Comparative Effectiveness Review
Number 265

Radiation Therapy for Metastatic Bone Disease: Effectiveness and Harms

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

Agency for Healthcare Research and Quality

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. 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 +
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.

Full Report

Skelly AC, Chang E, Bordley J, Brodt ED, Selph S, Fu R, Yu Y, Holmes R, Dana T, Stabler-Morris S, Riopelle D, Chou R. Radiation Therapy for Metastatic Bone Disease: Effectiveness and Harms. Comparative Effectiveness Review No. 265. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 75Q80120D00006.) AHRQ Publication No. 23-EHC026. Rockville, MD: Agency for Healthcare Research and Quality; August 2023. doi: https://doi.org/10.23970/AHRQEPCCER265. Posted final reports are located on the Effective Health Care Program search page.