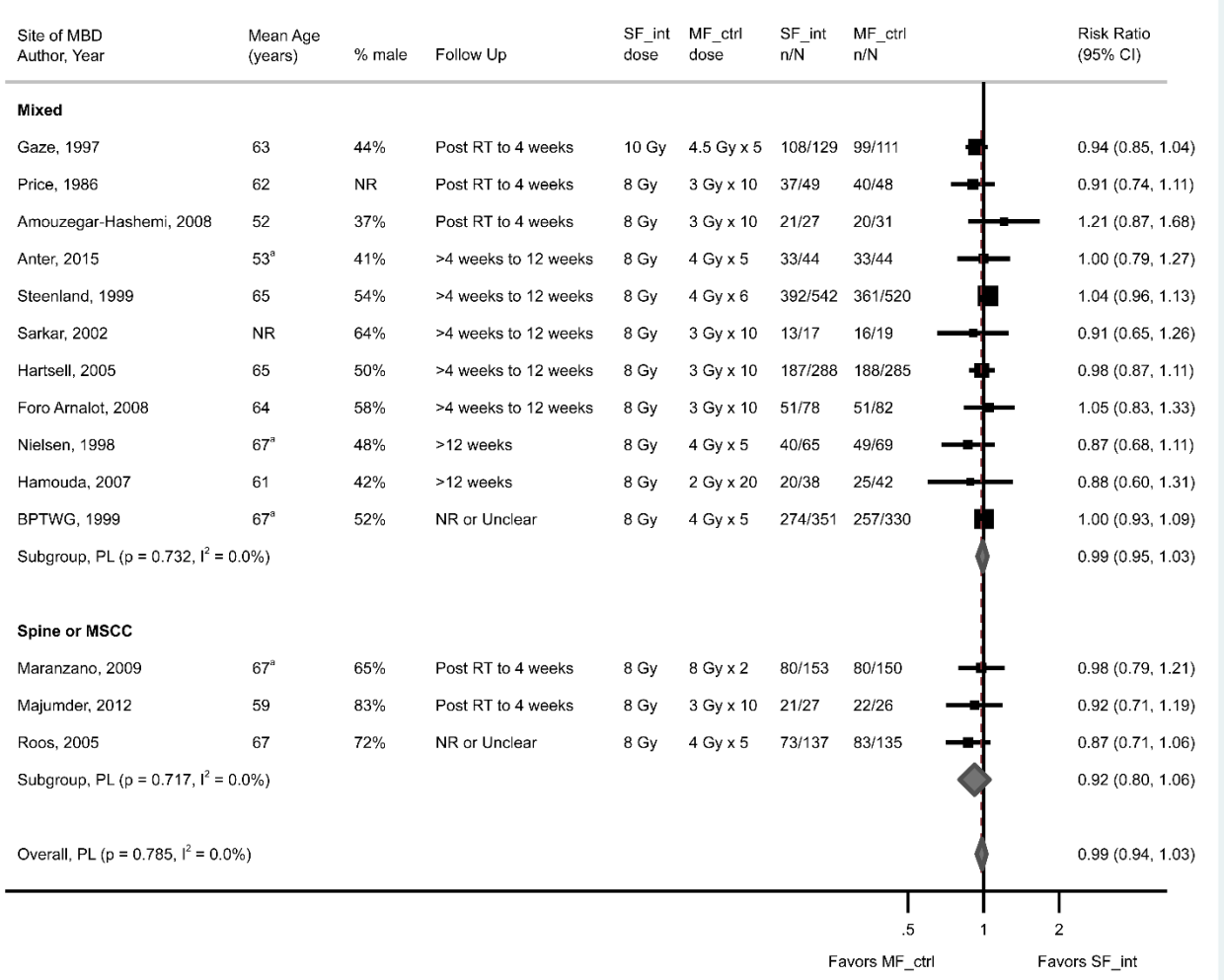
Appendix I. Forest Plots

Key Question 1: Dose-Fractionation Schemes

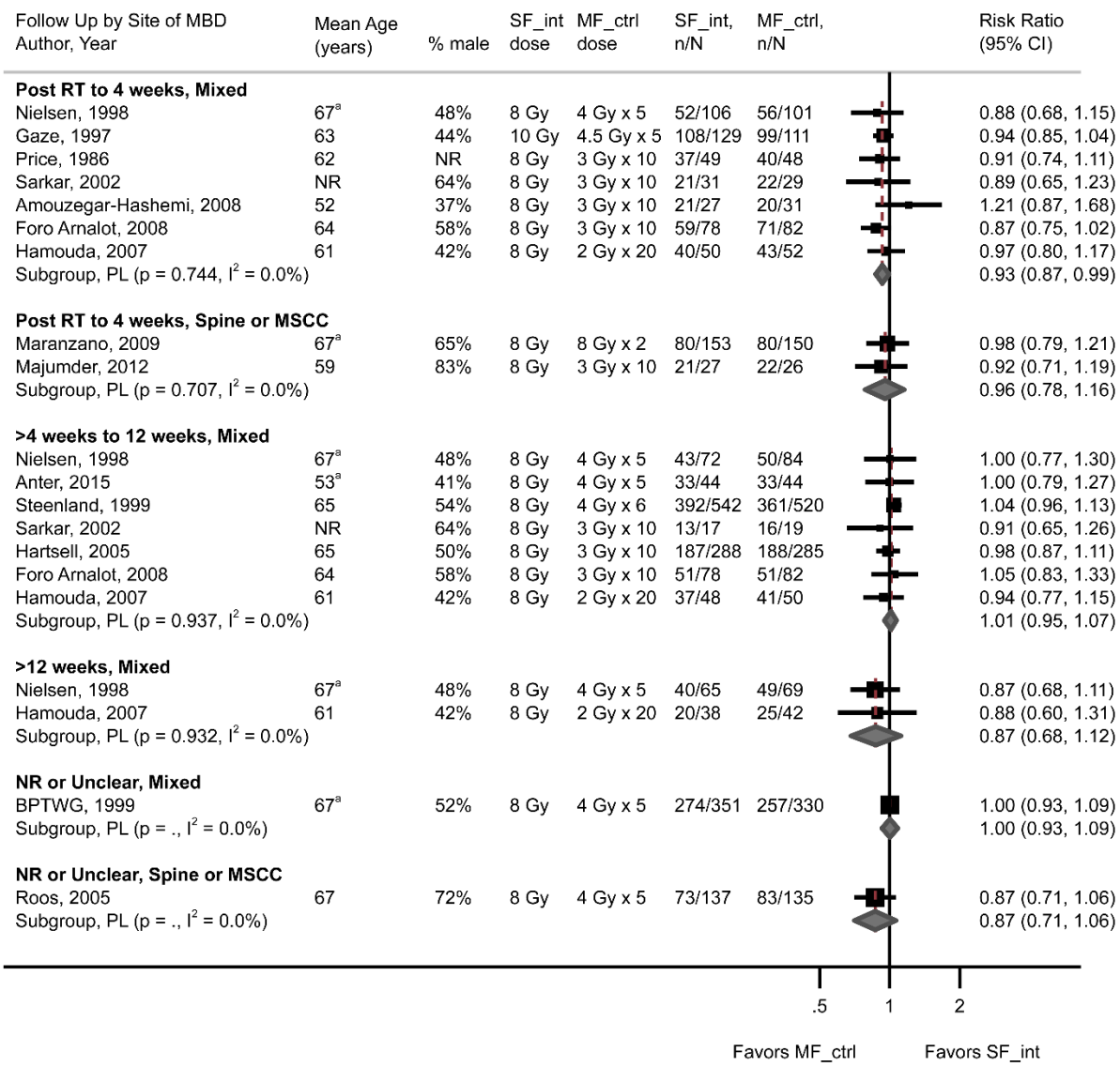
Single-Fraction Versus Multiple-Fraction EBRT

Figure I-1. Overall pain response: based on longest followup time, by site of MBD for SF versus MF EBRT



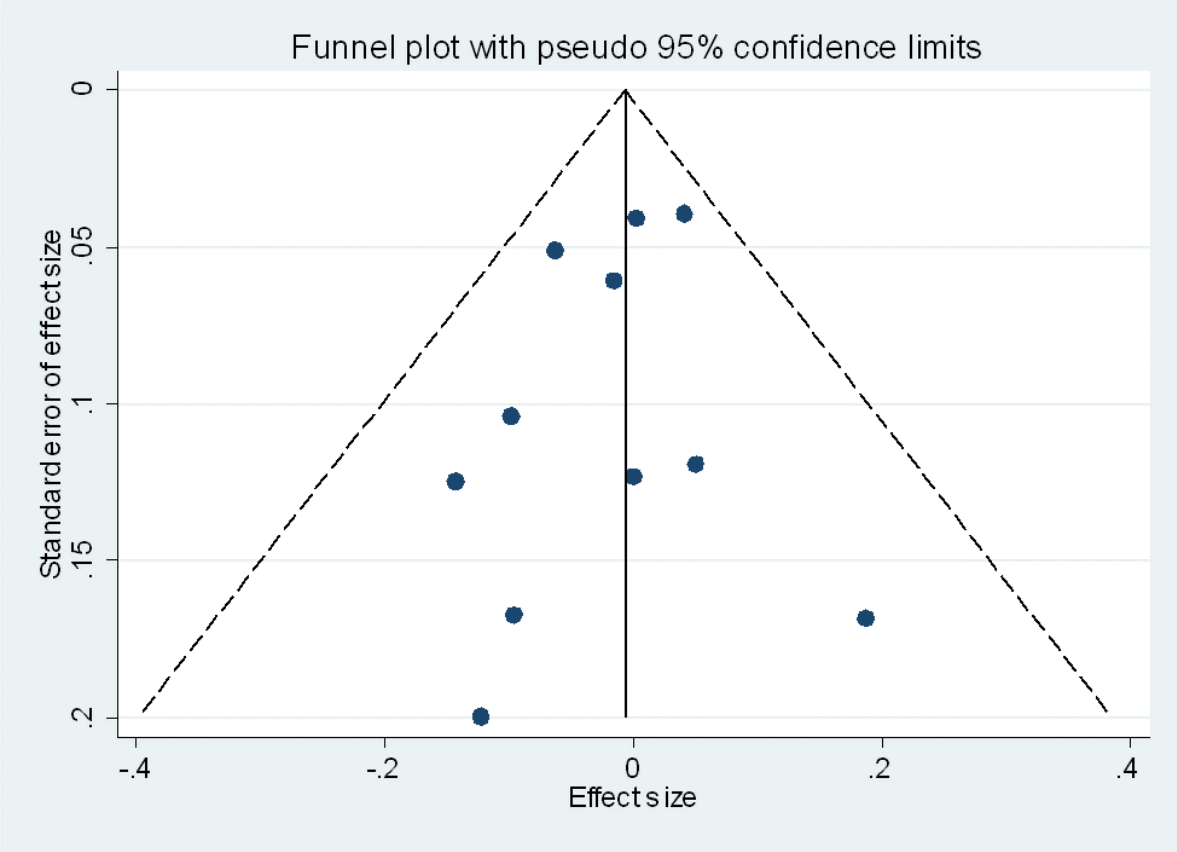
BPTWG Bone Pain Trial Working Group; CI = confidence interval; EBRT = external beam radiation therapy; MBD = metastatic bone disease; MF = multiple fraction; MF_ctrl = multiple fraction is the control; NR = not reported; PL = profile likelihood; RT = radiation therapy; SF = single fraction; SF_int = single fraction is the intervention.
a. Median age

Figure I-2. Overall pain response: by time frame, by site of MBD for SF versus MF EBRT



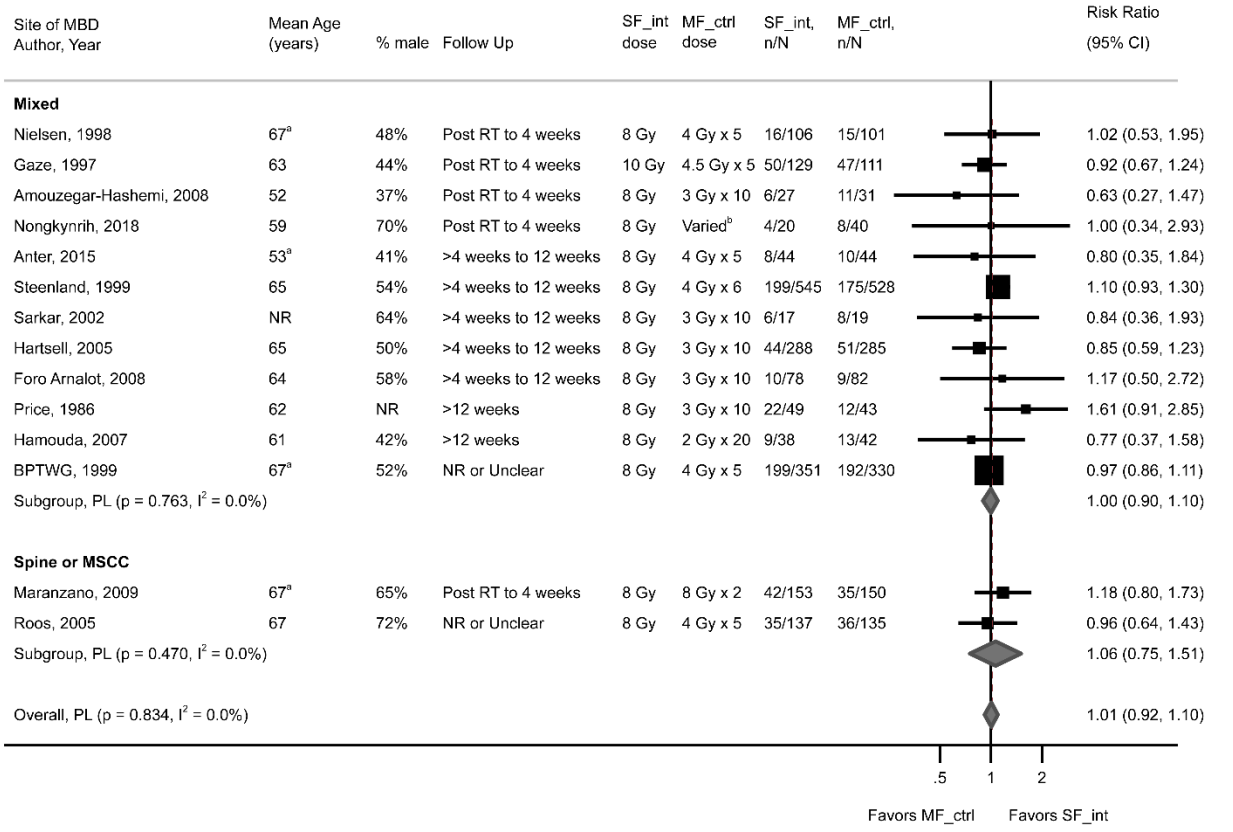
BPTWG Bone Pain Trial Working Group; CI = confidence interval; EBRT = external beam radiation therapy; MBD = metastatic bone disease; MF = multiple fraction; MF_ctrl = multiple fraction is the control; NR = not reported; PL = profile likelihood; RT = radiation therapy; SF = single fraction; SF int = Single Fraction is the intervention.
a. Median age

Figure I-3. Funnel plot for overall pain response based on last followup, for SF versus MF EBRT[a]



MF EBRT = multiple fraction external beam radiation therapy; SF EBRT = single fraction external beam radiation therapy.
[a] This funnel plot evaluates possible publication bias. The plot is considered symmetrical (i.e., none of the trials/dots lie outside the confidence limits (dashed lines)) and does not suggest publication bias. Egger's test for small study effects was not statistically significant (p=0.405) and is reported in the review text.

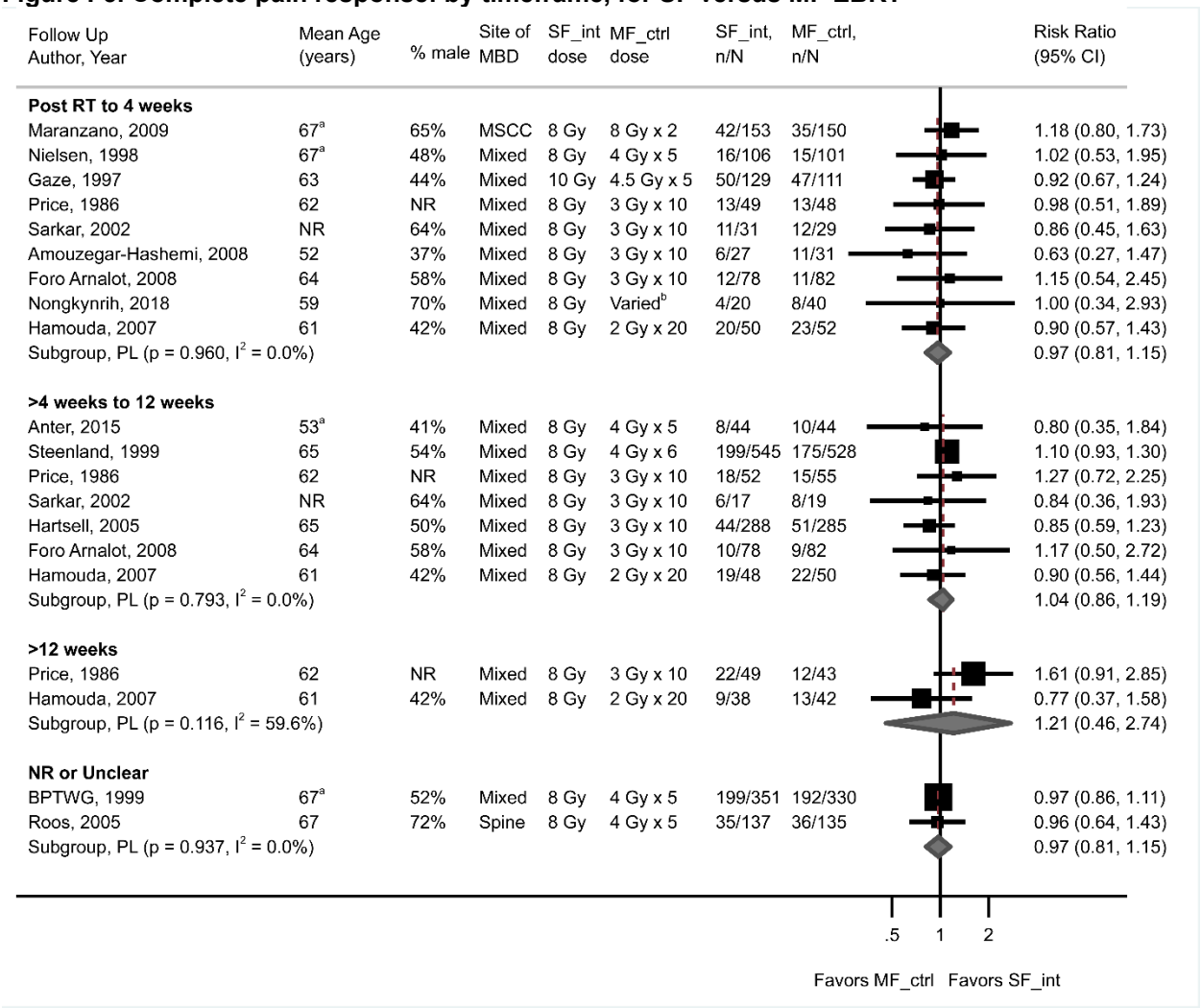
Figure I-4. Complete pain response: overall estimates for longest followup time, by site of MBD, for SF versus MF EBRT



BPTWG = Bone Pain Trial Working Group; CI = confidence interval; EBRT = external beam radiation therapy; MBD = metastatic bone disease; MF = multiple fractions; MF_ctrl = multiple fraction is the control; MSCC = metastatic spinal cord compression; NR = not reported; PL = profile likelihood; RT = radiation therapy; SF = single fractions; SF_int = Single Fraction is the intervention.

[a] Median age

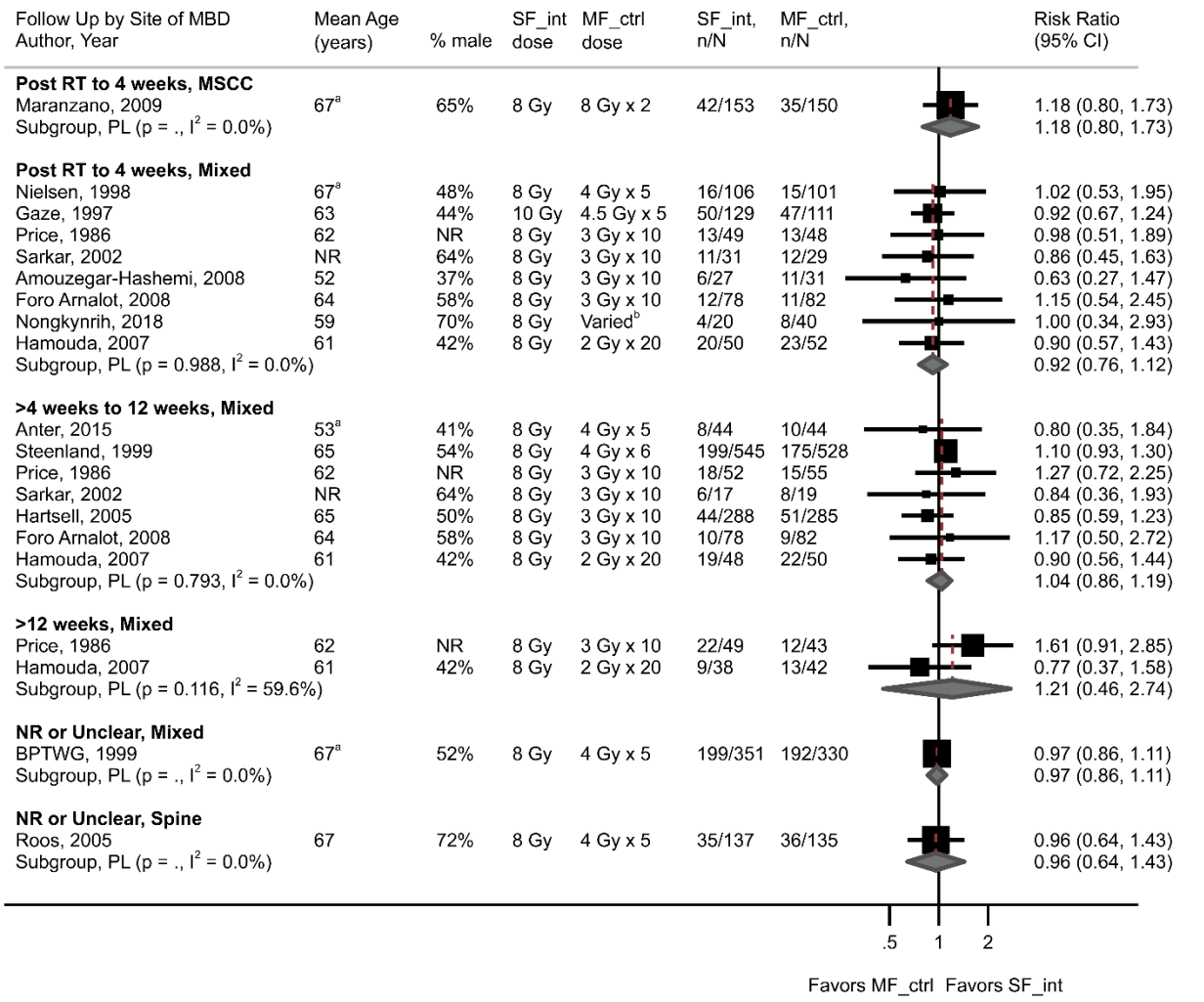
Figure I-5. Complete pain response: by timeframe, for SF versus MF EBRT



BPTWG = Bone Pain Trial Working Group; CI = confidence interval; EBRT = external beam radiation therapy; MBD = metastatic bone disease; MF = multiple fractions; MF_ctrl = multiple fraction is the control; MSCC = metastatic spinal cord compression; NR = not reported; PL = profile likelihood; RT = radiation therapy; SF = single fractions; SF_int = Single Fraction is the intervention.

[a] Median age

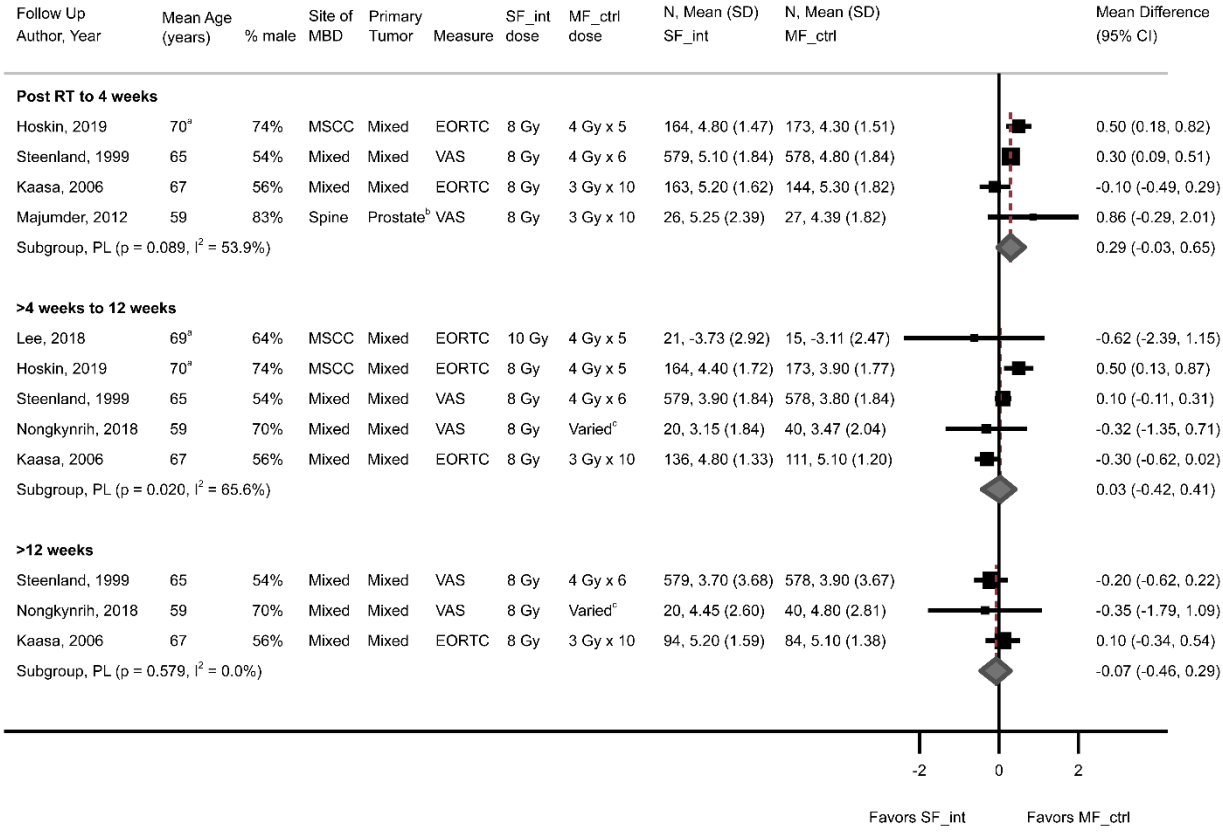
Figure I-6. Complete pain response: by timeframe, by site of MBD for SF versus MF EBRT



BPTWG = Bone Pain Trial Working Group; CI = confidence interval; EBRT = external beam radiation therapy; MBD = metastatic bone disease; MF = multiple fractions; MF_ctrl = multiple fraction is the control; MSCC = metastatic spinal cord compression; NR = not reported; PL = profile likelihood; RT = radiation therapy; SF = single fractions; SF_int = Single Fraction is the intervention.

[a] Median age

Figure I-7. Summary of pain scores (0-10 scale): SF versus MF EBRT



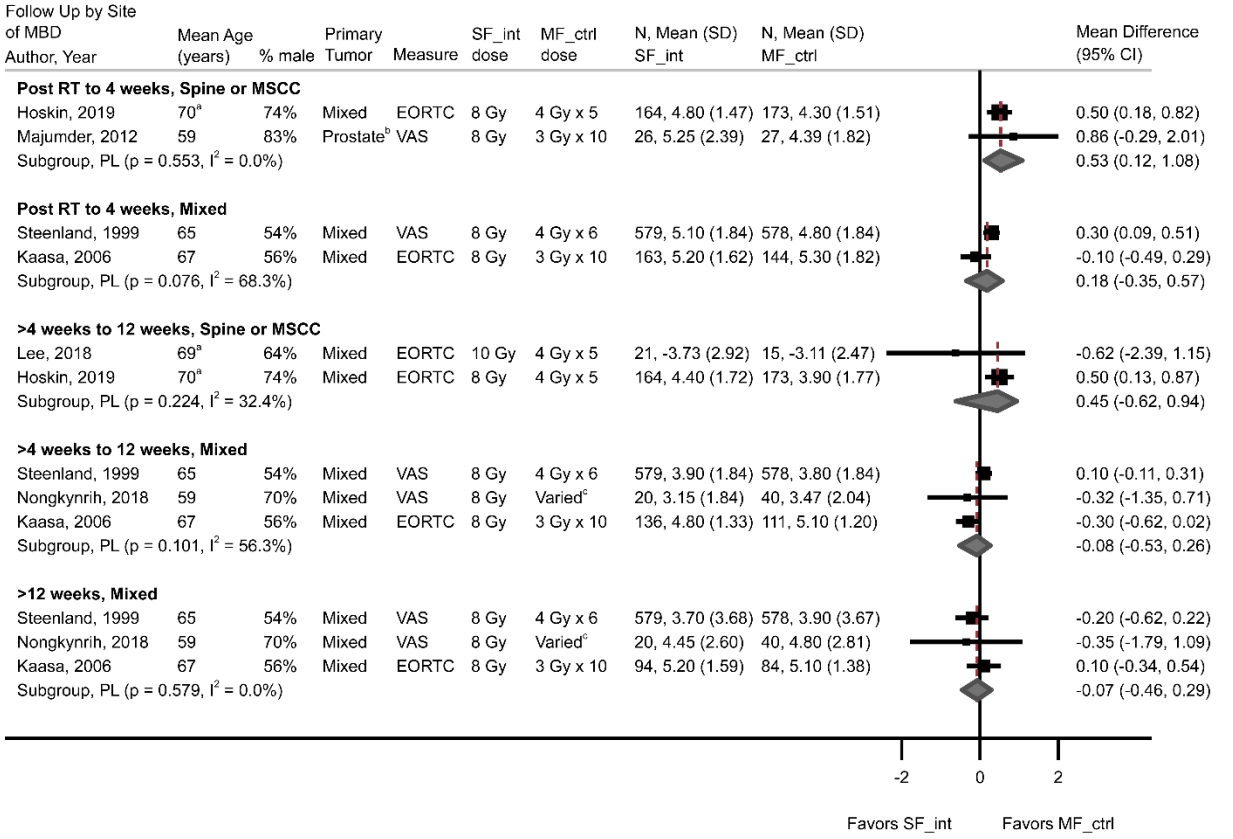
CI = confidence interval; EBRT = external beam radiation therapy; EORTC = European Organisation For Research And Treatment Of Cancer; MBD = metastatic bone disease; MF = multiple fractions; MF_ctrl = multiple fractions as control; PL = profile likelihood; RT = radiation therapy; SD = standard deviation; SF = single fraction; SF_int = single fractions as intervention; VAS = visual analog scale.

a. Median age

b. Prostate (80%) (breast 14%, cervix 3%, lung 3%)

c. 4 Gy x 5 (20 Gy) or 3 Gy x 10 (30 Gy)

Figure I-8. Summary of pain scores (0-10 scale): by time and site of MBD, for SF versus MF EBRT



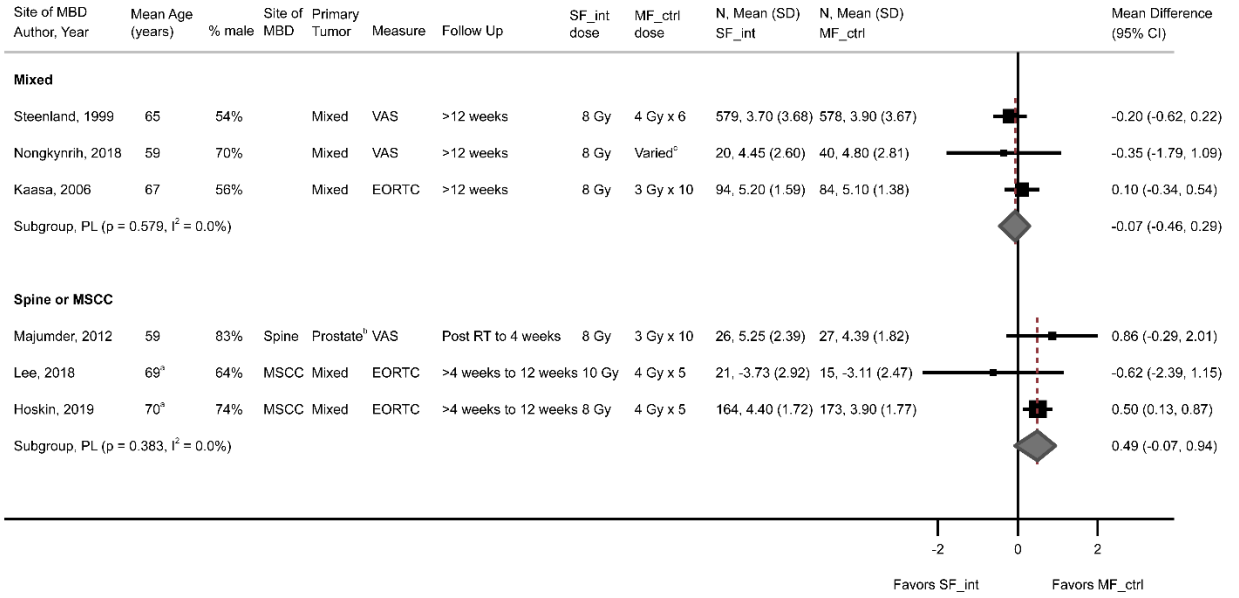
CI = confidence interval; EBRT = external beam radiation therapy; EORTC = European Organization for Research and Treatment of Cancer; MBD = metastatic bone disease; MF = multiple fraction; MF_ctrl = multiple fractions as control; MSCC = metastatic spinal cord compression; NR = not reported; PL = profile likelihood; RT = radiation therapy; SF = single fraction; SF_int = single fractions as intervention; VAS = visual analog scale.

[a] Median age

[b] Prostate (80%) (breast 14%, cervix 3%, lung 3%)

[c] 4 Gy x 5 (20 Gy) or 3 Gy x 10 (30 Gy)

Figure I-9. Summary of pain scores (0-10 scale): overall estimate for longest followup time, by site of MBD, for SF versus MF EBRT

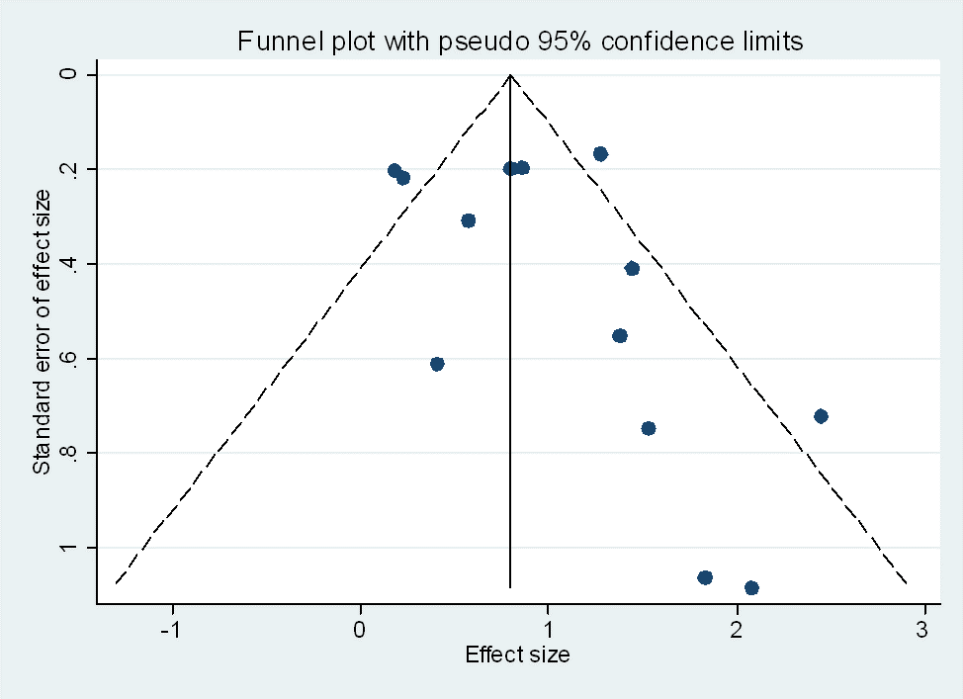


CI = confidence interval; EBRT = external beam radiation therapy; EORTC = European Organization for Research and Treatment of Cancer; MBD = metastatic bone disease; MF = multiple fraction; MF_ctrl = multiple fractions as control; MSCC = metastatic spinal cord compression; NR = not reported; PL = profile likelihood; RT = radiation therapy; SF = single fraction; SF_int = single fractions as intervention; VAS = visual analog scale.

[a] Median age

[b] Prostate (80%) (breast 14%, cervix 3%, lung 3%)

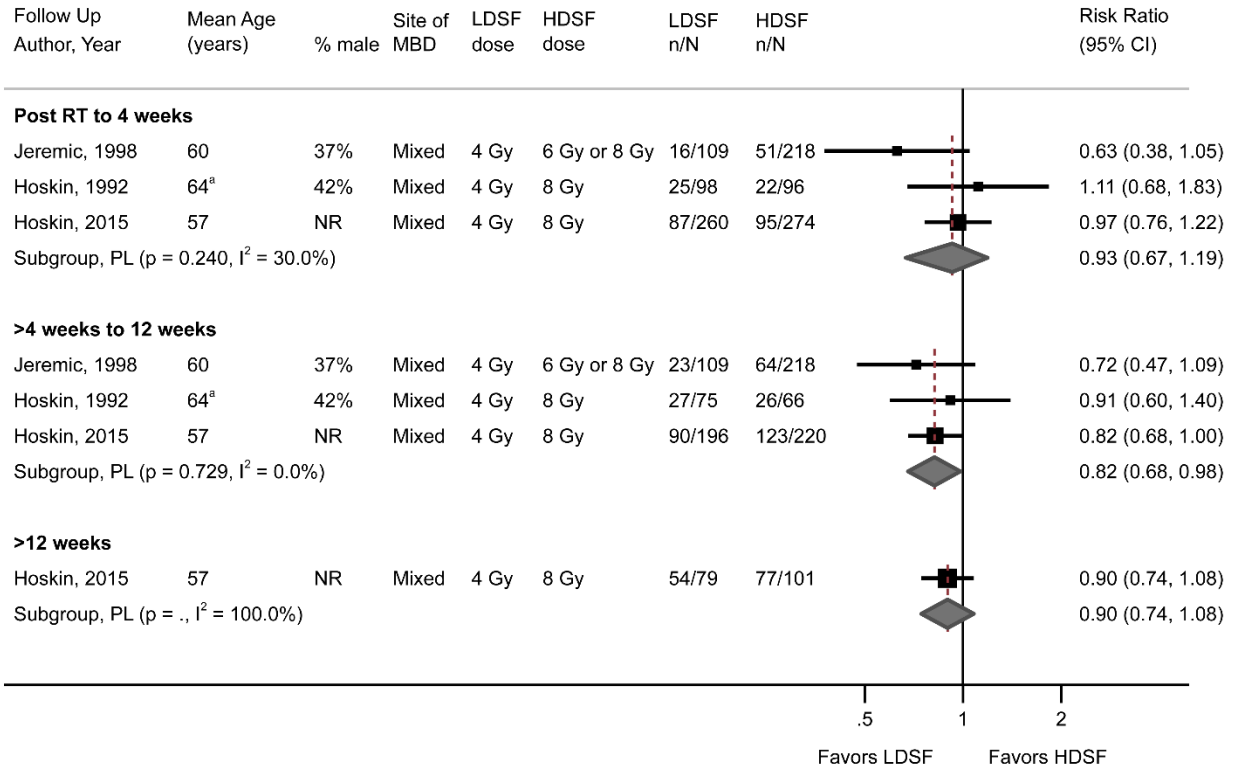
Figure I-10. Funnel plot analysis for the outcome of re-irradiation for studies comparing SF versus MF EBRT[a]



[a] This funnel plot evaluates possible publication bias. The plot is visually asymmetrical with 4 trials (represented by dots) lying outside of the pseudo 95% confidence limits (dashed lines) which may indicate some publication bias. Although Egger's test is not significant (p=0.221), it has low power to detect bias.

Comparison of Single Fraction Schemes for EBRT

Figure I-11. Complete pain response: by timeframe, for LDSF versus HDSF EBRT

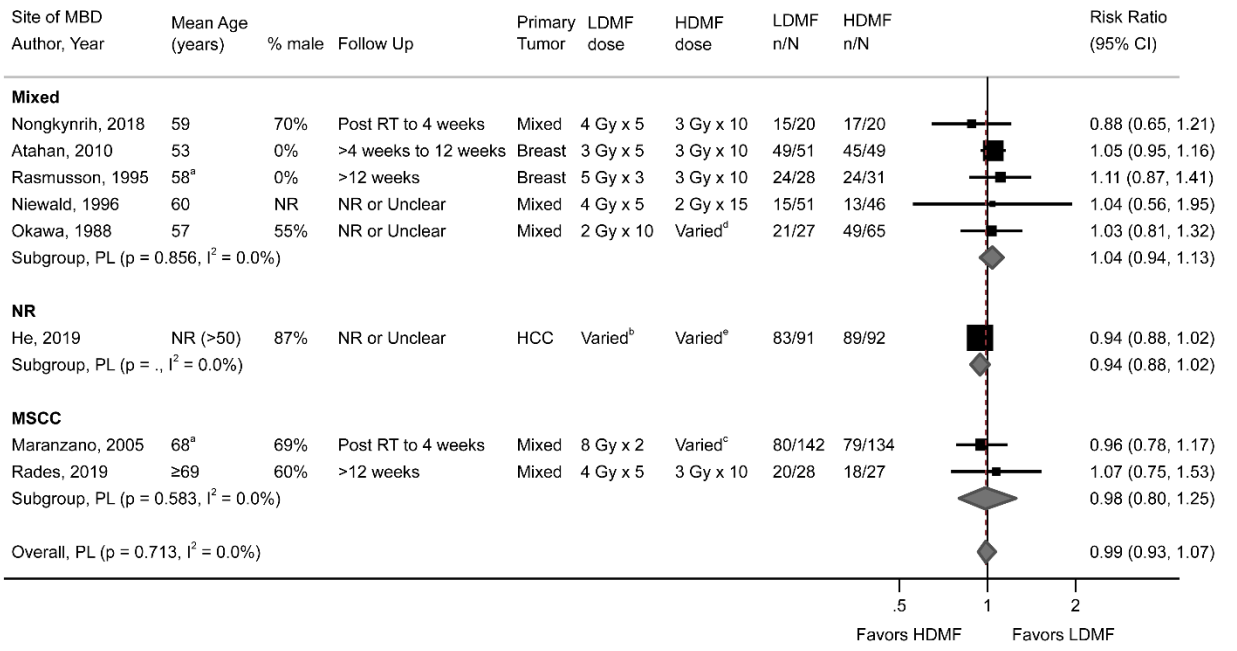


CI = confidence interval; EBRT = external beam radiation therapy; Gy = Gray; HDSF = higher total dose single fraction EBRT (control); LDSF = lower total dose single fraction EBRT (intervention); MBD = metastatic bone disease; NR = not reported; PL = profile likelihood.

[a] Median age

Comparison of Multiple Fraction Schemes for EBRT

Figure I-12. Overall pain response: overall estimate for longest followup time, by site of MBD for LDMF versus HDMF EBRT



CI = confidence interval; EBRT = external beam radiation therapy; HCC = hepatocellular carcinoma; HDMF = lower total dose multiple fraction EBRT control); LDMF = lower total dose multiple fraction EBRT (intervention); MBD = metastatic bone disease; MF = multiple fractions; MSCC = metastatic spinal cord compression; NR = not reported; PL = profile likelihood; RT = radiation therapy.

[a] Median age

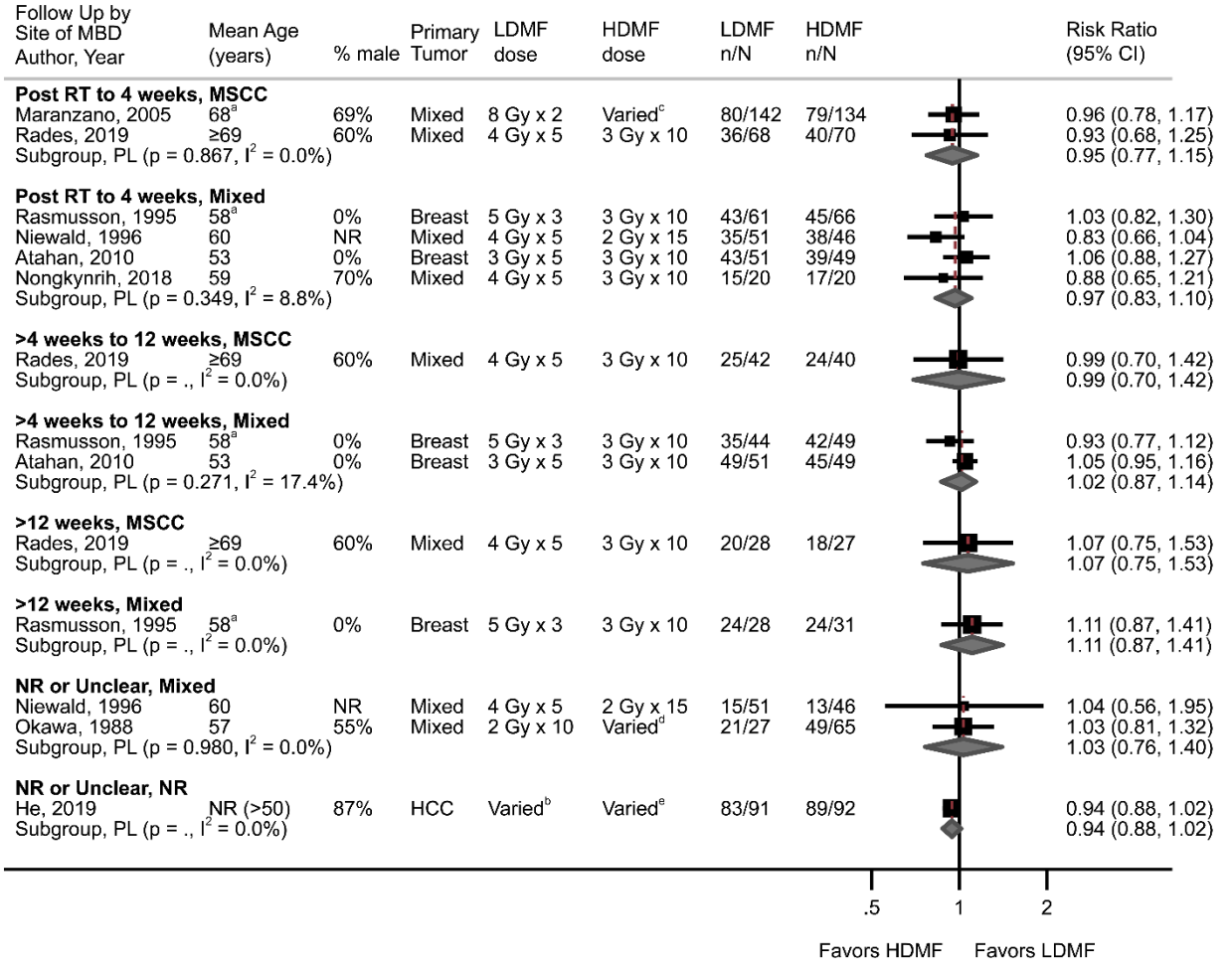
[b] 4 Gy x 7 or 4 Gy x 10

[c] 5 Gy x 3 & 3 Gy x 5 (30 Gy)

[d] 4.5 Gy x 5 (22.5 Gy) or 2 Gy x 15 (30 Gy)

[e] 2 Gy x 20 (40 Gy) or 2 Gy x 30 (60 Gy)

Figure I-13. Overall pain response: by timeframe, by site of MBD for LDMF versus HDMF EBRT



CI = confidence interval; EBRT = external beam radiation therapy; HCC = hepatocellular carcinoma; HDMF = lower total dose multiple fraction EBRT control); LDMF = lower total dose multiple fraction EBRT (intervention); MBD = metastatic bone disease; MF = multiple fractions; MSCC = metastatic spinal cord compression; NR = not reported; PL = profile likelihood; RT = radiation therapy.

[a] Median age

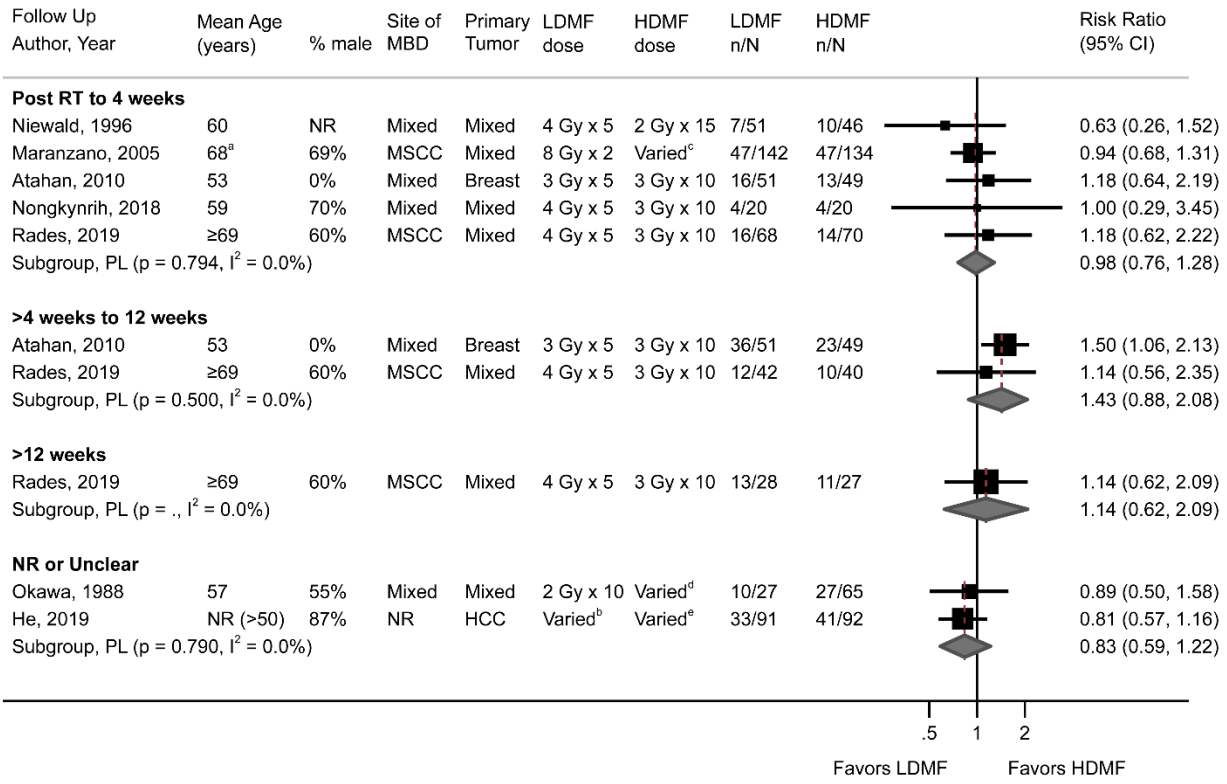
[b] 4 Gy x 7 or 4 Gy x 10

[c] 5 Gy x 3 & 3 Gy x 5 (30 Gy)

[d] 4.5 Gy x 5 (22.5 Gy) or 2 Gy x 15 (30 Gy)

[e] 2 Gy x 20 (40 Gy) or 2 Gy x 30 (60 Gy)

Figure I-14. Complete pain response: by timeframe for LDMF versus HDMF EBRT



CI = confidence interval; EBRT = external beam radiation therapy; HCC = hepatocellular carcinoma; HDMF = lower total dose multiple fraction EBRT control); LDMF = lower total dose multiple fraction EBRT (intervention); MBD = metastatic bone disease; MF = multiple fractions; MSCC = metastatic spinal cord compression; NR = not reported; PL = profile likelihood; RT = radiation therapy.

[a] Median age

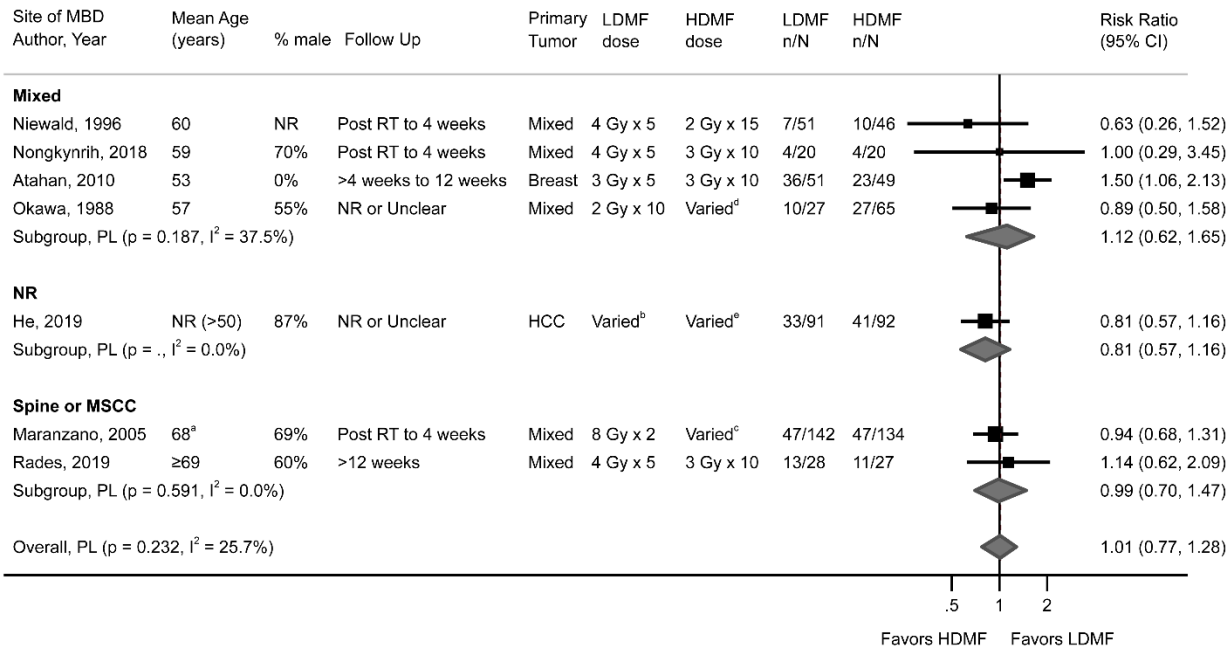
[b] 4 Gy x 7 or 4 Gy x 10

[c] 5 Gy x 3 & 3 Gy x 5 (30 Gy)

[d] 4.5 Gy x 5 (22.5 Gy) or 2 Gy x 15 (30 Gy)

[e] 2 Gy x 20 (40 Gy) or 2 Gy x 30 (60 Gy)

Figure I-15. Complete pain response: overall estimate by longest followup, by site of MBD for LDMF versus HDMF EBRT



CI = confidence interval; EBRT = external beam radiation therapy; HCC = hepatocellular carcinoma; HDMF = lower total dose multiple fraction EBRT control); LDMF = lower total dose multiple fraction EBRT (intervention); MBD = metastatic bone disease; MF = multiple fractions; MSCC = metastatic spinal cord compression; NR = not reported; PL = profile likelihood; RT = radiation therapy.

[a] Median age

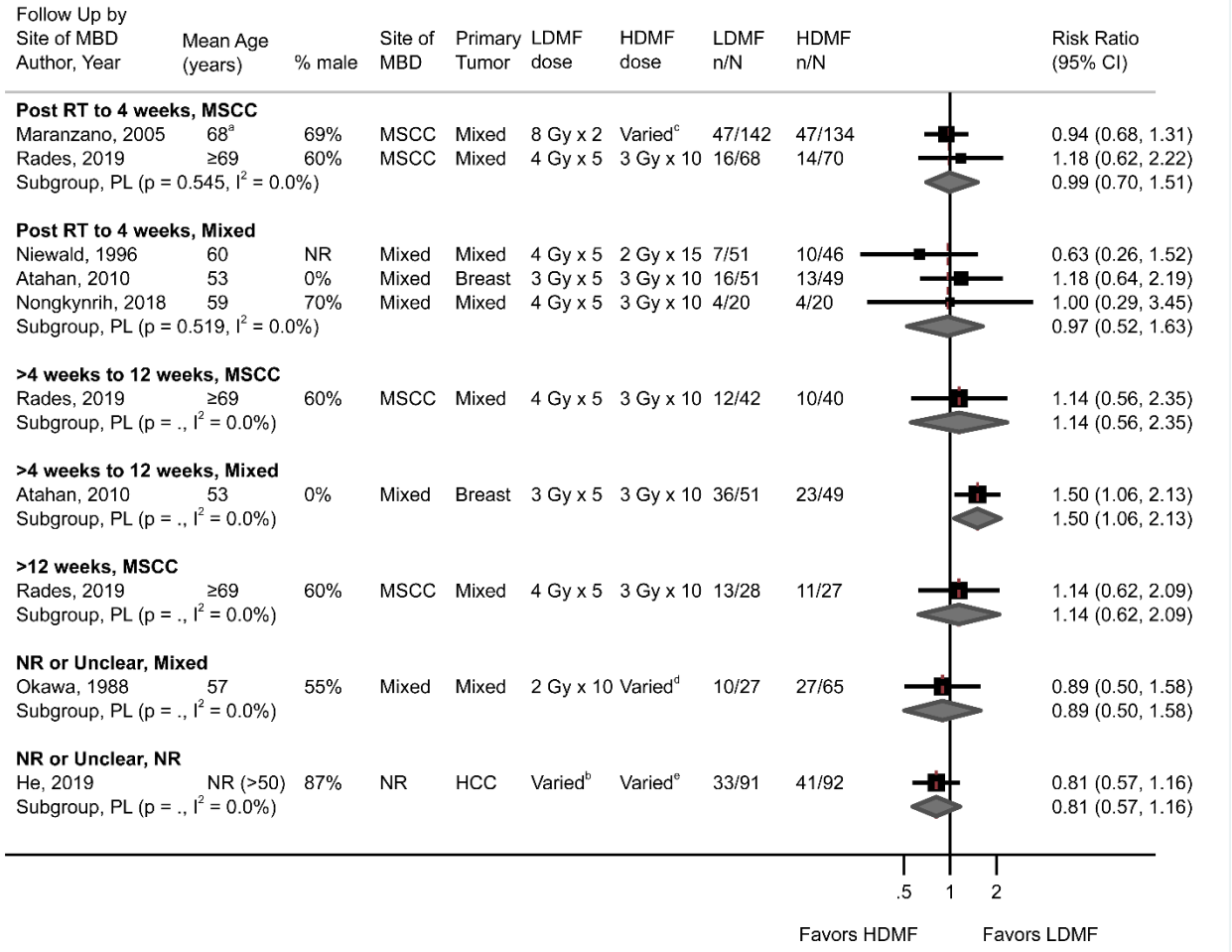
[b] 4 Gy x 7 or 4 Gy x 10

[c] 5 Gy x 3 & 3 Gy x 5 (30 Gy)

[d] 4.5 Gy x 5 (22.5 Gy) or 2 Gy x 15 (30 Gy)

[e] 2 Gy x 20 (40 Gy) or 2 Gy x 30 (60 Gy)

Figure I-16. Complete pain response: by timeframe, by site of MBD for LDMF versus HDMF EBRT



CI = confidence interval; EBRT = external beam radiation therapy; HCC = hepatocellular carcinoma; HDMF = lower total dose multiple fraction EBRT control); LDMF = lower total dose multiple fraction EBRT (intervention); MBD = metastatic bone disease; MF = multiple fractions; MSCC = metastatic spinal cord compression; NR = not reported; PL = profile likelihood; RT = radiation therapy.

[a] Median age

[b] 4 Gy x 7 or 4 Gy x 10

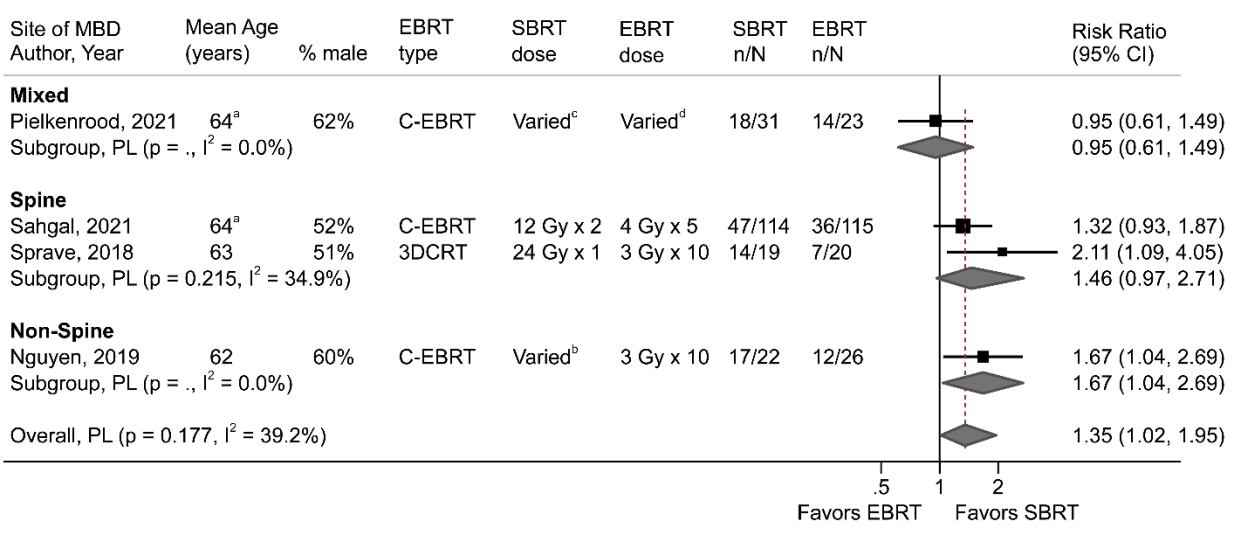
[c] 5 Gy x 3 & 3 Gy x 5 (30 Gy)

[d] 4.5 Gy x 5 (22.5 Gy) or 2 Gy x 15 (30 Gy)

[e] 2 Gy x 20 (40 Gy) or 2 Gy x 30 (60 Gy)

Key Question 1: SBRT Versus Conventional EBRT

Figure I-17. Overall pain response: based on longest followup time, by site of MBD for SBRT versus conventional EBRT



3DCRT = three-dimensional conformal radiation therapy; CI = confidence interval; C-EBRT = conventional external beam radiation therapy; MBD = metastatic bone disease; PL = profile likelihood; SBRT = stereotactic body radiation therapy

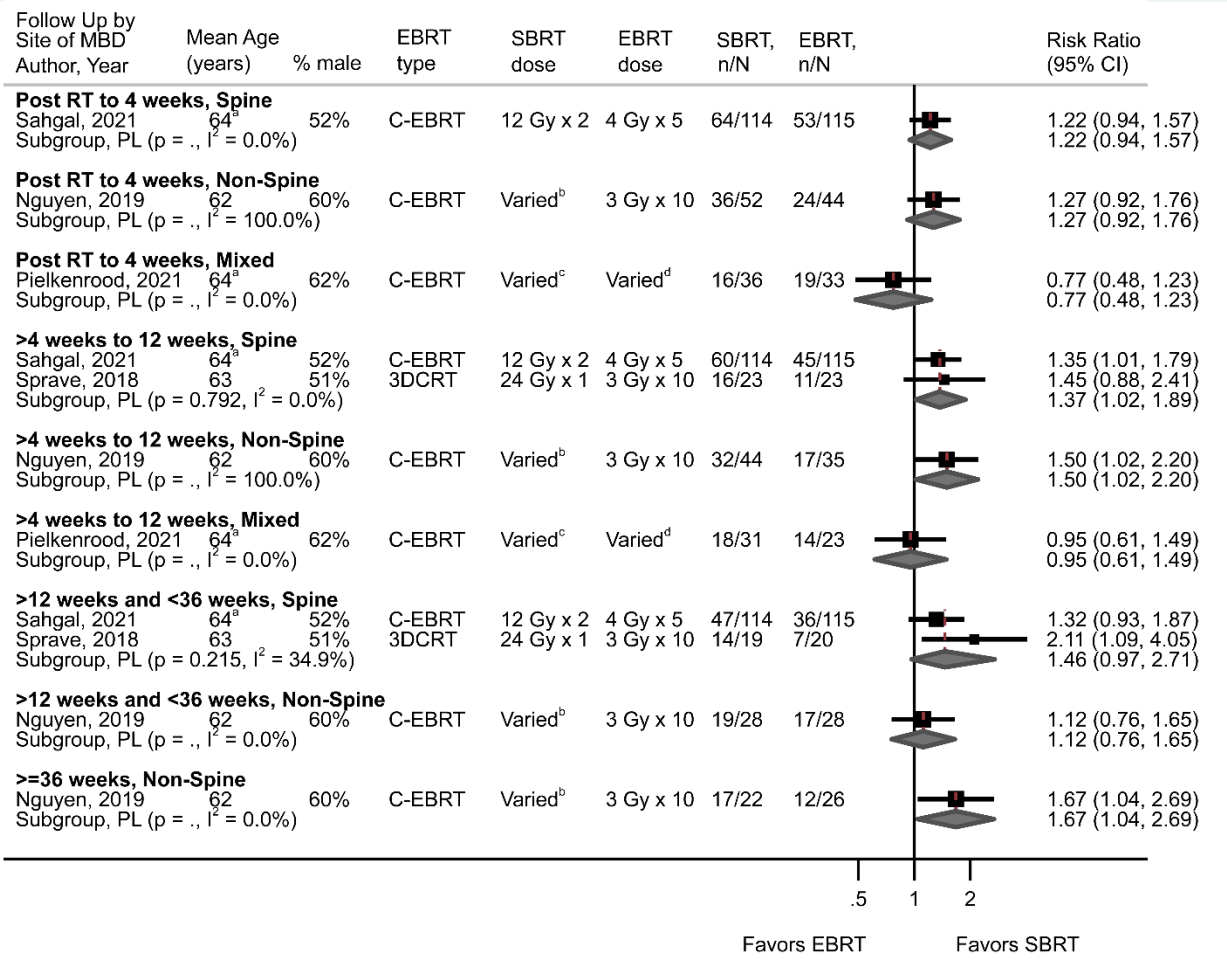
[a] Median age

[b] 12 Gy x 1 for lesions >4 cm or 16 Gy x 1 for lesions ≤4 cm

[c] 18 Gy x 1 or 10 Gy x 3 or 7 Gy x 5

[d] 8 Gy x 1 primarily; 4 Gy x 5 or 3G y x 10

Figure I-18. Overall pain response: by timeframe, by site of MBD for SBRT versus conventional EBRT



3DCRT = three-dimensional conformal radiation therapy; CI = confidence interval; C-EBRT = conventional external beam radiation therapy; MBD = metastatic bone disease; PL = profile likelihood; SBRT = stereotactic body radiation therapy

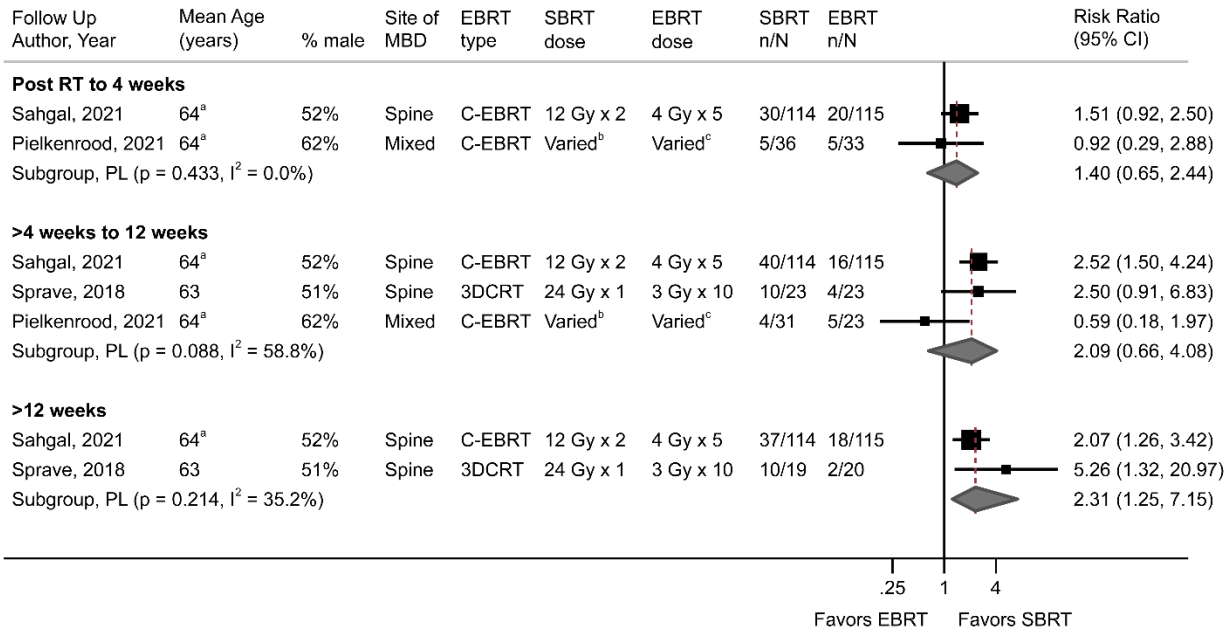
[a] Median age

[b] 12 Gy x 1 for lesions >4 cm or 16 Gy x 1 for lesions ≤4 cm

[c] 18 Gy x 1 or 10 Gy x 3 or 7 Gy x 5

[d] 8 Gy x 1 primarily; 4 Gy x 5 or 3G y x 10

Figure I-19. Complete pain response: by timeframe for SBRT versus conventional EBRT



3DCRT = three-dimensional conformal radiation therapy; CI = confidence interval; C-EBRT = conventional external beam radiation therapy; MBD = metastatic bone disease; PL = profile likelihood; SBRT = stereotactic body radiation therapy

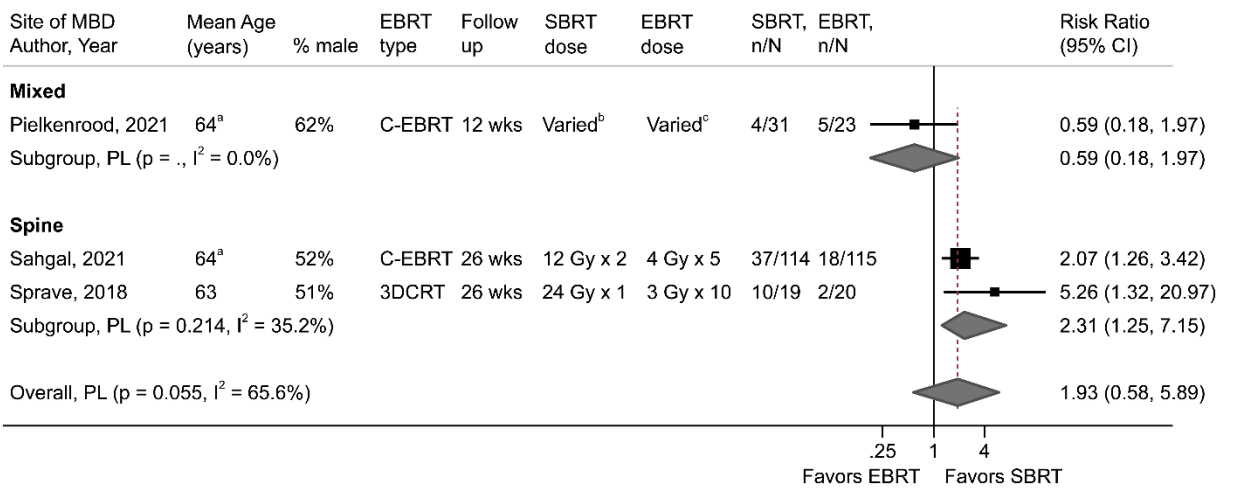
[a] Median age

[b] 12 Gy x 1 for lesions >4 cm or 16 Gy x 1 for lesions ≤4 cm

[c] 18 Gy x 1 or 10 Gy x 3 or 7 Gy x 5

[d] 8 Gy x 1 primarily; 4 Gy x 5 or 3G y x 10

Figure I-20. Complete pain response: by longest followup, by MBD site for SBRT versus conventional EBRT



3DCRT = three-dimensional conformal radiation therapy; CI = confidence interval; C-EBRT = conventional external beam radiation therapy; MBD = metastatic bone disease; PL = profile likelihood; SBRT = stereotactic body radiation therapy

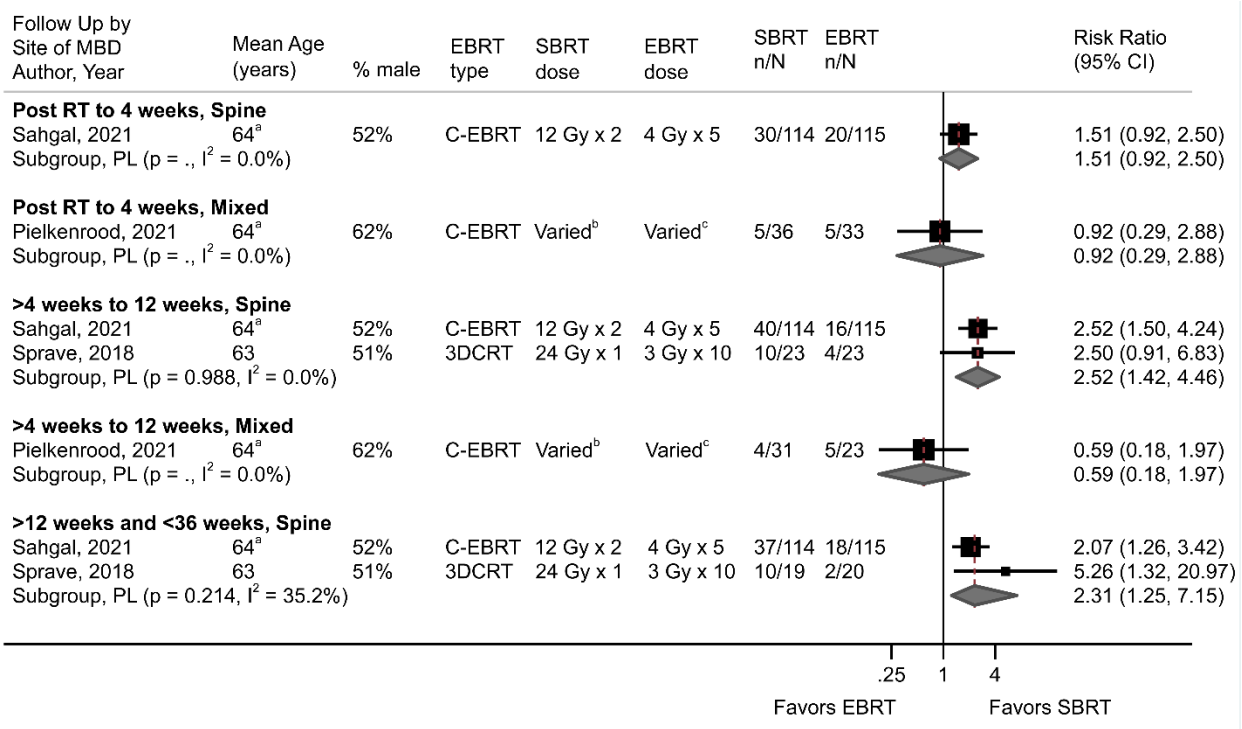
[a] Median age

[b] 12 Gy x 1 for lesions >4 cm or 16 Gy x 1 for lesions ≤4 cm

[c] 18 Gy x 1 or 10 Gy x 3 or 7 Gy x 5

[d] 8 Gy x 1 primarily; 4 Gy x 5 or 3G y x 10

Figure I-21. Complete pain response: by followup time and site of MBD for SBRT versus conventional EBRT



3DCRT = three-dimensional conformal radiation therapy; CI = confidence interval; C-EBRT = conventional external beam radiation therapy; MBD = metastatic bone disease; PL = profile likelihood; SBRT = stereotactic body radiation therapy

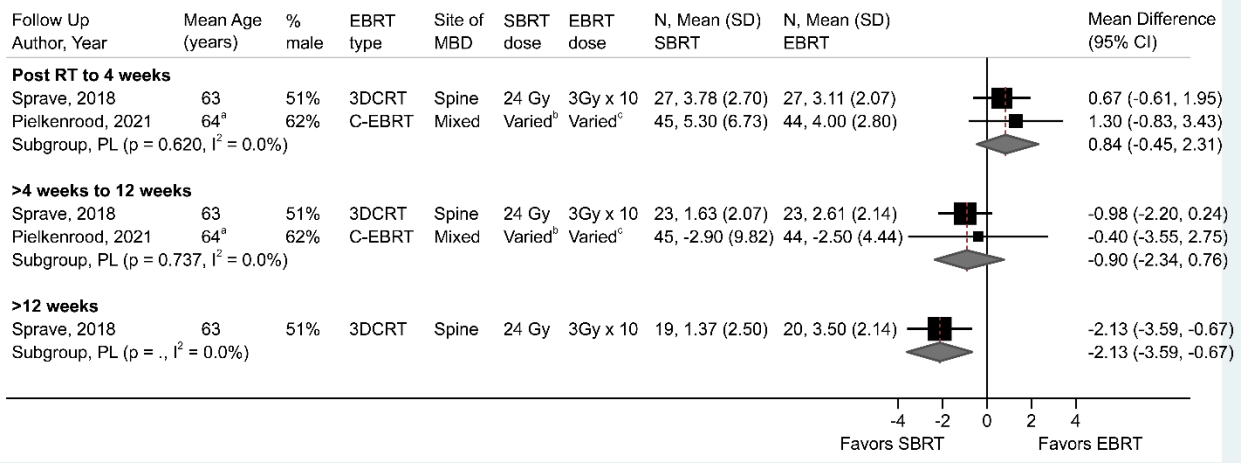
[a] Median age

[b] 12 Gy x 1 for lesions >4 cm or 16 Gy x 1 for lesions ≤4 cm

[c] 18 Gy x 1 or 10 Gy x 3 or 7 Gy x 5

[d] 8 Gy x 1 primarily; 4 Gy x 5 or 3G y x 10

Figure I-22. Pain intensity on a 0-10 scale: by timeframe for SBRT versus conventional EBRT



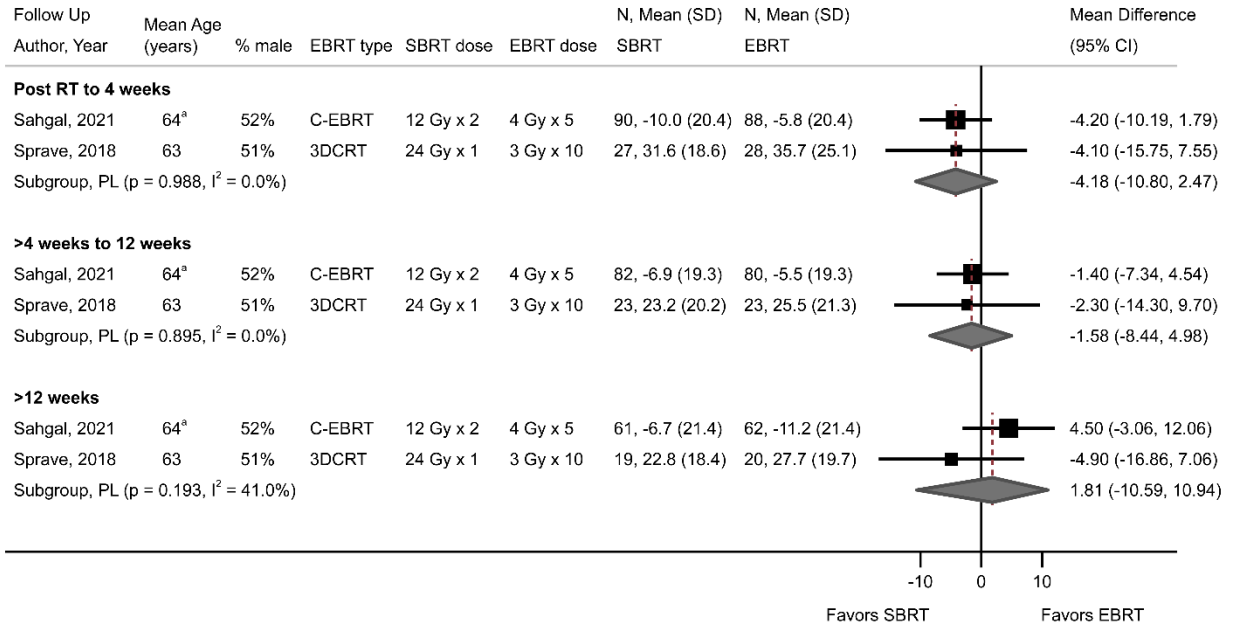
3DCRT = three-dimensional conformal radiation therapy; CI = confidence interval; C-EBRT = conventional external beam radiation therapy; MBD = metastatic bone disease; PL = profile likelihood; SBRT = stereotactic body radiation therapy

[a] Median age

[b] 18 Gy x 1 or 10 Gy x 3 or 7 Gy x 5

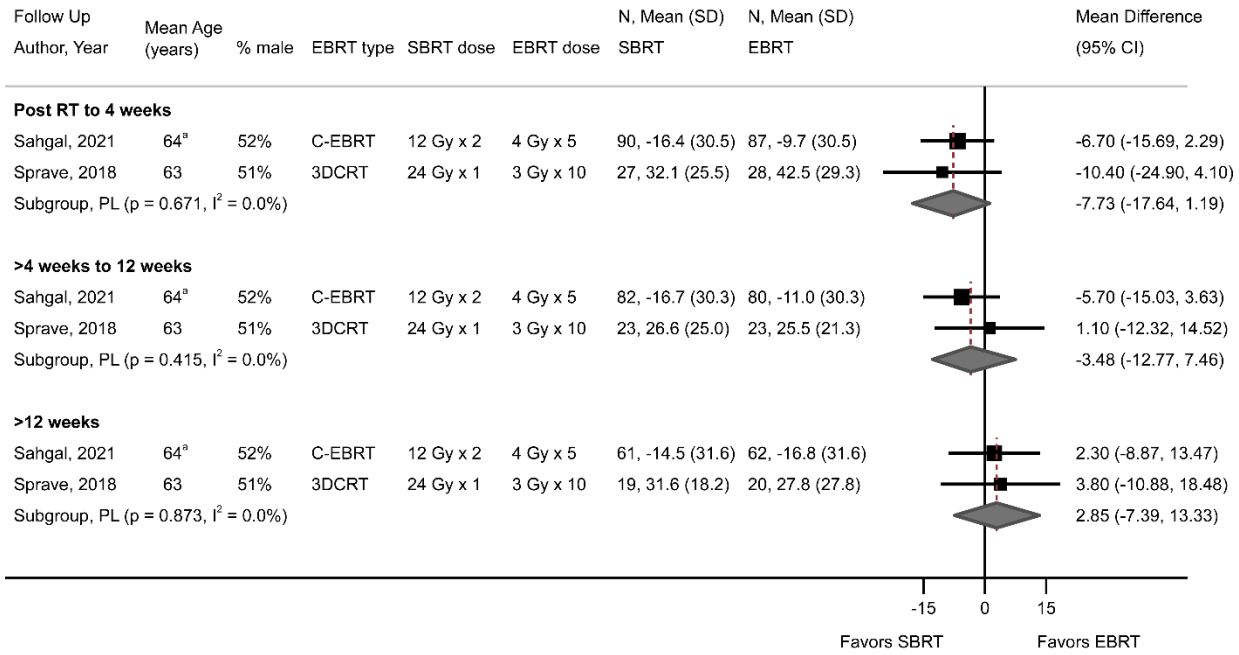
[d] 8 Gy x 1 primarily; 4 Gy x 5 or 3G y x 10

Figure I-23. EORTC QLQ-BM22 painful sites domain (0-100 scale, lower score means better quality of life): by timeframe for SBRT versus conventional EBRT



3DCRT = three-dimensional conformal radiation therapy; CI = confidence interval; C-EBRT = conventional external beam radiation therapy; EORTC QLQ-BM22 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Bone Metastases-22; PL = profile likelihood; SBRT = stereotactic body radiation therapy; SD = standard deviation.
[a] Median age

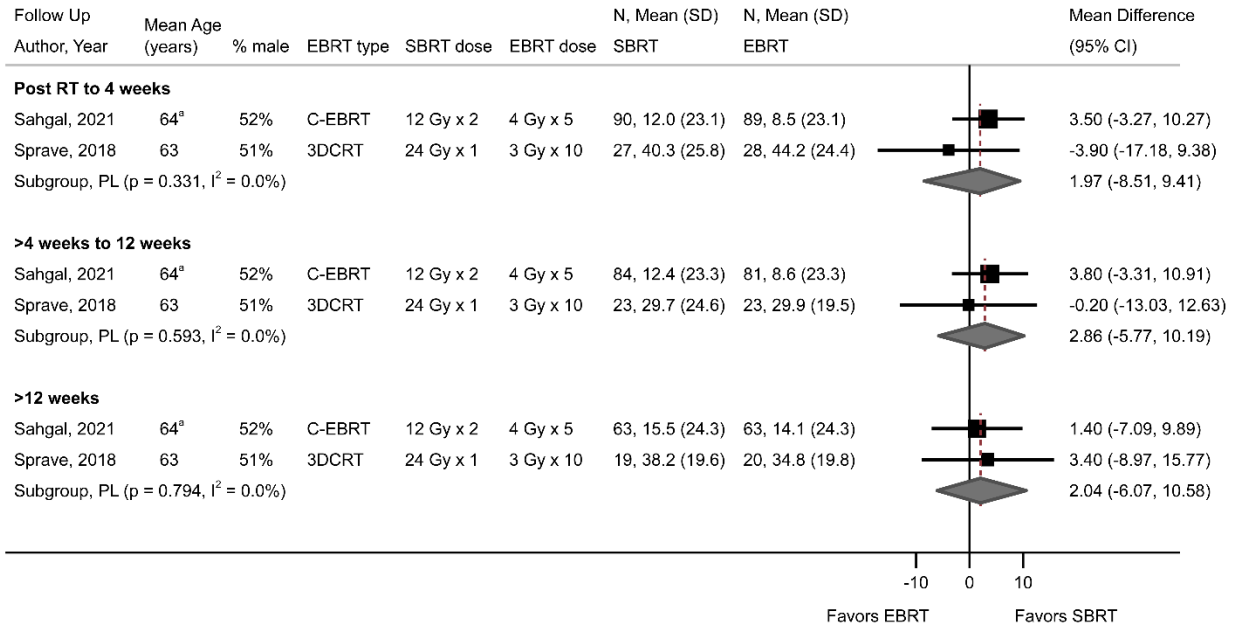
Figure I-24. EORTC QLQ-BM22 painful characteristics domain (0-100 scale, lower score means better quality of life): by timeframe for SBRT versus conventional EBRT



3DCRT = three-dimensional conformal radiation therapy; CI = confidence interval; C-EBRT = conventional external beam radiation therapy; EORTC QLQ-BM22 = European Organization for Research and Treatment of Cancer Quality of Life

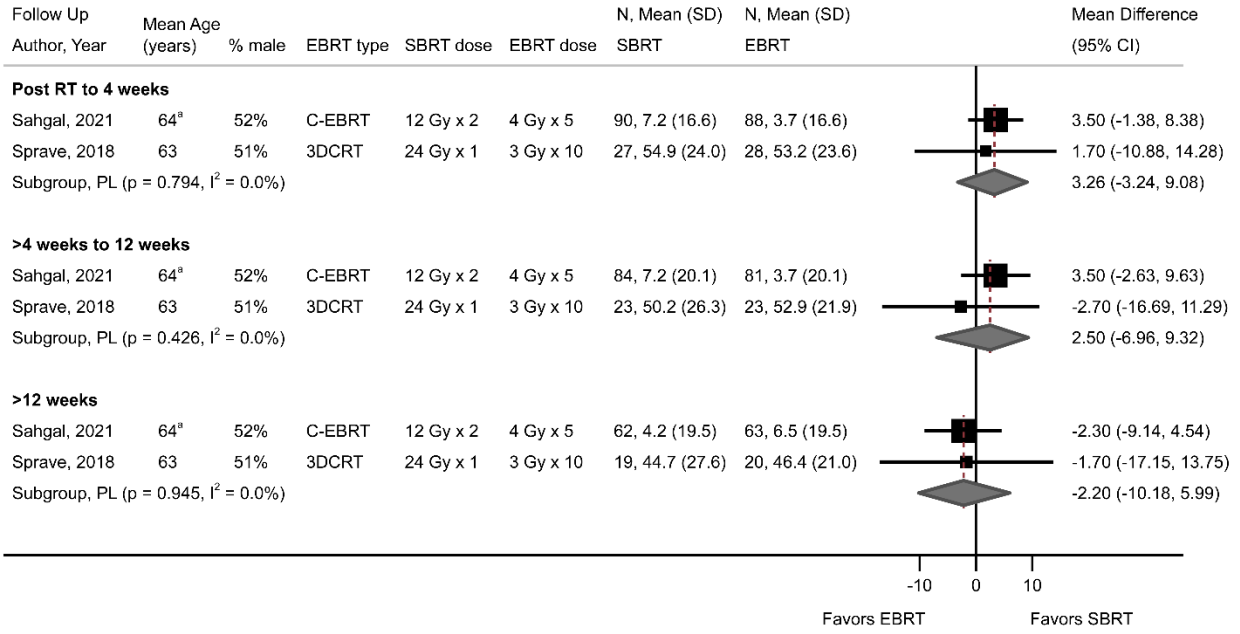
Questionnaire – Bone Metastases-22; PL = profile likelihood; SBRT = stereotactic body radiation therapy; SD = standard deviation.
[a] Median age

Figure I-25. EORTC QLQ-BM22 functional interference domain (0-100 scale, higher score means better quality of life): by timeframe for SBRT versus conventional EBRT



3DCRT = three-dimensional conformal radiation therapy; CI = confidence interval; C-EBRT = conventional external beam radiation therapy; EORTC QLQ-BM22 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Bone Metastases-22; PL = profile likelihood; SBRT = stereotactic body radiation therapy; SD = standard deviation.
[a] Median age

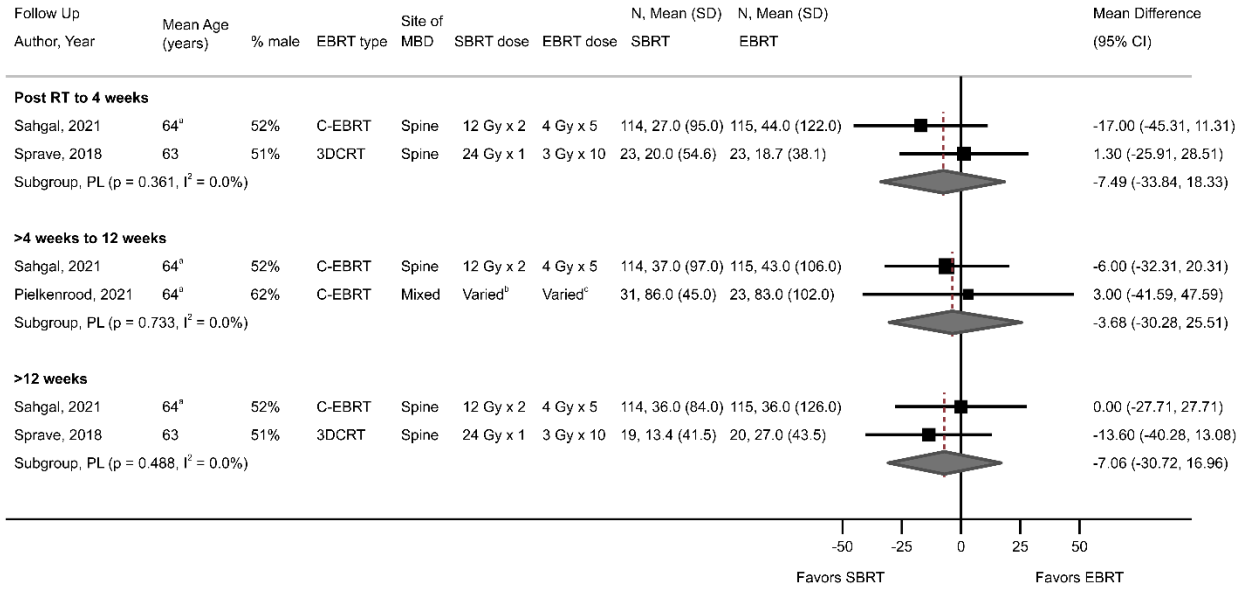
Figure I-26. EORTC QLQ-BM22 psychosocial aspects domain (0-100 scale, higher score means better quality of life): by timeframe for SBRT versus conventional EBRT



3DCRT = three-dimensional conformal radiation therapy; CI = confidence interval; C-EBRT = conventional external beam radiation therapy; EORTC QLQ-BM22 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Bone Metastases-22; PL = profile likelihood; SBRT = stereotactic body radiation therapy; SD = standard deviation.

[a] Median age

Figure I-27. OMED consumption: by followup time for SBRT versus conventional EBRT



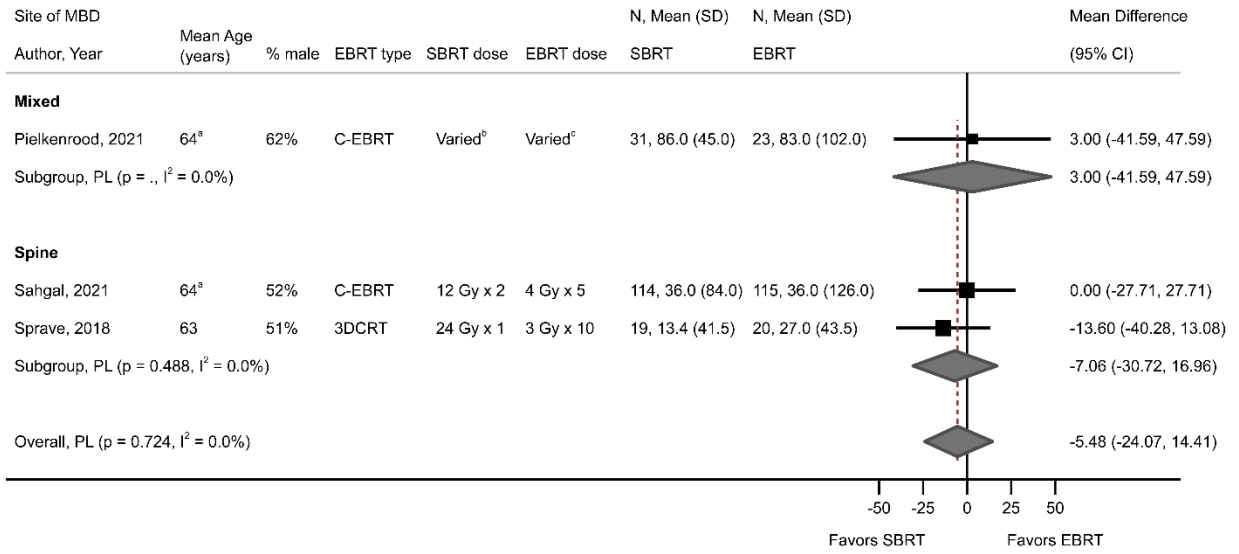
3DCRT = three-dimensional conformal radiation therapy; CI = confidence interval; C-EBRT = conventional external beam radiation therapy; EORTC QLQ-BM22 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Bone Metastases-22; OMED = oral morphine equivalent dose; PL = profile likelihood; SBRT = stereotactic body radiation therapy; SD = standard deviation.

[a] Median age

[b] 18 Gy x 1 or 10 Gy x 3 or 7 Gy x 5

[c] 8 Gy x 1 primarily; 4 Gy x 5 or 3 Gy x 10

Figure I-28. OMED consumption: at longest followup by site of MBD for SBRT versus conventional EBRT



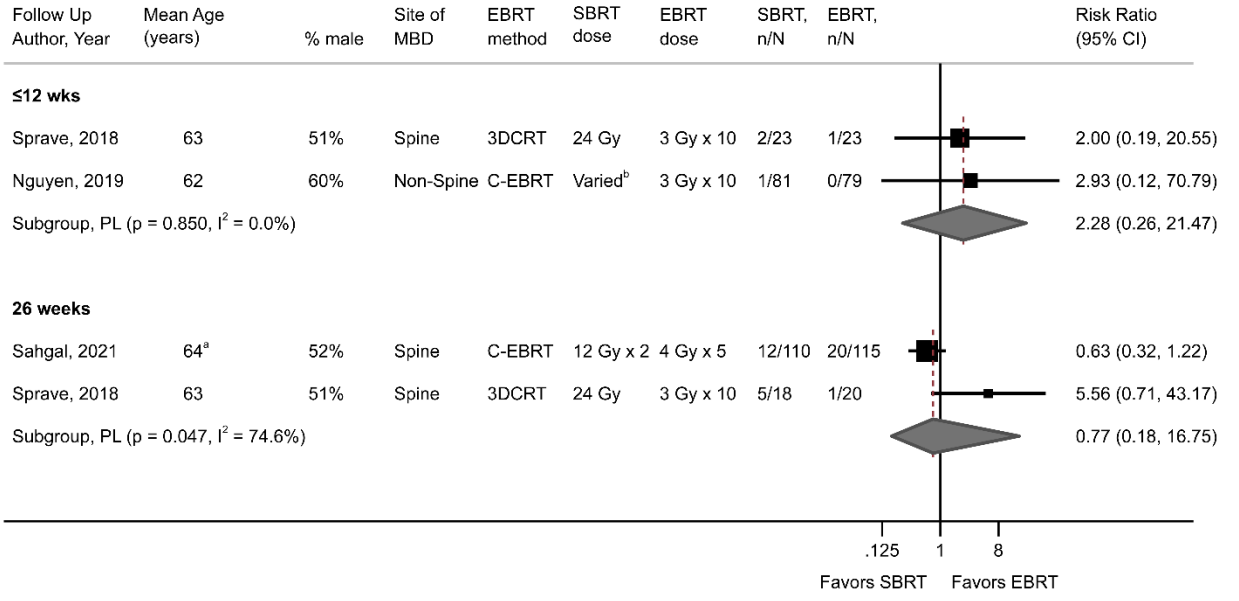
3DCRT = three-dimensional conformal radiation therapy; CI = confidence interval; C-EBRT = conventional external beam radiation therapy; EORTC QLQ-BM22 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Bone Metastases-22; OMED = oral morphine equivalent dose; PL = profile likelihood; SBRT = stereotactic body radiation therapy; SD = standard deviation.

[a] Median age

[b] 18 Gy x 1 or 10 Gy x 3 or 7 Gy x 5

[c] 8 Gy x 1 primarily; 4 Gy x 5 or 3 Gy x 10

Figure I-29. Pathological fractures: up to 12 and 26 weeks for SBRT versus conventional EBRT

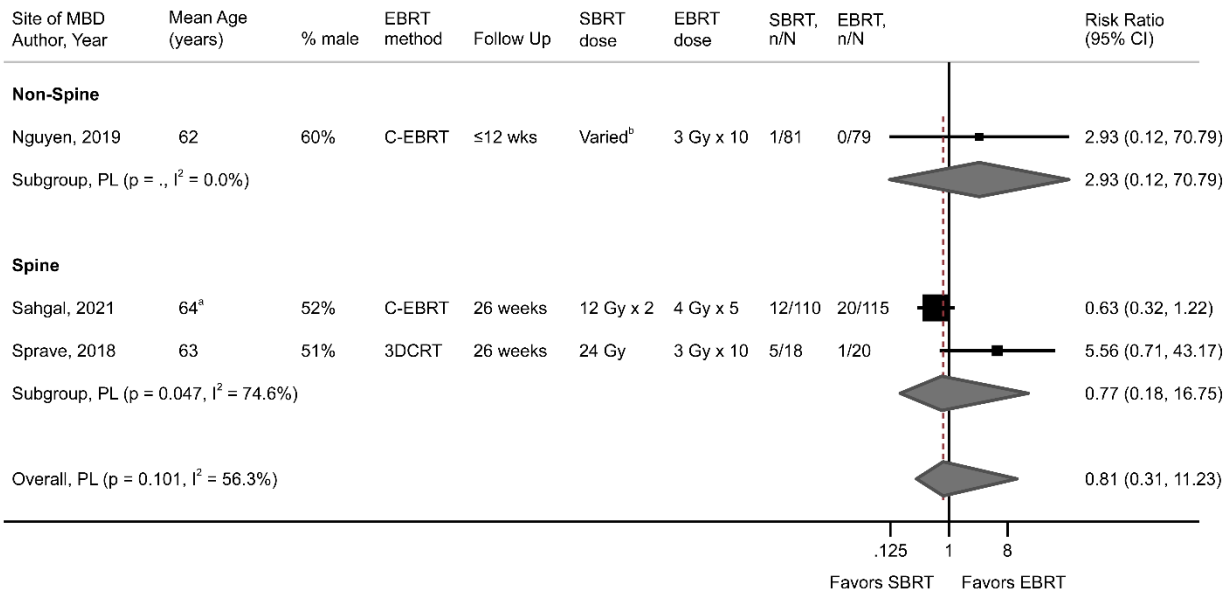


3DCRT = three-dimensional conformal radiation therapy; CI = confidence interval; C-EBRT = conventional external beam radiation therapy; EORTC QLQ-BM22 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Bone Metastases-22; PL = profile likelihood; SBRT = stereotactic body radiation therapy; SD = standard deviation.

[a] Median age

[b] 12 Gy x 1 for lesions >4 cm or 16 Gy x 1 for lesions ≤4 cm

Figure I-30. Pathological fractures: overall estimate for longest followup, by site of MBD for SBRT versus conventional EBRT



3DCRT = three-dimensional conformal radiation therapy; CI = confidence interval; C-EBRT = conventional external beam radiation therapy; EORTC QLQ-BM22 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Bone Metastases-22; PL = profile likelihood; SBRT = stereotactic body radiation therapy; SD = standard deviation.

[a] Median age

[b] 12 Gy x 1 for lesions >4 cm or 16 Gy x 1 for lesions ≤4 cm

Appendix J. Definitions of Magnitudes of Effect

Table J-1. Definitions for magnitude of effects, based on mean between-group differences

Effect Size	Definition
Small effect	• MD 0.5 to 1.0 points on a 0 to 10-point scale, 5 to 10 points on a 0 to 100-point scale • SMD 0.2 to 0.5 • RR/OR 1.2 to 1.4
Moderate effect	• MD >1 to 2 points on a 0 to10-point scale, >10 to 20 points on a 0 to 100-point scale • SMD >0.5 to 0.8 • RR/OR 1.5 to 1.9
Large effect	• MD >2 points on a 0 to10-point scale, >20 points on a 0 to 100-point scale • SMD >0.8 • RR/OR ≥2.0

MD = mean difference; OR = odds ratio; RR = risk ratio; SMD = standardized mean difference.

Appendix K. Appendix References

1. Treadwell JR, Singh S, Talati R, et al. A Framework for "Best Evidence" Approaches in Systematic Reviews. AHRQ Methods for Effective Health Care. (Prepared by the ECRI Institute Evidence-based Practice Center under Contract No. HHSA 290-2007-10063-I.) Agency for Healthcare Research and Quality (US). Report No.: 11-EHC046-EF. Rockville (MD): Jun 2011. https://www.ncbi.nlm.nih.gov/pubmed/21834173 PMID: 21834173.

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