SYSTEMATIC REVIEW

Assessing the Outcome of Stereotactic Body Radiation Therapy (SBRT) Compared to Conventional External Beam Radiotherapy (cEBRT) in Spinal Metastases Patient, Does SBRT Result in Better Quality of Life? – Systematic Review

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ABSTRACT

Introduction: Stereotactic Body Radiation Therapy (SBRT) is an alternative radiation therapy to Conventional External Beam Radiotherapy (cEBRT), which can deliver high doses of radiation to the tumor site and minimize side effects to surrounding healthy tissue. This study aims to evaluate the different outcomes of SBRT and cEBRT for patients with spinal metastases. **Materials and methods:** A literature search was conducted by the PRISMA guideline using multiple electronic databases: PubMed, ScienceDirect, Sage Journal, CENTRAL, and Web of Science. All studies that fulfilled our PICO criteria were included in this study. Case series, case reports, and reviews were excluded from this review. **Results:** Studies with a high risk of bias and not assessing the radiotherapy outcome were also excluded. The RoB2 and ROBINS-I tools were used to analyze the quality of the selected studies. Basic data (sample size, sex, and average age of each group) and the outcome summary were tabulated. Based on the inclusion criteria, four literatures were selected for this study. Two out of three studies found that SBRT was more successful in reducing pain. **Conclusion:** SBRT showed better pain control, OS, progression-free survival (PFS), incidence rate, local failure rate, and adverse event (AE) than cEBRT, but no significant difference in the quality of life.
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INTRODUCTION

The spine is a common location for bone metastases to occur. The spinal involvement occurs in up to 40% of patients with cancer as the disease progresses, with epidural compression occuring in 5-10% of cases.(1) Surgery is often used as one of the main management of cancer metastases in the spine. The main goals of surgery are spinal stabilization, restoration, and maintenance of overall alignment and decompression of nerve structures, especially for radioresistant tumors. (2) However, in some cases, surgical treatments were contraindicated or were declined by the patient; therefore, alternative treatments were employed.

One such option is Conventional External Beam Radiotherapy (cEBRT), a reliable alternative treatment modality for spinal metastases. Unlike surgery, cEBRT administers radiation in fractions, allowing for the recovery of normal tissues and thereby increasing the body's tolerance to therapy.(3) Stereotactic Body Radiation Therapy (SBRT) is an alternative to cEBRT. This radiation therapy's main advantage is the ability to deliver radiation to a much smaller specific area compared to cEBRT. Therefore, this therapy can deliver high doses of radiation to tumors while minimizing the dose delivered to surrounding healthy tissue. Treatment is fractionated into fewer sessions, typically one to five, with a total dose ranging from 8 to 30Gy.(4) Additionally, radiation intensity modulation further enhances the effectiveness of SBRT in reducing tumor size, thus minimizing radiation exposure to the surrounding tissue.(3)

Despite its promising result, there needs to be more comprehensive analysis comparing the effectiveness of SBRT and cEBRT in treating patients with spinal metastases. Therefore, the authors conducted a systematic review to summarize the results of available studies on the outcomes of SBRT and cEBRT in treating

patients with spinal metastases.

MATERIALS AND METHODS

Search strategy

This study was conducted based on the PRISMA guideline. In general, studies assessing the outcome of patients with spinal metastases treated with either cEBRT or SBRT were evaluated. Multiple electronic databases such as PubMed, ScienceDirect, Sage Journal, CENTRAL, and Web of Science search engines were used, and the search was done on Jan 24 2023. The search strategy for this study is listed in Table I. No filter was used in this search. The Population, Intervention, Comparison, and Outcome (PICO) concept was used in this study:

- P: Patients diagnosed with a cancer metastases on the spine
- I: Treated with either SBRT or cEBRT
- C: Comparing both treatments
- O: All possible outcome was summarized and tabulated

Table I: Search strategy

Database	Keyword
PubMed	((“Stereotactic” OR “conventional”) AND (“radiotherapy” OR “radiosurgery”)) AND (“spinal metastasis” OR “spinal metastases”)
ScienceDirect	((“Stereotactic” OR “conventional”) AND (“radiotherapy” OR “radiosurgery”)) AND (“spinal metastasis” OR “spinal metastases”)
Sage Journal	((“Stereotactic” OR “conventional”) AND (“radiotherapy” OR “radiosurgery”)) AND (“spinal metastasis” OR “spinal metastases”)
CENTRAL	#1 = (“Stereotactic” OR “conventional”) #2 = (“radiotherapy” OR “radiosurgery”) #3 = (“spinal metastasis” OR “spinal metastases”) #4 = #1 AND #2 AND #3
Web of Science	ALL = (((“Stereotactic” OR “conventional”) AND (“radiotherapy” OR “radiosurgery”)) AND (“spinal metastasis” OR “spinal metastases”))

Inclusion and exclusion criteria

All studies that fulfilled our PICO criteria were included in this study. Case series, case reports, and reviews were excluded from this study. Studies with a high risk of bias and not assessing the radiotherapy outcome were also excluded. All results from each study were tabulated and summarized. Search and screening for inclusion are conducted by two authors (ARH and EHK). Any dispute would be resolved by a third reviewer (KAIS).

Quality assessment

The quality of evidence for the included studies were assessed using appropriate tools. For RCTs, RoB2 tools by Cochrane was used. For non-RCTs, ROBINS-I was used.(5) The final score from each criterion was classified as low, unclear, or high risk of bias. Studies with an overall score of high risk of bias will be excluded from this study.

Data extraction

The studies were extracted using Microsoft Excel. The basic data was collected from each study including sample size, sex, and average age of each group, and the outcome summary was subsequently tabulated.

RESULTS

The search flow is depicted in Figure 1. Based on the search results, there were 2,842 search results and 16 studies obtained from manually searching other references. Of the 2,842 articles, 431 were obtained by PubMed search, 1,488 from ScienceDirect, 650 from Web of Science, 154 from Sage Journal, and 46 from CENTRAL. After removing duplicates, 2,231 unique articles were found. From those unique articles, 1,365 titles were found to be irrelevant; therefore, the abstracts of 866 remaining articles were reviewed, 853 abstracts were excluded, and 13 full articles were studied. Of the 13 articles, it was found that three studies discussed only the research protocol, three studies used combination therapy, not just radiation, one did not compare with SBRT, 1 was a case series, and 1 was an epidemiological study. The risk of bias was evaluated in each of the four final studies. Three had an unclear risk of bias, while one had a low risk.(6–9)

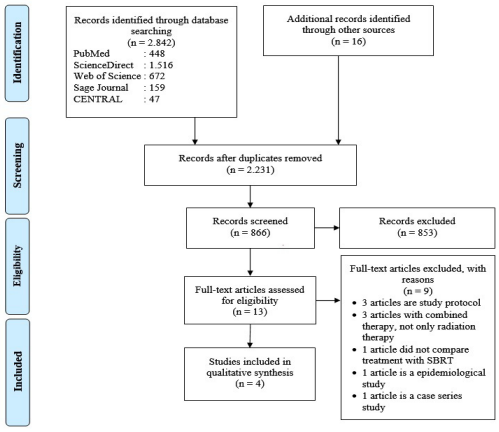

Figure 1: PRISMA Flow Diagram

The compilation results of each study's findings are qualitatively described in Table II. Cumulatively, 290 samples were treated with SBRT, and 296 were treated with cEBRT. Most patients were men, and most were over 60 years old.

Table II: Summary of results from included studies.

No	Author, Year	Study Design	SBRT		cEBRT		Summary of Results	
			Sample Size (% Male)	Age	Sample Size (%Male)	Age	QoL, Pain, and OS	Other Findings
1	Arjun Sahgal et al. 2021	RCT	114 (52%)	63 (56-72)	115 (53%)	65 (55-73)	QoL: No difference was found Pain: Analgesic consumption was higher in the SBRT group; Full response to pain was significantly higher in the SBRT group at 3-6 months (14% vs. 35%) OS: Higher in the SBRT group (89% vs 93%)	PFS: Higher in the SBRT group (86% vs 92%) Adverse Events: More frequent and severe in the cEBRT group Other finding: This study is the first published RCT comparing SBRT vs cEBRT, this study asserts the superiority of SBRT compared to cEBRT with better outcome even on longer term follow up (6 months)
2	Saskia van de Ven et. Al, 2019	NRCT	65 (51,4%)	64,4	66 (48,6%)	68.3	QoL: No difference was found Pain: Pain reduction was higher in the SBRT group at three months (43% vs. 56%) and six months (45% vs. 44%) OS: Higher in the SBRT group at one year (65% vs. 85%)	Physical function: No difference was found PFS: Higher in the SBRT group at one year (19% vs. 54%) Other Finding: The study analyzed patients with oligometastatic disease (<5 lesions within <3 organ) and found that the survival outcome are improving compared to previous studies. Indicating the need for more proper palliative care because such patients will have longer life expectancy
3	Bart J. Pilkenrood et. Al, 2020	RCT	45 (53%)	65 (61-72)	44 (70%)	64 (57-73)	QoL: No difference was found Pain: No difference was found OS: No difference found	Other finding: This study found that more patients prefers cEBRT compared to SBRT. One reason is because SBRT treatment requires the patient to wait for 1-2 weeks and an addition of MRI scan unlike cEBRT which can directly done upon visit on the patient's visit to oncologist.
4	Zeng KL, et al., 2022	RCT	66 (56,1%)	64 (32.4-90.3)	71 (46,5%)	65.4 (27-87,8)	QoL: Not reported Pain: Not Reported OS: No Difference Found	Local failure rate: Lower for SBRT at six months (2.8% vs. 11.2%) and two years (14.8% and 35.6%) Reirradiation rate: Lower for SBRT at six months (0% vs. 5.8%) and two years (8.2% and 22.4%) Vertebral Compression Fracture Incidence at 12 months: Less in the SBRT group (7.1% vs 9%) Other finding: This study focuses on the occurence of complication after treatment with either SBRT or cEBRT. Although the incidence is less on SBRT group. Grade 3 vertebral compression fracture occurs exclusively on SBRT group and none on cEBRT group.

SBRT = Stereotactic Body Radiotherapy
cEBRT = Conventional Body Radiotherapy
QoL = Quality of Life
OS = Overall Survival
PFS = Progression-Free Survival

Primarily, all studies assessed pain, quality of life (QoL), and effectiveness of radiotherapy. The effectiveness of radiotherapy was described by the overall survival (OS), adverse event (AE), or progression-free survival (PFS) rate. Based on the pain reduction, 3 out of 4 studies (Study by Arjun Sahgal: 14% vs 35%; Saskia van de Ven: 43% vs 56%; Bart J: -2,5 vs -2,9) found that SBRT was more successful in reducing pain than cEBRT. All studies found no difference in terms of quality of life. Two out of four studies found that SBRT had higher levels of OS but insignificantly (Study by Arjun Sahgal: 89% vs 93%; Study by Saskia van de Ven: 65% vs 85%;). The other study found no difference.(10–13)

Regarding PFS, one study (study by Saskia van de Ven) found a significant difference (54% vs 19%), while another found that SBRT was better (by Arjun Sahgal et al; 92% vs 82%) but not significantly. AEs were more common and severe in cEBRT than in SBRT. Incidence of vertebral compression fractures within one year after

radiation therapy is more frequent in cEBRT (Study by Zeng KL, et al; 9% vs 7,1%). One study assessed the local failure rate and reirradiation rate, and SBRT was better than cEBRT at six months (Study by Zeng KL et al; Local failure rate: 2,8% vs 11,2%; reirradiation rate: 0% vs 5,8%) and one year (Study by Zeng KL et al; Local failure rate: 14,8% vs 35,6%; reirradiation rate: 8,2% vs 22,4%).(10–13)

DISCUSSION

The pathomechanism of pain reduction after radiation therapy remains unclear. The analgetic effect given as a result of radiation action can be caused by stimulation of the ossification process, reduction in osteoclast activity in the bone microenvironment, and reduction of the osteolytic process due to cancer cell death.(14,15)

Bone pain due to cancer depends on three main mechanisms: tumor cells disrupt the physiological balance between osteoclasts and osteoblasts, and tumor cells tend to promote bone degradation by inducing osteoclasts' activity. Secondly, tumor cells may directly invade the nerve root and increase the expression of chemical mediators that stimulate nerve cells and pain signals. Thirdly, the muscles around the cancer will experience spasms, a physiological mechanism to maintain bone stability. The beneficial effect of radiation therapy on bone pain is related to its ability to reduce bone destruction. Radiation can prevent the activation of osteoclast cells and kill tumor cells. So that the size of the tumor will shrink, reducing pressure on nearby nerves and reducing pain.(16) Pain relief has been observed in some tumor patients, indicating a decrease in the activity of inflammatory cells and a decrease in the concentration of chemical mediators of pain in the irradiated area.(14)

Three studies compared the quality of life of the samples. The study by Sahgal et al., found that patients treated with SBRT felt better financial stability than those treated with cEBRT.(18) This is mainly due to the difference in days of treatment: 2 days for SBRT and five days for cEBRT. Interestingly, patients' perceptions of pain were similar in both treatment groups, reflecting the multidimensional nature of the overall assessment of the quality of life. The study by van de Ven et al., found that the quality of life in patients treated with SBRT was higher but not statistically significant (43% vs 56%). (10) This study also found that patient's pain responses/ perceptions were similar for SBRT and cEBRT.(14)

The QoL assessment is a subjective evaluation based on the assessment of pain, physical function, ability to do daily activity, general health, social functioning, and mental health. The subjective nature of QoL assessment might explain the similarities in outcome between both modalities. Although cEBRT results in worse OS, PFS, incidence rate, local failure rate, and AEs, the patients might not have felt the effects of recurrence or complications and therefore did not report a worsening in QoL.(19–21)

Underreporting of low QoL due to loss to follow-up or death might also affect the outcome of QoL assessment in both treatment groups. In the three studies assessing QoL in this systematic review, patients who died and were lost to follow-up were more prevalent in those treated with cEBRT, with a ratio of about 2:1.(10,18) Iovoli, J.A et.al showed that QoL remained stable after SBRT in NSCLC patient.(22)

Patients with SBRT have a higher overall survival rate, a lower local failure rate, and a lower reirradiation rate than conventional radiotherapy. One factor that leads to this advantage is that SBRT uses highly focused radiation guided by 3-dimensional imaging to deliver high doses of biologically effective dose (BED). Thus enabling better pain reduction caused by the tumor while reducing exposure to other surrounding structures. Also, this enables the shortening of treatment time, which can improve the quality of life of patients from a psychological perspective, provide a more effective radiotherapy method for radioresistant tumors, and reduce pain in the long term.(23)

Despite the advantages, SBRT also has risks to the patient, one of which is vertebral compression fractures. Several mechanisms cause vertebral compression fractures. Immediately after SBRT, the first mechanism is an intense acute inflammatory reaction, combined with a vascular effect associated with the high doses administered; SBRT leads to an increase in cell death due to the apoptotic process. This affects the bone matrix, which results in a weaker bone structure, easy structural failure, and an increased risk of vertebral compression fractures. Research shows that 68% of patients observed after receiving SBRT therapy will experience an acute inflammatory reaction in the tissue around the area exposed to the radiation. Radiation on the bone will change the collagen component of the bone and result in a loss of bone elasticity. The bone becomes more rigid and eventually loses its plasticity. These changes affect the ability of the vertebrae to withstand physiological loads, thereby increasing the risk of vertebral compression fractures.(24) The limitation of this study include the scarcity of studies directly comparing SBRT to cEBRT, making it hard to do meta-analysis or consistent comparison on a single parameter. Moreover, tools to evaluate certain parameters, such as quality of life itself, varied from studies to studies.

CONCLUSION

From the available studies, we conclude that SBRT is better than cEBRT. Significantly better outcomes in pain control, OS, PFS, incidence rate, local failure rate, and AE is consistent in the available studies but not in QoL.

Bias due to the subjective nature of QoL assessment or underreporting of worse QoL might skew the result favoring cEBRT.

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REFERENCES

1. Spratt DE, Beeler WH, de Moraes FY, Rhines LD, Gemmete JJ, Chaudhary N, et al. An integrated multidisciplinary algorithm for the management of spinal metastases: an International Spine Oncology Consortium report. Lancet Oncol. 2017;18(12):e720–30. doi: 10.1016/S1470-2045(17)30612-5
2. Eastley N, Newey M, Ashford RU. Skeletal metastases – The role of the orthopaedic and spinal surgeon. Surg Oncol. 2012 Sep;21(3):216–22. doi: 10.1016/j.suronc.2012.04.001
3. Joaquim AF, Ghizoni E, Tedeschi H, Pereira EB, Giacomini LA. Stereotactic radiosurgery for spinal metastases: a literature review. Einstein (Sro Paulo). 2013 Jun;11(2):247–55. doi: 10.1590/S1679-45082013000200020
4. Hall WA, Stapleford LJ, Hadjipanayis CG, Curran WJ, Crocker I, Shu H-KG. Stereotactic Body Radiosurgery for Spinal Metastatic Disease: An Evidence-Based Review. Int J Surg Oncol. 2011;2011:1–9. doi: 10.1155/2011/979214
5. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016 Oct 12;i4919. Available from: http://www.bmj.com/lookup/doi/10.1136/bmj.i4919
6. Sahgal A, Myrehaug SD, Siva S, Masucci GL, Maralani PJ, Brundage M, et al. Stereotactic body radiotherapy versus conventional external beam radiotherapy in patients with painful spinal metastases: an open-label, multicentre, randomised, controlled, phase 2/3 trial. Lancet Oncol. 2021;22(7):1023–33. doi: 10.1016/S1470-2045(21)00196-0
7. van de Ven S, van den Bongard D, Pielkenrood B, Kasperts N, Eppinga W, Peters M, et al. Patient-Reported Outcomes of Oligometastatic Patients After Conventional or Stereotactic Radiation Therapy to Bone Metastases: An Analysis of the PRESENT Cohort. Int J Radiat Oncol Biol Phys. 2020;107(1):39–47. doi: 10.1016/j.ijrobp.2019.12.041
8. Pielkenrood BJ, van der Velden JM, van der Linden YM, Bartels MMT, Kasperts N, Verhoeff JJC, et al. Pain Response After Stereotactic Body Radiation Therapy Versus Conventional Radiation Therapy in Patients With Bone Metastases—A Phase 2 Randomized Controlled Trial Within a Prospective Cohort. Int J Radiat Oncol Biol Phys. 2021;110(2):358–67. doi: 10.1016/j.ijrobp.2020.11.060
9. Zeng KL, Myrehaug S, Soliman H, Husain ZA, Tseng CL, Detsky J, et al. Mature Local Control and Reirradiation Rates Comparing Spine Stereotactic Body Radiation Therapy With Conventional Palliative External Beam Radiation Therapy. Int J Radiat Oncol Biol Phys. 2022;114(2):293–300. doi: 10.1016/j.ijrobp.2022.05.043
10. van de Ven S, van den Bongard D, Pielkenrood B, Kasperts N, Eppinga W, Peters M, et al. Patient-Reported Outcomes of Oligometastatic Patients After Conventional or Stereotactic Radiation Therapy to Bone Metastases: An Analysis of the PRESENT Cohort. Int J Radiat Oncol Biol Phys. 2020;107(1):39–47. Available from: https://doi.org/10.1016/j.ijrobp.2019.12.041
11. Sahgal A, Ma L, Weinberg V, Gibbs IC, Chao S, Chang UK, et al. Reirradiation human spinal cord tolerance for stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys. 2012;82(1):107–16. doi: 10.1016/j.ijrobp.2010.08.021
12. Zeng KL, Myrehaug S, Soliman H, Husain ZA, Tseng CL, Detsky J, et al. Mature Local Control and Reirradiation Rates Comparing Spine Stereotactic Body Radiation Therapy With Conventional Palliative External Beam Radiation Therapy. Int J Radiat Oncol Biol Phys. 2022;114(2):293–300. Available from: https://doi.org/10.1016/j.ijrobp.2022.05.043
13. Pielkenrood BJ, van der Velden JM, van der Linden YM, Bartels MMT, Kasperts N, Verhoeff JJC, et al. Pain Response After Stereotactic Body Radiation Therapy Versus Conventional Radiation Therapy in Patients With Bone Metastases—A Phase 2 Randomized Controlled Trial Within a Prospective Cohort. Int J Radiat Oncol Biol Phys. 2021;110(2):358–67. Available from: https://doi.org/10.1016/j.ijrobp.2020.11.060
14. Goblirsch M, Mathews W, Lynch C, Alaei P, Gerbi BJ, Mantyh PW, et al. Radiation Treatment Decreases Bone Cancer Pain, Osteolysis and Tumor Size. Radiat Res. 2004 Feb;161(2):228–34. doi: 10.1667/RR3108
15. Goblirsch MJ, Zwolak PP, Clohisy DR. Biology of Bone Cancer Pain. Clinical Cancer Research. 2006 Oct 15;12(20):6231s–5s. doi: 10.1158/1078-0432.CCR-06-0682
16. Felice F De, Piccioli A, Musio D, Tombolini V. The role of radiation therapy in bone metastases management. Oncotarget. 2017 Apr 11;8(15):25691–9. doi: 10.18632/oncotarget.14823
17. Sierko E, Hempel D, Zuzda K, Wojtukiewicz M. Personalized Radiation Therapy in Cancer

Pain Management. Cancers (Basel). 2019 Mar 19;11(3):390. doi: 10.3390/cancers11030390
18. Sahgal A, Myrehaug SD, Siva S, Masucci GL, Maralani PJ, Brundage M, et al. Stereotactic body radiotherapy versus conventional external beam radiotherapy in patients with painful spinal metastases: an open-label, multicentre, randomised, controlled, phase 2/3 trial. Lancet Oncol. 2021;22(7):1023–33. Available from: http://dx.doi.org/10.1016/S1470-2045(21)00196-0
19. Barzilai O, Versteeg AL, Sahgal A, Rhines LD, Bilsky MH, Sciubba DM, 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 29;125(5):770–8. Available from: https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncr.31870
20. Sprave T, Verma V, Forster R, Schlampp I, Bruckner T, Bostel T, et al. Quality of Life Following Stereotactic Body Radiotherapy Versus Three-Dimensional Conformal Radiotherapy for Vertebral Metastases: Secondary Analysis of an Exploratory Phase II Randomized Trial. Anticancer Res. 2018 Aug 30;38(8):4961–8. Available from: http://ar.iiarjournals.org/lookup/doi/10.21873/anticanres.12814
21. Guckenberger M, Mantel F, Sweeney RA, Hawkins M, Belderbos J, Ahmed M, et al. Long-Term Results of Dose-Intensified Fractionated Stereotactic Body Radiation Therapy (SBRT) for Painful Spinal Metastases. International Journal of Radiation Oncology*Biology*Physics. 2021 Jun;110(2):348–57. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0360301620347416
22. Iovoli AJ, Yu B, Ma SJ, Farrugia MK, Dexter EU, Yendamuri S, et al. Quality of Life After Stereotactic Body Radiation Therapy or Surgery for Early-Stage NSCLC: A Systematic Review. JTO Clin Res Rep. 2022 Nov;3(11):100417. doi: 10.1016/j.jtocrr.2022.100417
23. Zhang H, Li J, Yang X, Qiao R, Hu Y-C. Conventional Radiotherapy and Stereotactic Radiosurgery in the Management of Metastatic Spine Disease. Technol Cancer Res Treat. 2020 Jan 1;19:153303382094579. doi: 10.1177/1533033820945798
24. Faruqi S, Tseng C-L, Whyne C, Alghamdi M, Wilson J, Myrehaug S, et al. Vertebral Compression Fracture After Spine Stereotactic Body Radiation Therapy. Neurosurgery. 2018 Sep 1;83(3):314–22. doi: 10.1093/neuros/nyx493