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Original Article

Efficacy and safety of SBRT for spine metastases: A systematic review and *meta*-analysis for preparation of an ESTRO practice guideline

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ABSTRACT

Background and purpose: Advances in characterizing cancer biology and the growing availability of novel targeted agents and immune therapeutics have significantly changed the prognosis of many patients with metastatic disease. Palliative radiotherapy needs to adapt to these developments. In this study, we summarize the available evidence for stereotactic body radiotherapy (SBRT) in the treatment of spinal metastases.

Materials and methods: A systematic review and *meta*-analysis was performed using PRISMA methodology, including publications from January 2005 to September 2021, with the exception of the randomized phase III trial RTOG-0631 which was added in April 2023. Re-irradiation was excluded. For *meta*-analysis, a random-effects model was used to pool the data. Heterogeneity was assessed with the I^2-test, assuming substantial and considerable as $I^2 > 50$ % and $I^2 > 75$ %, respectively. A p-value < 0.05 was considered statistically significant.

Results: A total of 69 studies assessing the outcomes of 7236 metastases in 5736 patients were analyzed. SBRT for spine metastases showed high efficacy, with a pooled overall pain response rate of 83 % (95 % confidence interval [CI] 68 %-94 %), pooled complete pain response of 36 % (95 % CI: 20 %-53 %), and 1-year local control rate of 94 % (95 % CI: 86 %-99 %), although with high levels of heterogeneity among studies ($I^2 = 93$ %, $I^2 = 86$ %, and 86 %, respectively). Furthermore, SBRT was safe, with a pooled vertebral fracture rate of 9 % (95 % CI: 4 %-16 %), pooled radiation induced myelopathy rate of 0 % (95 % CI 0–2 %), and pooled pain flare rate of 6 % (95 % CI: 3 %-17 %), although with mixed levels of heterogeneity among the studies ($I^2 = 92$ %, $I^2 = 0$ %, and 95 %, respectively). Only 1.7 % of vertebral fractures required surgical stabilization.

Conclusion: Spine SBRT is characterized by a favorable efficacy and safety profile, providing durable results for pain control and disease control, which is particularly relevant for oligometastatic patients.

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Introduction

Skeletal metastases are among the most frequent sites of cancer spread, with the spine being the preferred site of tumor colonization [1] especially from lung, prostate or breast tumors. Spine metastases can have a substantial impact on patient's quality of life (QoL); they can cause pain, impair activities of daily living, and may threaten the spinal cord/cauda equina leading to neurological deficits [2].

The cornerstone of the management of spinal metastases is multidisciplinary co-operation. Conventional radiotherapy (CRT) has traditionally represented the preferred approach for a palliative intent, with the aim of providing adequate pain response with minimal toxicity [3,4]. CRT routinely uses low to intermediate total radiation doses delivered in few fractions (e.g. 8 Gray (Gy) delivered in single fraction, 20 Gy in 5 fractions or 30 Gy in 10 fractions), with lower biologically effective doses (e.g. 8 Gy in 1 fraction) associated with less durable pain control and/or need for re-irradiation [5,6].

In recent years, the treatment and prognosis of some metastatic cancer patients has changed dramatically with the introduction of new systemic strategies such as target therapies, immunotherapy, and 2nd and 3rd generation anti-androgens, which have led to substantial improvements in terms of overall survival (OS) with preserved QoL [5,6]. In this scenario, the role of radiotherapy has been challenged in order to provide a local treatment able to achieve long-term results not only in terms of pain relief but also in terms of local control and spinal stability.

Prospective and retrospective studies support the use of stereotactic body radiotherapy (SBRT) for spinal metastases as a safe and effective therapeutic option for both pain response and durable disease control, with the result that SBRT has been proposed as the preferred option not only for patients with oligometastatic disease, some of whom may be potentially curable with definitive metastasis-directed treatments, but also for selected patients requiring symptom palliation [7–11]. Following international guideline recommendations target volume delineation for spine SBRT differs from conventional external beam radiotherapy (EBRT), in that only a portion of the entire vertebral segment, based on the location of the macroscopic disease, is typically treated [1]. Using SBRT, clinicians can deliver dose-escalated and highly conformal treatments to the macroscopic tumor creating a steep dose gradient with a rapid dose fall-off outside the target, limiting the dose to nearby organs-at-risk such as the spinal cord or esophagus, resulting in an enhanced therapeutic ratio [6,12]. The present systematic review was performed in preparation for an ESTRO clinical practice guideline focused on 4 key questions:

1) What is the overall pain response rate, complete pain response rate and duration of pain response after SBRT for painful vertebral metastases? How does pain response after SBRT compare to conventional palliative radiotherapy?
2) What is the local control (LC) after SBRT for spine metastases? What is the role of spine SBRT in oligo-metastatic disease (OMD)?
3) What is the practice of spinal SBRT to optimize safety and efficacy according to available evidence?
4) What is the toxicity profile of spine SBRT?

An interdisciplinary panel of experts in spine SBRT generated statements and recommendations for best clinical practice spine SBRT using ASTRO clinical practice guideline methodology [2].

Methods

- Search strategy, selection process and eligibility criteria

A systematic literature search was performed using the Pubmed, Embase, and Cochrane databases. The Medical Subject Headings (MeSH) terms "SBRT," "stereotactic," "radiosurgery," or "SABR", were used in conjunction with "spinal," "spine," or "vertebral," and "metastasis," "metastases," or "metastatic" to conduct the search.

Publications between January 2005 to September 2021 were considered. The exception was the randomized phase II trial RTOG 0631 study that was published in April 2023, and which was added later due to its relevance. In May 2023, the ROBOMET trial results were presented at the European Congress of Radiotherapy and Oncology (ESTRO 2023), available only in abstract version at the time of the manuscript drafting. Due to the relevance of the study, the results are reported in Table 1, but the study was not included in the statistical analysis, due to the lack of details, which will be presumably provided in the full manuscript, once published. The review was done by two reviewers (RG, FC) independently and in case of discrepancy a triple check was performed by a third reviewer.

- Data collection process and items

The data collection process was performed by both reviewers independently. For the selected studies, six different groups of characteristics were created, including study characteristics, patient characteristics, metastasis characteristics, pain characteristics, technique characteristics, and outcome characteristics, including side effects. Manuscript characteristics included year of publication and study design (retrospective or prospective). For patient characteristics, the number of patients, the number of vertebral metastases, median age, median Karnofsky performance score (KPS), oligometastatic disease status, and primary tumor histology were extracted. For metastasis characteristics, the proportion of osteolytic metastases, unstable metastases, previously fractured metastases, use of the Spinal Instability Neoplastic Score (SINS), proportion of patients with pre-existing spinal cord compression, use of the Bilsky scale, and proportion of patients with stabilization or instrumentation surgery before SBRT were filtered out. Regarding pain characteristics, the focus was on the proportion of patients with pain before SBRT, median pain score before SBRT (numeric rating scale [NRS], visual analogue scale [VAS], brief pain inventory [BPI], or common terminology criteria for adverse events [CTCAE]), proportion of pain flare after SBRT, pain response rate, proportion of complete pain response, definition of pain response (BPI, VAS, NRS, or CTCAE), median time to pain response, and median time to pain progression. Radiotherapy technical characteristics included radiotherapy delivery technique, median number of radiotherapy fractions, range of radiotherapy fractions, median total dose, median single-fraction dose, use of image-guided radiotherapy (IGRT) (kV/kV, cone-beam computed tomography [CBCT], ExacTrac, Xsight, and magnetic resonance imaging [MRI]), use of rigid patient immobilization, and median planning target volume (PTV) size. Regarding outcome, including side effect data, median follow-up time, actuarial 1-year OS, actuarial 2-year OS, median OS, time to local recurrence, actuarial 1-year local metastasis control, actuarial 2-year metastasis control, proportion of patients with post-SBRT vertebral compression fracture, proportion of patients with post-SBRT surgical decompression/stabilization, proportion of patients with post-SBRT nerve root damage, proportion of patients with radiation induced myelopathy, and additional grade 3 (G3) toxicity were selected.

- Outcomes

The primary outcome was efficacy in terms of the pooled overall and complete pain response and 1-year LC as defined in the individual studies. The secondary outcome measure was safety, which included relevant toxicity such as the pooled pain flare rate, vertebral fracture rate and radiation induced myelopathy rate.

- Statistical Analysis:

Descriptive statistics (medians, means and percentages) were collected for baseline patients' and lesions' characteristics. T-test was applied to assess any potential significant predictive factor for clinical outcomes or adverse events incidence, assuming a p-value ≤ 0.05 as

statistically significant. All statistical analyses were carried out using Graphpad Prism v9.02 (Graphpad, San Diego, CA, USA).

For *meta*-analysis of the data, forest plots of the pooled overall and complete pain response, 1-year LC, fracture rate, radiation induced myelopathy rate and pain flare rate after SBRT for spine metastases in prospective studies were made. A random-effects model was used to pool the data.

Heterogeneity was assessed with the I^2 test. Substantial and considerable heterogeneity were defined as $I^2 > 50$ % and $I^2 > 75$ %, respectively. A p-value < 0.05 was considered statistically significant. R version 4.1.1 with "Rcurl", "metaphor", and "meta" packages were used for statistical analysis [12].

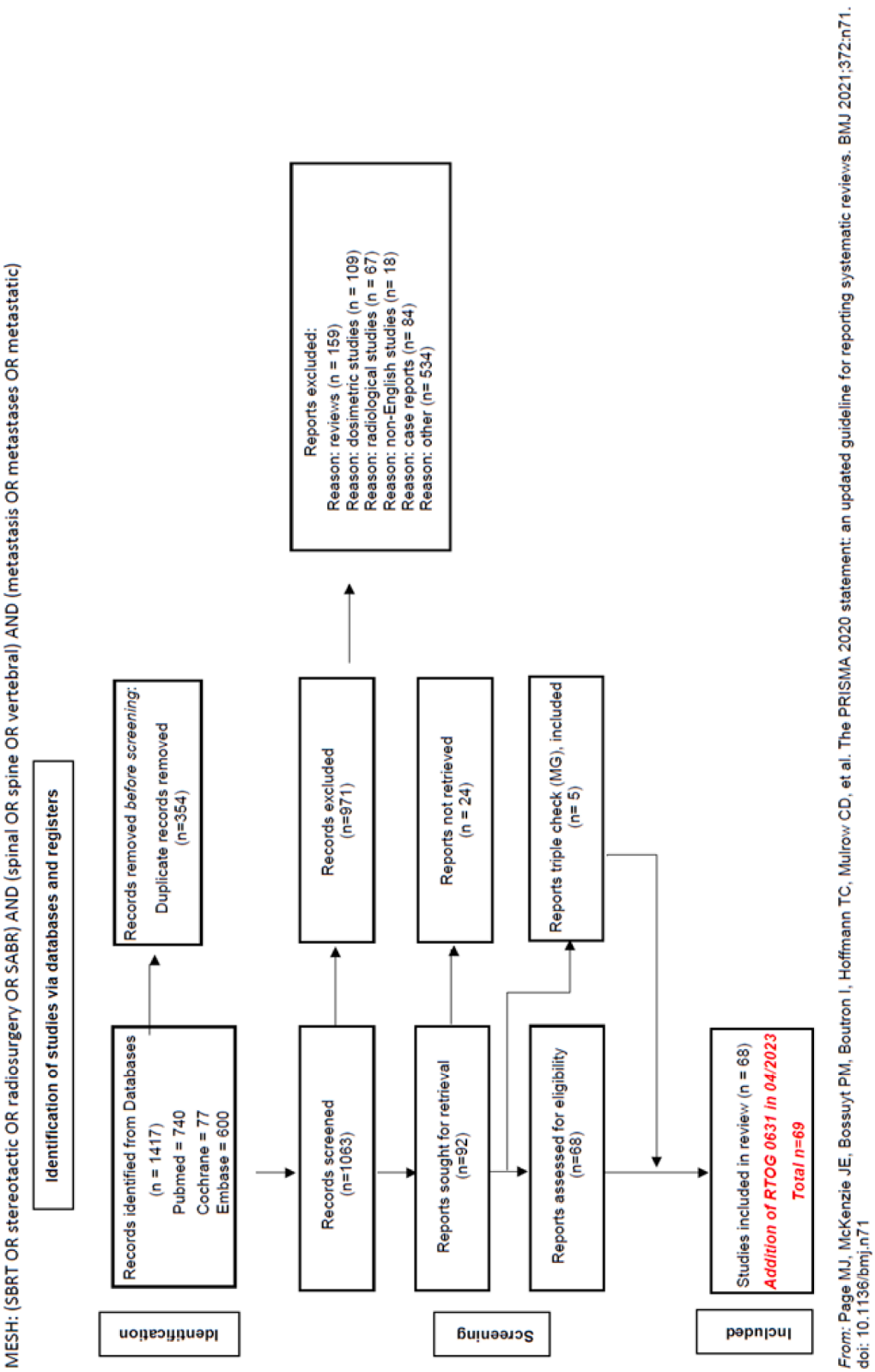


Fig. 1. PRISMA identification of studies. N = number, SBRT = stereotactic body radiotherapy, SABR = stereotactic ablative body radiotherapy.

Results

- Study selection

For the study selection, we applied the Preferred Reporting Items for Systematic Reviews and Meta-Analyses- strategy (PRISMA) [13], see Fig. 1.

During the initial stage of the literature search, a total of 1417 references were identified using the pre-specified MeSH terms. Specifically, 740 publications were retrieved from PubMed, 77 from Cochrane, and 600 from Embase. After removing 354 duplicates, the titles and abstracts of the remaining references were screened by two independent observers (FC and RG) for relevance. Reviews, planning studies, technical studies without clinical data, study protocols, abstracts, case reports, studies not published in English, and studies with fewer than 5 patients were excluded. In situations where a mixed population of previously irradiated and unirradiated patients was included, the outcomes regarding the previously unirradiated subset were analysed. For updated publications, those with the longest follow-up were included. As a result, 971 publications were excluded during the screening process and 92 publications were selected for further evaluation. Following a second review by the authors and a triple verification of 5 publications by MG, 68 studies were included in the initial systematic review. Including the RTOG 0631 study from April 2023 resulted in a final total of 69 studies [7,8,11,14,20,24–87].

- Risk of bias in studies

As prospective randomised trials have the highest level of evidence, the review and interpretation focused on the 4 prospective randomised trials published as of April 2023; the ROBOMET [13] study was presented as an abstract at ESTRO 2023, but was not included in our analysis due to it only being available in abstract form. In the interest of completeness, the abstract is included in the overview in the appendix (Table 1).

- Reporting bias

Overall, there was a lot of missing data in many of the studies examined, so that a certain reporting bias can be assumed for some categories.

- STUDY, PATIENT, METASTASIS, AND TECHNIQUE CHARACTERISTICS

Study characteristics, patient characteristics

Out of the total 69 studies, n = 14 were prospective, and as mentioned above the abstract of the prospective randomized ROBOMET trial was not included in the analysis. The majority of the studies were retrospective (55 studies), and the total number of patients included in these studies was 5736 with 7236 spinal lesions. The median age of the patients was 61 years (range 20.3–71), and the median performance score was 90 (range 70–100). The median proportion of oligometastatic patients was 90.5 % (range 13.4–100). The most frequent primary tumors were renal cell carcinoma, breast cancer, non-small cell lung cancer (NSCLC), and prostate cancer with 1064, 950, 865 and 553 cases, respectively.

Metastasis characteristics

In those reports with sufficient details, 48 % (range 26.5–92.5) of the metastases were osteolytic, and a median of 2.1 % were categorized as unstable (range 0–56). Pre-existing fractures were reported in a median of 19.8 % (range 0–63) of the patients, and the median proportion of patients with metastatic spinal cord compression was 8.7 % (range 0–100). Notably, 15 % (range 0–42) of the patients had previously undergone surgical stabilization or instrumentation before SBRT delivery. The Spinal Instability Neoplastic Score (SINS) was utilized in 22 studies, whereas the Bilsky Scale was employed in 19 studies to assess spinal stability prior to SBRT.

SBRT characteristics

SBRT delivery techniques varied across the studies, with volumetric modulated arc therapy (VMAT), intensity modulated radiation therapy (IMRT), CyberKnife and TomoTherapy used in 29, 24, 12 and 2 studies, respectively. In 79.7 % of all studies, the use of image-guided radiation therapy (IGRT) was mentioned, particularly cone beam computed tomography (CBCT) in 72.7 % of cases, ExacTrac in 21.8 %, and kilo voltage (kV) imaging in 14.5 %. Rigid patient immobilization was reported in 56 studies. The median total dose administered was 24 Gy (range 14–36), delivered in a median of 2 fractions (range 1–5). The median of the median planning target volumes (PTV) was 38 cm^3 (range medians 10.06–123.8).

- PRIMARY OUTCOME: Efficacy

Pain characteristics

Of the 14 prospective studies, 8 reported on overall pain response and 5 studies on complete pain response after SBRT. Among the selected studies, a median proportion of 81.4 % (range 19–100) of patients reported pain prior to undergoing SBRT. BPI, VAS, NRS, and CTCAE were employed as the primary definitions and measurement tools for pain. A median initial pain score of 6 on the NRS scale (range 4–7) was reported. The pooled overall pain response rate following SBRT was 83.2 % (95 % confidence interval [CI]: 41–100, $I^2 = 93$ %). The pooled complete pain response was 36 % (95 % CI: 20 %-53, $I^2 = 100$ %, Fig. 2). Furthermore, the median duration until pain response was 3 months (range 0.5–11.5).

Local control and overall survival

A total of 6 of the prospective studies reported on local control of SBRT for spine metastases. The 1-year local control rate was 94 % (95 % CI: 86 %-99 %, $I^2 = 100$ %, Fig. 2), with the majority ranking between 85 and 90 %. There was considerable heterogeneity among studies for 1-year LC ($I^2 = 86$ %). Median follow-up ranged between 3 and 80 months. Actuarial 1-year OS ranged between 23 % and 100 %, whereas 2-year OS ranged between 23 % and 89.9 %. Median OS ranged between 4 and 75.7 months.

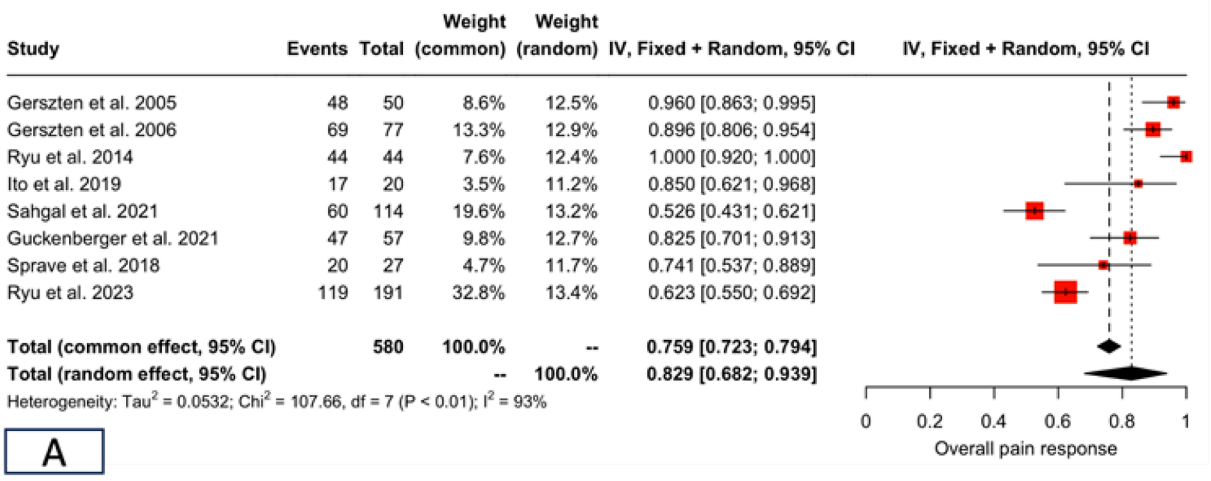
- SECONDARY OUTCOME: Safety

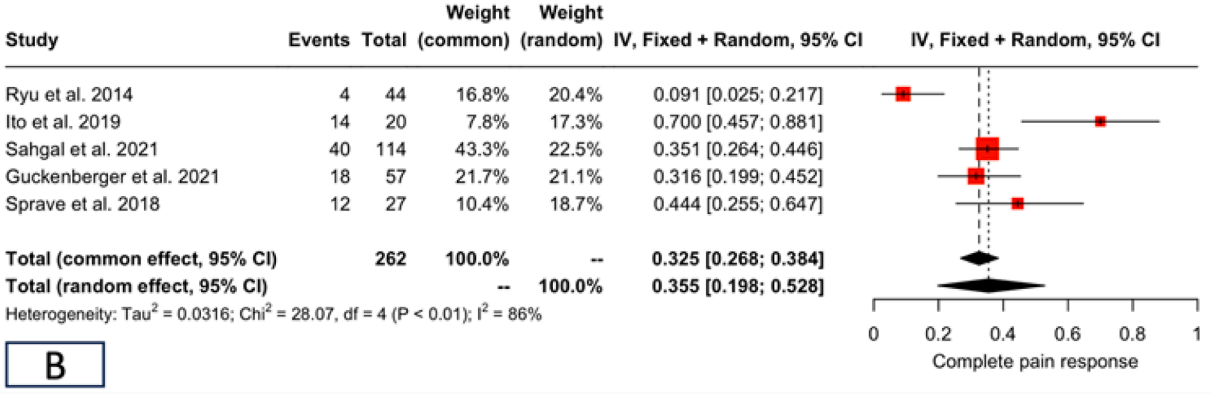
Toxicity

13 out of 14 prospective studies reported on post vertebral compression fractures. The pooled vertebral fracture rate was 9 % (95 % CI: 4 %-16 %, $I^2 = 100$ %, Fig. 2). Only 1.7 % of vertebral fractures required surgical stabilization. A total of 12 studies reported on radiation induced myelopathy. The pooled radiation induced myelopathy rate was 0 % (95 % CI 0–2 %, $I^2 = 100$ %, Fig. 3). Other toxicities of grade 3 or higher were reported in 13 studies (range 0–9 %). The pooled pain flare rate was 6 % (95 % CI: 3 %-17 %, $I^2 = 100$ %, Fig. 3).

In the subgroup analysis "One versus multiple fractions," no significant difference was observed in the comparison of 1-year LC, compression fracture rate, pain flare, pain response, and complete pain response, with p-values of 0.79, 0.69, 0.80, 0.58, and 0.51, respectively (Fig. 4).

Even though this sub-analysis could not show a significant difference in toxicity between single and fractionated irradiation, individual studies demonstrate high fracture rates with high-dose single irradiation [3,4].





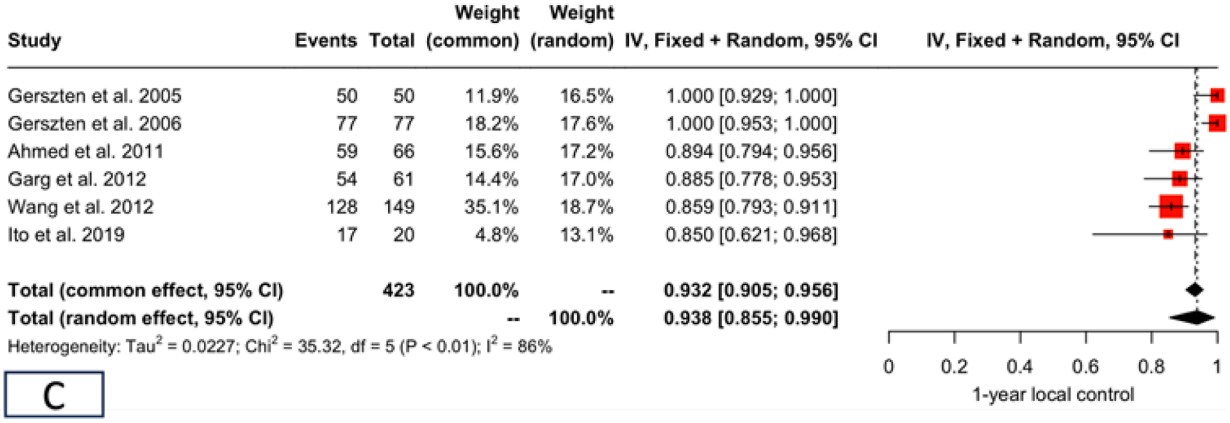


Fig. 2. Forest plot of primary endpoint parameters in prospective studies. A: Overall pain response, B: Complete pain response, C: 1-year local control.

Discussion

- **Pain Response**

Based on this systematic review, SBRT for vertebral metastases achieved high rates of pain response with a pooled overall response rate of 83 %, and a 36 % complete pain response rate. Of note, different scales for pain assessment have been employed. Additionally, pain flare after SBRT was infrequently observed, with a pooled incidence of 6 %. Pain response rates were not influenced by SBRT fractionation scheme,

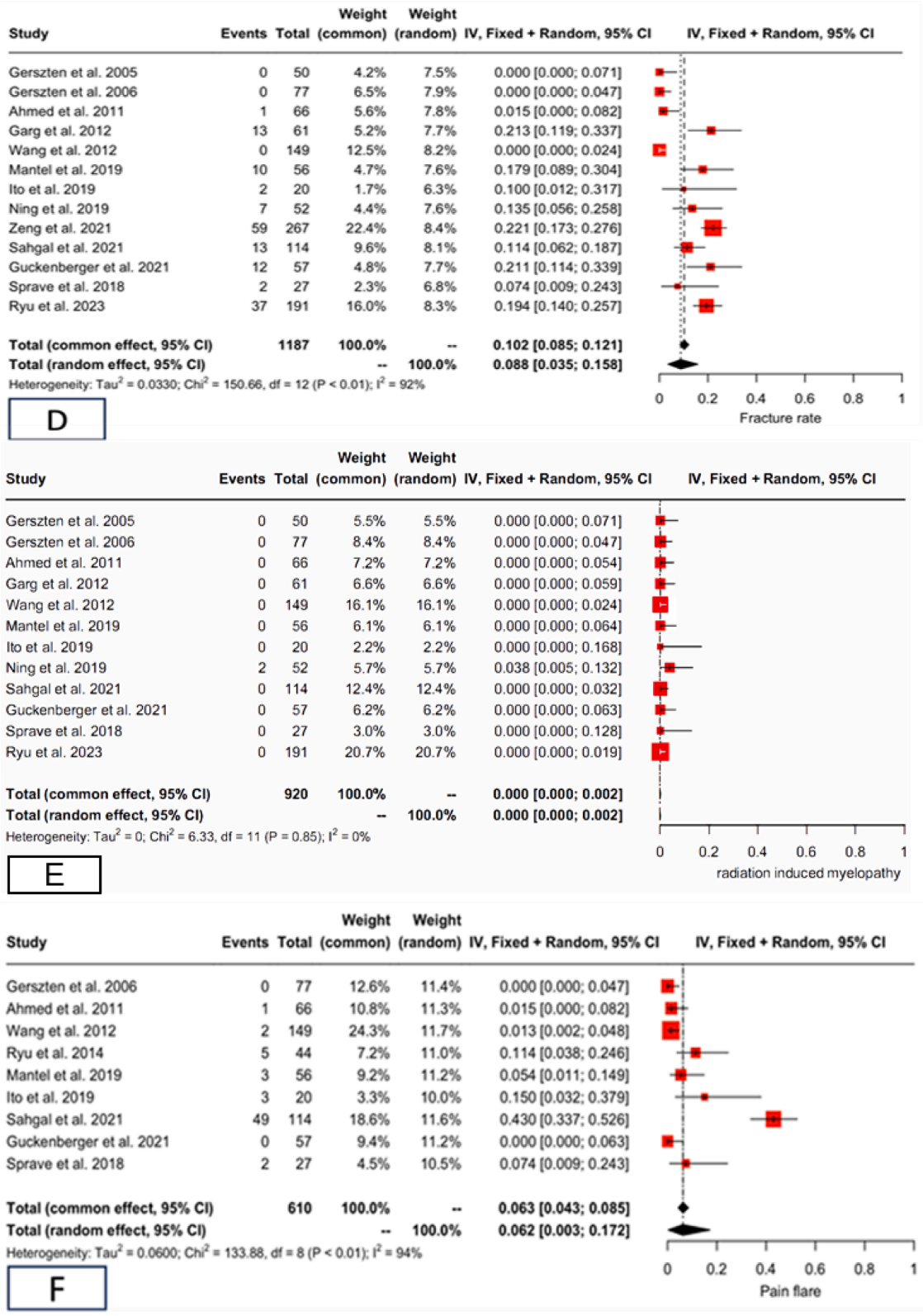


Fig. 3. Forest plots of secondary endpoints in prospective studies. D: Fracture rate, E: radiation induced myelopathy, F: Pain flare.

with no statistically significant differences between single fraction and multi-fraction regimens. These pain response rates appear favourable when compared to those observed after conventionally fractionated radiotherapy, where partial and complete pain response rates range between 14 and 62 % and 4–39 %, respectively [15,16].

Four randomized trials have been published reporting a comparison between SBRT and conventional radiotherapy for painful spinal metastases. In the study by Sahgal et al. (phase II/III) 229 patients were randomly assigned to 24 Gy/2 fractions vs 20 Gy/5 fractions with complete pain response at 3 months as primary endpoint. A statistically significant difference was observed in terms of complete pain response (35 % vs 14 %, p = 0.0002), and maintained at 6 months [5]. In

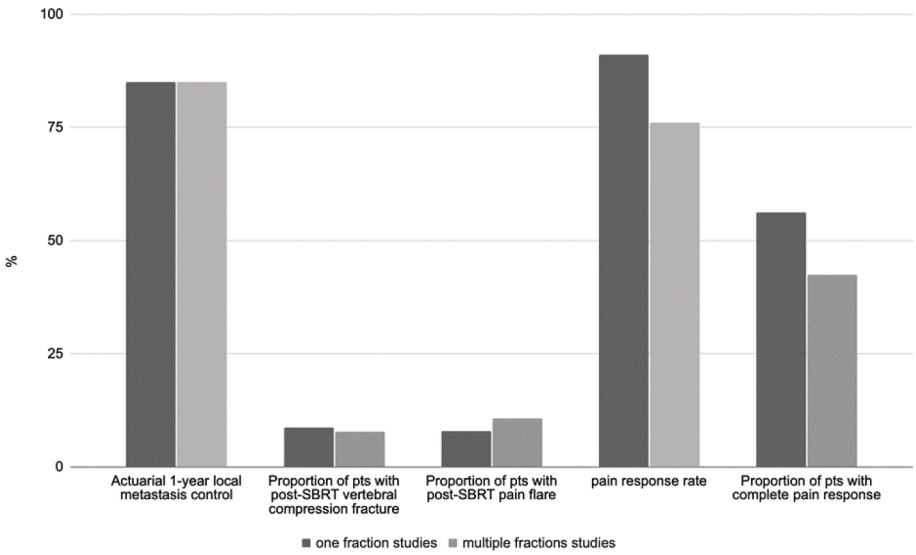


Fig. 4. Comparison of one versus multiple fractions. Pts = patients, SBRT = stereotactic body radiotherapy.

addition, a subsequent long-term analysis reported a significantly lower risk of local failure in the SBRT cohort with a consequent lower rate of re-irradiation [14]. Similarly, Sprave et al. (phase II, n = 55 patients) compared single-fraction (24 Gy) SBRT versus 3D-conformal conventional EBRT (10x3Gy), and found a non-significant difference in the primary end-point of complete pain response rate at 3-months (p = 0.057) that became significant at 6-months (p = 0.003) [6].

A phase II randomized trial at the University of Utrecht (n = 110) used the trial within a cohort methodology and compared various SBRT regimens with conventional radiotherapy including both spine and non-spine metastases. Similar outcomes in terms of overall pain response (40 % vs 32 %) were observed, but the inclusion of non-spine metastases makes it challenging to draw definitive conclusions.

Recently, Ryu et al. [9] published the outcomes of the RTOG 0631 randomized phase III trial, in which 339 patients were randomized 2:1 to single fraction SRS (16–18 Gy) vs conventional single fraction 8 Gy. No improvement in pain response was observed in the SRS cohort. The authors did observe an improvement in pain response after 12 months in the SBRT arm compared to the standard in which pain response plateaued, although with no statistically significant differences.

The ROBOMET trial, a randomized phase 3 trial for painful spine and non-spine metastases (8 Gy/1fx 3DCRT vs 20 Gy/1fx SBRT) reported no statistically significant differences in terms of 1-month complete pain response (37 % vs 33 %, p = 0.25), the primary endpoint of the trail. However, in a per-protocol analysis, SBRT outperformed conventional treatment in terms of complete pain response at 3 months (54 % vs 31 %, p = 0.048), with no significant differences in terms of toxicity incidence. Notably, spine metastases were a small proportion of the entire population of the trial, representing of the 28 % of the sample. The study is currently available in abstract version, only.

Globally, despite the heterogeneity of the data derived from these randomized studies, SBRT resulted in improved long-term pain control and it could be reasonably recommended for appropriately selected patients with longer life expectancy.

- **Oligometastatic Disease and Clinical Outcomes**

For some patients with oligometastatic disease, SBRT may represent a potentially curative therapeutic option while in others (e.g. with oligoprogression) it may be a helpful tool with which to postpone the start of, or the switch to, a new systemic agent. From the collected evidence, a median total dose of 24 Gy was delivered in a median of 2 fractions resulting in a pooled 1- year LC rate of 94 %. Notably, the majority of the studies included different primary histologies making it difficult to draw definitive conclusions on the radiosensitivity, as several studies have highlighted the need for higher doses in patients with radio-resistant histologies and for whom dose-escalation may lead to improved rates of LC [15,16]. Nonetheless, favorable LC rates are reported with SBRT doses lower than the "ablative" cut-off of BED_{10} = 100 Gy commonly applied to pulmonary or liver metastases [17–19]. While a multi-fraction regimen was the preferred approach in 53/69 studies, the optimal dose and fractionation schedule remains uncertain.

The impact of spine SBRT on overall survival could not be assessed due to the relatively short follow-up.

- **Adverse Events**

Vertebral compression fracture (VCF)

Our literature review found that only a small proportion of patients developed post-SBRT VCF (8,8%), with a very limited need for surgical decompression and/or stabilization (1,7%).

When compared to conventional radiotherapy, SBRT does not appear to increase the risk of VCF as reported from both the studies by Sprave et al. and Sahgal et al., in which no statistical differences between standard and experimental cohorts were recorded. This is in agreement with the results of our systematic review, where a very limited number of cases (about 1.7 %) required surgical stabilization. Of note, long-term results of the SC 24 trial, besides reporting a higher LC with reduced re-irradiation rates in the SBRT arm, recorded a higher incidence of VCF compared to the conventional EBRT although not reaching a statistical significance (p = 0.87). Notably, all the VCF occurred in the conventional arm were managed conservatively, while 3 out of 8 in the SBRT arm required surgical stabilization.

Among the risk factors potentially related to a higher probability of VCF, the impact of fractionation remains debatable. Although higher rates of VCF were observed in studies with single-fraction SBRT, no statistically significant differences with multi-fraction SBRT studies were observed in this systematic review. Several other risk factors have

been identified associated with a higher incidence of VCF such as osteolytic metastases, baseline fracture, mal-alignment, female sex, and older age, however, no conclusive correlations were observed [20,21].

Other toxicity

Radiation induced myelopathy is a very rare adverse event following spine SBRT. Total dose, dose per fraction and re-irradiation are traditionally considered as risk factors for this adverse event and recent modelling analyses by the Hypofractionation Treatment Effects in the Clinic report (HyTEC, [22]) provided safe dose constraints for spinal cord for de novo spine SBRT. The occurrence of SBRT-induced myelopathy was recorded in only 4 of the studies included in the present systematic review. The low incidence of this event reinforces the safety profile of spine SBRT, and highlights the need for further research in order to investigate the potential impact of concurrent systemic therapies.

Nerve root damage was also recorded in very few studies. Also for this peculiar adverse event, most of the evidence for SBRT dose tolerance are derived from brachial plexus limits for lung SBRT [23]. In general, further efforts are needed to provide recommendations for dose constraints for brachial and lumbosacral plexus based on robust dose-complication models. Also, the diagnosis and management of nerve root damage remains a matter of debate, especially in light of the characteristically irreversible clinical course.

Other grade 3 (G3) or higher adverse events are rarely reported in our review. Globally collected evidence highlights SBRT as a safe treatment with a very low incidence of severe adverse events.

- Heterogeneity

In all forest plots, with the exception of radiation induced myelopathy with $I^2 = 0$ %, the I^2 result shows heterogeneity (Fig. 2 and Fig. 3). This can be explained by the limitations, such as the different histologies, the use of radiosurgery and fractionated radiotherapy, and the rapid advancement of SBRT technologies in the recent years.

Limitations

This systematic review was limited by several factors. There was incomplete reporting with a lack of data points in many of the studies. Most studies included different histologies and both oligo- and polymetastatic patients were examined, resulting in heterogeneous study cohorts. Finally, a long time period of time from 2005 to 2021 was investigated and one additional study was included in 2023 - the technique and experience with stereotactic surgery in this period differs considerably and can, therefore, also have a significant impact on the outcome and tolerability of stereotactic radiotherapy.

Conclusion

The currently available data including 5 randomized trials of SBRT for spine metastases confirm that spine SBRT is an effective therapy for relieving pain with a low rate of reirradiation, and a favorable toxicity effect profile. Spine SBRT offers long-term local control, which is particularly relevant to oligometastatic patients. Centers looking to perform spine SBRT should acquire the necessary skills and knowledge, participate in various courses and the recently published guidelines including from ESTRO may provide guidance.

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

Table 1

Table 1: Overview of randomized trials. The ROBOMET study was presented on ESTRO 2023, but not included in the analysis, because only fully published studies were included. VCF = vertebral compression fracture, SBRT = stereotactic body radiotherapy, CRT = conventional radiotherapy, vs. = versus, mo = months, min = minimum, Gy = Gray. ITT = intention-to-treat.

Study parameter	CCTG SC.24/TROG 17.06	NRG / ROTG 0631	University Medical Center Utrecht	University of Heidelberg	ROBOMET(13)
Reference	https://doi.org/10.1016/S1470-2045(21)00196–0	https://doi.org/10.1001/jamaoncol.2023.0356	https://doi.org/10.1016/j.ijrobp.2020.11.060	https://doi.org/10.1016/j.radonc.2018.04.030	Abstract ESTRO 2023
Study type	Randomised, controlled, phase 2/3 trial	Randomized phase III trial	Phase 2 Randomized controlled trial within a prospective cohort	Randomized explorative phase II trial	Randomised phase III trial
Number of patients	229	339	110	55	126
Randomization	24 Gy in 2Fx vs 20 Gy in 5Fx	16 Gy / 18 Gy in 1Fx vs 8 Gy in 1Fx	1x18 Gy, 3x10 Gy or 5x7 Gy vs 1x8 Gy, 5x4 Gy or 10x3 Gy	24 Gy in 1Fx Vs 30 Gy in 10Fx	8 Gy in 1Fx Vs 20 Gy in 1Fx
Endpoint	Complete pain response @ 3 mo	Pain response @ 3 mo (min 3 points)	Pain response @ 3 mo (min 2 points)	Pain response @ 3 mo (min 3 points)	Complete pain response @ 1 mo
Major inclusion criteria	- Spinal metastases only - Pain (worst pain score of ≥ 2 of 10) - No more than 3 consecutive spinal segments	- Spinal metastases only – 1–3 separate sites - Each site involving max 2 contiguous segments - Epidural lesions at least a 3 mm gap from the spinal cord - Baseline pain score of at least 5	- Bone metastases and spinal metastases - No more than 2 painful lesions - No compression of spinal cord/cauda equina - No or mild neurologic signs - Pain score ≥ 3	- Spinal metastases only - Max. of two irradiated vertebral bodies per region - Max. of two different vertebral regions - Tumor distance > 3 mm to the spinal cord	- Painful bone metastases with min 2/10 pain score - Max. 3 painful locations
Major exclusion criteria	- Excluding seminoma and small-cell lung cancer	- Vertebral compression fractures with more than 50 % height loss and/	- Highly radiosensitive tumor (eg, lymphoma)	- Previous RT to the given irradiation sit	- Prior radiotherapy - Complicated bone

(*continued on next page*)

Table 1 (*continued*)

Study parameter	CCTG SC.24/TROG 17.06	NRG / ROTG 0631	University Medical Center Utrecht	University of Heidelberg	ROBOMET(13)
	- SINS > 12 - Prior RT, surgery - Neurological deficits	or bony retropulsion - Systemic or visceral metastases or uncontrolled primary tumors were excluded when the estimated survival time was longer than 6 months	- Lesions too large for SBRT (eg, >10 cm) - Previous CRT or SBRT on the same level - Need for surgical stabilization severe, worsening, or progressive neurologic deficits	- Multiple myeloma or lymphoma histology - Involvement of the cervical spine	metastases - Impending or existing fracture - Impending or existing spinal cord compression
VCF **SBRT vs. CRT**	11 % vs. 17 % (p = NR)	19.5 % vs. 21.6 % (p = 0.59)	No data available	New fractures in SBRT arm: 8.7 % @ 3mo 27.8 % @ 6mo	2 % vs 2 %
Complete pain response **SBRT vs. CRT**	35 % vs 14 % @3Mo **(p = 0.0002)** **32 %** **Vs** **16 % @6Mo (p = 0.0036)**	–	52.6 % Vs 10 % @ 6Mo (p = 0.002)	43.5 % vs. 17.4 % (52.6 % vs 10 % @ 6Mo (p = 0.003))	37 % vs 25 % (ITT analysis) (54 % vs 31 % @ 3 mo in pp analysis (p = 0.048))
Pain response **SBRT vs. CRT**	53 % vs. 39 % (p = NR)	41.3 % vs 60.5 % @3Mo (p = 0.01)	40 % vs 32 % @3Mo(p = 0.12)	69.6 % vs 47.8 % (73.3 % vs 35 % @ 6Mo (p = 0.02))	–
Pain reduction **SBRT vs. CRT**		−2.98 vs. −3.83	−2.9 vs. −2.5	−22.4 Vs −20.3	–

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