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Systematic Review

Single versus multifraction radiotherapy for spinal cord compression: A systematic review and meta-analysis

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ABSTRACT

Background: While multifraction radiotherapy (RT) regimens (MFRT) have been considered the standard of care in patients with metastatic epidural spinal cord compression (MESCC) with limited prognosis, recent randomized evidence has demonstrated that single fraction RT (SFRT) may be equivalent in terms of functional and overall outcomes. A systematic review and meta-analysis was conducted to determine the effects of SFRT compared to short course MFRT in patients with MESCC.

Methods: A search of OVID, EMBASE, and the Cochrane Central Register of Controlled Trials from inception to February 2018 was conducted. Randomized and prospective non-randomized trials comparing SFRT and short course MFRT for MESCC were included. Data were analyzed using a random effects model, and relative risks (RR) or hazard ratios (HR) were reported with corresponding 95% confidence intervals (CI). Quality of evidence was assessed using the GRADE criteria.

Results: Overall 1717 articles were reviewed. Three randomized trials were eligible for inclusion (n = 712 patients). The pooled treatment effect for SFRT versus MFRT with respect to motor response was RR = 0.96 (95% CI = 0.86–1.07, I^2 = 19%), HR = 1.00 (95% CI = 0.88–1.13, I^2 = 0%) for OS, and RR = 0.97, (95% CI = 0.85–1.11, I^2 = 61%) for bladder function. There was insufficient data to perform a meta-analysis on quality of life, toxicity or pain response, however available information suggests pain response appears similar between SFRT and MFRT. Overall quality of evidence was deemed moderate due to risk of bias.

There was no evidence of an observed difference with respect to motor response, bladder dysfunction and OS between SFRT and MFRT for MESCC in patients with a limited prognosis.

Metastatic extradural spinal cord compression (MESCC) is a devastating complication of advanced malignancy. It may cause a significant deterioration in overall physical function and quality of life (QOL). Published guidelines define MESCC as "compression of the dural sac and its contents (spinal cord and/or cauda equina) by an extradural tumour mass", with at least "indentation of the theca at the level of clinical features" required for diagnosis [1,2]. MESCC may therefore, be subclinical, or be accompanied by neurologic symptoms including pain, numbness, weakness, and loss of bowel and bladder sphincter control.

Patients presenting with MESCC are treated on an urgent or emergent basis, and the goal of therapy is to prevent paralysis, maintain or improve functional and ambulatory status, and relieve symptoms. In patients who have operable MESCC, randomized data supports the use of surgical decompression in select patients, followed by post-operative radiotherapy (RT) to control residual tumor [3]. Only about 10–15% of patients, however, are surgical candidates; most patients typically present with uncontrolled systemic disease, poor performance status, multiple comorbidities, and/or multi-level vertebral metastases, with limited motor function and ambulatory capacity [4]. These patients are treated with RT alone [4–6]. Given the poor prognosis of these patients, it is essential to balance provision of adequate RT dose to control tumors, along with patient convenience and treatment tolerability.

There has been significant investigation into comparing "long" (ten or more fractions) versus "short" (five fractions) course RT, with no observed difference in outcomes of motor response or survival [4–6]. A 2015 systematic review confirmed these findings, indicating no difference exists in ambulatory rates, motor function, or re-treatment rates [7]. Five fractions, however, may still

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consume significant time and resources for the patient, family, and health care system.

Consequently, the concept of limiting MESCC treatment to a single fraction of RT (SFRT) has been recently considered. Theoretically, SFRT has a lower biologically equivalent dose (BED), which may compromise extent and durability of tumor response. Retrospective studies have compared SFRT to multifraction (MFRT) regimens, and found that ambulatory rates and motor function were similar between 8 Gy in 1 fraction and 20 Gy in 5 fractions [5,8]. Randomized controlled trials (RCTs), including an Italian trial [9], ICORG 05-03 [10,11] and SCORAD- III [12], have been recently conducted to assess SFRT versus MFRT in patients with guarded prognosis and found no difference between arms in outcomes.

Despite these results, there is still some reluctance to use SFRT for MESCC. A variable patient population at baseline with respect to both pre-treatment motor status and prognosis, subjective grading of motor and ambulatory function, and large losses to follow up [9–12] in previous studies have all likely contributed to this. Clinical equipoise still exists in practice as to whether SFRT and MFRT generate equivalent outcomes in terms of ambulation post-treatment, duration of motor response, symptom relief, toxicity, QOL, and survival. Given the association between post-RT ambulatory status and survival, it is essential to determine whether a difference exists in motor response between SFRT and MFRT [13,14].

A systematic review and meta-analysis of the available literature was conducted to determine whether patients with MESCC treated with SFRT in comparison with short course MFRT have similar outcomes.

Methods

We conducted a systematic review using the methodology described in the *Cochrane Handbook for Systematic Reviews* [15]. The review aimed to investigate whether differences exist in MESCC patients receiving SFRT versus short course MFRT in the following domains: (i) motor response (in both ambulatory and non-ambulatory groups at baseline), (ii) overall survival (OS), (iii) bladder sphincter function, (iv) pain control and quality of life and (v) treatment-related toxicity [16]. Randomized and non-randomized prospective studies assessing SFRT compared to MFRT for MESCC were included. While in practice multi-fraction regimens administered for MESCC may vary between oncologists, this meta-analysis focuses on short course multi fraction regimens (one week or less) for MFRT, as studies have suggested equivalence between short and long course in patients with limited prognosis [4–7]. Studies of patients older than 18 years of age, with radiologic [17] or clinical (paresis, weakness, numbness, pain or loss of bowel or bladder function) evidence of MESCC due to a metastatic cancer were included. Studies were excluded if patients had no baseline assessment of motor function, if patients received surgical decompression or stereotactic body radiation therapy (SBRT), or if patients were randomized at time of local recurrence of previously treated spinal cord compression (recurrent disease).

The search was conducted in OVID (Medline Epub ahead of print, in-process and other non-indexed citations, OVID Medline –R Daily and Ovid Medline R from 1946 to Present), EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) (inception to February 2018), (search strategy outlined in Appendix A). Additionally, a further search was conducted of the American Society for Clinical Oncology (ASCO) and American Society for Therapeutic Radiation Oncology (ASTRO) meeting databases (from January 2014- January 2018) for presentation abstracts, as well as the National Institute of Health, Radiotherapy Oncology Group (RTOG), and NRG databases for ongoing and unpublished trials. Relevant articles were reviewed for additional references as part of the grey literature search. Two authors (EKD, JS) independently screened titles and abstracts and reviewed full texts of relevant studies from those included studies. A third party (AS) was selected to resolve any discrepancies. The *Cochrane Risk of Bias* [15] tool was used to assess bias within included studies, and authors were contacted for additional study information when necessary.

Meta-analyses were performed using random-effects models, with the Mantel-Hansel approach for binary outcomes and the inverse variance method for overall survival. The pooled treatment effect for motor response, bladder function and ambulation was estimated using relative risk (RR) reduction with corresponding 95% confidence intervals (CI), given that the expected rates of these outcomes are not well characterized post-RT for MESCC, making it difficult to interpret absolute risk reductions. Motor function was defined on either a Tomita or a modified Tomita scale for ambulatory capacity [9–12], and assessed motor response as maintenance of ambulatory status (excluding patients in the lowest category) or improvement in ambulatory status. Bladder dysfunction was characterized by physician-defined bladder abnormality or need for catheterization.

For OS, the pooled treatment effect for overall survival was estimated using hazard ratios (HR) with corresponding 95% CIs. When individual study hazard ratios were not provided, the Kaplan-Meier survival curves presented by authors in manuscripts [9] or presentations [12] were digitized using *GetData Graph Digitizer* (Cologne, Germany) [19] to extract individual patient data from the curves. The survival probabilities at a given time were then entered into *Tierney Trials 2007 Software* (London, United Kingdom) [20] to obtain an estimate of the HR and standard error.

Heterogeneity between studies was assessed by I^2 values. If the I^2 value was greater than 60% heterogeneity was determined to be substantial, between 40% and 60% deemed moderate, and if less than 40% designated as might not be important as per the *Cochrane Handbook of Systematic Reviews* [21]. Sensitivity analysis was also performed excluding studies with a high risk of bias to resolve any impact of bias on meta-analysis results. All statistical analyses were conducted in *Review Manager 5.3* using random effects models (Copenhagen, Denmark) [18].

We used the GRADE approach [15] to assess the quality of the evidence synthesized related to each outcome, and a summary of findings table was created in *GradePro software* (Hamilton, Canada) [22].

Results

Search results

The search was conducted in February 2018, and included all years from inception in EMBASE, MEDLINE and CENTRAL databases. We screened a total of 1717 articles (once duplicates were removed), including resources from EMBASE (507), MEDLINE (916), and CENTRAL (386) as well as grey literature databases (NIH (64), NRG (4), RTOG (9), ASCO (12) and ASTRO (12)). The sensitivity of the search strategy was validated by the return of the three known trials in MESCC comparing SFRT to MFRT, in the search results. Fifty-six (56) full texts were reviewed with two studies meeting inclusion criteria. Both of these studies were RCTs, one with final full text publication [9] and a second with final data accessed from a presentation (ASTRO 2014 Annual Meeting) as well as a full text publication reporting on QOL and pain outcomes [10,11]. One additional RCT abstract from the grey literature search met criteria, with data accessed from a presentation (ASCO 2017 annual meeting) [12]. Three RCTs were therefore included overall (see PRISMA diagram in Fig. 1). There were no prospective non-randomized trials that met inclusion criteria. Of the 54 excluded full text articles, relevant studies and reasons for exclusion are presented in the table of characteristics of excluded studies (Table 1).

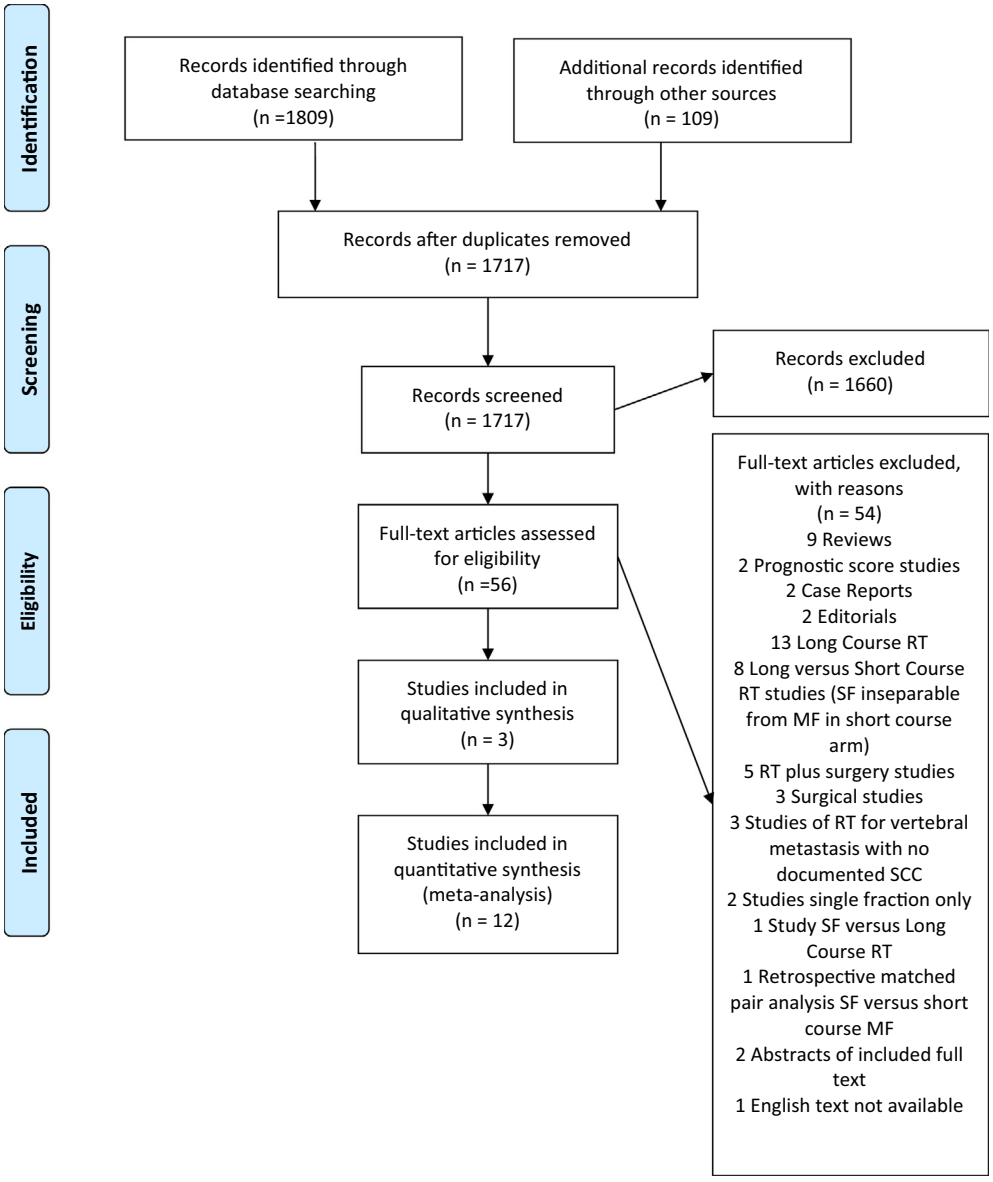


Fig. 1. PRISMA diagram of search results.

Table 1
Characteristics of excluded studies.

Study	Reason for exclusion	Reason for exclusion
Rades 2005 [5]	Retrospective review of short and long course RT regimens for SCC (1, 5, 10, 15, 20 fractions)	Retrospective nature may induce bias into fractionation decision Baseline motor function not documented
Rades 2015 [8]	Retrospective matched-pair analysis of SCC patients treated with 20 Gy/5 and 8 Gy/1 fraction from multi-center database	Retrospective nature may induce bias into RT regimen decision. Questionable documentation of baseline motor function and response in large multi-centre database
Giraldo 2017 [23]	Prospective evaluation of patients treated with 8 Gy for SCC	No comparison arm
Nguyen 2011 [24]	Prospective study comparing 8 Gy/1 (51%) versus 20 Gy/5 fractions (45%) for painful spinal metastasis	No radiologic or clinical assessment for SCC at baseline. Unknown how many patients had SCC versus vertebral metastasis only
Bone Pain Trial Working Party 1999 [25]	RCT of 8 Gy/1 versus 20/5 or 30 Gy/10 for comparison of pain control in skeletal metastasis	Predominantly non-spine skeletal metastasis. Baseline motor function and motor response not documented
Zaikova 2011 [26]	Retrospectively analysis of 58 patients undergoing surgery, 141 patients undergoing single fraction radiotherapy and 704 undergoing multiple fraction radiotherapy	Baseline motor function was not reported separately for patients in SF and MF groups. Retrospective nature may induce bias into RT regimen decision
Rades, 2011 [28]	Prospective study comparing long course (10 or more fractions) with short course (20 Gy/5 or 8 Gy/1 fraction) radiotherapy in SCC patients	Individual baseline and outcome motor function data were not provided separately for patients treated with 8 Gy/1

Table 2
Characteristics of Included studies.

	Maranzano 2009 [9]	ICORG 05-03 (Lee, 2018, Thirion 2014 [10,11])	SCORAD-III (Hoskin) 2017 [12]
Method	Prospective 1:1 Randomization of individual participants (n = 303) with SCC from multiple centres	Prospective 1:1 Randomization of individual participants (n = 116) with SCC from 5 radiotherapy centers; technique unknown but presumed central	Prospective 1:1 Randomization of individual participants (n = 694) with SCC from 47 radiotherapy centers; technique unknown but presumed central
Participants	Median age 67 Percent male: 65% Karnosky performance status 50-7: 60% Histology favourable (breast, prostate, small cell lung, hematology, seminoma): 30%	Median age 68.7 Percent male: 64% Proportion prostate cancer 24%, breast cancer 20%, Lung cancer 19%, other 63%	Median age 70 years Percent male: 73.5% Proportion prostate cancer 44%, breast cancer 11%, Lung cancer 17.5%, other 26.5% Performance status ECOG 0–2: 2.5%
Proportion ambulatory at baseline	65% ambulatory, 28% ambulatory with aid, 35% non-ambulatory	41.7% ambulatory, 25.3% ambulatory with aid, 33% non-ambulatory	66% (with or without walker)
Inclusion/exclusion	Inclusion: Diagnosis of malignancy, diagnostic MRI or CT confirming spinal cord compression, deemed inoperable or unsuitable for surgical intervention and without posterior bony protrusion into canal, life expectancy shorter than 6 months Exclusion Criteria: not meeting inclusion criteria	Inclusion: Histologically confirmed malignancy excluding hematologic malignancy or primary glioma, diagnostic MRI confirming spinal cord compression, deemed inoperable or unsuitable for surgical intervention, Karnosky Performance Status 30–100% Exclusion Criteria: Single site of bony metastasis with controlled primary site, prior radiotherapy to involved area of spine such that further radiotherapy would exceed cord tolerance	Inclusion criteria: histologic or cytologic confirmed malignancy, diagnosis of spinal cord compression, single field of RT can be used to treat SCC, life expectancy of at least 8 weeks Exclusion: surgical candidate or chemotherapy more appropriate, previous RT in field, prophylactic treatment in absence of gross disease, hematologic malignancy or primary glioma
Intervention	8 Gy/1 vs 16 Gy/2	10 Gy/1 vs 20 Gy/5	8 Gy/1 vs 20 Gy/5
Outcome	i) motor response (Tomita scale, ‘‘Ambulating without aid”, ‘‘Ambulating with aid” or ‘‘non-ambulating” or ‘‘paralyzed”), ii) bladder/bowel function, iii) survival and iv) pain response (requirement of pain medication) assessed	i) motor response (in-house modified Tomita scale, ‘‘Ambulating without aid”, ‘‘Ambulating with aid” or ‘‘bedbound”), ii) bladder/bowel function, iii) survival, iv) quality of life (EORTC QLQ-30) and v) pain (visual analog scale) assessed at 1, 5 weeks, and every 3 months thereafter	i) motor response (ambulatory status (AS) scale compatible with Tomita scale, with AS 1–2 ‘‘Walking without (1) or with (1) walker” versus AS 3–4 ‘‘non-ambulatory (3) or paralyzed (4)”, ii) bladder/bowel function, iii) overall survival, iv) adverse events, v) quality of life assessed at 4, 8, 12 weeks
Notes	Almost all patients evaluable at unspecified time point for motor response (however median duration of improvement reported) 16 mg dexamethasone given daily from day 1 until completion of treatment	76 patients evaluable (38 in SF and 38 in MF arm) at time of assessment at 5 weeks Distribution of patients between MF and SF arm respectively were ambulatory 47.4% and 57.9%, ambulatory with aid 28.9% and 15.8%, 23.7% and 26.3% non-ambulatory	340 patients evaluable (n = 176 in MF arm, n = 164 in SF arm) for primary assessment at 8 weeks
Risk of Bias	Judgement and support		
Random sequence generation (selection bias)	*Low risk*- Technique for sequencing of randomization was not stated, however given this was done centrally by a computer system and there are no differences at baseline between groups likely low risk	*Unclear risk*- technique for sequencing of randomization was not stated, but was centralized. Difference in baseline characteristics between groups in baseline ambulation rate, and differences in deaths between groups prior to first assessment, indicating small concern for bias (may also be due to small number of patients in each group)	*Probably Low risk*- Unclear risk, technique for sequencing of randomization was not stated, however baseline characteristics similar between groups so deemed low risk
Allocation concealment (selection bias)	*Low risk*- Patients were allocated by a centralized registration and investigators were inf	*Unclear risk*- method of allocation concealment was not stated, but was centralized. Difference in baseline characteristics between groups in baseline ambulation rate, and differences in deaths between groups prior to first assessment, indicating small concern for bias (may also be due to small number of patients in each group)	*Probably Low risk*- Unclear risk, method of allocation concealment not given, however baseline characteristics similar between groups so deemed low risk
Blinding of participants– (performance bias)	*High risk*- Patients not blinded to treatment due to ethical and resource concerns of sham radiotherapy. May affect performance in motor testing, patient reported outcomes and reporting of symptoms for adverse effects assessment	*High risk*- Patients not blinded to treatment due to ethical and resource concerns of sham radiotherapy. May affect performance in motor testing, patient reported outcomes and reporting of symptoms for adverse effects assessment	*High risk*- Patients not blinded to treatment due to ethical and resource concerns of sham radiotherapy. May affect performance in motor testing, patient reported outcomes and reporting of symptoms for adverse effects assessment
Blinding of outcome assessment – Subjective outcomes (detection bias)	*High risk*- Patients not blinded to treatment due to ethical and resource concerns of sham radiotherapy. May affect performance in motor testing, patient reported outcomes and reporting of symptoms for adverse effects assessment	*High risk*- Patients not blinded to treatment due to ethical and resource concerns of sham radiotherapy. May affect performance in motor testing, patient reported outcomes and reporting of symptoms for adverse effects assessment	*High risk*- Assessors not blinded to treatment. May affect assessment of subjective aspects of motor testing, adverse effects assessment
Blinding of outcome assessment – Objective outcomes (detection bias)	*Low risk*- Lack of blinding of assessors would not influence assessment of survival time	*Low risk*- Lack of blinding of assessors would not influence assessment of survival time	*Low risk*- lack of blinding of assessors would not influence assessment of survival time

Table 2 (*continued*)

	Maranzano 2009 [9]	ICORG 05-03 (Lee, 2018, Thirion 2014 [10,11])	SCORAD-III (Hoskin) 2017 [12]
Incomplete outcome data (attrition bias)	*Low risk* – Minimal loss to follow up (3 patients)	*Probably Low risk*- High losses to follow up, with losses balanced between arms (however more patients died (n = 20) in the SF group versus MF n = 10)	*Low risk*- High losses to follow up, however losses balanced between arms
Selective reporting (reporting bias)	*Probably Low Risk*-Motor response, bowel/ bladder, survival, pain response all reported Toxicity reported as a combination of total events for the group as well as between the two groups	*Probably Low Risk*-Includes data for motor response, bowel and bladder, quality of life, pain response. Survival reported only as "median survival of 4 months in both groups" thus far. Toxicity was reported as low overall without data for grade 1 and 2 events. "The reported overall toxicity (side effect rate) for the entire group of patients was low; there was one, Grade 3 acute side effect reported and two Grade 3 long-term side effects reported"	*Probably Low risk*- Motor response, bladder and bowel function, survival, toxicity and quality of life reported (final data not given in abstract)

Included studies

All three of the RCTs (Maranzano et al [9], ICORG 05-03 [10,11], and SCORAD-III [12]) included patients with MESCC who were not surgical candidates presenting with radiologic evidence of MESCC or cauda equina syndrome on MRI or CT scan). A summary of studies is found in Table 2. Maranzano et al included patients with a limited prognosis, specifically defined as less than 6 months life expectancy, as predicted by unfavourable histology or favourable histology with neurologic symptoms or low performance status [9]. SCORAD III included patients with 8 weeks or greater life expectancy, while ICORG05-03 did not specify a prognosis required to be included in the trial [10–12]. There were 327 patients included in Maranzano et al. [9], 112 in ICORG 05-03 [10,11] and 687 in SCORAD III [12], for a total of 1126 patients overall and 712 available for final assessment. All trials used conventional RT planning (field based or 3D conformal techniques). Dexamethasone, which is known to reduce neurologic symptoms of MESCC independently from radiotherapy (RT), was administered routinely in one study [9] at 16 mg daily, while the other two studies neither specified in their protocols nor reported on dexamethasone use. Overall, risk of bias appeared moderate (Figs. 2 and 3), with the main source of bias being related to blinding of patients and investigators.

In terms of SFRT and MFRT regimens, Maranzano et al. [9] compared a single 8 Gy fraction to 16 Gy in two fractions, ICORG 05-03 compared a single 10 Gy fraction to 20 Gy in five fractions [10,11] and SCORAD-III compared a single 8 Gy fraction to 20 Gy in five fractions [12]. Assuming an alpha/beta of 10 for tumour response, the MFRT arm of each study had an approximately equivalent BED, with 28.8 Gy using 16 Gy in two fractions [9] and 28 Gy using 20 Gy in 5 fractions [10–12]. These short course MFRT regimens were therefore considered roughly equivalent for the purpose of this analysis. In the SFRT arm of each study, the BED was 14.4 Gy for the 8 Gy regimen [9,12], and 20 Gy for the 10 Gy regimen [10,11]. Primary outcome assessments of motor and bladder func-

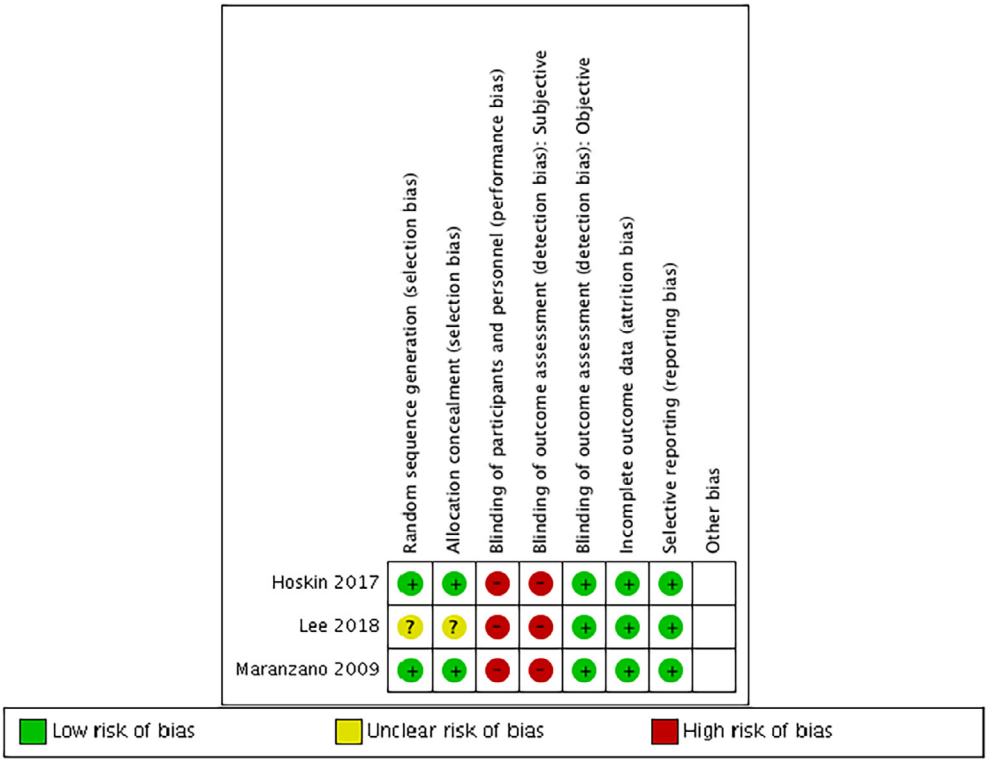


Fig. 2. Risk of bias of included RCTs by included study.

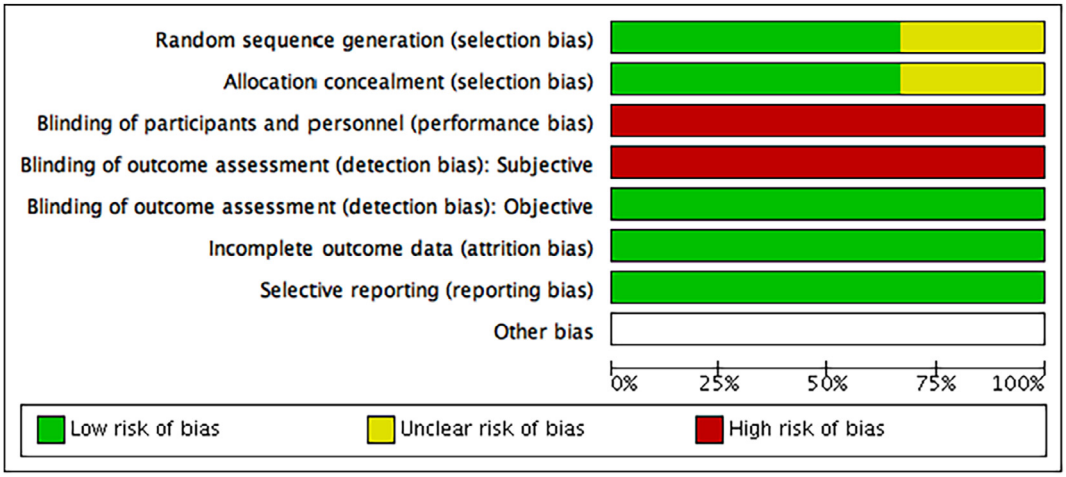


Fig. 3. Risk of bias of included RCTs by domain.

tion were reported as a mean duration of response in Maranzano et al. [9] and completed at 5 weeks in ICORG 05-03 [10,11] and at 8 weeks in SCORAD-III [12]. Pain [9–11] and quality of life [10–12] were assessed at the same time points in those studies, which included these outcomes. Summary of findings are presented for motor response, bladder dysfunction, survival and quality of life (QoL), and pain scores in Table 3.

Motor response

The pooled treatment effect across all 3 RCTs was RR = 0.96 (95% CI: 0.86–1.07) for motor response using the Tomita (or modified Tomita) scale with SFRT (n = 355) compared with MFRT (n = 364). A sensitivity analysis was conducted considering only those studies administering 8 Gy in 1 fraction for the SFRT arm (and therefore a larger BED difference between SFRT and MFRT), and the results were similar, RR = 0.93 (95% CI: 0.86–1.07) (n = 317 SFRT, n = 326 MFRT).

The effect of ambulatory status pre-treatment on motor response to SFRT or MFRT was assessed by sub-group analysis of two studies [9,12] for which individual patient data were available. In Maranzano et al., 65% of patients (SFRT n = 98 and MFRT n = 101), and in SCORAD III 66% of patients (SFRT n = 228 and MFRT n = 224) were ambulatory at baseline. For those patients who were ambulatory at baseline (including patients ambulating independently or with an aid), the RR was 0.96 (95% CI: 0.89–1.03) with SFRT versus MFRT in maintaining ability to ambulate. In the non-ambulatory group at baseline, RR for motor response was 0.74 (95% CI: 0.47–1.17) for SFRT versus MFRT.

Heterogeneity between studies was deemed not likely to be important for the assessment of motor response (I^2 of 19%). Overall, there was moderate quality evidence (due to risk of bias) for a preserved motor response in SFRT versus MFRT (Fig. 4a and b).

Bladder dysfunction

The risk of bladder dysfunction post-RT for SFRT (n = 355) versus MFRT (n = 364) was 0.97 (95% CI: 0.85–1.11). Subgroup analysis on post-RT bladder dysfunction based on bladder function prior to treatment could not be conducted, as individual patient data was only available for one study [12].

There was a substantial heterogeneity between the studies (I^2 of 61%), and few events (less than 300). Overall, there was low quality evidence (due to risk of bias and imprecision) to suggest bladder dysfunction is similar to slightly worse using SFRT versus MFRT (Fig. 4c).

Overall survival

Median survival was reported as 4 months for both groups in Maranzano et al (range 0–40 months, extrapolated from survival curves), 4 months for both groups in ICORG 05-03 (range not provided), and 12.4 weeks SFRT versus 13.7 weeks MFRT in SCORAD (minimum survival unknown- 204 weeks, extrapolated from survival curves).

Survival curves were provided for two of the trials [9,12]. Survival data could not be obtained from ICORG 05-03 [10,11]. After data extraction and construction of log hazard ratios, the pooled HR was 1.00 (95% CI: 0.88–1.13). (n = 498 SFRT, n = 492 MFRT). The risk of publication bias was deemed low, and there was no heterogeneity observed between the two studies (I^2 = 0%). Overall, from the available data, there was high quality evidence to suggest that survival rate is likely preserved in patients treated with SFRT versus MFRT (Fig. 4d).

Pain response

Pain response was reported in two of the studies (n = 188 SFRT and n = 185 MFRT total). Maranzano et al [9] reported percent of patients responding to radiotherapy in each group, determined by number of patients with de-escalation in pain medication requirement from major narcotics to minor narcotics, minor narcotics to analgesics, or analgesics to no pain medication, and reported an Odds Ratio = 1.04 (95% CI: 0.66–1.64) for SFRT versus MFRT. This suggests there was no clear difference in pain response between groups in Maranzano et al.

ICORG 05-03 [11] reported the median change in pain for the entire cohort by number on the visual analog scale as median decrease in 4.0–2.0 in the MFRT group versus 5.0–1.0 in the SFRT group. A formal analysis was not reported, and individual patient data on the number of responders could not be obtained from authors. Given the difference in method of pain reporting between the two studies and difficulty calculating a meaningful standardized mean difference, a meta-analysis was not conducted.

Quality of life

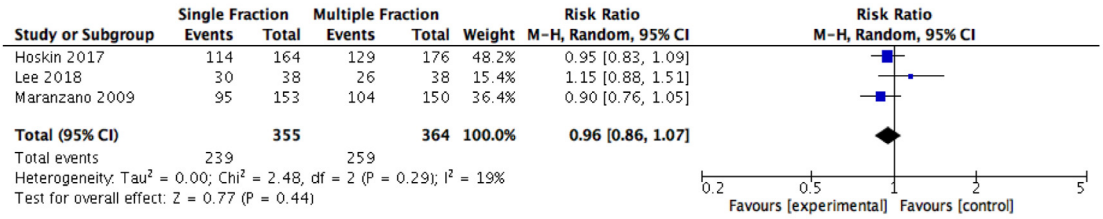
QOL data was measured in two of the studies using the EORTC-QLQ 30 [11,12]. ICORG 05-03 reported mean change from baseline in four domains [11] in a small number of patients (SFRT (n = 27) and MFRT (n = 24)) with average change in score presented for both arms. Improvement in summary scores from pre- to post-RT (excluding financial impact and global quality of life) was

Table 3
Summary of findings for SFRT compared to MFRT in patients with metastatic epidural spinal cord compression (MESCC).

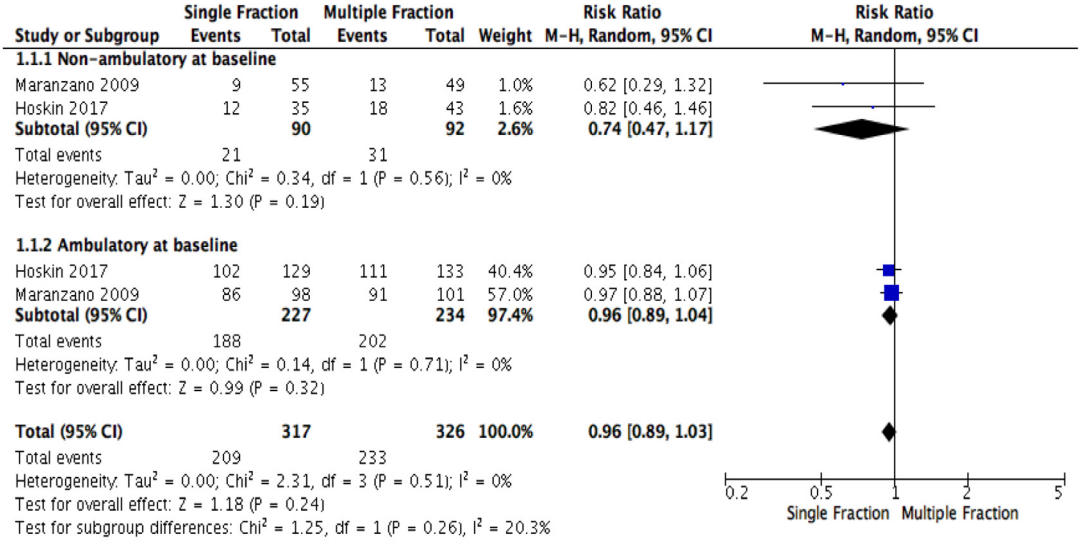
Outcome № of participants (studies)	Relative effect 95% CI)	Anticipated absolute effects (95% CI)		Difference	Certainty	What happens
Bladder Dysfunction Assessed: Patient or clinician reported, or requirement of catheterization № of participants: 696(3 RCTs)	**RR 0.97** (0.85–1.11)	79.6%	**77.2%** (67.7–88.4)	**2.4% fewer** (11.9 fewer to 8.8 more)	⊕⊕◯◯ LOW[a,b]	
Overall Survival Assessed: time in days from treatment follow up: median 4 months № of participants: 643 (2 RCTs)	**RR 1.00** (0.88–1.13)	100.0%	**100.0%** (88–100)	**0.0% fewer** (12 fewer to 13 more)	⊕⊕⊕⊕ HIGH	Median Survival: Maranzano 4 months in SFRT and MFRT, ICORG 0503 4 months in SFRT and MFRT, SCORAD 12.4 weeks SFRT vs 13.7 weeks MFRT (ranges not provided)
Motor Response Assessed: Tomita (modified) Scale (Ambulatory without aid, ambulatory with aid, non-ambulatory, paralyzed) follow up: range 1 days to 3 months № of participants: 719 (3 RCTs)	**RR 0.96** (0.86 to 1.07)	71.2%	**68.3%** (61.2 to 76.1)	**2.8% fewer** (10 fewer to 5 more)	⊕⊕⊕◯ MODERATE[a]	
Quality of Life **(QoL)** Assessed: EORTC QLQ-30 in ICORG 0503 up: median 5 weeks № of participants: 51 (1 RCT)	-			ICORG 0503 No difference between groups in QoL change when adjusted for baseline scores	⊕◯◯◯ VERY LOW[a,c]	Change in points Summary score: Increase 12.4 for SFRT versus 10.8 for MFRT (95% CI: 6.6–16.7) Physical functioning score: Decrease −3.3 for SFRT versus increase 8.1 for MFRT (95% CI: −6.5 to 10.6) Pain score: decrease −35.8 for SFRT versus −25.7 for MFRT (95% CI: −43.4 to −18.7) Global QoLscore: increase 9.0 for SFRT versus 2.2 for MFRT (95% CI: −3.2 to 14.0)
Pain Response Assessed: 1) Maranzano- (Discrete) Responder, Partial Responder, Non-responder 2) ICORG – (Continuous) Visual Analog Scale № of participants: 373 (2 RCTs)	Maranzano: OR = 1.04 (95% CI: 0.66–1.64) for SFRT versus MFRT ICORG: Median decrease on VAS of 5.0–1.0 in the SFRT versus 5.0–1.0 MFRT				⊕◯◯◯ VERY LOW[a,d]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio.
GRADE Working Group grades of evidence:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Explanations:
a. The risk of bias is deemed serious for subjective outcomes due to lack of blinding of both patients and assessors to treatment arm in all 3 trials. Which has the potential to affect both the performance of patients, as well as assessment of outcome by treating physician (for example, determination of whether patient is patient truly ambulatory without an aid). It is very difficult to blind patients in radiotherapy trials, as sham radiation is a costly use of resources and has ethical concerns (ie. required time for patients who already have difficulty with mobilization and not truly receiving the treatments). Other domains of risk of bias were deemed to be low, as while studies have significant loss to follow up patients were accounted for and arms were balanced, and allocation concealment and randomization were present in all 3 trials.
b. I2 test value is 61% suggesting heterogeneity may be a significant factor (possibly due to differences in definition of bladder dysfunction). Subgroup analysis was not possible with information provided. Confidence interval suggests less dysfunction with single fraction treatment but wide range still includes possibility of harm with single fraction.
c. Very small patient numbers in QoL assessment concerning for imprecision.
d. Pooled analysis is not possible due to variation in measurement methods (continuous vs discrete), difficult to make definitive conclusions. Small number of participants reported pain response in 1 trial.

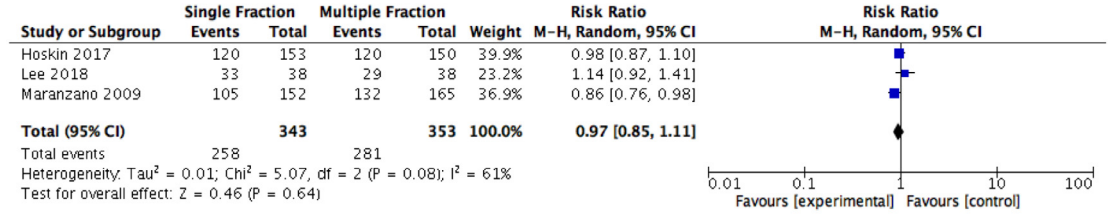
a.



b.



c.



d.

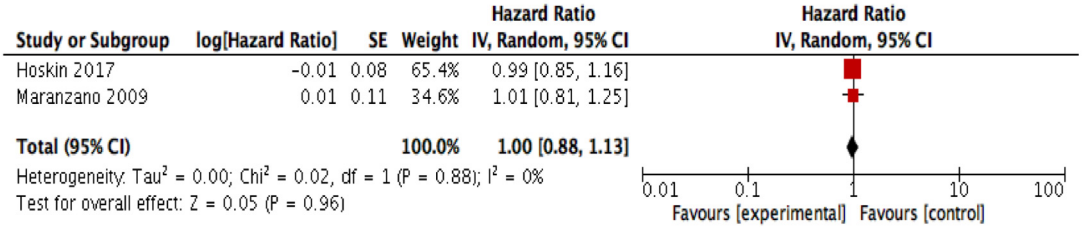


Fig. 4. Forest plot for each outcome assessed. A) Forest plot of motor response. B) Forest plot of ambulatory status post-treatment, analyzed by ambulatory status at baseline (ambulatory and non-ambulatory subgroups. C) Forest Plot for Risk of Bladder Dysfunction. D) Forest Plot of Overall Survival.

12.4 for SFRT versus 10.8 for MFRT with an absolute difference of 1.6 (95% CI: 6.6–16.7) favouring SFRT. Decrease or improvement physical functioning score was −3.3 for SFRT versus 8.1 for MFRT, with an absolute difference of 11.4 (95% CI: −6.5 to 10.6) in favour of MFRT. Improvement in pain signalled by a decrease in pain score was −35.8 for SFRT versus −25.7 for MFRT, with an absolute difference of 10.1 (95% CI: −43.4 to −18.7) in favour of SFRT. Improvement in global quality of life was 9.0 for SFRT versus 2.2 for MFRT, with an absolute difference of 6.8 (95% CI: −3.2 to 14.0) in favour of SFRT [11]. Confidence intervals for each score were wide, however, and after adjusting for pre-treatment pain scores, investigators reported no significant difference between groups. SCORAD-III likewise reported no significant difference in QoL scores between arms [12].

Toxicity

Reporting of toxicity was variable between studies. Maranzano et al. [9] reported toxicity for the entire study rather than by treatment arm, and ICORG 05-03 [10,11] reported "low" toxicity but did not report grade 1 and 2 events specifically, and divided the three grade 3 and 4 events that occurred by acute and late toxicity. Grade 1 and 2 toxicity was reported for diarrhea (14% vs 11%), fatigue (49% vs 55%) and skin erythema (12% vs 19%) in SCORAD-III [12] for SFRT and MFRT respectively, however grade 3 and 4 toxicity was reported as 20% in both groups. Therefore based on the available data, a meta-analysis was deemed to have minimal utility in providing meaningful information.

Discussion

Limiting RT for MESCC to one fraction has the potential to improve patient convenience and experience, improve access to RT (particularly in the setting of decreased mobility and strain on social resources), to expedite time to resuming systemic therapy and conserve resources for caregivers and the health care system. It also allows more readily for the opportunity to re-treat recurrent spinal cord compression if necessary. Due to limitations of the current available RCTs – in particular the large numbers of patients lost to follow up – it is difficult to draw definitive conclusions considering each study independently [9–12]. Only recently have RCTs investigated single versus multifraction treatment regimens, and this comparison has not been specifically addressed in a meta-analysis.

This review and meta-analysis has therefore addressed these disparities by pooling results from all known trials to assess outcomes in a larger number of patients. Overall, our results showed that there is no evidence of differences in motor response, bladder dysfunction or survival post-radiotherapy between SFRT and MFRT.

Considering the subgroup of patients who were ambulatory at baseline, maintenance of ambulation does not appear to differ between SFRT and MFRT. For the group of patients who were not ambulatory at baseline the result was less certain, with a confidence interval ranging from a large reduction in response to significant improvement in response. This is likely due to the small number of patients in this category, and therefore meaningful conclusions cannot be drawn for this group.

Risk of bladder dysfunction also did not appear to be different with use of SFRT or MFRT. There was significant heterogeneity observed between studies, which in part may be due to the variable definition of bladder dysfunction. Maranzano et al. [9] defined dysfunction as loss of sphincter control or catheterization, whereas in the other two studies the definition was not specified [10–12]. The quality of evidence for bladder dysfunction was deemed low due to risk of bias (due to lack of blinding), and concern for imprecision, yet these findings should be considered when determining appropriateness of SFRT versus MFRT.

There was no apparent effect in either direction for survival between SFRT and MFRT. While this important outcome appears to be preserved regardless of length of RT regimen, there is currently insufficient information on pain control, QOL and toxicity to induce definite conclusions between groups. Given the extremely poor prognosis in these patients, future studies should focus on QOL as a more relevant primary endpoint. This remains a challenge, however, given no validated measurement tool specific to QOL in MESCC patients currently exists, and we must rely on more general QOL assessment tools.

The three trials analyzed included patients with radiologic MESCC who were not candidates for surgery. Patients with any ambulatory status were eligible in each trial, and approximately two thirds of the patients in each trial were ambulatory at baseline. This may be an overestimate of motor capacity in the general MESCC population, which is not well defined. The significant losses to follow up in each trial also reaffirms the difficulties in accurately prognosticating patients with MESCC, and which patients may actually benefit from SFRT as compared to MFRT. However, with increased use of routine imaging for patients on systemic therapy, more patients may be identified at an early stage and present with ambulatory capacity intact in the future. This will be important and predicting post-treatment ambulatory rates and prognosis in future studies assessing RT doses in MESCC [13,14].

The majority of patients also had a limited prognosis. While only Maranzano et al. designated specific inclusion criteria of less than 6 months life expectancy, the patients in each study proved to have a very limited prognosis as demonstrated by the poor survival in both arms of each trial (approximately four months). Motor response assessment occurred at one to two months in these trials, and differences in the durability of response beyond that between the two regimens is unknown. Long term survival and symptom assessment is also unknown in this patient population. Therefore, these results cannot be directly applied in the case of patients who are expected to survive longer.

Ideally SFRT would be preferable for patient convenience, caregiver and health care system resources and to prevent delay in systemic therapy. The translation to effect on QOL with fewer treatments, however, is unknown. Only one study reported QOL data, and few patients completed questionnaires. Future studies of MESCC should incorporate QOL data robustly in order to capture the effect of RT fractionation regimens on other important domains which may be directly or indirectly associated with primary outcomes of motor and sphincter control.

While toxicity was not reported clearly between arms in two of the studies, there were no reports of patients not complying with the assigned treatment, or not completing RT. Both regimens tested in these studies were generally well tolerated with acceptable side effects, and patient adherence was not generally an issue [2,17].

The lack of difference in outcomes demonstrated between these regimens is consistent with retrospective reviews and a previous matched-pair analysis of SFRT versus MFRT for MESCC [5,8,23–26]. Although these results are reassuring in the uptake of SFRT, one must keep in mind the guarded prognosis of patients examined in these trials. Each study included patients with limited prognosis of a few months, and results therefore cannot be generalized to those patients with longer life expectancy who may require more durable control [13,14]. For example, Rades et al. have retrospectively reported higher local recurrences with both single and five fraction treatments for MESCC compared with long course radiotherapy regimens at up to 12 months [27]. Therefore, in patients with a more durable prognosis, for example 6–12 months

[27], dose escalation should be considered, potentially including the use of radiosurgery or stereotactic radiotherapy techniques [28]. Surgery must also be considered in patients with a favorable prognosis, as motor outcome and survival benefits have been demonstrated in this group [3].

Further studies would be valuable in investigating the impact of fractionation on durability of response, local recurrence, re-treatment, and QOL. As life expectancy improves with advances in oncology treatment, delineating the optimal management of MESCC will be of critical importance.

Despite the attempts of investigators of each study to perform well-conducted trials, overall the evidence was deemed moderate quality. Serious risk of bias for subjective outcomes resulted from a lack of ability to blind patients and outcome assessors to treatment arm. Sham radiotherapy is not generally allowed in RT trials, due to ethical concerns for patients and general health care resource burden. Therefore, a potential exists for preconceived ideas of treatment to impact patients' performance or judgment of assessors for subjective outcomes. While survival data may not have been affected by lack of blinding, the motor response, bladder function, pain response and QOL were all judged on scales with some aspect of subjectivity [29,30].

Maranzano et al. reported minimal losses to follow up, however it is not clear whether the trial only included those patients who survived until primary assessment, or assessed patients immediately post-treatment resulting in minimal losses [9]. Large losses to follow up, however, were detected in the ICORG 05-03 and SCORAD III trials [10–12]. While a lack of power due to small patient numbers in individual studies may be addressed by pooling data, these losses to follow up are concerning for potential bias in those patients assessed (i.e., better performers may have been available at or survived to the time of assessment). It is also reassuring that our sensitivity analysis which excluded ICORG 0503 results, the trial with the greatest losses to follow up (and also different size of SFRT BED), maintained the same results. Therefore while it is reassuring that losses to follow up were equal between arms in each study, this should still be kept in mind when considering SFRT versus MFRT as well as expected motor response rates in a group of MESCC patients.

While information on randomization and allocation concealment was not provided for the ICORG 05-03 study [10,11], one would assume risk of bias should be low owing to the central randomization process for this multicenter trial, however at baseline patients in the two groups who survived until assessment were different in ambulatory status, and unequal in the number of patients who died prior to the 5 week motor response assessment. Overall the losses to follow up were similar however, between arms, so attrition bias was not detected. It is thought the small differences in baseline status could be due to the small number of patients randomized in this study.

Overall, we acknowledge MESCC studies are difficult to conduct given the limitations of the population and challenges in blinding of radiotherapy regimens. We believe the data extracted is nonetheless extremely valuable and our results should be considered despite these biases when making treatment decisions.

There are nevertheless limitations of this meta-analysis, including the lack of fully published data for two of the RCTs. We attempted to minimize this bias through contacting investigators, and when unsuccessful using raw data from large conference presentations (ASTRO and ASCO annual meetings), trial registries, and abstracts. While fully published data is clearly preferable to allow detection of bias in individual studies, reviews of previous meta-analysis and surveys of authors have also indicated it is important to include unpublished data to minimize other forms of bias (i.e., publication bias) [31,32]. There are a very limited number of randomized studies in SFRT for MESCC, further emphasizing importance of considering all available data. If the final data is published at a later date, an updated meta-analysis could certainly be performed. In the interim the authors acknowledge that these results should be applied with caution given the lack of some fully published data.

Secondly, survival information was extrapolated from survival curves to allow a meta-analysis of data, which is less accurate than calculating hazard ratios from individual patient data. We feel this review provides important information regardless of this issue, and all possible steps were taken to minimize risk of bias within the review and clarify the certainty of evidence.

Finally, each of the RCTs focused on patients with a relatively poor prognosis, which must be considered when contemplating which regimen a patient should receive. Prognosis may be challenging to predict in MESCC patients, however, a number of factors have been suggested in the literature and should be referenced in this scenario. For example, Bollen et al. conducted a systematic review of studies in patients with spinal metastasis and found that performance status, primary tumor type, as well as American Society of Anesthesiology (ASA) status (a measure of physical fitness) were strongly associated with survival on multivariable analysis [33]. On the other hand, however, they also found strong evidence for no association of survival with age, number and location of spinal metastasis, and pathologic fracture. Systemic burden of disease, the availability of systemic therapies, and spinal stability should likewise be considered [34]. Once prognosis has been estimated, the appropriate treatment can be pursued, and the International Spine Oncology Consortium has developed an algorithm to assist with navigating treatment options for MESCC patients. For example, the algorithm may assist with decisions of which patients will benefit from standard external beam radiotherapy (EBRT) for MESCC (i.e., MFRT or SFRT), whether a more aggressive intervention such as surgery or radiosurgery should be implemented, or alternatively whether patients are too unwell to achieve benefit from even EBRT and best supportive care should be considered.

We acknowledge that despite the results of the recent trials and this meta-analysis, the uptake of SFRT for MESCC by radiation oncologists may be variable, in keeping with the cautious uptake of SFRT for painful bone metastasis despite several randomized studies demonstrating no detriment to pain control with de-escalation of dose [35,36]. For example, uptake may be affected by geographic location of training and practice, type of practice, membership affiliation, and other factors [35,36]. We anticipate that dissemination of knowledge through presentations, conferences and multidisciplinary collaboration will be critical in encouraging translation of the results of this meta-analysis to clinical practice.

In conclusion, the use of SFRT (8–10 Gy) most likely results in similar outcomes for motor response, bladder dysfunction and overall survival to MFRT, in the setting of MESCC in patients who are not surgical candidates and who have a limited prognosis. This is particularly reassuring in that SFRT can be considered a convenient and viable option in this patient group, where other factors such as performance status or geographic location, may make the use of MFRT undesirable. Firm conclusions cannot be drawn for SFRT versus MFRT in terms of pain control, QOL or toxicity due to incomplete data, and difficulty synthesizing data across studies. These questions should, however, be emphasized in future studies of MESCC moving forward. The results of this MA should also be applied with caution given the lack of fully published data in two of the trials. Furthermore, while the results of this meta-analysis indicate SFRT preserves response and survival for patients with limited prognosis, further research focusing on long-term outcomes and requirement of re-treatment is necessary before SFRT can be implemented safely in patients with a better prognosis.

Disclosures

There are no relevant conflicts of interest to disclose.

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All authors contributed to completion of this manuscript and have approved its submission.

Appendix A

Search strategy

OVID MEDLINE (Medline Epub ahead of print, in-process and other non-indexed citations, OVID Medline –R Daily and Ovid Medline R from 1946 to Present)
#1 "spinal cord compression/ or "(spinal adj1 cord adj1 compression).tw (12,811)
#2 "cauda equina/ (3150)
#3 "cauda equina.tw (4106)
#4 "exp spinal cord neoplasms/ (10,359)
#5 "(spine or spinal or vertebra or epidural) adj3 (compression or cancer or malignancy or metastasis or tumor or neoplasm).tw (20,627)
#6 "exp RADIOTHERAPY, CONFORMAL/ or exp RADIOTHERAPY PLANNING, COMPUTER ASSISTED/ or exp RADIOTHERAPY DOSAGE/ or exp RADIOTHERAPY, COMPUTER-ASSISTED/ (68,777)
#7 "(radiation or radiotherapy) adj3 (fraction or dose).tw (36,995)
#8 "exp animals/ not humans.sh (4,423,824)
#9 1–5 (39752)
#10 6 and 7 (97942)
#11 9 and 10 (925)
#12 11 not 8 (916)
EMBASE (OvidSp interface)
#1 "spinal cord compression/dm,rt,th [Disease Management, Radiotherapy, Therapy] (613)
#2 "spinal cord tumor/ or spinal cord cancer/ (8883)
#3 "exp cauda equina/" or cauda equina.tw (6147)
#4 spinal cord compression.tw (6819)
#5 "(spine or spinal or vertebra or epidural) adj3 (compression or cancer or malignancy or metastasis or tumor or neoplasm)" (14,093)
#6 "cancer radiotherapy/ (37,628)
#7 "(radiation or radiotherapy) adj3 (fraction or dose).tw (54,236)
#9 or/1–5 (26,966)
#10 or 6 and 7 (91,864)
#11 9 and 10 (507)
Cochrane Central Register of Controlled Trials (CENTRAL)
#1 MeSH term [spinal cord compression] explode all trees (117)
#2 MeSH term [cauda equine] (16)
#3 Spin* near (metastasis or neoplasm or vertebra* or malignancy or tumor) (48)
#4 1 or 2 or 3 (181)
#5 MeSH term [radiotherapy] explode selected trees [[radiotherapy dosage], explode selected trees radiotherapy dose fractionation] and [radiotherapy, computer-assisted] (1403)
#6 #4 and #5 (385) in Trials

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