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Systematic Review

Stereotactic body radiation therapy versus conventional external beam radiotherapy for spinal metastases: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Introduction: This study aimed to compare SBRT and cEBRT for treating spinal metastases through a systematic review and meta-analysis of randomized controlled trials (RCTs).
Methods: PubMed, EMBASE and Cochrane Library were searched up to 6 May 2023 for RCTs comparing SBRT and cEBRT for spinal metastases. Overall and complete pain response, local progression, overall survival, quality of life and adverse events were extracted. Data were pooled using random-effects models. Results were reported as risk ratios (RRs) for dichotomous outcomes, and hazard ratios (HRs) for time-to-event outcomes, along with their 95% confidence intervals (CIs). Heterogeneity was evaluated using the I^2 statistic.
Results: Three RCTs were identified involving 642 patients. No differences were seen in overall pain response comparing SBRT and cEBRT (RR at 3 months: 1.12, 95% CI, 0.74–1.70, p = 0.59; RR at 6 months: 1.29, 95% CI, 0.97–1.72, p = 0.08). Only two of three studies presented complete pain response data. SBRT demonstrated a

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statistically significant improvement in complete pain response compared to cEBRT (RR at 3 months: 2.52; 95% CI, 1.58–4.01; P < 0.0001; RR at 6 months: 2.48; 95% CI, 1.23–4.99; P = 0.01). There were no significant differences in local progression and overall survival. Adverse events were similar, except for any grade radiation dermatitis, which was significantly lower in SBRT arm (RR 0.17, 95% CI 0.03–0.96, P = 0.04).
Conclusion: SBRT is a safe treatment option for spine metastases. It may provide better complete pain response compared to cEBRT. Additional trials are needed to determine the potential benefits of SBRT in specific patient subsets.

The management of bone metastases remains a therapeutic challenge, as they often result in debilitating pain and a decline in patients' quality of life (QoL) [1]. Compared to non-spine bone metastases, spine metastases are unique in that they could lead to irreversible neurological complications such as radiculopathy and spinal cord compression if not managed in a timely fashion. Radiotherapy (RT) has been a cornerstone in the treatment of spinal metastases, with conventional external beam radiotherapy (cEBRT) being the long-standing standard of care [2–3]. However, as technology has advanced, SBRT has emerged as a promising treatment option for these patients due to its ability to deliver highly conformal, ablative doses of radiation to the tumor while sparing surrounding healthy tissue [4]. This precision may allow for better local control, which is crucial in preventing tumor progression, while also having the potential to reduce complications, such as radiation myelopathy or vertebral collapse [5–7].

While spinal SBRT has shown promising results in terms of efficacy and safety, the economic considerations of employing such technologies for palliation remain a concern [8]. Moreover, it has long been questioned whether an increase in radiation dose to the tumor may lead to increased pain control, while maintaining acceptable toxicities [9–11].

The current state of the art in spinal radiotherapy highlights a need for a systematic comparison of these two techniques to identify the most effective and safest treatment option for patients with spinal metastases. There have been several meta-analyses published to answer this question [12–15]. Recently, a full publication from a previous abstract of the largest randomized controlled study became available [11]. To offer valuable insights that can inform clinical decision-making and guide future research on the optimal treatment strategies for patients with spinal metastases, we conducted this systematic review and meta-analysis to investigate the effectiveness and safety of spinal SBRT compared to cEBRT in terms of pain response, toxicities, local control, QoL and survival outcomes.

Materials and methods

The analysis was performed and findings were reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline [16]. Two reviewers (SL and HW) independently performed the literature search, assessed study eligibility, extracted the relevant data, and performed the risk-of-bias assessment following the strategies stated below. Any disagreement between the reviewers was resolved through discussion and consensus, or arbitration by the third reviewer (AC).

Studies were identified through a systematic search on Embase, MEDLINE, and Cochrane Central Register of Controlled Trials (CENTRAL). A literature search was conducted on 6 May 2023 from inception to date of search for articles investigating the use of spinal SBRT for the treatment of metastasis due to any primary cancer. A combination of the following search terms was used: "cancer," "radiotherapy," and "stereotactic." The detailed search strategies for each database are summarized in the supplementary materials. Reference lists of relevant studies were also reviewed for possibly suitable articles.

Articles were included if [1] the study was a randomized controlled trial (RCT), [2] the study compared SBRT for the treatment of spinal metastasis in cancer patients, and included in the meta-analyses only if [3] the study compared SBRT with cEBRT. We excluded non-human studies, studies that did not provide quantified data or sufficient statistical parameters for analysis, and studies reporting exclusively on patients aged < 18 years. If an RCT included both spine and non-spine metastases but results were reported separately, this study would be included as well. Duplicate reports and studies covering overlapping populations were excluded. In cases where the same study population was reported on more than once, we included the most recent article.

Data from the included studies were extracted and included the first author's name, year of publication, sample size (both randomized and included in analysis), and cancer sites, dose-fractionations and techniques of SBRT and cEBRT, and the scoring systems employed for rating pain. The extraction encompassed all grades of toxicities. Notably, this data extraction was conducted solely from the published manuscripts, as individual patient data were not obtained. Where necessary, standard deviations and standard errors were derived from the reported *p*-values, following the guidelines provided in the Cochrane Handbook for Systematic Reviews of Interventions [17].

We used the Cochrane risk-of-bias tool for randomized trials to evaluate the quality of each included study [18]. This tool was specifically developed for use in reviewing RCTs, which may have certain methodological challenges such as selective outcome reporting.

The GRADE approach (Grading of Recommendations, Assessment, Development and Evaluations) to evaluated the quality (certainty) of the overall body of evidence was used [19]. All GRADE domains were assessed (methodological limitations, inconsistency, imprecision, indirectness and publication bias), and a summary is presented in Supplementary table S1).

The primary outcome was the overall pain response rate at 3 months. Secondary outcomes included complete pain response at 3 months, overall and complete pain response at 6 months, local progression, overall survival (OS), treatment toxicities, and QoL.

The study findings were summarized in Table 1. We calculated pooled relative risk (RRs) and 95% confidence intervals (CIs) for dichotomous outcomes (including pain response and local progression) for the analyzed studies. We calculated hazard ratios (HRs) and 95% CIs for OS. We employed a random-effects model to calculate the meta-analytic summary estimate, along with 95% CIs [20]. This analytic approach accounts for statistical heterogeneity between studies, which may arise from variations in patient characteristics across studies, the interventions used, and the outcome assessments [20]. Heterogeneity between effect estimates among studies was quantified by two statistical tests: the Cochran's Q statistical test for between-study variability and the I^2 statistic for the proportion of total variation across studies due to statistical heterogeneity instead of chance [21].

All *p*-values were two-tailed, and p-values of < 0.05 were considered statistically significant. The analyses and graphs were generated using Review Manager (RevMan) [Computer program] (Version 5.4. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2015).

Results

The literature search yielded a total of 4,044 studies. After removing 1,006 duplicates, the remaining 3,038 studies were screened by title and abstract using the inclusion/exclusion criteria. Of these, three studies, published between 2018 and 2023, met the inclusion criteria (Fig. 1)

Table 1
Study Characteristics for the Included Studies.

First Author (Year)	Sample size randomized and included in analysis	Primary Cancer sites	Sites of spinal metastases	SBRT dose-fractionations (BED Gy_{10})	cEBRT dose-fractionations (BED Gy_{10})	Maximum number of spinal segments	Criteria for spinal stability	Scoring system for pain	Scoring system for toxicities	Quality of life assessment tool
Sprave (2019) (9)	60 randomized, 55 analyzed in per-protocol population	*Lung: 34.5% Breast: 30.9% Renal: 7.2% Others: 27.3%	*Thoracic: 38.2%Lumbar: 60.0%Other: 1.8%	24 Gy in 1 daily fractions (81.6 Gy_{10})	30 Gy in 10 daily fractions (39 Gy_{10})	2	Not reported	BPI	CommonTerminology Criteria for Adverse Events (v.4.03)	EORTC QLQ-BM22,EORTC QLQ-C30,EORTC QLQ-FA13
Sahgal (2021) (10)	229 randomized, 223 analyzed in per-protocol population	Lung: 26.6% Breast: 21.8% Renal: 8.7% Melanoma: 3.1%Others: 39.8%	Cervical: 8.3% Thoracic: 48.5% Lumbar 36.2% Sacral: 5.2% Other: 1.8%	24 Gy in 2 daily fractions (52.8 Gy_{10})	20 Gy in 5 daily fractions (28 Gy_{10})	2	SINS Score < 12	BPI	Common Terminology Criteria for Adverse Events version4.0	EORTC QLQ- C30, EORTC QLQ-BM22
Ryu (2023) (11)	353 randomized, 339 analyzed in per-protocol population	NR	*Cervical: 5.9% Thoracic: 50.1% Lumber: 44.0%	16 or 18 Gy in 1 fraction (41.6 or 50.4 Gy_{10})	8 Gy in 1 fraction (14.4 Gy_{10})	3	No vertebral compression fracture and collapse $\leq$ 50%	Numerical Rating Pain Scale	Common Toxicity Criteria Adverse Events, version 3.0,	FACT-G, EQ-5D, BPI

*Per-protocol population was reported.
Abbreviations: BPI = Brief Pain Inventory; SINS = Spinal Instability Neoplastic Score; EORTC = European Organization for the Research and Treatment of Cancer.

[9–11]. Among these, one study implemented a two-fraction SBRT regimen [10], while the other two utilized a single-fraction SBRT (Tables 1 and 2) [9,11]. Two studies adhered to a 1:1 patient allocation to either the intervention or control arm, whereas in the case of Ryu et al., patients were randomized in a 2:1 ratio favoring the SBRT group [9–11]. Across all three studies, no significant differences were noted in patient characteristics between the two arms. Sprave et al. reported the outcomes of the same cohort in three separate articles, each focusing on pain response, QoL, and local control and pathological fractures [9,22–23]. The raw data from Ryu et al. beyond what was presented in the published manuscript were not available for analysis.

A total number of 642 patients were included. The most common primary cancer sites were lung and breast cancers in Sprave et al. and Sahgal et al., whereas these were not reported by Ryu et al. Sprave et al. and Sahgal et al. assessed pain by Brief Pain Inventory (BPI), whereas Ryu et al. used a numerical rating pain scale. All studies used the Common Terminology Criteria of Adverse Events (CTCAE) to grade the severity of toxicities, albeit using different versions. The dose fractionations used for SBRT varied across studies, including single fraction (24 Gy in Sprave et al. and 16 or 18 Gy in Ryu et al.) and two fractions (24 Gy in 2 fractions in Sahgal et al.). The dose fractionations used for cEBRT include 30 Gy in 10 fractions, 20 Gy in 5 fractions, and 8 Gy in a single fraction.

Using the Risk of Bias Tool 2.0, the studies of Sahgal et al. and Sprave et al. were rated as having a low risk of bias. The RTOG 0631 study by Ryu et al. was rated as having "some concerns" due to a high number of missing data at 3 months (Fig. 2). The GRADE Working Group grades of evidence is described in the Supplementary Table S1.

The pooled risk ratio (RR) of 1.12 (95% CI, 0.74–1.70, p = 0.59, I^2 73%) revealed a statistically non-significant difference between SBRT and cEBRT in overall pain response at 3 months (Fig. 3A). The pooled overall pain response at 3 months was 36.8% in the SBRT arm and 36.3% in the cEBRT arm.

For the complete pain response at 3 months, only studies of Sprave et al. and Sahgal et al. were included in the meta-analysis on this outcome due to data availability. SBRT was associated with statistically significant improvement in complete pain response rates at 3 months compared to cEBRT (RR, 2.52; 95% CI, 1.58–4.01; P < 0.0001; I^2 0%) (Fig. 3B). The pooled complete pain response at 3 months was 34.7% in the SBRT arm and 13.8% in the cEBRT arm.

At the 6-month follow-up, there was still no statistical difference in overall pain response between SBRT and cEBRT. The pooled RR was 1.29 (95% CI, 0.97–1.72; P = 0.08; I^2 9%) (Fig. 3C). The pooled overall pain response at 6 months was 26.3% in the SBRT arm and 22.8% in the cEBRT arm.

The estimates from Sprave et al. and Sahgal et al. revealed that the complete pain response at 6 months favored SBRT compared to cEBRT (RR, 2.48; 95% CI, 1.23–4.99; P = 0.01; I^2 24%) (Fig. 3D). The pooled complete pain response rate at 6 months was 32.6% in the SBRT arm and 13.8% in the cEBRT arm. The pooled results demonstrated that SBRT performed better in providing complete pain relief over a sustained period of time.

Only Sahgal et al. and Ryu et al. reported outcomes of local progression. Sahgal et al. assessed patients with magnetic resonance imaging (MRI) at 3 and 6 months after treatment [10]). On the other hand, Ryu et al. arranged follow-up MRI at 3, 6, 12 and 24 months after treatment [11]. The number of progression events were reported at the sixth month in Sahgal et al, and at the twelfth month in Ryu et al. Pooling the two studies, a total of 23 out of 173 patients (13.3%) had local progression events in the SBRT arm, whereas 28 out of 153 patients (18.3%) had local progression events in the cERBT arm. The meta-analysis showed no significant difference in the number of local progression events for patients treated with SBRT versus cEBRT (pooled RR 0.51, 91% CI 0.16–1.64; P = 0.26, I^2: 68%) (Fig. 3E).

No significant difference was detected in OS between the SBRT and cEBRT groups (pooled HR 0. 92, 95% CI 0.73–1.15, P = 0.46, I^2: 0%)

(Fig. 3F).

The pooled analysis of adverse events revealed comparable safety profiles between SBRT and cEBRT (Table 3). The forest plots of these events are shown in the supplementary Fig. S1A-I. Fatigue of grade ≥ 2 showed a risk ratio (RR) of 1.11 (95% CI 0.49–2.51, P = 0.79). Pain flare also occurred, presenting an RR of 1.32 (95% CI 0.93–1.87, P = 0.11). Likewise, the incidence of all pain-related events of grade ≥ 2 demonstrated an RR of 1.10 (95% CI 0.69–1.77, P = 0.68). Dysphagia of grade ≥ 2 was observed with an RR of 1.82 (95% CI 0.31–10.69, P = 0.51), whereas esophagitis of the same severity showed an RR of 0.48 (95% CI 0.06–3.85, P = 0.49). Nausea and vomiting of grade ≥ 2 had RRs of 1.14 (95% CI 0.16–7.93, P = 0.90) and 2.51 (95% CI 0.46–13.8, P = 0.29), respectively. Any grade radiation dermatitis was the only adverse event that showed a significantly RR of 0.17 (95% CI 0.03–0.96, P = 0.04), favoring the SBRT arm. All cases of radiation dermatitis were grade 1 except one case with grade 2 in Ryu et al. in the cEBRT arm. The other two studies reported no instances of grade ≥ 2 radiation dermatitis. Compression fracture was reported in all three studies. Sahgal et al. and Sprave et al. reported the number of patients over the total number of patients, whereas Ryu et al. performed a competing risk analysis excluding patients who were lost to follow-up or died. Therefore, its results could not be pooled together with the other two studies. At 6 months, no difference in any grade compression fracture was observed pooling the results of Sahgal et al. and Sprave et al. (RR of 1.50 (95% CI 0.18–12.5, P = 0.71).

The three RCTs utilized different patient-reported outcome measurements to assess the QoL of patients with spine metastases; therefore, only a narrative description of the results was performed. The QoL results of Sprave et al.'s study were reported in a separate publication. All three included RCTs reported QoL outcomes. Sprave et al. used European Organization for the Research and Treatment of Cancer Quality of Life Questionnaires (EORTC QLQ)-BM22, QLQ-FA13, and QSC-R10. Sahgal et al. also used EORTC QLQ-BM22, in addition to EORTC QLQ-C30. Ryu et al. used FACT-G and EQ-5D index score, and the BPI. These trials did not report any significant differences between two arms for the various domains of QoL, except for the financial domain assessed using EORTC QLQ-C30 instrument in Sahgal et al., which found that patients in the SBRT arm might have improved perception of financial burden at the 4th week assessment (mean change in score from baseline −5.9 for SBRT versus + 1.5 for cEBRT; p = 0.03). However, this effect was not sustained at 3 months and 6 months.

Discussion

Our study summarized the evidence from the all RCTs comparing the effectiveness of SBRT and cEBRT in the management of spinal metastases, including the recently published results of RTOG 0631 [9–11]. We showed that, in patients with previously unirradiated spinal bone metastases without cord compression, no significant difference in overall pain response, QoL, local progression event, adverse events and OS

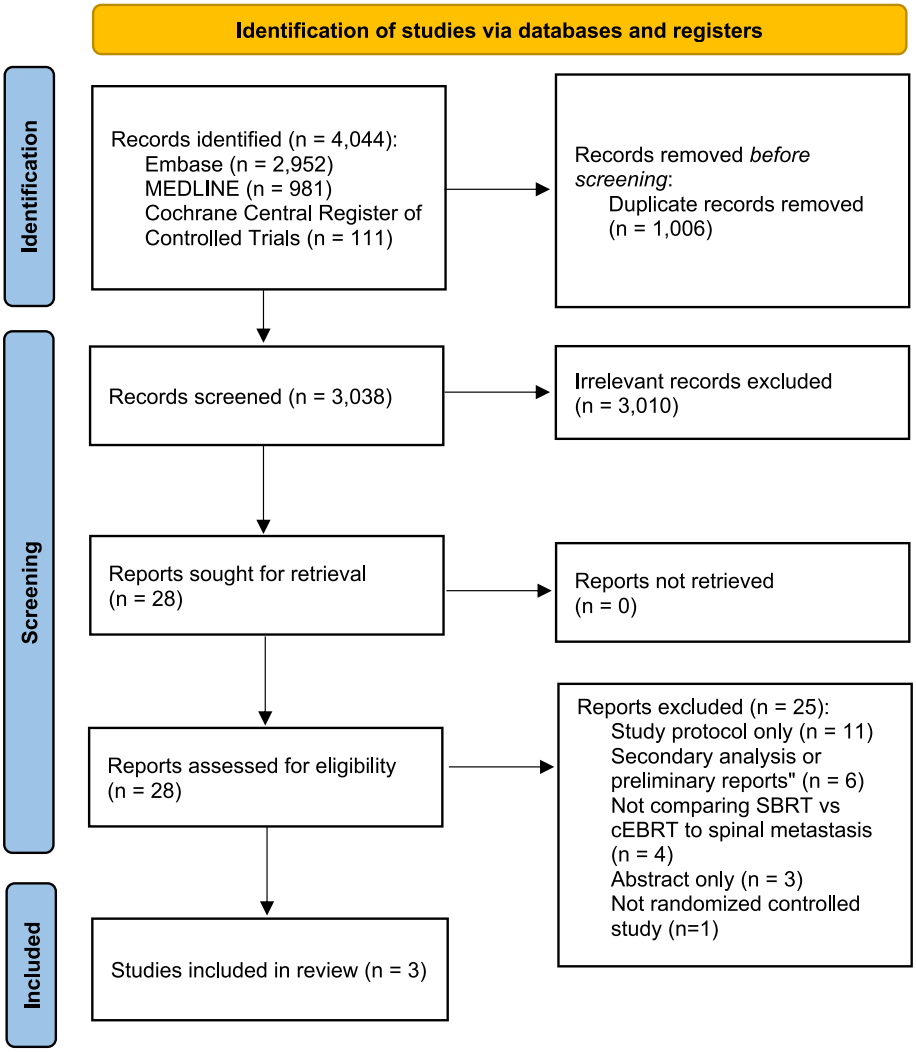

Fig. 1. PRISMA Flow Diagram of Study Selection.

Table 2
Outcomes Assessment of the Included Studies.

First Author (Year)	Overall pain response at 3 months		Complete pain response at 3 months		Overall pain response at 6 months or beyond		Complete pain response at 6 months		Local progression*	
	SBRT	cEBRT	SBRT	cEBRT	SBRT	cEBRT	SBRT	cEBRT	SBRT	cEBRT
Sprave et al. (2018)(9)	53.3%	36.7%	33.30%	13.30%	46.70%	23.30%	33.30%	6.70%	NR	NR
Sahgal et al. (2021)(10)	52.6%	39.1%	35.10%	13.90%	41.20%	31.30%	32.50%	15.70%	2.6%	10.4%
Ryu et al. (2023)(11)	26.3%	33.8%	NR	NR	15.70%	15.40%	NR	NR	33.9%	42.3%

Ryu et al. reports local progression event at 12 months, while Sahgal et al. reports at 6 months.
Abbreviations: cEBRT, conventional external beam radiotherapy; NR, not reported; SBRT, stereotactic body radiation therapy.

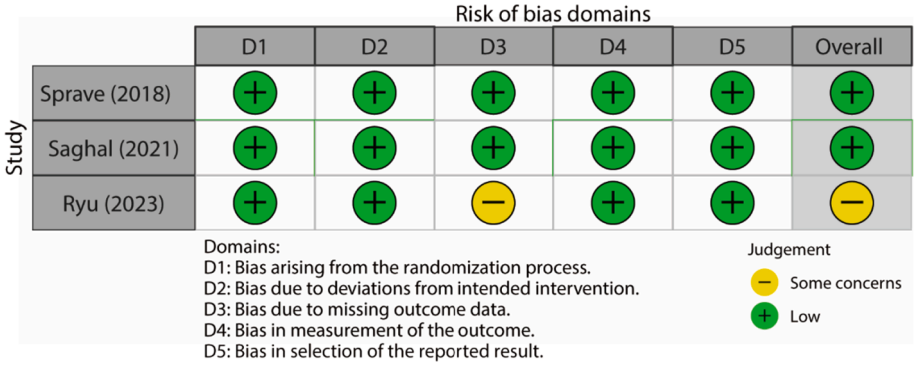

Fig. 2. Risk-of-Bias Assessment.

between SBRT and cEBRT were observed. However, there is a possibility that SBRT may be associated with a significant improvement in complete pain response at 3 and 6 months from the pooled estimates of the studies of Sahgal et al. and Sprave et al.

Our up-to-date systematic review that analyzed results on pain response (complete pain response and overall pain response) were consistent with those of the previous systematic reviews on painful bone metastasis, although these were not specifically assessing patients with spinal metastasis [12–15]). It is important to note that complete pain response data were not available for study by Ryu et al [11]. It remains uncertain whether the benefits of complete pain response for SBRT demonstrated in this meta-analysis will persist if future data from Ryu et al. are reported and included in future meta-analyses. Ryu et al. is the largest RCT among the three [11]; therefore, its results carry a significant weight on the meta-analyses. Another controversy is that Ryu et al. used Numerical Rating Pain Scale of ≥ 3 points improvement to define pain response [11], whereas Sahgal et al. and Sprave et al. used the international consensus on palliative radiotherapy endpoints (ICPRE) [9–10], which defines partial pain response as ≥ 2 points compared to baseline without an increase in analgesics, or no worsening of the worst pain score and a reduction of oral morphine equivalent consumption of at least 25% [24]. Although Ryu et al.'s main results on pain response remained unchanged in the sensitivity analysis re-categorizing response based on ICPRE [11], caution needs to be exercised when comparing results with the other two studies and interpreting the pooled estimates. When interpreting the results, it is also essential to consider patient selection, as certain subgroups, such as those with a higher baseline pain score and a greater extent of vertebral collapse, may not derive the same benefits from SBRT because there could be a mechanical pain component that may be less treatable by radiotherapy of any modality [25–26].

Our meta-analysis showed that patients receiving SBRT had a lower risk of radiation dermatitis. To our knowledge, this is an interesting finding that has not been previously reported in the literature. A possible explanation is that SBRT can achieve better conformity to the planning target volume (PTV) with lower skin doses that could not be otherwise achieved with two- to four-field 3D-conformal radiotherapy. However, this conclusion needs to be further validated in larger studies, as there were only a small number of events and, therefore, the 95% CI was very wide.

The effectiveness and safety of treatments of spinal metastases could be dependent on many factors, for example the size of the tumour, radiosensitivity of the tumour subtype, presence of pre-existing pathological vertebral collapse, number of contiguous spinal segment involved, whether subsequent systemic treatment was initiated after radiotherapy and presence of neuropathic pain [25]. Imbalance of any of the above factors between the two groups may underestimate or overestimate the therapeutic effect of the treatment arms. Sahgal et al. stratified patients based on radiosensitivity and presence of mass-type tumour [10]. Only patients with a stable spine, defined as < 12 points on the Spinal Instability Neoplastic Score (SINS), were included. On the other hand, Ryu et al. only stratified based on number of metastases, intended radiotherapy dose (16 Gy versus 18 Gy) and radiosensitivity [11]. The definition for spinal stability of Ryu et al. was also different compared to Sahgal et al., where patients with $\leq 50\%$ of vertebral collapse and no compression fracture was included in the study [10]. Sprave et al. did not have any stratification in their study design and did not specify any criteria for spinal stability [9].

Furthermore, the lower pain response observed in the SBRT arm of the study of Ryu et al. merits additional discussion. The pain response in the SBRT arm of Ryu's study (41.3%) falls below the rates reported in older studies using fractionated radiotherapy (around 60%) [27], and also lower than those reported in the studies by Sahgal et al. and Sprave et al. (53% and 59.2% respectively) [9–10]. It is worth considering whether this observation merely reflects the different scoring system used in the study, or whether it suggests a fundamentally different patient population. Patients in the SBRT arm of Ryu et al. had a higher median baseline pain score of 7 compared to 5 in Sahgal et al. Besides, a larger proportion of patients in the SBRT arm of Ryu et al. had a baseline performance status of 2 (22% versus 7% in Sahgal et al.). However, the proportion of radioresistant tumours were less in the study of Ryu et al. (13.9% versus 26% in Sahgal et al.) [10–11]. Further clinical trials are needed to understand the complex interactions of how these factors influence pain response rates.

Within the studies included in our meta-analysis, each author

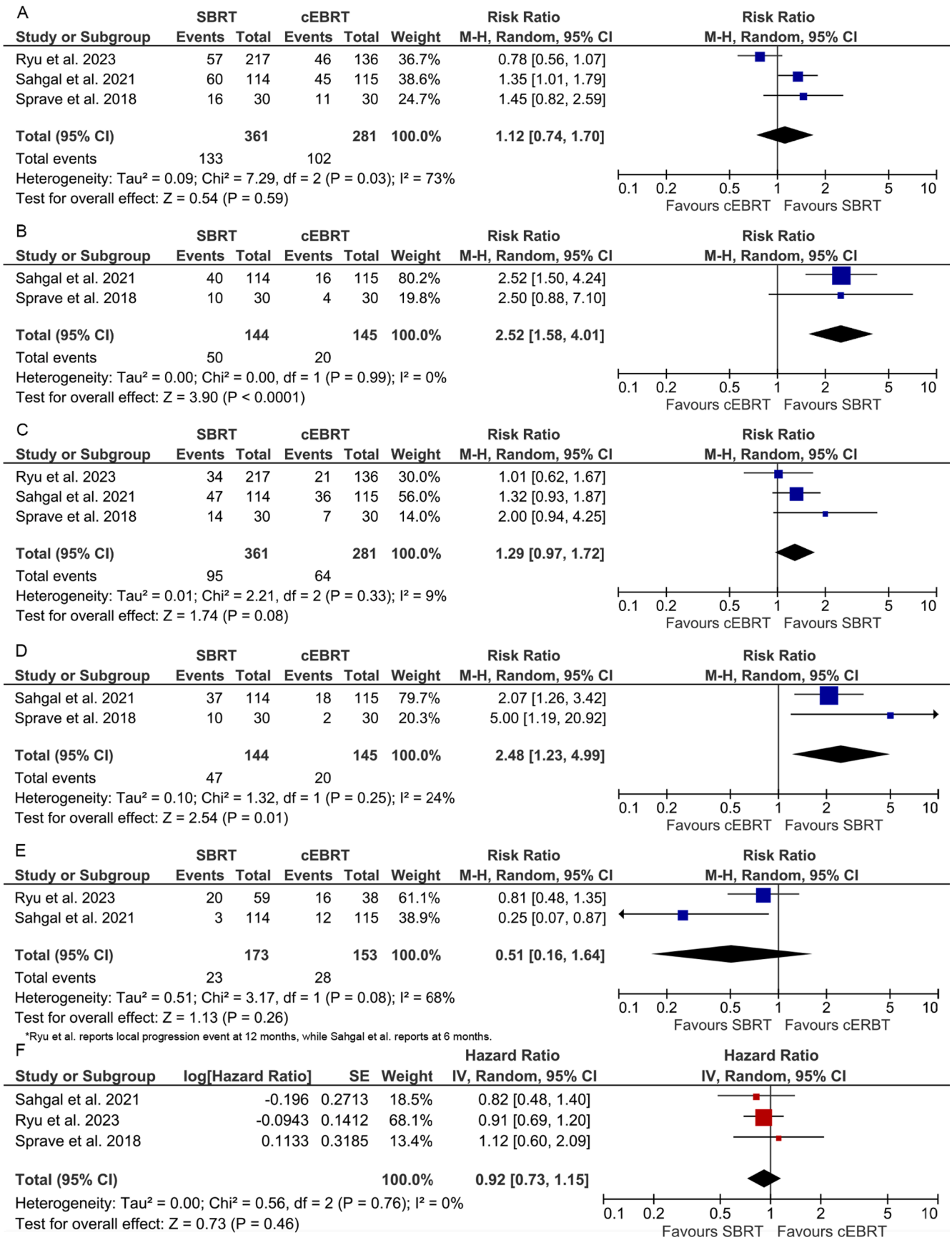

Fig. 3. Forest plots of comparison: SBRT versus cEBRT (intention-to-treat analysis). Outcomes: (A) Overall pain response at 3 months. (B) Complete pain response at 3 months. (C) Overall pain response at 6 months. (D) Complete pain response at 6 months. (E) Local progression event. (F) Overall survival at 6 months.

Table 3
Toxicity Assessment of the Included Studies.

First Author (Year)	Vertebral compression fracture		Fatigue ≥ grade 2		Dysphagia ≥ grade 2		Nausea ≥ grade 2		Vomiting ≥ grade 2		Pain ≥ grade 2		Pain flare		Esophagitis ≥ grade 2		RD ≥ grade 1	
	SBRT	cEBRT	SBRT	cEBRT	SBRT	cEBRT	SBRT	cEBRT	SBRT	cEBRT	SBRT	cEBRT	SBRT	cEBRT	SBRT	cEBRT	SBRT	cEBRT
Sprave et al. (2018)(9)	27.8%	5.0%	7.4%	7.1%	0%	3.6%	NR	NR	0%	3.6%	NR	NR	7.4%	0%	NR	NR	3.7%	17.9%
Sahgal et al. (2021)(10)	10.9%	17.4%	0%	0.9%	1.8%	0%	0.9%	2.6%	NR	NR	6.4%	7.8%	42.9%	33.0%	1.8%	1.7%	NR	NR
Ryu et al. (2023)(11)	19.5%	21.6%	6.4%	5.1%	1.0%	0%	4.5%	1.7%	3.0	0	16.8%	13.7%	NR	NR	0%	1.7%	0	1.7%

Abbreviations: cEBRT, convention external beam radiotherapy; NR, not reported; RD, radiation dermatitis; SBRT, stereotactic body radiation therapy.

outlined different planning techniques for cEBRT. Sahgal et al. permitted standard fields with parallel-opposed anterior-posterior beam arrangements and 3-dimensional conformal radiotherapy (3D CRT) with up to four beams, where the target vertebrae were contoured as the clinical target volume with a 1–2 cm margin added for PTV and beam penumbra [10]. Ryu et al. incorporated either 2-dimensional or 3D CRT at the treating physician's discretion, encompassing the entire vertebral body of the involved index spine, including one vertebra above and one below [11]. Similarly, Sprave et al. implemented a 3DCRT approach, irradiating the involved vertebrae and the ones immediately above and below with either three or four anteroposterior/posteroanterior beams [9]. The volume-expanded PTV in the study of Sahgal et al. may be smaller than the studies of Ryu et al. and Sprave et al, which could be one of the reasons which enhanced the relative pain response benefit of SBRT to cEBRT.

The preservation of QoL and OS is another critical aspect in the management of spinal metastases. Our review has shown that SBRT neither adversely affects nor improves these outcomes compared to cEBRT. This is an important finding, as it demonstrates that the benefits of SBRT in terms of complete pain response do not come at the cost of reduced QoL or survival. Interestingly, despite a higher chance of complete pain relief at the site treated by SBRT, this does not necessarily affect the overall patient's perception of pain from their disease and symptom burden. This highlights the importance of robustly designed and powered trials incorporating cancer-specific QoL assessment, such as the Spine Oncology Study Group Outcomes Questionnaire (SOSGOQ2.0), in spinal metastases-specific radiotherapy trials [28].

While the local control rates were similar between the two arms in the meta-analyses, interpretation of the results need to be taken carefully because of the heterogeneity in the doses used for SBRT and cEBRT, and differences in the timing of when local progression was assessed. In the original publications, patients were assessed at 12 months in RTOG 0631, whereas Sahgal et al. assessed patients at 6 months. There have been other studies published that showed that local control can be improved with dose escalation. Zeng et al. analyzed the long-term results of a cohort of patients treated in the study of Sahgal et al. This study showed that patients treated with the SBRT arm had a significantly lower rate of local failure compared to the cEBRT arm (SBRT 6.1% versus cEBRT 28.4% at 12 months $p < 0.001$) [29]. Moreover, analysis of a prospective cohort of patients treated with SBRT showed that a higher dose of 28 Gy in 2 fractions achieved better local control compared to 24 Gy in 2 fractions [30]. This suggests that the optimal dosage and schedule of SBRT might play a pivotal role in achieving better local control, a topic that deserves further exploration in future randomised studies. Improved local control is especially important in the oligometastatic setting, as this may translate to an overall survival benefit as suggested in the SABR-COMET trial [31].

Heterogeneity in study endpoints and differences in the timing when patients were assessed across the three studies caused uncertainties in interpreting the results of this meta-analysis. Moving forward, an update of the ICPRE should be performed in order to review whether the existing efficacy endpoints are relevant and appropriate for patients treated with SBRT. For example, durability of pain response has been argued to be a more comprehensive assessment of pain relief for patients compared to overall and complete pain response at a specific time point [32]. Definitions of toxicities specific to spinal SBRT, such as pain flare and compression fractures, should also be aligned. An agreed set of endpoints for efficacy and toxicity will allow more meaningful comparisons of future RCTs investigating SBRT versus cEBRT or different SBRT techniques, doses or fractionation schedules.

Future RCTs are needed to better define when and how SBRT should be performed in patients with painful spinal metastases. Before these results are available, an individual participant level meta-analysis of the three studies would be helpful to guide clinical practice. Getting the complete pain response rates at 3 and 6 months from the recently published RTOG study will enhance the results of the current meta-

analysis. When participants' pain scores and data on analgesic consumption are available, the definition for pain response can be aligned across the studies. Subgroup analyses can also be performed to generate hypothesis on which patients benefit from SBRT. A relationship between radiation dose and pain response may also be observed. Furthermore, risk factors for pain flares and compression fractures after radiotherapy may be identified with a larger sample size.

Strengths of our study include the comprehensive and up-to-date analysis of RCTs, providing a more reliable estimate of the comparative effectiveness of SBRT and cEBRT for spinal metastases. However, there are limitations in our study, such as the small number of RCTs performed to be included in this analysis, and heterogeneity in the stratification of patients, doses of EBRT and SBRT employed in the studies, and definitions of study endpoints.

In conclusion, our study indicates that SBRT is a viable treatment option for spinal metastases, which may offer improved complete pain response up to 6 months after treatment without increased risks of adverse events. However, no differences in overall pain response, local control, QoL, and OS were observed compared to cEBRT. Before more RCTs or additional results from an individual participant level meta-analysis of the three studies are available, the decision between SBRT and cEBRT for painful spine metastases should be individualized based on a thorough evaluation of the patients' prognosis and preferences.

CRediT authorship contribution statement

Henry C.Y. Wong: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing. **Shing Fung Lee:** Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing. **Adrian Wai Chan:** Conceptualization, Methodology, Investigation, Formal analysis, Writing – review & editing. **Saverio Caini:** Conceptualization, Methodology, Writing – review & editing. **Peter Hoskin:** Writing – review & editing. **Charles B. Simone:** Conceptualization, Methodology, Writing – review & editing. **Peter Johnstone:** Conceptualization, Methodology, Writing – review & editing. **Yvette van der Linden:** Writing – review & editing. **Joanne M. van der Velden:** Writing – review & editing. **Emily Martin:** Writing – review & editing. **Sara Alcorn:** Writing – review & editing. **Candice Johnstone:** Writing – review & editing. **J. Isabelle Choi:** Writing – review & editing. **Gustavo Nader Marta:** Writing – review & editing. **Eva Oldenburger:** Writing – review & editing. **Srinivas Raman:** Writing – review & editing. **Agata Rembielak:** Writing – review & editing. **Vassilios Vassiliou:** Writing – review & editing. **Pierluigi Bonomo:** Writing – review & editing. **Quynh-Nhu Nguyen:** Writing – review & editing. **Edward Chow:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Samuel Ryu:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2023.109914.

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