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Comparative Efficacy of Single-Fraction versus Multi-Fraction Stereotactic Body Radiotherapy for Spinal Metastases: A Meta-Analysis

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Abstract

Objective: This study compares the efficacy of stereotactic body radiotherapy (SBRT) in patients with spinal metastases, focusing on single-fraction (SF-SBRT) versus multifraction (MF-SBRT) regimens. **Methods:** A literature search was conducted across PubMed, Web of Science, Cochrane Library, Scopus, and Embase. Data analysis was performed using Engauge Digitizer, RevMan, and STATA software. **Results:** Fifteen studies were analyzed. SF-SBRT had a higher incidence of local failure but a lower rate of vertebral compression fractures (VCFs) compared to MF-SBRT. No significant differences were found in overall survival rates. The 1-year and 2-year local control rates for SBRT were 87% and 80%, with overall survival rates at 63% and 47%. **Conclusions:** SF-SBRT offers convenience and rapid relief, while MF-SBRT may provide better long-term control. Regimen selection should be based on the patient's clinical situation and preferences to optimize outcomes.

Keywords stereotactic body radiotherapy; spinal metastases; local control; overall survival; meta-analysis

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1 Introduction

The vertebral column is the most common site for the metastasis of malignant neoplasms, with approximately 70% of all bone metastases occurring in the spine[1]. Patients with spinal metastases often present with low back pain or vertebral fractures as initial symptoms. As the metastases progress, they can lead to spinal cord compression, with metastatic epidural spinal cord compression (MESCC) occurring in about 8% to 20% of cases[2].

Stereotactic body radiotherapy (SBRT), characterized by its non-coplanar, multi-angular, and focused irradiation techniques, represents a precision approach in oncological treatment[3]. This method involves accurate positioning, meticulous planning, and precise delivery of highly conformal, ablative radiation doses to the tumor while minimizing exposure to surrounding healthy tissue[4]. SBRT not only enhances local control, crucial for halting tumor progression, but also potentially reduces the risk of complications such as radiation-induced myelopathy or vertebral collapse[5,6]. Compared to conventional external beam radiotherapy (cEBRT), SBRT offers better protection of normal tissues and organs, superior pain relief, and improved control over local metastases[7]. Tumors such as melanoma, renal cell carcinoma, sarcoma, and those recurring after cEBRT remain particularly susceptible to the therapeutic effects of SBRT[8,9].

The efficacy of radiotherapy is significantly influenced by the fractionation of radiation doses, which can be delivered in either single or multiple fractions. Despite the clinical importance of dose fractionation in spinal SBRT, there is considerable variation in the dose-fractionation schemes employed. Randomized controlled trials (RCTs) specifically investigating the optimal strategy for pain management, local tumor control, and side effects are notably lacking.

2 Methods

2.1 Inclusion Criteria

The treatment must involve the use of stereotactic radiosurgery (SRS) or SBRT for patients diagnosed with spinal metastases, including those treated after decompression surgery or following the failure of conventional external beam radiotherapy (cEBRT). Publications must report at least one measurable outcome relevant to the study objectives. Studies authored by the same individual but reporting data from distinct institutions are eligible for inclusion.

2.2 Exclusion Criteria

Studies focused on metastatic tumors located outside the spinal region, research involving primary spinal tumors, non-metastatic, or benign spinal conditions were excluded. Article types limited to reviews and case reports were also excluded, as well as publications with insufficient data to allow for the extraction of relevant outcomes. Non-English language publications were excluded as well.

2.3 Descriptive Data

Comprehensive descriptive information was collected, including the author's name, year of publication, number of vertebral bodies affected by the tumor, patient cohort size, primary tumor histology, radiation dosage and fractionation scheme, duration of follow-up, prior decompression surgery, history of conventional external beam radiotherapy (cEBRT), and the type of publication. These details are systematically summarized in Table 1.

Table1. Baseline Characteristics of All Included Studies

Author/ Year	Study Type	Lesions	Mean age(range)	Main Histology	Dose /SF	Dose /MF	Follow-up(Mon)（range）	Prior RT	Prior Surgery
Bate 2015**[35]**	R	SF:38 MF:31	59.8 (29-81)	Renal(26%) Breast(24%) Lung(16%)	23/1 22/1 20/1 16/1	10/2 9/3 6/5	10	30（43%）	21（30%）
Bernstein 2016**[36]**	P	SF:10 MF:17	58.4(33.4-79.4)	Thyroid(100%)	18/1 16/1	30/5 27/3	28.9	8 (29%)	8 (29%)
Bishop 2015**[37]**	R	SF:146 MF:130	59 (17-88)	Renal(38%) Lung(14%) Thyroid(10%)	18/1 24/1	27/3	19	163 (49%)	NA
Cunha 2012**[38]**	R	SF:36 MF:131	57 (18-90)	Renal(29%) Breast(23%) Lung(20%)	20-22/1 8-18/1	18-24/2 20-27/3 30/4 23-35/5	7.4 (0.4-37.3)	54 (32%)	NA
Ghia 2016**[39]**	P	SF:21 MF:26	62 (38–75)	Renal (100%)	24/1	27/3 30/5	23	NA	15 (32%)
Hashmi 2016**[40]**	R	SF:148 MF:99	62 (18–89)	Breast(29.1%) Lung(16.6%) Kidney(13.1%)	8–15.9/1 16–18/1 18–22/1	2–5/per FX 6–6.9/per FX 7–7.9/per FX 8–8.9/per FX 9–20/per FX	8.1 (0.1–52.6)	247 (100%)	113 (46%)
Ho 2016**[41]**	P	SF:14 MF:24	60 (22–88)	Renal (26%) Breast(18%) Lung (8%)	24/1 18/1 16/1	27/3 30/5 20/5	69(9–145)	17 (45%)	16 (42%)
Isabelle 2015**[42]**	R	SF:141 MF:46	60.20 (33-87.67)	Renal（100%）	10-18/1 20-24/1	18-24/2 18-30/3 25-30/4 25-30/5	8.02(0.03-75.99)	34（18%）	0（0%）
Isabelle 2016**[43]**	P	SF:37 MF:63	NA	Renal(32%) Lung(30%) Breast(15%)	12-24/1	20-24/2 24-35/3-5	7.3(0.6-67.6)	23 (23%)	0（0%）
Kumar 2017**[44]**	R	SF:20 MF:10	65 (40-89)	Thyroid（17%） Colon（13%） Breast（13%）	24/1	27-30/3-5	20 (5-40)	NA	NA
Laufer 2013**[45]**	R	SF:40 MF:146	58.9 （14.8–81.4）	Renal（22%） Sarcoma（18%） Prostate（13%）	24/1	30/5-6 27/3	11（1.5–63.2）	91（49%）	186（100%）
Park 2014**[46]**	R	SF:1 MF:58	NA	Breast(18.7%) Liver(13.6%) Stomach(11.9) Lung(11.9)	18/1	21-26/3-5 27/3; 27/5 28-30/3-5 32-35/5	7.4(1.1-42.5)	14 (23.7%)	NA
Randa 2016**[47]**	P	SF:18 MF:51	58 (20-80)	Renal(53%) Sarcoma(20%) Thyroid(9%)	16/1 18/1 20/1 24/1	30/5 27/3	30(1-145)	69 (100%)	31 (47%)
Sahgal 2013**[48]**	R	SF:209 MF:201	57.55 (18-90)	Renal(55%) Breast(13%) Lung(10%)	8-17/1 18-26/1	18-26/2 18-35/3 25-35/4 25-35/5	11.5(0.03 - 113)	94 (23%)	NA
Folker 2014**[49]**	R	SF:68 MF:52	54 (25-84)	Sarcomas（100%）	18-24/1	24-36/3-6	12.3 (1-80.7)	33（28%）	12（10%）

R:retrospective studies P:prospective cohort studies

2.4 Primary Outcomes

- **Post-radiation vertebral compression fracture (VCF):** Identified through imaging as either the emergence of a new vertebral body fracture or the exacerbation of an existing

fracture subsequent to SBRT.

- **Radiation failure:** Defined as imaging-documented progression of spinal tumors following SBRT, irrespective of the fractionation regimen employed.
- **Cumulative incidence of overall survival:** The probability of patient survival over time following SBRT.

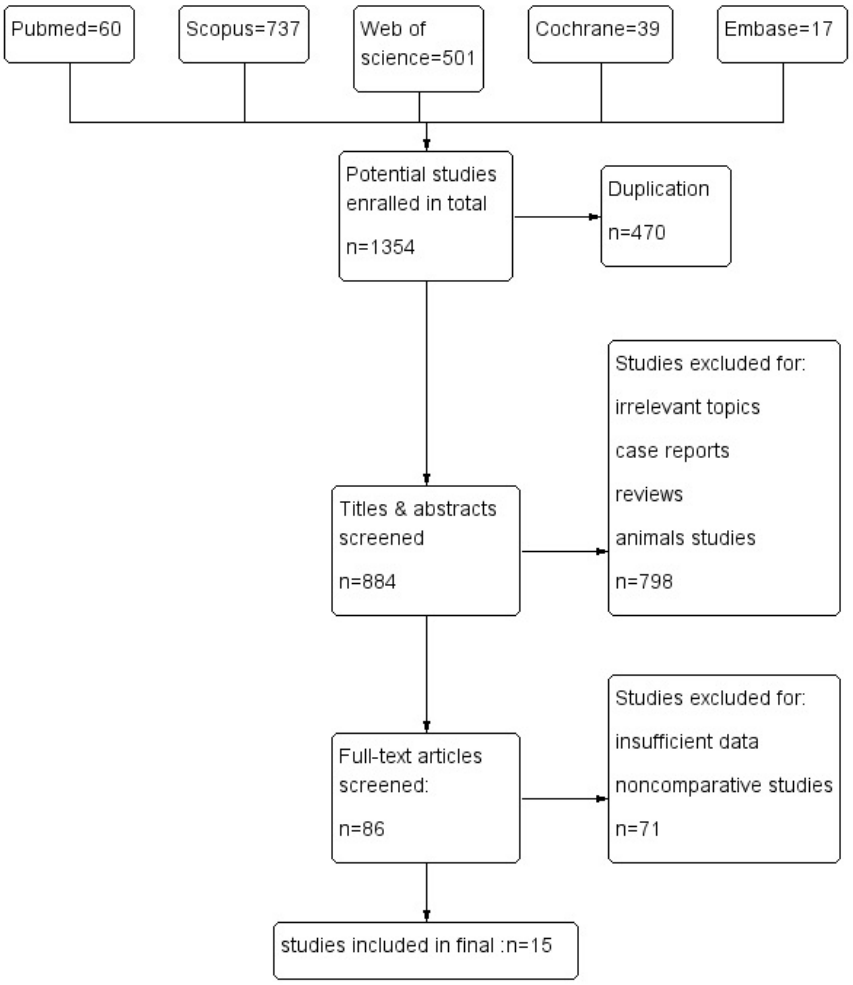

Figure 1: Flow diagram for the process of included studies identification

2.5 Secondary Outcomes

- **Actuarial overall survival rate:** Reported at both 1-year and 2-year intervals post-SBRT.
- **Actuarial local control rate:** Also reported at 1-year and 2-year intervals post-treatment.

2.6 Data Analysis

Statistical analyses were conducted using Review Manager (RevMan) and STATA version 13. Vertebral compression fractures (VCFs) and local failure were analyzed as dichotomous outcomes,

reported with odds ratios (ORs) and 95% confidence intervals (CIs). Time-to-event outcomes were expressed using hazard ratios (HRs). The choice between the random-effects model and the fixed-effects model was determined by the level of heterogeneity among the studies, with the random-effects model applied when heterogeneity was significant ($I^2 > 50\%$) and the fixed-effects model used otherwise ($I^2 < 50\%$). For studies lacking sufficient data, statistical transformations were performed, or indirect data were extracted using Engauge Digitizer software.

2.7 Quality Assessment

The quality of non-randomized controlled studies was evaluated using the Newcastle-Ottawa Scale (NOS), which employs a star system with a maximum of 9 stars to assess three critical aspects: the selection of study groups, the comparability of the groups, and the ascertainment of outcomes for cohort studies[15]. The processes of data extraction, analysis, and quality assessment were independently conducted by two unbiased clinicians. In cases of disagreement, a third party was consulted to resolve the issue.

3 Results

This study adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the Methodological Quality of Systematic Reviews) guidelines[16]. Our initial search across five major databases yielded 1,354 articles. After removing 470 duplicates, 884 unique articles were retained for further review. A thorough screening of titles and abstracts led to the exclusion of 798 articles, which were deemed irrelevant due to their nature as reviews, case reports, or basic science experiments. Detailed full-text reviews of the remaining 86 articles resulted in the inclusion of 15 studies that met our predefined inclusion and exclusion criteria. This final cohort consisted of 10 retrospective studies and 5 prospective cohort studies; no randomized controlled trials (RCTs) were included.

3.1 Quality Assessment

Quality assessment was conducted using the Newcastle-Ottawa Scale (NOS), with articles scoring 7 or higher deemed high-quality. Among the 15 included studies, 9 received a score of 7 stars, 5 were awarded 8 stars, and 1 achieved the maximum score of 9 stars. Consequently, all included studies were classified as high-quality according to the NOS criteria (Table 2).

3.2 Main Outcomes

- **Post-radiation Vertebral Compression Fracture (VCF):** Analysis of 8 articles documenting 1,077 lesions revealed no heterogeneity ($I^2 = 0\%$), supporting the use of the fixed-effects model. The results showed that multifraction (MF) treatments were significantly more likely to result in post-radiation vertebral compression fractures compared to single-fraction (SF) treatments ($P \leq 0.001$, OR = 1.82, 95% CI = 1.26 to 2.63) (Figure 2).

Table2. Newcastle-Ottawa Scale Scores of All Included Studies.

Study/Year	Study Type	Selection	Comparability	Exposure
Bate 2015**[35]**	R	☆☆☆☆	☆	☆☆
Bernstein 2016**[36]**	P	☆☆☆	☆☆	☆☆☆
Bishop 2015**[37]**	R	☆☆☆	☆☆	☆☆
Cunha 2012**[38]**	R	☆☆☆	☆☆	☆☆
Ghia 2016**[39]**	P	☆☆☆☆	☆	☆☆
Hashmi 2016**[40]**	R	☆☆☆	☆☆	☆☆
Ho 2016**[41]**	P	☆☆☆☆	☆☆	☆☆☆
Isabelle 2015**[42]**	R	☆☆☆	☆☆	☆☆☆
Isabelle 2016**[43]**	P	☆☆☆	☆	☆☆☆
Kumar 2017**[44]**	R	☆☆☆	☆☆	☆☆
Laufer 2013**[45]**	R	☆☆☆	☆☆	☆☆☆
Park 2014**[46]**	R	☆☆☆	☆	☆☆☆
Randa 2016**[47]**	P	☆☆	☆☆	☆☆☆
Sahgal 2013**[48]**	R	☆☆☆	☆☆	☆☆☆
Folker 2014**[49]**	R	☆☆☆☆	☆☆	☆☆

R:retrospective studies P:prospective cohort studies

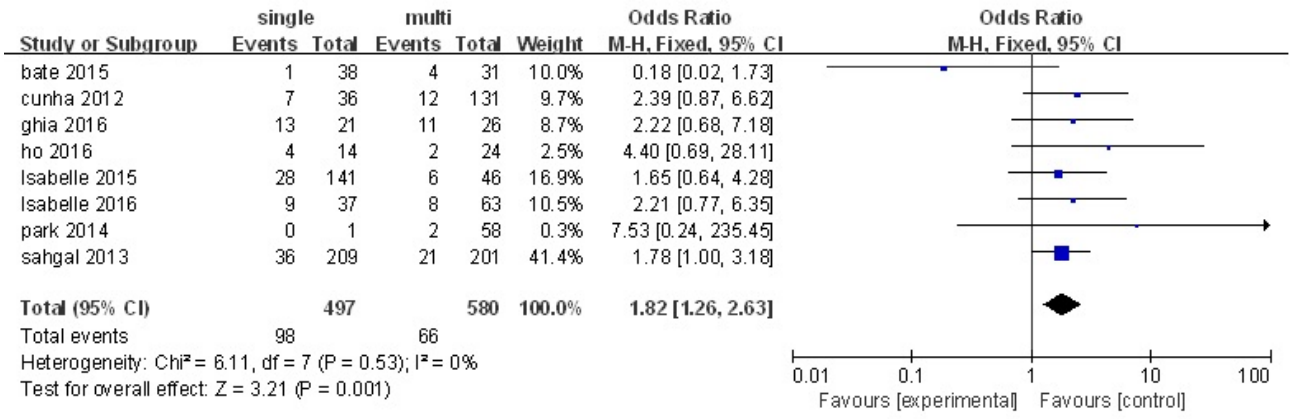

Figure 2: Comparison of Post-radiation Vertebral Compression Fracture in SF and MF Groups in the Meta-analysis

- **Local Failure:** An analysis of 7 articles covering 755 lesions demonstrated low heterogeneity (I^2 = 18%). Using the fixed-effects model, the findings indicated that SF treatments had a higher propensity for local failure compared to MF treatments (P = 0.0007, OR = 0.48, 95% CI = 0.31 to 0.73) (Figure 3).
- **Cumulative Incidence of Overall Survival:** The analysis of 4 articles encompassing 235 patients revealed no heterogeneity (I^2 = 0%), and thus the fixed-effects model was applied. The data indicated no significant difference in the cumulative incidence of overall survival between SF and MF treatments (P ≥ 0.50, HR = 0.89, 95% CI = 0.63 to 1.25) (Figure 4).

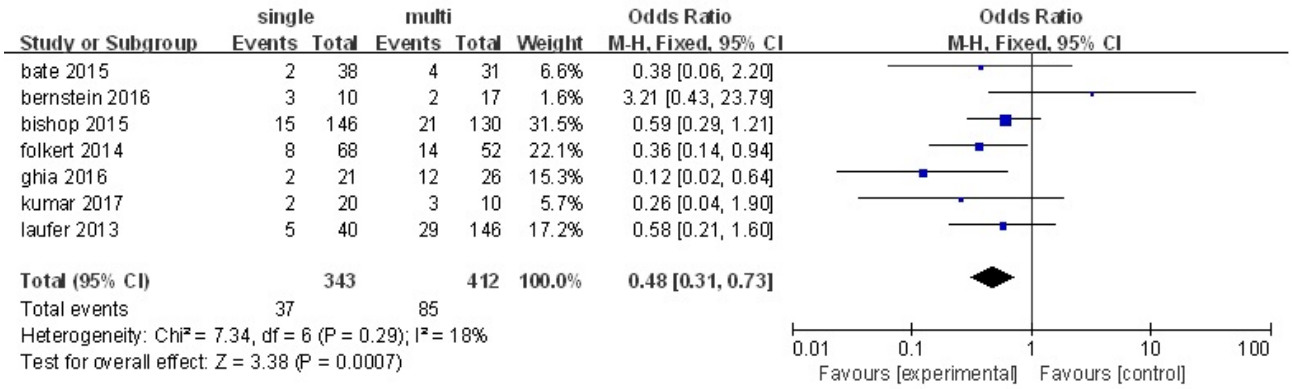

Figure 3: Comparison of Post-radiation Local Failure in SF and MF Groups in the Meta-analysis

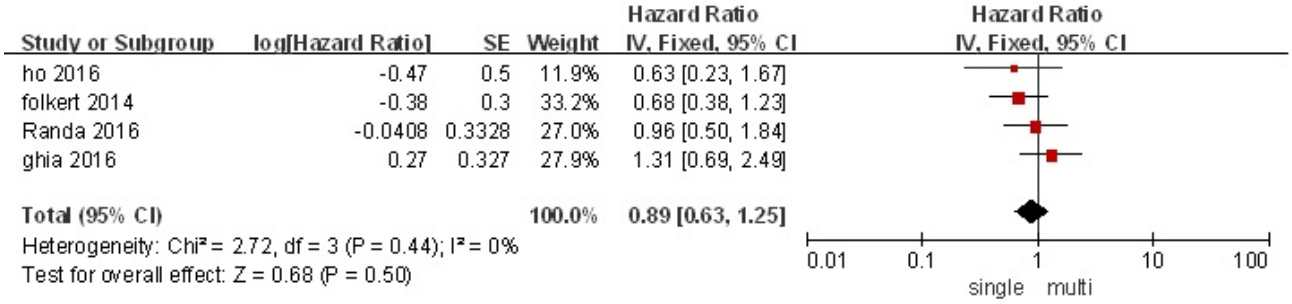

Figure 4: Comparison of Post-radiation Cumulative Incidence of Overall Survival in SF and MF Groups in the Meta-analysis

3.3 Secondary Outcomes

- **One-Year Actuarial Local Control Rate:** Analyzing data from 9 articles involving 1,037 lesions, we encountered low heterogeneity (I^2 = 24.8%), which supported the use of the fixed-effects model. The computed one-year actuarial local control rate was 87% (95% CI = 0.85 to 0.89) (Figure 5 A).

- **Two-Year Actuarial Local Control Rate:** Data from 7 articles covering 868 lesions also exhibited low heterogeneity (I^2 = 24.5%). Despite this, the random-effects model was employed, resulting in a two-year actuarial local control rate of 80% (95% CI = 0.78 to 0.83) following SBRT (Figure 5 B).

- **One-Year Actuarial Overall Survival Rate:** An assessment of 6 articles detailing the outcomes of 576 patients indicated moderate heterogeneity (I^2 = 66.0%), necessitating the use of the random-effects model. The calculated one-year actuarial overall survival rate post-SBRT was approximately 63% (95% CI = 0.55 to 0.70) (Figure 6 A).

- **Two-Year Actuarial Overall Survival Rate:** Analysis of 6 articles involving 544 patients revealed significant heterogeneity (I^2 = 72.7%), leading to the application of the random-

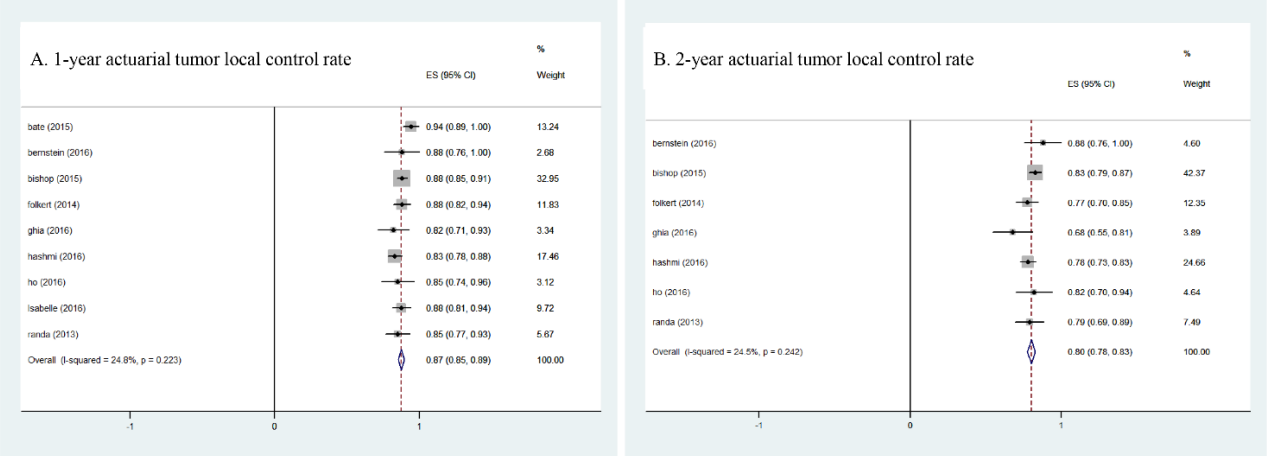

Figure 5: Actuarial Local Control Rate following SBRT, as derived from the statistical analysis conducted in the included studies. 5A. One-Year Actuarial Local Control Rate. 5B. Two-Year Actuarial Local Control Rate.

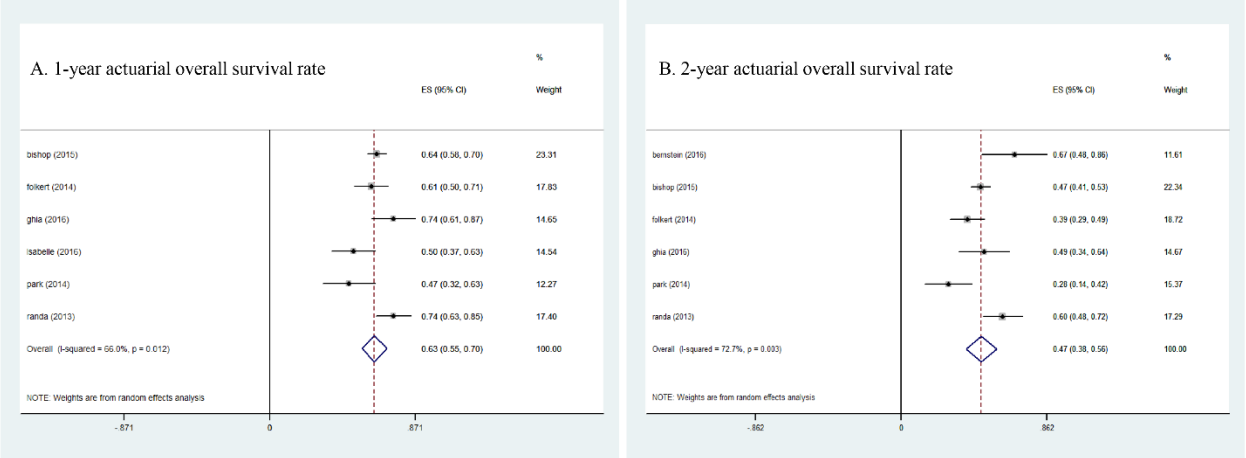

Figure 6: Actuarial Overall Survival Rate following SBRT, as derived from the statistical analysis conducted in the included studies. 6A. One-Year Actuarial Overall Survival Rate. 6B. Two-Year Actuarial Overall Survival Rate.

effects model. The two-year overall survival rate post-SBRT was determined to be around 47% (95% CI = 0.38 to 0.56) (Figure 6 B).

4 Conclusion

This study highlights the nuanced differences between single-fraction and multifraction SBRT in the management of spinal metastases. While both treatment regimens exhibit distinct biological effects, they do not significantly differ in terms of overall survival rates. Single-fraction SBRT offers advantages in treatment duration and cost-effectiveness, potentially improving pa-

tient compliance. However, the choice between single-fraction and multifraction SBRT should be individualized based on the patient's clinical context, taking into account the risk of vertebral compression fractures and the institution's capacity to manage potential complications. Despite the absence of randomized controlled trials in this area, our findings contribute valuable insights to the current understanding of SBRT fractionation. Future research should prioritize the inclusion of RCTs to further validate these observations and support evidence-based decision-making in the treatment of spinal metastases.

5 Discussion

5.1 Comparative Efficacy of cEBRT and SBRT

Conventional external beam radiotherapy (cEBRT) remains a cornerstone of radiotherapeutic practice, typically delivering doses ranging from 1 to 4 Gy per fraction, with 1.8 to 2 Gy being the most common regimen. This approach allows for a broad range of radiation therapy targets to be treated at relatively low dose fractions[17]. A 2012 meta-analysis evaluating the comparative efficacy of different cEBRT fractionation patterns in treating bone metastases across various sites found that pain control rates were equivalent across the fractionation schedules[12]. However, spinal metastases present a unique challenge, requiring a dual-focused approach: precise control of the radiation dose for effective tumor targeting and stringent protection of adjacent normal tissues, particularly the spinal cord. In this complex therapeutic landscape, Stereotactic Body Radiotherapy (SBRT) offers distinct advantages. SBRT's capability for high precision and targeted radiation delivery makes it a superior modality for managing spinal metastases, enhancing treatment efficacy while minimizing risks to critical structures around the tumor site. This underscores the pivotal role of SBRT in contemporary management.

5.2 Advantages of SBRT in Spinal Metastases

SBRT is renowned for its precision in delivering high radiation doses directly to the target volume while preserving the integrity of adjacent high-risk organs, especially the spinal cord. This advanced modality allows for an intense, focused dose ranging from 6 to 30 Gy, distributed across 1 to 5 fractions. These regimens leverage the differential radiobiological sensitivity of normal and tumor tissues, with an alpha/beta (α/β) ratio of 2 for the spinal cord to minimize risk and an α/β ratio of 10 for tumor tissue to maximize therapeutic effect. This distinction underscores SBRT's capability to achieve significant tumor control while adhering to stringent safety margins for the protection of critical structures[18].

5.3 Challenges in Dose Fractionation for SBRT

Despite its advantages, the optimal dose-fractionation schedule for spinal SBRT remains a topic of ongoing debate. Clinical practices vary widely, with single-fraction regimens delivering 16 24 Gy, alongside schedules of 24 27 Gy in 3 fractions, and 30 35 Gy over 4 5 fractions[19-21].

Current evidence does not definitively favor one fractionation pattern over another in terms of efficacy. The incidence of vertebral compression fractures (VCFs) following spinal SBRT has been quantitatively assessed in two significant multicenter analyses, reporting VCF rates ranging from 6% to 14%. About half of these fractures were new occurrences post-SBRT, while the remainder involved pre-existing conditions that worsened following treatment. These observations suggest a nuanced balance between therapeutic efficacy and the risk of adverse effects such as VCF[22,23].

5.4 Vertebral Compression Fractures and Associated Risks

Tseng et al.[24] reported cumulative incidences of VCF following SBRT, documenting rates of 8.5% at 1 year and 13.8% at 2 years among 145 patients with 279 metastatic lesions. Their findings identified lytic tumors and spinal malalignment as significant predictors of VCF. In comparison, the SC.24 trial revealed a VCF rate of 11% in the SBRT-treated cohort, versus 17% in those receiving cEBRT, suggesting a differential impact of radiotherapy modality on the risk of VCF.

Vertebral compression fractures are a recognized complication following radiation therapy, primarily due to the high doses of radiation that can induce necrosis, cellular injury, vascular fibrosis, collagen degradation, and other biomechanical alterations. These changes collectively compromise bone integrity, weakening it and increasing susceptibility to fractures[25]. A 2007 meta-analysis highlighted variability in the incidence of VCFs after spinal SBRT, noting that these rates exceed the traditional baseline of around 3% seen with conventional radiotherapy[26]. The time between SBRT and the onset of VCFs varies, ranging from 2.5 to 25 months, with the highest risk occurring within the first 3 months.

5.5 Clinical Outcomes and Local Control Rates

Multifraction SBRT leverages the differential capacity for DNA repair in normal versus tumor cells to mitigate radiation-induced damage. This approach narrows the therapeutic window between effective antitumor doses and the tolerance levels of critical adjacent structures, such as the spinal cord and esophagus. Consequently, it enables the delivery of higher total doses to the tumor while minimizing harm to surrounding healthy tissues, particularly beneficial for treating larger tumors or those close to vital organs, and in cases requiring retreatment[27].

Compared to cEBRT, SBRT demonstrates superior local control, with tumor control rates ranging from 61% to 86% at one year[28], and an average one-year survival rate of 76%[29]. For vertebral metastases from solid tumors, SBRT is recommended at doses exceeding an equivalent of 18 Gy in a single fraction (biologically effective dose, BED_{10} = 50 Gy_{10}). High-dose SBRT regimens for de novo spine metastases include 20 Gy in one fraction, 24 Gy in one fraction, 12 Gy in two fractions, 10 Gy in three fractions, and 7 Gy in five fractions. These schedules are associated with expected local control rates of 80% to 90% at one to two years[30,31].

In a randomized phase III trial involving 117 oligometastatic patients, 56% of whom had spinal metastases, a comparison was made between single-fraction SBRT delivering 24 Gy and fractionated SBRT delivering 27 Gy in three fractions. The study found that the higher-dose,

single-fraction SBRT resulted in improved local control[32]. Based on this study and supporting evidence, we recommend a dose exceeding the equivalent of 18 Gy in a single fraction (BED_{10} = 50 Gy_{10}) to achieve sustained local control in oligometastatic patients. However, higher doses increase the risk of VCFs, particularly with single-fraction regimens such as 24 Gy. The decision to use such a regimen depends on an institution's ability to manage potential complications, prompting some clinicians to opt for fractionated SBRT delivered over 2 5 fractions. In our analysis, the one-year local control rate was 87%, with a one-year survival rate of 63%, consistent with previous findings[33,34].

5.6 Future Directions for SBRT Research

Our study reveals that the two SBRT fractionation patterns—single-fraction and multifraction—exhibit distinct biological effects, yet do not significantly differ in terms of overall survival rates. From a patient perspective, single-fraction SBRT offers advantages in treatment duration and cost-effectiveness, potentially improving patient compliance compared to the multifraction approach. Despite the absence of randomized controlled trials (RCTs) as a reference, these findings provide valuable evidence to the existing literature. Future research should focus on integrating more RCTs to validate these observations and strengthen the evidence supporting SBRT fractionation choices.

Conflict of Interest: The authors declare that they have no conflict of interest.
Data Availability Statements: The data underlying this article will be shared on reasonable request to the corresponding author.

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