National Institute for Health and Care Excellence

Draft for consultation

Metastatic spinal cord compression

[M] Radiotherapy

NICE guideline number tbc

Evidence reviews underpinning recommendations 1.1.21, 1.10.1 to 1.10.10 and research recommendation 1 in the NICE guideline

March 2023

Draft for consultation

These evidence reviews were developed by NICE

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Radiotherapy

Review question

How effective is radiotherapy, including both fractionated and unfractionated radiotherapy, for the management of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Introduction

External beam radiotherapy is widely used for the treatment of painful spinal metastases. A variety of regimen and techniques have been used, and there is some uncertainty over which are the most appropriate. Radiotherapy regimens range from a single dose of 8Gy to fractionated regimens delivered in multiple doses. Different techniques have also been used: for example stereotactic radiotherapy delivers a precise focused dose compared to conventional external beam radiotherapy – but it is unclear whether this leads to improved outcomes.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Adults with: • metastatic spinal disease • direct malignant infiltration of the spine Adults with confirmed spinal cord or nerve root compression because of: • metastatic spinal disease • direct malignant infiltration.
Intervention	Radiotherapy (RT): • Unfractionated RT (including stereotactic techniques) • Fractionated RT
Comparison	• No RT (with or without surgery) • Repeated single site treatments versus one multi-site treatment • Surgery with post-op RT versus RT alone • Different fractionation • Different dosage • Different RT technique

Outcome	**Critical**
	• Health related quality of life
	• Neurological and functional status including:
	  ○ Bowel & bladder function
	  ○ Mobility or ambulatory status
	• Overall survival
	• Pain
	
	Important

	• Treatment related morbidity • Spinal stability (especially in those who did not have surgery) • Fitness for subsequent anti-cancer therapy

RT: radiotherapy.

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness

Included studies

Nineteen studies were included in this review reporting results from 13 randomised controlled trials (Hoskin 2019 [SCORAD-III trial], Howell 2013 [RTOG 97-14 trial], Lee 2018 [ICORG 05-03 trial], Majumder 2012, Maranzano 2005, Maranzano 2009, Patchell 2005, Rades 2016 [SCORE-2 trial], Rades 2018 [SCORE-2 trial], Rades 2019 [SCORE-2 trial], Roos 2005 [TROG 96-05 trial], Sahgal 2021, Sprave 2018 – a, b, c [IRON-1 trial], Sprave 2018 d, e, f [NCT- 02358720], Steenland 1999 [Dutch bone metastasis trial]).

The included studies are summarised in Table 2.

Four randomised controlled trials (Howell 2013 [RTOG 97-14], Majumder 2012, Roos 2005 [TROG 96-05], Steenland 1999 [Dutch Bone Metastasis trial]) compared single fraction radiotherapy to multiple fraction radiotherapy in patients with spinal metastases (without evidence of cord compression).

Three randomised controlled trials (Hoskin 2019 [SCORAD-III trial]), Lee 2018 [ICORG 05-03 trial], Maranzano 2009), compared single fraction radiotherapy to multiple fraction or split-course radiotherapy in patients *with* metastatic spinal cord compression.

One randomised controlled trial (Sprave 2018 a, b, c [IRON-1 trial]) compared image guided intensity modulated radiotherapy (IMRT) to conventional radiotherapy (CRT) in patients with spinal metastases (without evidence of cord compression).

Two randomised controlled trials (Sahgal 2021, Sprave 2018 d, e, f [NCT- 02358720]) compared stereotactic ablative body radiotherapy (SABR) to CRT in patients with spinal metastases (without evidence of cord compression).

Two randomised controlled trials compared different regimens of radiotherapy (Maranzano 2005, Rades 2016 [SCORE-2 trial], Rades 2018, Rades 2019 [SCORE-2 trial]) in patients *with* metastatic spinal cord compression; and 1 randomised controlled trial compared surgery + radiotherapy to radiotherapy alone (Patchell 2005) in patients with metastatic spinal cord compression.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies.

Study/trial	Population	Intervention	Comparison	Outcomes
Hoskin 2019 (SCORAD-III trial) RCT Australia and United Kingdom	N=686. Patients with MRI or CT confirmed metastatic spinal cord compression. Age, median, years (range): single fraction 70 (23 to 96); multiple fraction 70 (33 to 95). Mean and SD not reported. Sex: female n=183, male n=503.	Single fraction RT 8 Gy in 1 fraction beginning on day of simulation.	Multiple fraction RT 20 Gy in 5 fractions.	• Health related quality of life • Functional status • Overall survival • Pain • Treatment related morbidity
Howell 2013 RCT United States	N=235. Patients with painful spinal metastases. Age, median, years (range): Single fraction 69 (36 to 92); multiple fraction 68 (33 to 91). Mean and SD not reported. Sex: female n=105, male n=129.	Single fraction RT 8 Gy in 1 fraction.	Multiple fraction RT 30 Gy in 10 fractions.	• Survival • Pain • Treatment related morbidity • Treatment failure
Lee 2018 (ICORG 05-03 trial)	N=104. Patients with MRI documented metastatic spinal cord compression/ cauda equina not	Single fraction RT 10 Gy in 1 fraction beginning on day of simulation.	Multiple fraction RT 20 Gy in 5 fractions beginning on day of simulation.	• Health related quality of life • Functional status • Pain

Study/trial	Population	Intervention	Comparison	Outcomes
RCT Ireland and Northern Ireland	proceeding with surgical decompression. Age, mean, years (SD): 66.7 (13.1) (not reported by group). Sex: female n=38, male n=66.			• Treatment related morbidity
Majumder 2012 RCT India	N=64. Patients with histopathologically proven primary malignancy having symptomatic secondary deposits to the vertebra. Age, median, years (range): multiple fraction 58 (55.64); single fraction 60 (56.64). Mean and SD not reported. Sex: female n=11, male n=53.	Single fraction RT 8 Gy in 1 fraction.	Multiple fraction RT 30 Gy in 10 fractions.	• Pain • Treatment related morbidity
Maranzano 2005 RCT Italy	N=300 randomised (n=276 assessable). Patients with MRI or CT diagnosed metastatic spinal cord compression and short life expectancy. Age, median, years (range): short course 66 (30-87); split course 68 (34-89). Mean and SD not reported. Sex: female n=85, male n=191.	Short course RT 16 Gy in 2 fractions over 1 week.	Split course RT 30 Gy in 8 fractions over 2 weeks.	• Functional status • Pain • Survival • Treatment related morbidity

Study/trial	Population	Intervention	Comparison	Outcomes
Maranzano 2009 RCT Italy	N=303. Patients with MRI or CT confirmed metastatic spinal cord compression with a short life expectancy. Age, median, years (range): single fraction 67 (33-87); multiple fraction 67 (39-87). Mean and SD not reported. Sex: female n=106, male n=197.	Single fraction RT 8 Gy in 1 fraction.	Split course RT 16 Gy in 2 fractions.	• Functional status • Pain • Bowel and bladder function • Overall survival • Treatment related morbidity
Patchell 2005 RCT United States	N=101. Patients with metastatic spinal cord compression. Age, median, years (range): Surgery + RT 60; RT only 60. No further details reported. Sex: female n=31, male n=70.	Surgery plus radiotherapy Direct decompressive surgery within 24 hours of randomisation followed by RT (30 Gy in 10 fractions administered 14 days after surgery).	Radiotherapy only 30 Gy in 10 fractions beginning within 24 hours of randomisation.	• Mobility or ambulatory status • Overall survival • Functional status • Bowel and bladder function • Pain
Rades 2016, Rades 2018, Rades 2019 (SCORE-2 trial) RCT Germany	N=203. Patients with MRI or CT confirmed metastatic spinal cord compression but no previous surgery or radiotherapy to spinal cord. Poor or intermediate survival prognosis. Age, years, n:	20 Gy in 5 fractions	30 Gy in 10 fractions	• Functional status • Pain

Study/trial	Population	Intervention	Comparison	Outcomes
	≤ 68 n=103, ≥ 68 n=100. Mean and SD not reported. Sex: female n=79, male n=124.			
Roos 2005 (TROG 96-05 trial) RCT Australia, New Zealand, United Kingdom	N=272. Patients with painful spinal metastases and life expectancy of at least 6 weeks. Age, median, years (range): single fraction 67 (29-86); multiple fraction 68 (32-89). Mean and SD not reported. Sex: female n=76, male n=196.	Single fraction RT 8 Gy in 1 fraction.	Multiple fraction RT 20 Gy in 5 fractions.	• Pain • Treatment failure • Adverse events
Sahgal 2021 RCT Canada and Australia	N=229. Patients with painful MRI-confirmed spinal metastases. Age, n: 18 to 59 n=83; 60 to 69 n=61; ≥70: n=85. Sex: female n=109, male n=120.	Stereotactic ablative body RT 24 Gy in 2 consecutive daily fractions.	Conventional RT 20 Gy in 5 daily fractions.	• Health related quality of life • Overall survival • Progression free survival • Pain • Treatment related morbidity
Sprave 2018 a, b, c (IRON-1 trial) RCT Germany	N=60. Patients with spinal metastases with indication for palliative radiotherapy. Age, mean, years (SD): IMRT: 66.1 (10.5); conventional RT: 62.5 (11.8).	Image guided intensity modulated RT (IMRT) 30 Gy in 10 fractions.	Conventional RT 30 Gy in 10 fractions	• Health related quality of life • Functional status • Pain • Treatment related morbidity

Study/trial	Population	Intervention	Comparison	Outcomes
	Sex: female n=27, male n=33.			
Sprave 2018 d, e, f (NCT-02358720) RCT Germany	N=55 Histologically confirmed tumour diagnosis, with secondary diagnosed solitary/multiple spinal bone metastases and indication for radiotherapy of the spinal bone metastases. Age, mean, years (SD): Stereotactic body RT 61 (8.2); conventional RT 63.9 (10.8). Sex: female n=27, male n=28.	Stereotactic ablative body RT High dose single-fraction stereotactic ablative body radiation therapy (24 Gy to the 80% isodose line).	Conventional RT 30 Gy in 10 fractions.	• Health related quality of life • Functional status • Pain • Treatment related morbidity
Steenland 1999 (Dutch Bone Metastasis trial) RCT Netherlands	N=1157. Patients with painful bone metastases from a solid tumour. Age, mean, years (SD): single fraction 65 (SD not reported); multiple fraction 65 (SD not reported). Sex: female n=533, male n=624.	Single fraction RT 8 Gy in 1 fraction.	Multiple fraction RT 24 Gy in 6 fractions.	• Treatment related morbidity

CT: computed tomography; Gy: Gray; IMRT: image guided intensity modulated radiotherapy; RCT: randomised controlled trial; MRI, magnetic resonance imaging; RT: radiotherapy, SD: standard deviation.

See the full evidence tables in appendix D and the forest plots in appendix E.

Economic evidence

Included studies

One economic study was identified which was relevant to this review question. (Turner 2018) The study compared surgery and radiotherapy to radiotherapy alone.

A single economic search was undertaken for all topics included in the scope of this guideline. See supplement 2 for details.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in supplement 2.

Summary of the evidence

People with painful spinal bone metastases (but no evidence of spinal cord compression)

Single fraction verses multiple fraction radiotherapy

There was very low to low quality evidence of no important difference between single fraction radiotherapy and multiple fractions in terms of pain reduction, spinal stability and overall survival. There was very low quality evidence of an important benefit with single fraction radiotherapy which had fewer treatment related adverse events than multiple fractions.

IMRT verses 3D-CRT

There was no evidence of an importance difference between IMRT and 3D-CRT in terms of quality of life, pain response, treatment related morbidity or overall survival in one small trial. This evidence was very low quality.

SABR verses conventional radiotherapy

There was an important benefit with SABR when compared to conventional RT (EBRT or 3D-CRT) in reducing pain. There was no evidence of important differences in quality of life, treatment related morbidity or overall survival. This evidence was all low quality.

People with metastatic spinal cord compression

Single fraction verses multiple fraction radiotherapy

There was moderate to high quality evidence of no important difference between single fraction radiotherapy and multiple fractions in terms of neurological and functional status, quality of life, pain, overall survival and treatment toxicity.

Short course verses split or long course radiotherapy

There was low to high quality evidence of no important difference between short course radiotherapy and split or long course radiotherapy in terms of neurological and functional status, pain response and treatment related morbidity.

Surgery plus radiotherapy verses radiotherapy alone

There was moderate to high quality evidence of an important benefit for surgery + radiotherapy over radiotherapy alone for neurological and functional status (ability to walk, continence and muscle strength).

See appendix F for full GRADE tables.

Summary of included economic evidence

Table 3: Economic evidence profile of an economic evaluation of the addition of radiotherapy for people undergoing surgery for metastatic spinal cord compression

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectiveness	
Turner 2018 Surgery and radiotherapy versus radiotherapy	Potentially serious limitations[1]	Directly applicable[2]	Radiotherapy arm was based on modelling using values from Patchell 2005	-£12,839	0.32 QALYs	Surgery and radiotherpay dominant[3]	Various deterministic sensitivity analyses always favoured surgery and radiotherapy

[1] *Limited exploration of uncertainty.*
[2] *UK NHS perspective with QALYs valued using EQ-5D questionnaire scored using the UK population value set*
[3] *Surgery and radiotherapy both less costly and more effective*

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence Statement

Turner 2018 was a cost utility analysis which reported outcomes in terms of cost per QALY gained for surgery and radiotherapy versus radiotherapy alone in people with symptomatic spinal metastases.

The study found surgery and radiotherapy to be cost saving and health improving compared to radiotherapy alone. This was robust to deterministic sensitivity analysis. The study was deemed to be directly applicable to the review question with potentially serious methodological limitations.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Health related quality of life, pain and neurological and functional status were chosen as critical outcomes because untreated malignant spinal disease can impact on quality of life due to

severe pain and impaired neurological and functional status. Overall survival was also a critical outcome because radiotherapy can potentially prolong life.

The committee agreed that treatment related morbidity is an important outcome, due to side effects of radiotherapy, and is an important consideration when choosing radiotherapy dose and fractionation. Spinal stability was also an important outcome, because different radiotherapy doses and fractionations may have differing impact on re-ossification rates of unstable spinal bone metastases. Fitness for subsequent anti-cancer therapy was an important outcome because morbidity due to radiotherapy could delay further anti-cancer therapy until the person recovers fitness.

The quality of the evidence

The quality of the evidence for outcomes was assessed with GRADE and ranged from very low to high. The main issues that lowered the quality of the evidence were risk of bias as per Cochrane RoB 2 and imprecision of the effect estimates. In one case evidence quality was downgraded for indirectness because the study included some people with non-spinal bone metastases.

The committee considered the quality of evidence was sufficient to make recommendations on fractionation and on SABR for painful spinal metastases. They used their clinical experience to make recommendations where there was a lack of evidence on the timing of radiotherapy, radiotherapy for people with asymptomatic spinal metastases and the use of SABR for MSCC.

Benefits and harms

Radiotherapy and fertility

The committee agreed that the impact on future fertility of both the cancer and the radiotherapy treatment should be discussed with the person and, if appropriate (for example, depending on age and preferences), a referral should be made to a fertility. The committee discussed that treatment of MSCC is usually urgent and fertility treatment can take time to organise and undertake in practice and that it is therefore important to bear in mind that MSCC treatment should not be delayed awaiting further discussions with a fertility specialist. They also acknowledged that radiotherapy fields for MSCC would usually not affect the gonads so, urgent radiotherapy treatment might not impact as much on fertility as radiotherapy does for other cancers which is another reason why urgent treatment should not be delayed.

Radiotherapy to treat painful spinal metastases or DMI of the spine and prevent MSCC

Evidence supported the recommendation for single fraction radiotherapy in people with painful spinal metastases (without MSCC). Single fraction radiotherapy appeared as effective as multiple fractions in terms of reducing pain but with fewer adverse effects. Although the evidence was very low quality, the committee discussed that a strong recommendation was supported because single fractionation would likely be more acceptable to patients with fewer visits and transfers required to complete the treatment. There was limited evidence from 2 small RCTs that stereotactic ablative body radiotherapy (SABR) is more effective than conventional radiotherapy in reducing pain for people with spinal metastases without MSCC. Although the evidence was very low quality the committee agreed that the ability of SABR to deliver a precise dose while sparing damage to healthy tissue supported their recommendation. The committee agreed that this could be an option for a subgroup of people who have a good overall prognosis because they can tolerate this radiotherapy and it would not be too

risky. They also discussed that those with limited metastatic disease (based on expertise they thought that usually up to 3 discrete metastases would be considered standard for oligometastases) could benefit from this. They agreed that this number would balance the potential that all cancer sites could be controlled with an acceptable level of toxicity.

Although there was a lack of evidence about the impact of radiotherapy on stem cell harvest in people with haematological cancers, the committee agreed that in their experience it could lower the chance of a successful procedure. For this reason they recommended a discussion with the relevant haematology MDT whenever this was being considered to allow for careful consideration of the risks and benefits for each individual.

Radiotherapy to treat MSCC

Although there was no evidence on the timing of radiotherapy for people with MSCC, the committee agreed that MSCC can be an oncologic emergency and rapid access to radiotherapy would be needed in some cases to prevent neurological impairment (as soon as possible and within 24 hours). The committee discussed that in patients with MSCC who are not candidates for surgery, radiotherapy may help prevent further neurological damage and alleviate pain. In this situation radiotherapy should be given urgently – unless the person already has prolonged paraplegia or tetraplegia and their pain is controlled or their overall prognosis is poor. In these cases, the benefits of radiotherapy are unlikely to outweigh the harms.

There was evidence that single fractionation was as effective as multiple fractions for people with MSCC, but with the benefit of increased patient convenience and reduced costs. The committee agreed that a strong recommendation was appropriate based on the evidence and because this would lead to less time spent in multiple hospital visits which can be particularly important in a patient group with reduced life expectancy. This would also use fewer resources in relation to appointments and staff time.

The committee agreed, based on their experience, that it can be technically difficult to treat multilevel disease in a single dose and that radiologists avoid large single dose treatment fields which cover a large proportion of the spinal cord due to toxicity. For these reasons in some cases multiple fraction radiotherapy would be more appropriate.

The committee agreed to make a research recommendation stereotactic ablative body radiotherapy for the treatment of MSCC, given a lack of evidence about its use in this indication.

Radiotherapy for asymptomatic spinal metastases

There was a lack of evidence about the use of radiotherapy in people with asymptomatic spinal metastases. The committee agreed that benefits of radiotherapy were less clear cut in this population whereas the harms of radiotherapy are known. They recommended radiotherapy only in limited circumstances: for those with limited metastatic disease (where radiotherapy could be used to control disease), for those with radiological spinal cord compression (where presumably radiotherapy may prevent progression to symptomatic MSCC) and for those in a randomised trial.

Postoperative radiotherapy

There was evidence showing that radiotherapy and surgery had an important benefit in relation to neurological and functional status over radiotherapy alone. The committee noted also that this is now routine practice in most services and is suitable for most people with MSCC post surgery. To standardise this practice and based on the evidence they recommended that postoperative radiotherapy should be offered.

Further radiotherapy

The committee also discussed retreatment with radiotherapy in people who had previously had radiotherapy. No evidence was identified so the committee, based on experience, decided to recommend this treatment option in some cases but also to highlight some of the factors linked to treatment toxicity (dose, timing and volume of treatment field) that should be taken into account when making decisions about whether or not to offer further radiotherapy treatment.

Providing urgent radiotherapy services

The committee discussed that their recommendation regarding radiotherapy within 24 hours would require some configuration of services that would help enable this to happen. Based on experience they therefore recommended that MSCC services need to ensure that radiotherapy and simulator facilities are available for urgent (within 24 hours) daytime sessions, 7 days a week. This would enable treatment to be given within this timeframe.

Cost effectiveness and resource use

The economic evidence showed that giving post-operative radiotherapy to people who have undergone surgery will be cost saving and health improving compared to radiotherapy alone. These savings and health improvements are largely being driven through people being ambulant for longer periods of time, improving quality of life and reducing costs to community services which are involved with non-ambulant people.

Stereotactic ablative body radiotherapy (SABR) is not widely used for painful spinal metastases in the NHS and would represent a change in practice. The technology is already available in the NHS for other cancers and all cancer centres will already have access to this technology. These recommendations will increase the use of stereotactic ablative body radiotherapy but this is similar in cost to alternative radiotherapy and the committee agreed this will not lead to a significant resource impact. There may be an initial cost of setting up pathways for people with painful spinal metastases to access SABR, as these are not currently established, but this will be a one-off cost and would not lead to significant resource impact. There was also evidence that SABR will reduce pain leading to reduced use of analgesics and other treatments for pain, decreasing costs and increasing quality of life. The committee therefore concluded that SABR was likely to be cost neutral or potentially cost saving once the initial set-up costs had been incurred.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.1.21, 1.10.1 to 1.10.10 and research recommendation 1 on the effectiveness of stereotactic ablative body radiotherapy in the treatment of MSCC, in the guideline.

References – included studies

Effectiveness

Hoskin 2019 [SCORAD-III trial]

Hoskin P, Hopkins K, Misra V, et al. Effect of Single-Fraction vs Multifraction Radiotherapy on Ambulatory Status Among Patients With Spinal Canal Compression From Metastatic Cancer: the SCORAD Randomized Clinical Trial. JAMA 322, 2084-2094, 2019

Howell 2013 [RTOG 97-14 trial]

Howell D, James J, Hartsell W, et al. Single-fraction radiotherapy versus multifraction radiotherapy for palliation of painful vertebral bone metastases - Equivalent efficacy, less toxicity, more convenient: A subset analysis of Radiation Therapy Oncology Group trial 97-14. Cancer 119, 888-896, 2013

Lee 2018 [ICORG 05-03 trial]

Lee K, Dunne M, Small C, et al. (ICORG 05-03): prospective randomized non-inferiority phase III trial comparing two radiation schedules in malignant spinal cord compression (not proceeding with surgical decompression); the quality of life analysis. Acta Oncologica, 1-8, 2018

Majumder 2012

Majumder D, Chatterjee D, Bandyopadhyay A, et al. Single Fraction versus Multiple Fraction Radiotherapy for Palliation of Painful Vertebral Bone Metastases: A Prospective Study. Indian Journal of Palliative Care, 18, 202-6, 2012

Maranzano 2005

Maranzano E, Bellavita R, Rossi R, et al. Short-course versus split-course radiotherapy in metastatic spinal cord compression: results of a phase III, randomized, multicenter trial. Journal of Clinical Oncology 23: 3358-65, 2005

Maranzano 2009

Maranzano E, Trippa F, Casale M, et al. 8Gy single-dose radiotherapy is effective in metastatic spinal cord compression: results of a phase III randomized multicentre Italian trial. Radiotherapy and Oncology 93, 174-9, 2009

Patchell 2005

Patchell R, Tibbs P Regine W, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet 366, 643-8, 2005

Rades 2016 [SCORE-2 trial]

Rades D, Šegedin B, Conde-Moreno A, et al, Radiotherapy With 4 Gy × 5 Versus 3 Gy × 10 for Metastatic Epidural Spinal Cord Compression: final results of the SCORE-2 Trial (ARO 2009/01). Journal of Clinical Oncology 34, 597-602, 2016

Rades 2018 [SCORE-2 trial]

Rades D, Conde-Moreno A, Cacicedo J et al. Comparison of Two Radiotherapy Regimens for Metastatic Spinal Cord Compression: subgroup Analyses from a Randomized Trial. Anticancer Research 38, 1009-1015, 2018

Rades 2019 [SCORE-2 trial]

Rades D, Segedin B, Conde-Moreno A, et al. Patient-Reported Outcomes-Secondary Analysis of the SCORE-2 Trial Comparing 4 Gy x 5 to 3 Gy x 10 for Metastatic Epidural Spinal Cord Compression. International Journal of Radiation Oncology, Biology, Physics, 105, 760-764, 2019

Roos 2005 [TROG 96-05 trial]

Roos D, Turner S, O'Brien, P, et al. Randomized trial of 8 Gy in 1 versus 20 Gy in 5 fractions of radiotherapy for neuropathic pain due to bone metastases (Trans-Tasman Radiation Oncology Group, TROG 96.05). Radiotherapy and Oncology 75, 54-63, 2005

Sahgal 2021

Sahgal A, Myrehaug S, Siva S, et al. Stereotactic body radiotherapy versus conventional external beam radiotherapy in patients with painful spinal metastases: an open-label, multicentre, randomised, controlled, phase 2/3 trial. Lancet Oncology 22, 1023-1033, 2021

Sprave 2018a [IRON-1 trial]

Sprave T, Verma V, Förster R et al. Radiation-induced acute toxicities after image-guided intensity-modulated radiotherapy versus three-dimensional conformal radiotherapy for patients with spinal metastases (IRON-1 trial): first results of a randomized controlled trial. Strahlentherapie und Onkologie 194, 911-920, 2018

Sprave 2018b [IRON-1 trial]

Sprave T, Verma V, Förster R et al. Quality of Life and Radiation-induced Late Toxicity Following Intensity-modulated Versus Three-dimensional Conformal Radiotherapy for Patients with Spinal Bone Metastases: results of a Randomized Trial. Anticancer Research 38, 4953-4960, 2018

Sprave 2018c [IRON-1 trial]

Sprave T, Verma V, Förster R, et al. Bone density and pain response following intensity-modulated radiotherapy versus three-dimensional conformal radiotherapy for vertebral metastases - secondary results of a randomized trial. Radiation Oncology, 13, 212, 2018

Sprave 2018d [NCT - 02358720]

Sprave T, Verma V, Forster R, et al, Quality of Life Following Stereotactic Body Radiotherapy Versus Three-Dimensional Conformal Radiotherapy for Vertebral Metastases: Secondary Analysis of an Exploratory Phase II Randomized Trial. Anticancer Research 38, 4961-4968, 2018

Sprave 2018e [NCT - 02358720]

Sprave T, Verma V, Forster R, et al, Randomized phase II trial evaluating pain response in patients with spinal metastases following stereotactic body radiotherapy versus three-dimensional conformal radiotherapy. Radiotherapy and Oncology 128, 274-282, 2018

Sprave 2018f [NCT - 02358720]

Sprave T, Verma V, Forster R, et al, Local response and pathologic fractures following stereotactic body radiotherapy versus three-dimensional conformal radiotherapy for spinal metastases - a randomized controlled trial. BMC Cancer 18, 859, 2018

Steenland 1999 [Dutch Bone Metastasis trial]

Steenland E, Leer J, van Houwelingen H, et al. The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. Radiotherapy and Oncology, 52, 101-109, 1999

Economic

Turner 2018

Turner I, Kennedy J, Morris S, et al. Surgery and radiotherapy for symptomatic spinal metastases is more cost effective than radiotherapy alone: a cost utility analysis in a UK Spinal Center. World Neurosurgery, 109, e389-e397, 2018.

Appendices

Appendix A Review protocols

Review protocol for review question: How effective is radiotherapy, including both fractionated and unfractionated radiotherapy, for the management of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Table 4: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42021288035
1.	Review title	Radiotherapy for the management of spinal metastases, direct malignant infiltration or associated spinal cord compression
2.	Review question	How effective is radiotherapy, including both fractionated and unfractionated radiotherapy, for the management of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?
3.	Objective	To establish the effectiveness of radiotherapy, including both fractionated and unfractionated radiotherapy, for the management of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Cumulative Index to Nursing and Allied Health Literature (CINAHL) • Database of Abstracts of Reviews of Effects (DARE) • Embase • Epistemonikos • International Health Technology Assessment (IHTA) database

ID	Field	Content
		• MEDLINE & MEDLINE In-Process Searches will be restricted by: • Date: 1990 onwards (see rationale under Section 10) • English language studies • Human studies Other searches: Inclusion lists of systematic reviews With the agreement of the guideline committee the searches will be re-run between 6-8 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Radiotherapy in the management of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression.
6.	Population	Inclusion: Adults with: • metastatic spinal disease • direct malignant infiltration of the spine • Adults with confirmed spinal cord or nerve root compression because of metastatic spinal disease or direct malignant infiltration. Exclusion: • Adults with suspected metastatic spinal disease and suspected direct malignant infiltration of the spine. • Adults with spinal cord compression because of primary tumours of the spinal cord, meninges or nerve roots.

ID	Field	Content
		• Adults with spinal cord compression because of non-malignant causes. • Adults with primary bone tumours of the spinal column. • Children and young people under the age of 18.
7.	Intervention	Radiotherapy (RT): • Unfractionated RT (including stereotactic techniques) • Fractionated RT
8.	Comparator	• No RT (with or without surgery) • Repeated single site treatments versus one multi-site treatment • Surgery with post-op RT versus RT alone • Different fractionation • Different dosage • Different RT technique
9.	Types of study to be included	Experimental studies (where the investigator assigned intervention or control) including: • Randomised controlled trials • Systematic reviews/meta-analyses of randomised controlled trials. In the absence of controlled trials reporting critical outcomes for each of the interventions & comparators, studies using the following designs will be included: Observational studies (where neither control nor intervention were assigned by the investigator) including: • Systematic reviews of observational studies. • Prospective and retrospective cohort studies • Case control studies • Before and after study or interrupted time series
10.	Other exclusion criteria	Inclusion: • Full text papers • Observational studies should adjust for baseline differences in patient groups in their analyses

ID	Field	Content
		Exclusion: • Conference abstracts • Articles published before 1990. MRI has regularly used in diagnosis since the early 1990s. IMRT was not commercially available until 1994. • Papers that do not include methodological details will not be included as they do not provide sufficient information to evaluate risk of bias/ study quality • Studies using qualitative methods only • Non-English language articles
11.	Context	Metastatic spinal cord compression in adults: risk assessment, diagnosis and management (2008) NICE guideline will be updated by this review question

12.	Primary outcomes (critical outcomes)	• Health related quality of life
		• Neurological and functional status including:
		  ○ Bowel & bladder function
		  ○ Mobility or ambulatory status
		• Overall survival
		• Pain

13.	Secondary outcomes (important outcomes)	• Treatment related morbidity • Spinal stability (especially in those who did not have surgery) • Fitness for subsequent anti-cancer therapy
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary.

ID	Field	Content
		The full set of records will not be dual screened because the population, interventions and relevant study designs are relatively clear and should be readily identified from titles and abstracts. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Risk of bias of individual studies will be assessed using the preferred checklist as described in Developing NICE guidelines: the manual. Quality assessment of individual studies will be performed using the following: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs • ROBINS-I for non-randomised studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Data Synthesis Where possible, pair wise meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios for dichotomous outcomes. Peto odds ratio will be used for outcomes with zero events Mean differences or standardised mean differences will be calculated for continuous outcomes.

ID	Field	Content
		Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. In the case of serious or very serious unexplained heterogeneity (remaining after pre-specified subgroup and stratified analyses) meta-analysis will be done using a random effects model. Default MIDs will be used for risk ratios and continuous outcomes only, unless the committee pre-specifies published or other MIDs for specific outcomes. For risk ratios: 0.8 and 1.25. For continuous outcomes: MID is calculated by ranking the studies in order of SD in the control arms. The MID is calculated as +/- 0.5 times median SD. For studies that have been pooled using SMD (meta-analysed): +0.5 and -0.5 in the SMD scale are used as MID boundaries. Validity The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/
17.	Analysis of sub-groups	Evidence will be stratified by: • Primary cancer type • Ambulant vs non ambulant patients • Bony instability / vertebral collapse on MRI Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.

ID	Field	Content			
18.	Type and method of review	X	Intervention		
			Diagnostic		
			Prognostic		
			Qualitative		
			Epidemiologic		
			Service Delivery		
			Other (please specify)		
19.	Language	English			
20.	Country	England			
21.	Anticipated or actual start date	01 November 2021			
22.	Anticipated completion date	23 August 2023			
23.	Stage of review at time of this submission	Review stage		Started	Completed
		Preliminary searches			
		Piloting of the study selection process			
		Formal screening of search results against eligibility criteria			
		Data extraction			
		Risk of bias (quality) assessment			
		Data analysis			
24.	Named contact	5a. Named contact National Guideline Alliance 5b Named contact e-mail metastaticspinal@nice.org.uk 5e Organisational affiliation of the review			

ID	Field	Content
		National Institute for Health and Care Excellence (NICE) and National Guideline Alliance
25.	Review team members	NGA Technical Team
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance, which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
29.	Other registration details	
30.	Reference/URL for published protocol	National Guideline Alliance. Radiotherapy for the management of spinal metastases, direct malignant infiltration or associated spinal cord compression. PROSPERO 2021 CRD42021288035 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021288035
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Humans; Radiation Oncology; Spinal Cord Compression; Spinal Neoplasms

ID	Field	Content	
33.	Details of existing review of same topic by same authors		
34.	Current review status	X	Ongoing
			Completed but not published
			Completed and published
			Completed, published and being updated
			Discontinued
35.	Additional information		
36.	Details of final publication	www.nice.org.uk	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation

Appendix B Search strategy (clinical/economic)

Literature search strategies for review question: How effective is radiotherapy, including both fractionated and unfractionated radiotherapy, for the management of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Database: Medline – OVID interface

#	Searches
1	exp spinal cord neoplasms/ or Spinal Neoplasms/
2	((spine or spinal or vertebr*) adj2 (adeno* or cancer* or carcinoma* or intraepithelial* or intra epithelial* or malignan* or neoplas* or tumo?r*)).tw.
3	((spine or spinal or vertebr*) and (metast* or oligometast*)).tw.
4	or/1-3
5	*spinal cord compression/
6	((cauda equina or cervical* or cervicothoracic or cord* or coccyx or duralsac* or dural sac* or intervertebr* or lumbar or lumbosac* or lumbo sac* or medulla* or orthothoracic or sacral or sacrum or spinal or spine* or thecal sac* or thoracic or vertebr* or epidural or extradural or extra dural or ((axon* or neuron* or nerve*) adj2 root)) and (collaps* or compress* or pinch* or press*) and (adeno* or cancer* or carcinoma* or chordoma* or intraepithelial* or intra epithelial* or malignan* or metast* or neoplas* or oligometast* or tumo?r*)).tw.
7	(myelopath* or myeloradiculopath* or radiculopath*).tw,hw. or (radicular adj2 (disorder* or syndrome*)).tw.
8	(mescc or mscc).tw.
9	or/5-8
10	exp radiotherapy/ or (((bucky or bio?radiant) adj2 (radiation or ray or therap* or treat*)) or hypophysis radiat* or (interstitial adj2 radiat*) or irradiat* or ((radiat* or rt) adj2 (beam centration or fraction* or repair* or therap* or treat* or unfraction*)) or 3D?CRT or radio?hypophysectom* or ((radio* or roentgen) adj2 (therap* or treat*)) or radio?therap* or therapeutic radiology or (stereotactic adj3 (radiat* or radio*)) or sbrt).tw.
11	or/4,9-10
12	exp radiotherapy/ or (((bucky or bio?radiant) adj2 (radiation or ray or therap* or treat*)) or hypophysis radiat* or (interstitial adj2 radiat*) or irradiat* or (radiat* adj2 (beam centration or fraction* or repair* or therap* or treat* or unfraction*)) or 3D?CRT or radio?hypophysectom* or ((radio* or roentgen) adj2 (therap* or treat*)) or radio?therap* or therapeutic radiology).tw.
13	11 and 12
14	(animals not humans).sh. or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ or (rat or rats or mouse or mice).ti.
15	13 not 14
16	limit 15 to yr="2005 -Current"
17	limit 16 to english language
18	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
19	(experimental or non?random*).tw. or experimental study/ use emez
20	or/18-19
21	meta-analysis/ or meta-analysis as topic/ or systematic review/
22	(meta analy* or metanaly* or metaanaly* or ((evidence or systematic*) adj2 (overview* or review*))).ti,ab. or (bibliograph* or data extraction or hand search* or manual search* or reference list* or relevant journals or (search adj (criteria or strategy)) or (search* adj4 literature) or study selection or systematic search or (bids or cancerlit or cinahl or cochrane or embase or medline or psychinfo or psychlit or psycinfo or psyclit or pubmed or science citation index)).ab. or cochrane.jw.
23	or/21-22
24	or/20,23
25	17 and 24
26	COMPARATIVE STUDIES/ or FOLLOW-UP STUDIES/ or TIME FACTORS/ or chang$.tw. or evaluat$.tw. or reviewed.tw. or prospective$.tw. or retrospective$.tw. or baseline.tw. or cohort.tw. or case series.tw.
27	(17 and 26) not 25

Health economics search

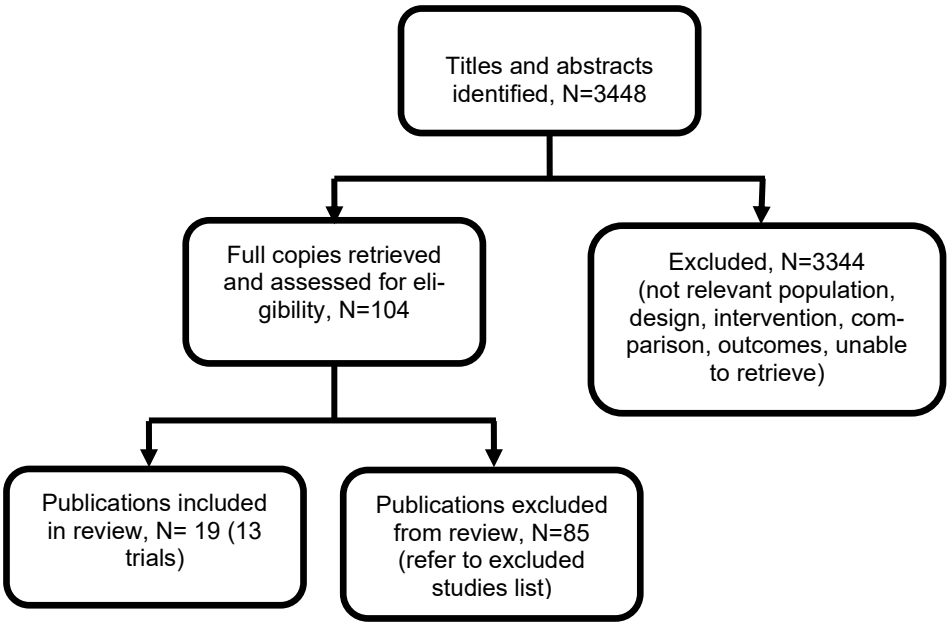
Database: Medline – OVID interface

#	Searches
1	exp Spinal Cord Neoplasms/ or Spinal Neoplasms/
2	((spine or spinal or vertebr*) adj2 (adeno* or cancer* or carcinoma* or intraepithelial* or intra epithelial* or malignan* or neoplas* or tumo?r*)).tw.
3	((spine or spinal or vertebr*) and (metast* or oligometast*)).tw.
4	or/1-3
5	Spinal Cord Compression/
6	((cauda equina or cervical* or cervicothoracic or cord* or coccyx or duralsac* or dural sac* or intervertebr* or lumbar or lumbosac* or lumbo sac* or medulla* or orthothoracic or sacral or sacrum or spinal or spine* or thecal sac* or thoracic or vertebr* or epidural or extradural or extra dural or ((axon* or neuron* or nerve*) adj2 root)) and (collaps* or compress* or pinch* or press*) and (adeno* or cancer* or carcinoma* or chordoma* or intraepithelial* or intra epithelial* or malignan* or metast* or neoplas* or oligometast* or tumo?r*)).tw.
7	(myelopath* or myeloradiculopath* or radiculopath*).tw,hw. or (radicular adj2 (disorder* or syndrome*)).tw.
8	(mescc or mscc).tw.
9	or/5-8
10	((adeno* or cancer* or carcinoma* or intraepithelial* or intra epithelial* or malignan* or metast* or neoplas* or tumo?r*) adj3 (escap* or infiltrat* or invasiv* or metast* or spread*) adj5 (cauda equina or cervical* or cervicothoracic or cord* or coccyx or duralsac* or dural sac* or intervertebr* or lumbar or lumbosac* or lumbo sac* or medulla* or orthothoracic or sacral or sacrum or spinal or spine* or thecal sac* or thoracic or vertebr* or epidural or extradural or extra dural or ((axon* or neuron* or nerve*) adj2 root))).tw.
11	or/4,9-10
12	Economics/ or Value of life/ or exp "Costs and Cost Analysis"/ or exp Economics, Hospital/ or exp Economics, Medical/ or Economics, Nursing/ or Economics, Pharmaceutical/ or exp "Fees and Charges"/ or exp Budgets/
13	(cost* or economic* or pharmacoeconomic*).ti.
14	(budget* or financ* or fee or fees or price* or pricing* or (value adj2 (money or monetary))).ti,ab.
15	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
16	or/12-15
17	11 and 16
18	limit 17 to english language
19	limit 18 to yr="2005 -Current"

Appendix C Effectiveness evidence study selection

Study selection for: How effective is radiotherapy, including both fractionated and unfractionated radiotherapy, for the management of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: How effective is radiotherapy, including both fractionated and unfractionated radiotherapy, for the management of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Table 5: Evidence tables

Hoskin, 2019 (SCORAD-III trial)

Hoskin P, Hopkins K, Misra V, et al. Effect of Single-Fraction vs Multifraction Radiotherapy on Ambulatory Status Among Patients With Spinal Canal Compression From Metastatic Cancer: the SCORAD Randomized Clinical Trial. Journal of the American Medical Association, 322, 2084-2094, 2019

Study details

Country/ies where study was carried out	UK and Australia
Study type	Randomised controlled trial (RCT). Multicentre, non-inferiority, randomised clinical trial.
Study dates	February 2008 to April 2016, with final follow-up in September 2017.
Inclusion criteria	• Aged at least 18 years • estimated life expectancy greater than 8 weeks • proven diagnosis of spinal canal or cauda equina (C1-S2) compression on magnetic resonance imaging or computed tomographic scan, with single or multiple sites of compression. • histological or cytological confirmation of malignancy was required, but not for patients with clinical evidence of prostate cancer, who had to have a serum prostate-specific antigen level greater than 100 µg/L. Additional inclusion criteria (supplemental data): • able to give written informed consent • willing and able to complete assessment forms.
Exclusion criteria	• Patients able to undergo surgery or chemotherapy or if they had haematological malignancies or glioma • prophylactic treatment in the absence of radiological spinal canal compression • previous radiotherapy targeting the spine. Additional exclusion criteria (supplemental data): • patients known to be pregnant.
Patient characteristics	Age, median, years (range): single fraction 70 (23 to 96); multi-ple fraction 70 (33 to 95). Mean and SD not reported. Sex: female n=183, male n=503.

	Type of malignancy, primary tumour: Prostate: Single-fraction radiotherapy: 152 (44%); Multifraction radiotherapy: 152 (45%); Lung: Single-fraction radiotherapy: 66 (19%); Multifraction radiotherapy: 66 (19%); Breast: Single-fraction radiotherapy: 39 (11%); Multifraction radiotherapy: 40 (12%); Gastrointestinal: Single-fraction radiotherapy: 35 (10%); Multifraction radiotherapy: 38 (11%); Kidney: Single-fraction radiotherapy: 11 (3%); Multifraction radiotherapy: 12 (4%); Skin: Single-fraction radiotherapy: 9 (3%); Multifraction radiotherapy: 6 (2%); Bladder: Single-fraction radiotherapy: 7 (2%); Multifraction radiotherapy: 4 (1%); Other (gynaecologic, head and neck, sarcoma, unspecified): Single-fraction radiotherapy: 26 (8%); Multifraction radiotherapy: 23 (7%) Level of compression: *Reported as number of spinal cord compression sites:* Single: Single-fraction radiotherapy: 303 (88%); Multifraction radiotherapy: 311 (91%); Multiple: Single-fraction radiotherapy: 42 (12%); Multifraction radiotherapy: 30 (9%) Location of metastasis in spine, treatment site: Thoracic: Single-fraction radiotherapy: 232 (67%); Multifraction radiotherapy: 230 (67%); Lumbar: Single-fraction radiotherapy: 72 (21%); Multifraction radiotherapy: 65 (19%); Thoracic and lumbar: Single-fraction radiotherapy: 17 (5%); Multifraction radiotherapy: 16 (5%); Sacrum (S1 and S2): Single-fraction radiotherapy: 9 (3%); Multifraction radiotherapy: 6 (2%); Cervical vertebrae: Single-fraction radiotherapy: 7 (2%); Multifraction radiotherapy: 10 (3%); Cervical and thoracic: Single-fraction radiotherapy: 5 (1%); Multifraction radiotherapy: 8 (2%); Lumbar and sacrum: Single-fraction radiotherapy: 3 (1%); Multifraction radiotherapy: 4 (1%); Not reported: Single-fraction radiotherapy: 0; Multifraction radiotherapy: 2 (1%) Other metastases: Nonskeletal metastases: Single-fraction radiotherapy: 159 (46%); Multifraction radiotherapy: 156 (46%) Evidence of bony instability / vertebral collapse on MRI: Not reported. Mobility (ambulant or not): *Reported as ambulatory status:* Grade 1 (ambulatory without the use of walking aids): Single-fraction radiotherapy: 76 (22%); Multifraction radiotherapy: 77 (23%); Grade 2 (ambulatory with walking aids): Single-fraction radiotherapy: 152 (44%); Multifraction radiotherapy: 146 (43%); Grade 3 (unable to walk): Single-fraction radiotherapy: 91 (26%); Multifraction radiotherapy: 90 (26%); Grade 4 (absence or flicker of motor power in any muscle group): Single-fraction radiotherapy: 26 (8%); Multifraction radiotherapy: 28 (8%)
Intervention(s)/control	Single-fraction radiotherapy: 8 Gy of radiotherapy in a single fraction *versus* multifraction radiotherapy: 20 Gy of external beam radiotherapy in 5 fractions over 5 consecutive days (daily from Monday to Friday). "Megavoltage radiotherapy was delivered to the compression site with a margin of at least 1 vertebral level above and below. The dose was prescribed at cord depth, using magnetic resonance imaging or imaging at simulation. It was mandated that treatment began within 48 hours of a decision to treat

	based on diagnostic imaging up to 7 days prior to commencement of treatment. Supportive care was given according to local practice, including steroids and analgesics" (p. 2085).
Duration of follow-up	1, 4, 8, 12 and 52 weeks. Median follow-up, weeks (IQR): 13.3 (12-50).
Sources of funding	University College London, Cancer Research UK Cancer, the Council Queensland, UK National Institute of Health Research.
Sample size	N=686 (single-fraction radiotherapy: n=345; multiple fraction radiotherapy: n=341)

Study arms: single fraction radiotherapy (n=345) versus multi-fraction radiotherapy (n=341)

Outcomes

Outcome	Single fraction radiotherapy, n=345	Multiple fraction radiotherapy, n=341
Health related quality of life - EORTC QLQ-C30 Global health (standardised mean differences at 2 months between groups, adjusted for baseline values, range 0 –100, higher scores are better)	−0.13 (1 sided 97.5% CI −0.38 to ∞), p value for noninferiority = .12	
Health related quality of life - EORTC QLQ-C30 Physical functioning (standardised mean differences at 2 months between groups, adjusted for baseline values, range 0 – 100, higher scores are better)	−0.12 (1 sided 97.5% CI −0.35 to ∞), p value for noninferiority = .09	
Health related quality of life - EORTC QLQ-C30 Emotional functioning (standardised mean differences at 2 months between groups, adjusted for baseline values, range 0 – 100, higher scores are better)	−0.18 (1 sided 97.5% CI −0.41 to ∞), p value for noninferiority = .19	
Neurological and functional status - ability to walk after treatment (8-week ambulatory response rate, patients with Grade 1 or 2 ambulatory status, per protocol analysis - data available for 342/686 patients [single fraction 115/166; multiple fraction 128/176])	−3.9% (1 sided 95% CI −12.0% to ∞, *p* value for noninferiority = 0.7	
Neurological and functional status - normal bladder function (at any time point, results adjusted for bladder function at baseline, sex, age, baseline AS, primary tumour, number of SSC sites, the extent of metastases at baseline and extent of metastases)	n=184/316	n=211/322
Neurological and functional status - normal bowel function after treatment (at any time point, results adjusted for bowel function at baseline, sex, age, baseline AS, primary tumour, number of SSC sites, the extent of metastases at baseline and extent of metastases)	n=112/315	n=118/322

Outcome	Single fraction radiotherapy, n=345	Multiple fraction radiotherapy, n=341
Overall survival (event is death from any cause): single fraction	n=266/345	n=263/341
Pain - pain score (standardised mean difference between groups at 8 week follow-up)	SMD 0.12 (1 sided 97.5% CI ∞ to 0.38, p value for noninferiority = 0.28	
Treatment related morbidity – Grade 3 or 4 adverse events (number of patients who experienced an adverse event):	n=71/345	n=70/341

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low. *Single-fraction radiotherapy: 166 patients included in intention-to-treat analysis; Multifraction radiotherapy: 176 patients included in intention-to-treat analysis. Post hoc sensitivity analysis indicates results not biased by missing data.*
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low. *Trial protocol available as supplementary data.*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Howell, 2013 (RTOG 97-14 trial)

Howell D, James J, Hartsell W, et al. Single-fraction radiotherapy versus multifraction radiotherapy for palliation of painful vertebral bone metastases - Equivalent efficacy, less toxicity, more convenient: A subset analysis of Radiation Therapy Oncology Group trial 97-14. Cancer 119, 888-896, 2013

Study details

Country/ies where study was carried out	United States
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	• Patients with painful vertebral bone metastases if any of the treated sites were at the cervical, thoracic, or lumbar spine • treated for no more than 3 separate sites (multiple spine sites were allowed).
Exclusion criteria	• Patients with spinal cord compression • a Karnofsky performance status <40.
Patient characteristics	Age, median, years (range): Single fraction 69 (36 to 92); multiple fraction 68 (33 to 91). Mean and SD not reported. Sex: female n=105, male n=129. Type of malignancy, primary tumour: SFRT: 69 (36 to 92); MFRT: 68 (33 to 91) Level of compression: Patients with spinal cord compression were excluded. Location of metastasis in spine, treatment site: Cervical: SFRT: 12 (10%); MFRT: 7 (6%); Thoracic: SFRT: 44 (35%); MFRT: 40 (36%); Lumbar: SFRT: 63 (51%); MFRT: 58 (53%); Multiple sites: SFRT: 5 (4%); MFRT: 6 (5%) Evidence of bony instability / vertebral collapse on MRI: Not reported Mobility (ambulant or not): Not reported (treatment site weight bearing: SFRT: 48 (39%); MFRT: 36 (32%); non-weight bearing: SFRT: 76 (61%); MFRT: 75 (68%)

Intervention(s)/control	Single-fraction radiotherapy 8 Gy in 1 fraction *versus* multiple fraction radiotherapy 30 Gy in 10 fractions *Bisphosphonates, non-narcotic analgesics and narcotics were permitted.*
Duration of follow-up	3 months follow-up for pain, retreatment rates and overall survival followed up at 3, 6, 12, 36 and 60 months.
Sources of funding	Radiation Therapy Oncology Group (RTOG) grant and Community Clinical Oncology Program grant from the National Cancer Institute.
Sample size	N=235 (single fraction radiotherapy n=124; multiple fraction radiotherapy: n=111)

Study arms: Single fraction radiotherapy (n=124) versus multiple fraction radiotherapy (n=111)

Outcomes

Outcome	Single fraction radiotherapy, n=124	Multiple fraction radiotherapy, n=111
Overall survival (event is death from any cause; median follow-up 11 months):	**n=116/124**	**n=102/111**
Pain - complete or partial pain response (follow-up 1 to 3 months):	**n=54/77**	**n=47/76**
Treatment related morbidity - grade 2 to 4 adverse events:	**n=3/124**	**n=5/111**

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns. No information about allocation concealment.
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low. 93% patients received treatment within protocol borders, 96% received the total protocol dose, 99% received all fractions, and 99% did not have any treatment delays (no reasons given for differences to protocol).
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low

Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High. Outcome data not reported for all participants. Missingness could depend on outcome values and may not be balanced between groups.
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably yes
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns. Subjective outcomes could have been influenced by knowledge of the intervention received.
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High. Risk of bias due to allocation concealment and missing outcome data.
Overall bias and Directness	Overall Directness	Directly applicable

Lee, 2018 (ICORG 05-03 trial)

Lee K, Dunne M, Small C, et al. (ICORG 05-03): prospective randomized non-inferiority phase III trial comparing two radiation schedules in malignant spinal cord compression (not proceeding with surgical decompression); the quality of life analysis. Acta Oncologica, 1-8, 2018

Study details

Country/ies where study was carried out	Ireland and Northern Ireland (five sites).
Study type	Randomised controlled trial (RCT) 1:1 ratio
Study dates	January 2006 - April 2014.
Inclusion criteria	• 18 years or over • MRI-documented MSCC/cauda equina (MRI of the entire spine performed) • histologically proven malignancy (other than leukemia, myeloma, lymphoma, germ cell tumors, or primary tumors of the spine or vertebral column)

	• Karnofsky performance status 30 • written informed consent. In order to fulfill the definition of MSCC, patients were required to be symptomatic with radiological presence of a mass that touches, displaces, indents the spinal cord, or leads to complete loss of definition of spinal cord. Patients with two compression levels were eligible for inclusion.
Exclusion criteria	• Previous irradiation of relevant spinal segment • solitary bone metastasis with controlled primary site • patient deemed suitable for neurosurgical intervention.
Patient characteristics	N=104 (n=117 randomised – n=8 unable to complete baseline assessments, n=5 found to be ineligible after randomisation. Not all patients were included in the quality of life analysis. Age, mean, years (SD): 66.7 (13.1) (not reported by group). Sex: female n=38, male n=66. Type of malignancy, n: Breast – not analysed 3; analysed 19; total 22; lung – not analysed 14; analysed 4; total 18; Prostate – not analysed 8; analysed 17; total 25; other – not analysed 22; analysed 17; total 39; *p* <.0005 Level of compression: Cervical - not analysed 2, analysed 1, total 3; cervical–thoracic – not analysed 0, 2, total 2; thoracic - not analysed 26, analysed 44, total 70; lumbar - not analysed 17, analysed 9, total 26; lumbar-sacral - not analysed 1, analysed 0, total 1; sacral -not analysed 1; analysed 1, total 2. Muscle weakness: No - not analysed 8, analysed 27, total 35; yes - not analysed 39, analysed 30, total 69 (66) – *p* = .002 Mobility: Unaided - not analysed 13, analysed 32, total 45; with walking aid - not analysed 14, analysed 11, total 25; bed-bound - not analysed 20, analysed 14, total 34; *p* = .014 Pain VAS, mean (SD): not analysed 4.4 (3.5), analysed 4.6 (3.4), total 4.5 (3.4); *p* = .775 QLQ-C30 summary score (excluding financial impact and global quality of life), mean (SD): not analysed 49.3 (17.8), analysed 56.5 (16.3), total 53.2 (17.3); *p* = .036 QLQ-C30 physical functioning score, mean (SD): not analysed 26.0 (25.3), analysed 43.9 (32.1), total 35.8 (30.5); *p* = .002 QLQ-C30 pain score, mean (SD): not analysed 75.9 (31.2), analysed 69.0 (30.9), total 72.1 (31.1); *p* = .264.
Intervention(s)/control	Control: 20 Gy in five daily fractions, beginning on day of simulation. Experimental: A single 10 Gy fraction, delivered on day of simulation. • Radiotherapy fields defined to include anatomic area of spinal cord compression with a suitable margin, typically one to two vertebrae above and below the level of compression. • All patients simulated (conventional/CT) and underwent accurate localization of the treatment area on the treatment unit.

	• All patients treated with a linear accelerator or cobalt unit. • Field arrangement was at the discretion of the simulating physician. • If a direct posterior field was indicated, prescription was at cord depth. This was defined as the depth of the posterior border of the vertebral body. The depth of the posterior border of the vertebral body was calculated from diagnostic MRI images.
Duration of follow-up	• All patients followed up until death or for a median of 7 months (range: 1–103 months) from the end of RT. • Outcome assessment questionnaires completed prior to treatment; and at 5 weeks, 3 months and every 3 months thereafter from completion of treatment.
Sources of funding	St. Luke's Institute of Cancer Research and the Health Research Board.
Sample size	N=104 (n=44 not analysed for QoL outcome; n=57 analysed for QoL outcome). Control n=28/59; experimental n=29/58. n=8 patients unable to or declined to complete QoL questionnaire at baseline; n=5 patients in control group were too ill or died before the five fractions were delivered (1 patient had no baseline QoL completed); n=30 patients died before 5-week follow-up; 1 patient in control group lost to follow up; n=12 patients unable to or declined to complete the QoL questionnaire due to weakness, tiredness, illness or choice.

Study arms: 10 Gy in 1 fraction (n=58, external beam radiotherapy, delivered on day of simulation) versus 20 Gy in 5 fractions (n=59, external beam radiotherapy, five daily sessions, beginning on day of simulation).

Outcomes

Outcome	Single fraction radiotherapy, n=36	Multiple fraction radiotherapy, n=37
Neurological and functional status – ability to walk after treatment	**n=28/36**	**n=24/37**

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

intended interventions (effect of assignment to intervention)		
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns. 55% of patients analysed for QOL data. Missingness could have depended on outcome value.
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably yes
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns. Subjective or patient reported outcomes could have been influenced by knowledge of the intervention received.
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns. Risk of bias due to missing outcome data, and lack of blinding with regards to patient reported outcomes.
Overall bias and Directness	Overall Directness	Directly applicable

Majumder, 2012

Majumder D, Chatterjee D, Bandyopadhyay A, et al. Single Fraction versus Multiple Fraction Radiotherapy for Palliation of Painful Vertebral Bone Metastases: A Prospective Study. Indian Journal of Palliative Care, 18, 202-6, 2012

Study details

Country/ies where	India.

study was carried out	
Study type	Randomised controlled trial (RCT)
Study dates	July 2010 to May 2011.
Inclusion criteria	Histopathologically proven primary malignancy having symptomatic secondary deposits to the vertebra.
Exclusion criteria	• > 75 years • Karnofsky performance status < 40 • Features of cord compression
Patient characteristics	Age, median, years (range): multiple fraction 58 (55.64); single fraction 60 (56.64). Mean and SD not reported. Sex: female n=11, male n=53. Karnofsky Performance Status, n: 40 - multiple fraction 10, single fraction 12; 50 – multiple fraction 13, single fraction 10; 60 – multiple fraction 5, single fraction 4; 70 – multiple fraction 5, single fraction 5. Primary cancer, n: Breast – multiple fraction 3, single fraction 6; cervix - multiple fraction 2, single fraction 0; lung - multiple fraction 1, single fraction 1; prostate - multiple fraction 27, single fraction 24. Metastasis, n: cervical - multiple fraction 2, single fraction 1; lumbar - multiple fraction 18, single fraction 20; sacral - multiple fraction 3, single fraction 2; thoracic - multiple fraction 10, single fraction 8.
Intervention(s)/control	Multiple fraction RT - 30 Gy in 10 weeks vs Single fraction RT - 8 Gy in 1 fraction.
Duration of follow-up	Patients were followed every week of treatment and at the end of 1 month of treatment. For the patients of single fraction arm telephonic follow-up was done weekly up to 1 month for response assessment.
Sources of funding	None reported.
Sample size	Randomised: N=64. (intervention n=33, control n=31). Lost to follow-up: n=12 (multiple fractions n=7, single fraction n=4).
Other information	To assess "... pain response in patients with vertebral metastases after treating them with various radiation fractionations and to compare the toxicity profile in the treatment arms." Patients' pain was evaluated just before start of treatment using Visual Analogue Scale (VAS) for assessment of pain intensity. A 10 cm straight line was drawn with 0 at one end and 10 at other end. Patient was asked to mark his or her present pain intensity assuming 10 as worst pain and 0 to be no pain. Then patients were planned for radiation treatment. Clinically tender spines were first identified and vertebral levels were anatomically found out. Superior and inferior field borders were kept on one uninvolved vertebra on both sides. Lateral borders taken touching tips of transverse processes. Field borders were marked by metal wires and X-ray done.

	After confirmation of desired field borders by radiologic picture plans were accepted. Endpoints are defined as follows: Complete response: Complete subjective response without analgesic increase. Partial response: Reduction of 2 or more points (0-10 point scale) without analgesic increase. Pain progression: Increase in pain score 2 or more points with stable analgesic.

Study arms: 30 Gy in 10 fractions over 2 weeks (n=33) versus 8 Gy in a single fraction (n=31)

Outcomes

Outcome	Single fraction radiotherapy, n=31	Multiple fraction radiotherapy, n=33
Pain - complete or partial pain response (follow-up 1 to 3 months)	**n=25/31**	**n=27/33**
Treatment related morbidity - grade 2 to 4 adverse events	**n=3/31**	**n=12/33**
Treatment related morbidity - treatment discontinuation due to adverse events	**n=0/31**	**n=0/33**

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably yes
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Maranzano, 2005

Maranzano E, Bellavita R, Rossi R, et al. Short-course versus split-course radiotherapy in metastatic spinal cord compression: results of a phase III, randomized, multicenter trial. Journal of Clinical Oncology 23: 3358-65, 2005

Study details

Country/ies where study was carried out	Italy.
Study type	Randomised controlled trial (RCT) 1:1 randomisation ratio.
Study dates	February 1998 - November 2002.
Inclusion criteria	• Diagnosis of MSCC by MRI or CT. • No criteria indicating a primary surgical approach (ie, none of the following was present: diagnostic doubt, spinal instability, a vertebral body collapse causing bone impingement on the cord or nerve roots, or previous irradiation in the same area). • Short life expectancy (< 6 months) because of unfavorable histologies (ie, lung, kidney, GI, head and neck carcinoma, melanoma, or sarcoma) or favorable histologies (ie, lymphoma, seminoma, myeloma, and breast or prostate carcinoma) provided that motor or sphincter dysfunction and/or low performance status were also manifest. • Informed consent provided.
Exclusion criteria	None reported.
Patient characteristics	Age, median, years (range): short course 66 (30-87); split course 68 (34-89). Mean and SD not reported. Sex: female n=85, male n=191. Karnofsky performance status: ≤40 - total n=96, short course n=46, split course n=40; 50 -70 – total 143, short course 76, split course 67; 80-100 – total n=47, short course 20, split course n=27. Back pain: Yes – total n=262, short course n=136, split course n=126; no – total n=14, short course n=6, split course n=6.

	Motor function: Able to walk – total n=184, short course n= 93, split course n=91 (without support – total n=107, short course n=51, split course n=56; with support – total n=77, short course n=42, split course n=35); unable to walk – total – n=92, short course n=49, split course n=43 (not able to walk – total n=75, split course n=40, short course n=35; paraplegic – total n=17, short course n=9, split course n=8). Sphincter control: Normal – total n=246, short course n=126, split course n=120; abnormal – total n=29, short course n=16, split course n=13. Histology: Favourable – total n=99, short course n=50, split course n=49; unfavourable – total n=177, short course n=92, split course n=63. 24 patients not assessable as a result of early death (n=17) or lost to follow-up (n=7)
Interven-tion(s)/con-trol	Short course RT: 8 Gy, 6-day rest, and then 8 Gy, to a total dose of 16 Gy in 1 week). Split-course RT: 5 Gy x 3, 4-day-rest, and then 3 Gy x 5, to a total dose of 30 Gy in 2 weeks) All patients treated with fields covering the upper abdomen (ie, fields between T8 and L3 with an area of ≥ 100 cm2) received oral or parenteral adjuvant antiemetics (a 5-hydroxitriptamine-3 receptor antagonist) 30 to 60 minutes before each RT fraction. Emergency RT started within 24 hours of radiologic diagnosis and delivered from a 4- to 18-MV linear accelerator. Two vertebral bodies above and below the involved vertebrae and paravertebral mass were included in the treatment portal. Parenteral dexamethasone administered from first day of clinical-radiologic diagnosis until 4 to 5 days after the end of RT, and then tapered off during 10 days. No responders continued taking corticosteroids.
Duration of follow-up	Median follow-up was 33 months (range, 4 to 61 months).
Sources of funding	Not reported.
Sample size	N=300 randomised (n=276 assessable/included in outcomes analysis). Short course n=142. Split course n=134.

Study arms: short-course radiotherapy (total dose of 16 Gy in 1 week = 8 Gy, 6-day rest, and then 8 Gy), n=142 versus split-course radiotherapy (total dose of 30 Gy over 2 weeks - 3 fractions of 5 Gy, then 4-day-rest, then 5 fractions of 3 Gy), n=134

Outcomes

Outcome	Short-course RT (total dose of 16 Gy in 1 week), n=142	Split-course RT (total dose of 30 Gy over 2 weeks), n=134
Neurological and functional status - ability to walk (measured after treatment) – all patients	n=97/142	n=95/134
Neurological and functional status - normal sphincter control (measured after treatment)	n=128/142	n=119/134
Pain - complete or partial pain response - all patients ('complete' = without pain; 'partial' = pain responsive to 'minor' analgesics)	n=80/142	n=79/134
Treatment related morbidity - Grade 3 or higher adverse events (number of patients experiencing an adverse event)	n=3/142	n=5/134
Spinal stability - in field recurrence (number of patients with an event, diagnosed by MRI performed as a result of symptomatic progression: presence of neurologic signs/symptoms suggesting myelo-radicular compression	n=5/142	n=0/134

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably yes
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Maranzano, 2009

Maranzano E, Trippa F, Casale M, et al. 8Gy single-dose radiotherapy is effective in metastatic spinal cord compression: results of a phase III randomized multicentre Italian trial. Radiotherapy and Oncology 93, 174-9, 2009

Study details

Country/ies where study was carried out	Italy (13 sites).
Study type	Randomised controlled trial (RCT) 1:1 randomisation ratio.
Study dates	November 2002 - September 2007.
Inclusion criteria	• Metastatic spinal cord and/or cauda equina compression diagnosed by MRI or CT in patients with progressive neoplastic disease. • No criteria indicating a primary surgical approach (there were neither diagnostic doubts, nor spinal instability, bony compression causing MSCC, nor previous irradiation in the same area). • Patients with a short life expectancy (66 months) because of (a) the presence of unfavourable histologies (lung, kidney, gastrointestinal and head and neck carcinoma, melanoma, sarcoma), or (b) favourable ones (lymphoma, seminoma, myeloma, and breast or prostate carcinoma) provided that motor/sphincter dysfunction and/or low performance status were also manifested. • Informed consent.
Exclusion criteria	None reported.
Patient characteristics	Age, median, years (range): single fraction 67 (33-87); multiple fraction 67 (39-87). Mean and SD not reported. Sex: female n=106, male n=197. Karnofsky performance status, score, n: ≤40 short course 25, single dose 22; 50 – 70 short course 86, single dose 96; 80 – 100 short course 39, single dose 35. Back pain, yes, n: short course 134; single dose 137. Back pain, no, n: short course 16; single dose 16.

	Ambulatory, n: total - short course 101, split course 98 (walking without support - short course 59, single dose 55, walking with support – short course 42, single dose 43). Not ambulatory, n: total – short course 49, single dose 55 (not walking – short course 40, single dose 38; paraplegic – short course 9, single dose 17. Sphincter control, normal, n: short course 135; single dose 127. Sphincter control, abnormal, n: short course 15, single dose 26. Histology – favourable, n: short course 48; single dose 43. Histology – unfavourable, n: short course 102; single dose 110.
Intervention(s)/control	Single fraction RT (8 Gy) versus Short course RT (8 Gy x 2 with 6 days rest in between two doses with a total dose of 16 Gy in 1 week. Radiotherapy started within 24/48 h of radiologic diagnosis and delivered by a 4–18 MV linear accelerator. General recommendations for physicians participating in the trial were as follows: (1) radiation portals centred on the site of epidural compression and extended two vertebral bodies above and below; (2) paravertebral mass included in the treatment portal according to MRI and/or CT definition; (3) radiotherapy field defined on a treatment simulator and dose prescribed at cord depth as measured by MRI or CT scans and/or simulator lateral radiograph; (4) cervical spine lesions treated with opposed lateral fields, thoracic spine with a simple posterior field, or with two opposed antero-posterior fields and differential dose contribution (in the ratio of 2–3 to 1 in favour of the posterior field), and lumbar spine with opposed antero-posterior fields which were, if necessary, differently weighted at RT isocentre. All patients treated with fields covering the upper abdomen (fields between T8 and L3 with an area of P100 cm2) received oral or parenteral adjuvant antiemetics (a 5-hydroxytriptamine receptor [5-HT3] antagonist) 30–60 min before each RT fraction (single dose n=55, short course n=59). Parenteral dexamethasone (8 mg x 2/day) was administered from the first day of clinical-radiologic diagnosis until 4–5 days after the end of RT, and then tapered off over 10 days. No responders continued steroids.
Duration of follow-up	Median follow-up = 31 months (range, 4–58). Overall survival measured from date of randomisation to date of death from any cause.
Sources of funding	Not reported.

Sample size	N=327 randomised, n=303 assessable (n=21 lost to follow-up, n=3 early deaths, details on groups to which these patients were allocated are not reported clearly). Intervention (single dose of 8 Gy) n=153 assessable. Control (2 x 8 Gy) n=150 assessable.

Study arms: 8 Gy single dose (n=153) versus 8 Gy x 2 short course (n=150)

Outcomes

Outcome	Single fraction radiotherapy, n=153	Multiple fraction radiotherapy, n=150
Neurological and functional status - ability to walk after treatment	**n=95/153**	**n=104/150**
Neurological and functional status - normal bowel function after treatment	**n=130/153**	**n=131/150**
Overall survival (event is death from any cause)	**n=153/153**	**n=150/150**
Pain - complete or partial pain response	**n=80/153**	**n=80/150**
Treatment related morbidity: Grade 3 or 4 adverse events	**n=0/153**	**n=2/150**

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns. Outcome data available for around 66% of patients. Missingness could depend

		on outcome values but appears balanced between groups.
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Patchell, 2005

Patchell R, Tibbs P Regine W, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet 366, 643-8, 2005

Study details

Country/ies where study was carried out	United States (7 sites).
Study type	Randomised controlled trial (RCT) Stratified according to treating institution, tumour type, ambulatory status, and relative stability of the spine. Randomisation within strata by permutated blocks was done separately at each institution with a computerised technique, which ensured immediate randomisation at study entry.
Study dates	September 1992 to December 2002.
Inclusion criteria	• At least 18 years old • Tissue-proven diagnosis of cancer (not of CNS or spinal column origin) • MRI evidence of MESCC • General medical status good enough to be acceptable surgical candidates

	• Expected survival of at least 3 months. • At least one neurological sign or symptom of MESCC (including pain). • Not totally paraplegic for longer than 48 hours before study entry. Confirmation of MESCC: MESCC defined radiographically as a true displacement of the spinal cord (by an epidural mass) from its normal position in the spinal canal. MESCC had to be restricted to a single area, which could include several contiguous spinal or vertebral segments. Before randomisation, all patients had imaging of the entire spinal cord. The imaging technique consisted of MRI with whole spine sagittal T1 and T2 imaging and axial T1 imaging. Additional MRI techniques were used as clinically appropriate. There was a central review of all MRI scans for confirmation of MESCC.
Exclusion criteria	• Patients with a mass that compressed only the cauda equina or spinal roots. • Patients with multiple discrete compressive lesions (unless they had one area of compression and multiple non-compressive lesions). • Patients with certain radiosensitive tumours (lymphomas, leukaemia, multiple myeloma, and germ-cell tumours) • Patients with pre-existing or concomitant neurological problems not related directly to their MESCC (eg, brain metastases). • Patients with previous MESCC and those who had received spinal radiation such that they were unable to receive the study dose.
Patient characteristics	Age, median, years (range): Surgery + RT 60; RT only 60. No further details reported. Sex: female n=31, male n=70. Primary tumours (n): lung – radiation 13, surgery 13; breast - radiation 6, surgery 7; prostate - radiation 10, surgery 9; other genitourinary - radiation 6, surgery 5; gastrointestinal - radiation 4, surgery 2; melanoma - radiation 3, surgery 3; head and neck – radiation 2, surgery 1; unknown -radiation 3, surgery 5; other radiation 4, surgery 5. Walking at entry (n): Radiation 35; surgery 34. Continent at entry (n): Radiation 32; surgery 30. Median Frankel score at entry: Radiation D; surgery D. D=ambulatory but with neurological symptoms. Median ASIA score at entry: Radiation 90; surgery 89. Spinal level of compression – Cervical - radiation 5, surgery 8; T1-T6 – radiation 18, surgery 20; T7-T12 – radiation 28, surgery 22. Position of spinal tumour - anterior – radiation 33, surgery 28; lateral - radiation 11, surgery 9; posterior – radiation 7, surgery 13. Unstable spine – radiation 18, surgery 20. Median time between diagnosis of primary tumour and development of MESCC, months: radiation 7; surgery 3. Median time between development of motor symptoms and treatment of MESCC, days: radiation 12; surgery 10 days.

Interven-tion(s)/con-trol	**Radiotherapy only:** • 30 Gy (3 x 10 fractions). • Started within 24 hours of randomisation. • Treatments delivered to a port that encompassed one vertebral body above and below the visible lesion. • Protocol compliance monitored through central review of radiotherapy treatment plans. **Direct decompressive surgery followed by radiotherapy:** Operation within 24 hours of randomisation. RT delivered as per intervention group, within 14 days after surgery. Surgical technique: Protocol did not specify operative techniques or fixation devices. However, the aim of surgery was to provide immediate direct circumferential decompression of the spinal cord. The operation was tailored for each patient depending on the level of the spine involved and the patient's circumstances. In general, for anteriorlylocated tumours the approach in the cervical spine was anterior, and in the thoracic and lumbar spine, depending on the tumour location, the approach was through a transversectomy or anterior approach. For laterally-located tumours, a lateral approach was used, and for posteriorly-located tumours, a laminectomy was done and any other posterior elements involved were removed. Stabilisation of tumours in all locations was performed if spinal instability was present; cement (methyl methacrylate), metallic rods, bone grafting, or other fixation devices were used. Within 1 month of treatment Phillip Tibbs reviewed operative reports and William Regine reviewed plans for post-surgery radiotherapy to monitor protocol compliance. Patients were given radiotherapy, as in the radiation group, within 14 days after surgery. Steroids given on same schedule for both groups. When diagnosed, all patients were given 100 mg dexamethasone immediately, then 24 mg every 6 h until the start of radiotherapy or surgery. Corticosteroids were then reduced and continued until completion of radiotherapy. Patients with severe diabetes or other relative contraindications to high-dose corticosteroids were treated with reduced doses when appropriate.
Duration of follow-up	All time dependent endpoints measured from the day of randomisation until death or last follow up. Overall median follow-up times were 102 days (IQR 0–1940) in the surgery + RT group and 93 days (IQR 0–1117 days) in the radiation group (p=0.10). Patients had neurological assessments before treatment, weekly during radiotherapy, and within 1 day after completion of treatment. Patients then had regular study follow-up assessments every 4 weeks until the end of the trial or

	death. Patients were also reassessed at any time they had symptoms suggestive of neurological progression.
Sources of funding	Grants from - National Cancer Institute (RO1 CA55256), and National Institute for Neurological Disorders and Stroke (K24 NS502180).
Sample size	N=101 randomised. Surgery plus radiotherapy n=50. Radiotherapy alone n=51.
Other information	The trial was stopped early after a comparison of ambulatory rates between the two groups using a Cochran-Mantel-Haenszel statistic based on ambulatory status. This comparison yielded a p value of 0.001, which fell below the predetermined significance level for early termination of the trial according to the O'Brien Fleming rule ($p < 0.0054$). Because of proven superiority of surgical treatment, the data safety and monitoring committee deemed the trial should be stopped early. Spinal stability was ascertained according to Cybulski's guidelines. Patients with pathological spine fractures or evidence of bone in the spinal canal were also judged to have spinal instability. Protocol violations occurred with five patients. In the surgery group, three patients did not receive postoperative radiotherapy and a fourth patient stopped radiotherapy before receiving the complete course. In the radiation group, one patient was treated with surgery as well as postoperative radiotherapy. **Outcome measurement:** Ambulatory status results calculated as follows using 2 methods: • Combined ambulatory rate = Percentage of patients who maintained or regained ability to walk immediately after completion of radiotherapy. • Ambulatory time after treatment to give a measure of long-term success. Patients were deemed ambulatory if they could take at least two steps with each foot unassisted (4 steps total), even if a cane or walker was needed. Corticosteroid use assessed by calculating and comparing mean daily dexamethasone equivalent doses. Pain relief assessed by calculating and comparing mean daily morphine equivalent doses.

Study arms: direct decompressive surgery followed by radiotherapy (n=50, radiotherapy consisted of 30 Gy in 10 fractions administered 14 days after surgery) versus radiotherapy alone (n=51, radiotherapy consisted of 30 Gy in 10 fractions)

Outcomes

Outcome	Surgery + radiotherapy, n=50	Radiotherapy alone n=51
Neurological and functional status - ambulant after treatment - all patients	n=42/50	n=29/51
Neurological and functional status - ambulant after treatment – patients ambulatory at study entry, n=69	n=32/34	n=26/35
Neurological and functional status - ambulant after treatment - patients non ambulatory at study entry, n=32	n=10/16	n=3/16
Neurological and functional status - maintenance of continence (time to incontinence), median, days	156	17
Neurological and functional status - maintenance of muscle strength (time ASIA score was maintained), median, days	566	72
Neurological and functional status - maintenance of functional ability (time Frankel score was maintained), median, days	566	72
Pain - median [IQR] daily equivalent dose of morphine, mg	0.4 (IQR 0.0–60.0)	4.8 (IQR 0.0–200.0)
Treatment related morbidity - 30 day mortality	3/50	7/51

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Rades, 2016 (SCORE-2 trial)

Rades D, Šegedin B, Conde-Moreno A, et al, Radiotherapy With 4 Gy × 5 Versus 3 Gy × 10 for Metastatic Epidural Spinal Cord Compression: final results of the SCORE-2 Trial (ARO 2009/01). Journal of Clinical Oncology 34, 597-602, 2016

Study details

Country/ies where study was carried out	Germany
Study type	Randomised controlled trial (RCT). Stratified for ambulatory status, time developing motor deficits before RT, and type of primary tumour.
Study dates	July 2010 and May 2015.
Inclusion criteria	• MRI (or CT) confirmed diagnosis of MESCC. • Motor deficits of lower extremities because of MESCC of the thoracic or lumbar spinal cord • No previous surgery or RT to parts of the spinal cord affected by MESCC. Poor or intermediate survival prognosis (defined as a total prognostic score of less than or equal to 35 points in a validated scoring system).
Exclusion criteria	Patients with other severe neurologic disorders including symptomatic brain metastases were not included.
Patient characteristics	Age, years, n: ≤ 68 n=103, ≥ 68 n=100. Mean and SD not reported. Sex: female n=79, male n=124. Ambulatory status before RT *p* = .99 Ambulatory without aid, n: total = 52; 4 Gy x 5 = 26; 3 Gy x 10 = 26. Ambulatory with aid, n: total 65; 4 Gy x 5 = 32; 3 Gy x 10 = 33. Not ambulatory, n: total 86; 4 Gy x 5 = 43; 3 Gy x 10 = 43. Time developing motor deficits before RT, days, n: *p* = .99 1-7 – total = 92; 4 Gy x 5 = 46; 3 Gy x 10 = 46. 8-14 total = 53; 4 Gy x 5 = 26; 3 Gy x 10 = 27 > 14 – total = 58; 4 Gy x 5 = 29; 3 Gy x 10 = 29. Type of primary tumor, n : *p* = .99 Breast cancer – total = 32; 4 Gy x 5 = 16; 3 Gy x 10 = 16.

	Prostate cancer – total = 32; 4 Gy x 5 = 16; 3 Gy x 10 = 16. Myeloma/lymphoma – total = 16; 4 Gy x 5 = 8; 3 Gy x 10 = 8. Lung cancer – total = 58; 4 Gy x 5 = 29; 3 Gy x 10 = 29. Other tumors – total = 65; 4 Gy x 5 = 32; 3 Gy x 10 = 33. ECOG performance status (ECOG: Eastern Cooperative Oncology Group), n: *p* = .57 1-2 – total = 69; 4 Gy x 5 = 31; 3 Gy x 10 = 38. ≥ 3 – total = 134; 4 Gy x 5 = 70; 3 Gy x 10 = 64. Number of involved vertebrae, n: *p* = .97 1-2 – total = 111; 4 Gy x 5 = 55; 3 Gy x 10 = 56. ≥ 3 – total = 92; 4 Gy x 5 = 46; 3 Gy x 10 = 46. Other bone metastases at time of RT, n: *p* = .89 No – total = 28; 4 Gy x 5 = 13; 3 Gy x 10 = 15. Yes – total = 175; 4 Gy x 5 = 88; 3 Gy x 10 = 87. Visceral metastases at time of RT, n: *p* = .99 No – total = 46; 4 Gy x 5 = 23; 3 Gy x 10 = 23. Yes – total = 157; 4 Gy x 5 = 78; 3 Gy x 10 = 79. Interval from tumour diagnosis to MESCC, months: *p* = .66 ≤ 5 - total = 106; 4 Gy x 5 = 55; 3 Gy x 10 = 51. > 5 – total = 97; 4 Gy x 5 = 46; 3 Gy x 10 = 51. Administration of bisphosphonates: . 97 No – total = 119; 4 Gy x 5 = 59; 3 Gy x 10 = 60. Yes – total = 84; 4 Gy x 5 = 42; 3 Gy x 10 = 42.
Interven-tion(s)/con-trol	4 Gy x 5 in 1 week versus 3 Gy x 10 in 2 weeks. RT performed with a linear accelerator and 6 to 18MeV photons. In the 4 Gy x 5 group, 61 patients (60.4%) were treated with 18 MeV photons alone, 14 patients (13.9%) with lower energies alone, and 26 patients (25.7%) with mixed energies, compared with 22 patients (21.6%), 60 patients (48.8%), and 20 patients (19.6%), respectively, in the 3 Gy 3 10 group (P = .53, x2 test). Treatment volumes encompassed one normal vertebra above and below the metastatic lesions. Three-dimensional conformal RT was performed in 68 patients (67.3%) of the 4 Gy x 5 group and 73 patients (71.6%) of the 3 Gy x 10 group (P=.71, x2 test). The other patients were treated with a single posterior field or opposed fields.
Duration of follow-up	1 month.
Sources of funding	Merck Serono.
Sample size	N=203 randomised. 4 Gy x 5 n=101; 3 Gy x 10 n=102.

	Lost to follow-up: 4 Gy x 5 n=1; 3 Gy x 10 n=2. Died prior to 1 month follow-up: 4 Gy x 5 n=22; 3 Gy x 10 n=23. Analysed: 4 Gy x 5 n=78; 3 Gy x 10 n=77.
Other information	Local progression free survival and overall survival both counted from the last day of RT. Local progression free survival defined as freedom from both deterioration of motor deficits during or directly after RT and in-field recurrence of MESCC during follow-up. **Results also reported from:** **Rades 2018 [SCORE-2 trial]** Rades D, Conde-Moreno A, Cacicedo J et al. Comparison of Two Radiotherapy Regimens for Metastatic Spinal Cord Compression: subgroup Analyses from a Randomized Trial. Anticancer Research 38, 1009-1015, 2018 **Rades 2019 [SCORE-2 trial]** Rades D, Segedin B, Conde-Moreno A, et al. Patient-Reported Outcomes-Secondary Analysis of the SCORE-2 Trial Comparing 4 Gy x 5 to 3 Gy x 10 for Metastatic Epidural Spinal Cord Compression. International Journal of Radiation Oncology, Biology, Physics, 105, 760-764, 2019

Study arms: 4 Gy x 5 in 1 week (n=101) versus 3 Gy x 10 in 2 weeks (n=102)

Outcomes

Outcome	Short course radiotherapy, n=101	Long course radiotherapy n=102
Neurological and functional status - ambulatory status (1 month follow-up)	n=56/78	n=57/77
Neurological and functional status - motor deficits improved or stable (1 month follow-up)	n=68/78	n=69/77
Overall survival (6 months follow-up)	n=9/101	n=9/102
Pain - complete or partial pain response (1 month follow-up)	n=36/101	n=40/102
Treatment related morbidity - grade 3 or 4 acute toxicity Grade 3 acute toxicity	n=0/101	n=0/102

Critical appraisal – Cochrane RoB 2

Section	Question	Answer

Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns. For some outcomes/timepoints relatively large numbers of patients had been lost to follow-up or died.
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably yes
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Roos, 2005 (TROG 96-05 trial)

Roos D, Turner S, O'Brien, P, et al. Randomized trial of 8 Gy in 1 versus 20 Gy in 5 fractions of radiotherapy for neuropathic pain due to bone metastases (Trans-Tasman Radiation Oncology Group, TROG 96.05). Radiotherapy and Oncology 75, 54-63, 2005

Study details

Country/ies where study was carried out	Australia, New Zealand, and UK.
Study type	Randomised controlled trial (RCT) 2 arm, 1:1 randomisation ratio, stratification by centre.
Study dates	February 1996 - December 2002.
Inclusion criteria	• Pathologically confirmed malignancy. • Plain X-ray or bone scan evidence of bone metastasis at the index site. • Pain or dysaesthesia predominantly of a neuropathic nature • Life expectancy at least six weeks. • Able to complete the pain assessments. • Written informed consent. Computed tomography and/or magnetic resonance imaging of the index site were not mandatory, reflecting contemporary palliative RT practice in Australasia at the time of trial conception.
Exclusion criteria	• Metastasis within the distribution of the neuropathic pain (shaft of femur metastasis with L2 neuropathic pain). • Prior radiotherapy to the index site. • Clinical or radiological evidence of compression of the spinal cord or cauda equina. • Pathological fracture of long bone(s) at index site. • Change in systemic therapy within 6 weeks before, or anticipated within 4 weeks after, commencing radiotherapy. • Neuropathic pain due primarily to extra-skeletal tumour (pre-sacral recurrence of rectal carcinoma).
Patient characteristics	Age, median, years (range): single fraction 67 (29-86); multiple fraction 68 (32-89). Mean and SD not reported. Sex: female n=76, male n=196. Primary site: single dose group - lung n=45, prostate n=38, breast n=9, other n=45; multiple fraction group – lung n=39, prostate n=41, breast n=14, other n=41. Systematic treatment at randomisation: single dose group – chemotherapy n=3, hormonal therapy n=34; multiple fraction group – chemotherapy n=9, hormonal therapy n=42. Index site: single dose group – spine n=117, rib n=17, other n=3; multiple fraction group – spine n=124, rib n=8; other n=3. Pre-treatment index pain severity: single dose group – none n=1, mild n=28, moderate n=56, severe n=51, unknown n=1; multiple fraction group – none n=0, mild n=20, moderate n= 59, severe n=54, unknown n=2. NB. ‘none’ = mild pain at randomisation but no pain at pre-treatment assessment due to increased analgesia.

	Pre-treatment index pain analgesia (patients may be in more than 1 category): single dose group – none n=6, non-opioid analgesic n=87, corticosteroid n=27, n=adjuvant analgesic n=22, opioid n=107; multiple fraction group - none n=6, non-opioid analgesic n=95, corticosteroid n=24, n=adjuvant analgesic n=19, opioid n=108. NB. Non opioid analgesic = non-steroidal anti-inflammatory drug or paracetamol; adjuvant analgesic = anti-convulsant or anti-depressant. Concurrent pain elsewhere: single dose group n=47; multiple fraction group n=38.
Intervention(s)/control	Single dose of 8 Gy versus 20 Gy in 5 fractions. Non-index sites could be treated with RT at clinicians' discretion. The protocol specified use of photon or electron RT as appropriate. The spine was to be treated with direct fields prescribed to 5 cm depth (D5); ribs with direct fields to applied dose (Dmax); other sites with parallel opposed fields to mid-plane. A simulator or portal film was required for correlation with diagnostic imaging of the putative index site in the eligibility audits. Other treatment details were according to clinicians' usual practice. Source data verification of the RT prescription and treatment records was carried out for all patients. The dosimetric consequences of prescription point protocol violations were classified using TROG criteria as minimal/per protocol (within ± 5% of protocol dose), minor/acceptable (> 5–10% variation) or major/unacceptable (> 10% variation). Ten patients did not receive per protocol fractionation because of early death (4), cord compression while awaiting RT (3, erroneous diagnosis for 1), patient refusal (2), prior RT to the index site (1). All patients were treated with megavoltage photons or electrons except one who had orthovoltage photons due to linac waiting time. Patients randomized to 20/5 waited significantly longer to commence RT than patients randomized to 8/1 (PZ0.0043), reflecting departmental scheduling constraints with fractionated treatment (20/5 median 5 days, range 0–41 days; 8/1 median 2, range 0–34). More patients on 8/1 than 20/5 had concurrent RT to other sites, but the difference was not significant (p = 0.079). Source data verification of the RT prescription and treatment records for all patients was commenced late in the trial when it became evident that compliance with the protocol prescription point and treatment technique may be in question. Protocol violations were detected in 57 patients (21%). These comprised prescription of postero-anterior spine fields to other than D5 (range Dmax to D9) (47 patients), non-protocol technique (parallel opposed spine fields) (8) and electron fields prescribed to 95% rather than Dmax (2). Major dose violations were detected in 17 patients (6%). There were no significant differences between arms (P = 0.66 for all violations; PZ0.46 for major violations).
Duration of follow-up	Patients followed until death or close-out date of trial. No further details provided.

Sources of funding	Royal Adelaide Hospital Special Purposes Fund Grant-In-Aid; and National Health and Medical Research Council Research Grant 981871.
Sample size	N=272 randomised. Single fraction n=137; multiple fractions n=135.
Other information	Pain assessment = patient reported (in person at clinic visits, by telephone or, rarely, by post), using validated diagrams to show areas of pain (rated as severe, moderate, mild or none). Analgesics recorded at assessments scheduled pre-treatment, 2 and 4 weeks after commencement of RT, at 2 and 3 months, then three monthly until treatment failure or death. Response defined as an improvement in pain score by at least 1 grade with no increase in analgesia for the index pain. Complete response defined as a change in pain score from severe, moderate, or mild to none with no analgesia or adjuvant analgesia for the index pain. Treatment failure = first of any of: worsening in pain score by at least one category and/or significant increase in analgesia (> 50% increase in dose; change from non-opioid to opioid), re-irradiation, progression/development of pathological fracture, or development of clinical cord/cauda equina compression. Acute side effects of RT graded according to the Radiation Therapy Oncology Group (RTOG) criteria and recorded at four weeks as the worst grade experienced since commencing RT. ‘Flare effect’ (defined as a temporary increase in pain at the index site within a week of commencing RT) added to the case record form as a protocol amendment 15 months after trial activation and was recorded for 194 patients. This was graded mild, moderate, severe increase in pain. Changes in systemic anti-cancer treatment since randomization, development of new pathological fracture or progression of vertebral crush fracture, and spinal cord/cauda equina compression at the index site were also recorded. Re-treatment was at clinicians’ discretion. The reasons for not re-treating were recorded following a protocol amendment 15 months after trial activation. Patients followed up to death or the close-out date except for two lost to follow-up. Nine patients remained alive without failure at the close-out date (median follow-up 11 months, range 3–77) and one ineligible patient was lost to follow-up from the date of RT. Twenty patients (7%) were found to have eligibility infringements, 10 per arm, either at eligibility audit or from systematic checking of the case record forms. Of those with another metastasis along the distribution of neuropathic pain, three also probably did not have genuine NBP. Although there were instances

	where the dermatome(s) recorded on the case record forms did not match the truly involved spinal level, no cases of 'geographical miss' with RT fields were detected. Reasons why patients were not assessable – no radiotherapy given – single fraction 3/137, multiple fractions 2/135; early death (within 32 days) – single fraction 7/137, multiple fractions 6/135; no follow-up/non-compliance – single fraction 2/137; multiple fractions 4; no pre-treatment assessment – single fraction 0/137, multiple fractions 1/135; masked by other pain or changes in analgesia/systemic therapy – single fraction 6/137, multiple fractions 7/135

Study arms: Single 8 Gy fraction (n=44) versus 20 Gy in 5 fractions (n=46)

Outcomes

Outcome	Single fraction radiotherapy, n=137	Multiple fraction radiotherapy, n=135
Overall survival (event is death from any cause; median follow-up 11 months):	n=126/137	n=122/135
Pain - complete or partial pain response (follow-up 1 to 3 months):	n=73/137	n=83/135
Treatment related morbidity - moderate or severe flare effect	n=12/137	n=4/135
Spinal stability - cord compression (median follow-up 11 months)	n=9/137	n=8/135
Spinal stability - fractures (median follow-up 11 months)	n=6/137	n=5/135

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low. Protocol violations were identified however there was no significant differences between groups and these deviations were consistent with what could occur outside the trial context.
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by	Probably no

Section	Question	Answer
	knowledge of intervention received?	
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable. *Included some patients who did not have spinal metastases (rib, ilium, skull, and clavicle: - 8 Gy in single fraction n=20/137; 20 Gy in 5 fractions n=11/35.)*

Sahgal, 2021

Sahgal A, Myrehaug S, Siva S, et al. Stereotactic body radiotherapy versus conventional external beam radiotherapy in patients with painful spinal metastases: an open-label, multicentre, randomised, controlled, phase 2/3 trial. Lancet Oncology 22, 1023-1033, 2021

Study details

Country/ies where study was carried out	Canada and Australia
Study type	Randomised controlled trial (RCT) Open-label, multicentre, randomised controlled, phase 2/3 trial.
Study dates	January 2016 to September 2019
Inclusion criteria	• Aged 18 years or older • painful MRI-confirmed spinal metastases (defined as a worst pain score of ≥2 of 10, according to the Brief Pain Inventory [BPI]) • not intending to change pain medications on the first day of protocol radiotherapy treatment • no more than three consecutive spinal segments in the radiotherapy treatment volume site • an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 • metastases arising from a solid primary tumour (excluding seminoma and small-cell lung cancer) • Spinal Instability in Neoplasia Score (SINS) of 12 or less • received no previous radiotherapy that would compromise the study interventions

	• undergone no previous spinal surgical procedures at the study target volume site • no neurological deficits resulting from malignant epidural spinal cord or cauda equina compression.
Exclusion criteria	"Systemic chemotherapy was not allowed at least 1 week before and after study radiotherapy delivery, and centre guidelines applied with respect to non-cytotoxic systemic therapy, with the proviso that no systemic anticancer therapy (excluding endocrine therapy) be administered within 24 h before or after radiotherapy" (p. 1024). Exclusion criteria reported at https://clinicaltrials.gov/ct2/show/NCT02512965: • Patients who have a pacemaker, such that MRI cannot be performed or treatment cannot be delivered safely • prior treatment with any radionuclide within 30 days prior to randomization • prior radiation to the spinal segment intended to be treated with protocol radiotherapy such that the protocol therapy cannot be delivered as intended • prior surgery to the spinal segment intended to be treated with protocol radiotherapy • patients who have received chemotherapy within 1 week prior to administration of protocol radiotherapy or who are expected/planned to receive chemotherapy within one week of completing protocol radiotherapy. Centre guidelines regarding administration of targeted non-cytotoxic therapy must be followed with the proviso that no systemic anticancer therapy should be administered within 24 hours prior to and post-radiotherapy Endocrine therapy may be administered during radiotherapy as per the discretion of the treating physician • spine instability as judged by a Spinal Instability Neoplastic Score (SINS) of more than 12 • symptomatic spinal cord compression or cauda equina syndrome resulting from bony compression or epidural compression of the spinal cord and cauda equina, respectively • pregnant or lactating women.
Patient characteristics	Age, n: 18 to 59 n=83; 60 to 69 n=61; ≥70: n=85. Sex: female n=109, male n=120. Type of malignancy, primary tumour: Breast: Conventional external beam radiotherapy: 27 (23%); Stereotactic body radiotherapy: 23 (20%); Genitourinary (excluding renal cell carcinoma): Conventional external beam radiotherapy: 25 (22%); Stereotactic body radiotherapy: 21 (18%); Lung: Conventional external beam radiotherapy: 26 (23%); Stereotactic body radiotherapy: 35 (31%); Gastrointestinal: Conventional external beam radiotherapy: 15 (13%); Stereotactic body radiotherapy: 14 (12%); Renal cell: Conventional external beam radiotherapy: 7 (6%); Stereotactic body radiotherapy: 13 (11%); Head and neck: Conventional external beam radiotherapy: 3 (3%); Stereotactic body radiotherapy: 5 (4%); Melanoma: Conventional external beam radiotherapy: 5 (4%); Stereotactic body radiotherapy: 2 (2%); Other: Conventional external beam radiotherapy: 7 (6%); Stereotactic body radiotherapy: 1 (1%)

	Level of compression: *Reported as extent of epidural disease‡* Unknown: Conventional external beam radiotherapy: 0; Stereotactic body radiotherapy: 4 (4%); None: Conventional external beam radiotherapy: 56 (49%); Stereotactic body radiotherapy: 61 (54%); Low grade: Conventional external beam radiotherapy: 53 (46%); Stereotactic body radiotherapy: 47 (41%); High grade: Conventional external beam radiotherapy: 6 (5%); Stereotactic body radiotherapy: 2 (2%) *or* Location of metastasis in spine, treatment site: *Spinal location of target vertebrae:* Cervical: Conventional external beam radiotherapy: 8 (7%); Stereotactic body radiotherapy: 11 (10%); Thoracic: Conventional external beam radiotherapy: 61 (53%); Stereotactic body radiotherapy: 50 (44%); Lumbar: Conventional external beam radiotherapy: 42 (37%); Stereotactic body radiotherapy: 41 (36%); Sacral: Conventional external beam radiotherapy: 4 (3%); Stereotactic body radiotherapy: 8 (7%) Evidence of bony instability / vertebral collapse on MRI: *Reported as Spinal Instability in Neoplasia score (SINS)†* 0 to 6: Conventional external beam radiotherapy: 46 (40%); Stereotactic body radiotherapy: 57 (50%); 7 to 12: Conventional external beam radiotherapy: 69 (60%); Stereotactic body radiotherapy: 57 (50%); Median SINS score (range): Conventional external beam radiotherapy: 7 (6 to 8); Stereotactic body radiotherapy: 7 (5 to 8) *Location:* Junctional: Conventional external beam radiotherapy: 47 (41%); Stereotactic body radiotherapy: 48 (43%); Mobile spine: Conventional external beam radiotherapy: 31 (27%); Stereotactic body radiotherapy: 33 (29%); Semi-rigid: Conventional external beam radiotherapy: 34 (30%); Stereotactic body radiotherapy: 27 (24%); Rigid: Conventional external beam radiotherapy: 3 (3%); Stereotactic body radiotherapy: 4 (4%) *Pain:* Mechanical pain: Conventional external beam radiotherapy: 28 (24%); Stereotactic body radiotherapy: 19 (17%); Occasional pain (not mechanical): Conventional external beam radiotherapy: 87 (76%); Stereotactic body radiotherapy: 93 (83%); Pain-free lesion: Conventional external beam radiotherapy: 0; Stereotactic body radiotherapy: 0 *Bone lesion:* Osteolytic: Conventional external beam radiotherapy: 45 (39%); Stereotactic body radiotherapy: 50 (45%); Mixed (osteolytic and osteoblastic): Conventional external beam radiotherapy: 40 (35%); Stereotactic body radiotherapy: 29 (26%); Osteoblastic: Conventional external beam radiotherapy: 30 (26%); Stereotactic body radiotherapy: 33 (29%) *Spinal alignment:* Subluxation or translation present: Conventional external beam radiotherapy: 0; Stereotactic body radiotherapy: 1 (1%); Deformity (kyphosis or scoliosis): Conventional external beam radiotherapy: 3 (3%); Stereotactic body radiotherapy: 3 (3%); Normal: Conventional external beam radiotherapy: 112 (97%); Stereotactic body radiotherapy: 108 (96%) *Vertebral body collapse:* ≥50% collapse: Conventional external beam radiotherapy: 3 (3%); Stereotactic body radiotherapy: 1 (1%); <50% collapse: Conventional external beam radiotherapy: 37 (32%); Stereotactic body radiotherapy: 25 (22%); No collapse with ≥50% body involvement: Conventional external beam radiotherapy: 35 (30%); Stereotactic body radiotherapy: 21 (19%); None of the above: Conventional external beam radiotherapy: 40 (35%); Stereotactic body radiotherapy: 65 (58%)

	Posterolateral element involvement: Bilateral: Conventional external beam radiotherapy: 38 (33%); Stereotactic body radiotherapy: 31 (28%); Unilateral: Conventional external beam radiotherapy: 48 (42%); Stereotactic body radiotherapy: 44 (39%); None of the above: Conventional external beam radiotherapy: 29 (25%); Stereotactic body radiotherapy: 37 (33%) *(Baseline SINS source forms were missing for two (2%) of 114 patients in the stereotactic body radiotherapy group).* Mobility (ambulant or not): Not reported
Intervention(s)/control	Conventional external beam radiotherapy; total dose 20 Gy delivered in five consecutive daily fractions by either a parallel-opposed pair (anteroposterior and posteroanterior fields), or a three-dimensional conformal technique allowing the delivery of up to four beams. Intensity-modulated radiotherapy and volumetric-modulated arc therapy were not permitted in the conventional external beam radiotherapy group. *versus* Stereotactic body radiotherapy; total dose of 24 Gy delivered in two consecutive daily fractions, according to standard spinal stereotactic body radiotherapy techniques specified in the study protocol and the radiotherapy quality assurance (RTQA) manual.
Duration of follow-up	1, 3 and 6 months after last radiotherapy fraction treatment (median follow-up was 6.7 months; IQR 6.3 to 6.9).
Sources of funding	Canadian Cancer Society (Canada) and National Health and Medical Research Council (Australia and New Zealand).
Sample size	N=229 (Conventional external beam radiotherapy: n=115; Stereotactic body radiotherapy: n=114)
Other information	• Each centre required a minimum of two investigators to be credentialed by central review of a protocol-specific spinal stereotactic body radiotherapy treatment plan. • The painful spinal metastasis was identified as the radiation study target vertebral segment volume site by the radiation oncologist based on patient history, patient physical examination, and interpretation of the baseline spine MRI. ‡"The extent of epidural disease is at the target level and represents the worst extent of epidural disease; low grade refers to grade 1a, 1b, and 1c on the malignant epidural spinal cord compression scale, and high grade refers to grade 2 or 3" (p. 1027). †"The SINS ranges from 0 to 18, with higher values indicating greater instability; a SINS score of 0–6 is classified as stable, 7–12 as potentially unstable, and 13–18 as unstable" (p. 1027).

Study arms: External beam radiotherapy (n=115) versus stereotactic body radiotherapy (n=114)

Outcomes

Outcome	1 month, External beam radiotherapy, N = 115	1 month, Stereotactic body radiotherapy, N = 114	3 month, External beam radiotherapy, N = 115	3 month, Stereotactic body radiotherapy, N = 114	6 month, External beam radiotherapy, N = 115	6 month, Stereotactic body radiotherapy, N = 110
Complete response No of events	n = 20 ; % = 17	n = 30; % = 26	n = 16 ; % = 14	n = 40 ; % = 35	n = 18 ; % = 16	n = 37 ; % = 32
Partial response No of events	n = 33 ; % = 29	n = 34 ; % = 30	n = 29 ; % = 25	n = 20 ; % = 18	n = 18 ; % = 16	n = 10 ; % = 9
Stable pain No of events	n = 38 ; % = 33	n = 26 ; % = 23	n = 34 ; % = 30	n = 27 ; % = 24	n = 32 ; % = 28	n = 26 ; % = 23
Progressive pain No of events	n = 14 ; % = 12	n = 9 ; % = 8	n = 14 ; % = 12	n = 7 ; % = 6	n = 8 ; % = 7	n = 5 ; % = 4
Mean daily OME consumption (mg) OME = oral morphine equivalents Mean (SD)	44 (122)	27 (95)	43 (106)	37 (97)	36 (126)	36 (84)
Death No of events	*empty data*	*empty data*	*empty data*	*empty data*	n = 30 ; % = 26	n = 26 ; % = 23
Radiation site-specific progression-free survival rates No of events	n = 99 ; % = 86	n = 105 ; % = 92	n = 79 ; % = 69	n = 86 ; % = 75	*empty data*	*empty data*
Overall survival No of events	n = 102 ; % = 89	n = 106 ; % = 93	n = 84 ; % = 73	n = 88 ; % = 77	*empty data*	*empty data*
Grade 3 adverse event No of events	*empty data*	*empty data*	*empty data*	*empty data*	n = 5 ; % = 4	n = 5 ; % = 5
Vertebral compression fracture of any grade No of events	*empty data*	*empty data*	*empty data*	*empty data*	n = 20 ; % = 17	n = 12 ; % = 11

Outcome	1 month, External beam radiotherapy, N = 115	1 month, Stereotactic body radiotherapy, N = 114	3 month, External beam radiotherapy, N = 115	3 month, Stereotactic body radiotherapy, N = 114	6 month, External beam radiotherapy, N = 115	6 month, Stereotactic body radiotherapy, N = 110
Global quality of life change score from baseline Mean (SD)	0.4 (21.4)	3.1 (21.4)	3 (27.3)	2.9 (27.3)	5.9 (30)	0.8 (30)

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High. Patients in the stereotactic body radiotherapy group had higher oral analgesic intake at baseline (mean daily OME 184.4 [SD 816.7]) than those in the conventional external beam radiotherapy group (69.5 [SD 105.4])
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably yes. For patient-reported outcomes.
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Sprave, 2018a (IRON-1 trial)

Sprave T, Verma V, Förster R et al. Radiation-induced acute toxicities after image-guided intensity-modulated radiotherapy versus three-dimensional conformal radiotherapy for patients with spinal metastases (IRON-1 trial): first results of a randomized controlled trial. Strahlentherapie und Onkologie 194, 911-920, 2018

Study details

Country/ies where study was carried out	Germany
Study type	Randomised controlled trial (RCT) Prospective, randomised, single centre, explorative pilot trial
Study dates	November 2016 to May 2017
Inclusion criteria	• Histologically confirmed tumour and spinal bone metastases • indication for palliative radiotherapy of vertebral bone metastases, including pain and/or neurological deficits In addition to the above, inclusion criteria were: • Aged 18 to 85 years • a Karnofsky performance score ≥ 50 (ECOG ≤2) • ability to provide written informed consent (Sprave 2018a and b)
Exclusion criteria	• Patients with significant neurological or psychiatric disorders precluding informed consent • previous radiotherapy to the same irradiation site • radiosensitive (multiple myeloma or lymphoma) histology. Number or location of metastases were not specific criteria for inclusion or exclusion, nor was the presence of spinal cord compression (Sprave 2018a and b).
Patient characteristics	Age, mean, years (SD): IMRT: 66.1 (10.5); conventional RT: 62.5 (11.8). Sex: female n=27, male n=33. Type of malignancy, primary tumour: Lung: IMRT: 11 (36.7%); 3DCRT: 16 (53.3%); Breast: IMRT: 7 (23.3%); 3DCRT: 6 (20%); Prostate: IMRT: 6 (20%);

	3DCRT: 1 (3.3%); Other (renal cancer, gastrointestinal stromal tumour, carcinoma of unknown primary, melanoma, mesothelioma, pancreatic cancer): IMRT: 6 (20%); 3DCRT: 7 (23.3%) Level of compression: Presence of spinal cord compression was not a specific inclusion or exclusion criteria (Sprave 2018a and b) *or* Location of metastasis in spine, treatment site: Cervical: IMRT: 4 (13.3%); 3DCRT: 5 (16.7%); Thoracic: IMRT: 15 (50%); 3DCRT: 15 (50%); Lumbar: IMRT: 11 (36.7%); 3DCRT: 10 (33.3%) (Sprave 2018); Sacrum: IMRT: 0 (0%); 3DCRT: 3 (10%) (Sprave 2018 a and b) *(Number of metastases: 1: IMRT: 17 (56.7%); 3DCRT: 10 (33.3%); 2: IMRT: 14 (13.3%); 3DCRT: 9 (30%); 3: IMRT: 9 (30%); 3DCRT: 11 (36.7%))* *(Distant metastases at baseline: Visceral: IMRT: 14 (46.7%); 3DCRT: 10 (33.3%); Lung: IMRT: 7 (23.3%); 3DCRT: 6 (20%); Brain: IMRT: 4 (13.3%); 3DCRT: 5 (16.7%); Tissue: IMRT: 5 (16.7%); 3DCRT: 5 (16.7%)* Evidence of bony instability / vertebral collapse on MRI: Not reported Mobility (ambulant or not): Not reported
Intervention(s)/control	**Intensity modulated radiotherapy (IMRT):** image-guided radiotherapy by means of step-and-shoot IMRT, VMAT, or helical TomoTherapy; administered in 10 fractions of 3 Gy *versus* **Conventional 3-dimensional conformal radiotherapy (3DCRT):** most commonly delivered two or three anteroposterior 6 MV individually formed beams; administered in 10 fractions of 3 Gy In addition, patients were taking medication including sleeping medication, psychiatric medication, opiates and NSAIDs at baseline.
Duration of follow-up	3 months (Sprave 2018) and 6 months (Sprave 2018 a and b).
Sources of funding	None.
Sample size	N=60 (IMRT: n=30; 3DCRT: n=30)
Other information	Results also reported from: Sprave 2018a (Sprave, T, Verma, V, Förster, R et al. (2018) Bone density and pain response following intensity-modulated radiotherapy versus three-dimensional conformal radiotherapy for vertebral metastases - secondary results of a randomized trial. Radiation oncology (London, England) 13(1): 212). Sprave 2018b (Sprave, T, Verma, V, Förster, R et al. (2018) Quality of Life and Radiation-induced Late Toxicity Following Intensity-modulated Versus Three-dimensional Conformal Radiotherapy for Patients with Spinal Bone Metastases: results of a Randomized Trial. Anticancer research 38(8): 4953-4960).

Study arms: IMRT (N = 30) versus 3DCRT (N = 30)

Outcomes

Outcome	IMRT, 3 month, N = 20	IMRT, 6 month, N = 18	3DCRT, 3 month, N = 19	3DCRT, 6 month, N = 12
Bone density (Hounsfield Units) Mean (SD)	90.5 (134.2)	124 (166)	35 (87.1)	132 (157.7)
Pathological fractures No of events	n = 3 ; % = 15	n = 3 ; % = 16.7	n = 2 ; % = 10.5	n = 2 ; % = 16.7
Complete response No of events	n = 10 ; % = 50	n = 7 ; % = 41.2	n = 5 ; % = 26.3	n = 3 ; % = 25
Partial response No of events	n = 4 ; % = 20	n = 5 ; % = 29.4	n = 4 ; % = 20.1	n = 4 ; % = 33.3
Pain progression No of events	n = 1 ; % = 5	n = 2 ; % = 11.8	n = 3 ; % = 15.8	n = 3 ; % = 25
Intermediate pain No of events	n = 5 ; % = 25	n = 3 ; % = 17.7	n = 7 ; % = 36.8	n = 2 ; % = 16.7
1-2 No of events	n = 59 ; % = 40.1	n = 11 ; % = 31.4	n = 85 ; % = 57.8	n = 17 ; % = 48.6
3-4 No of events	n = 2 ; % = 1.4	n = 1 ; % = 2.9	n = 1 ; % = 0.7	n = 6 ; % = 17.1
Painful sites Mean (SD)	24.3 (24.1)	28.6 (22.6)	32.6 (23)	31.1 (25.5)
Pain characteristics Mean (SD)	31.1 (42.1)	35.3 (35.2)	31 (25)	29.6 (29.7)
Functional interference Mean (SD)	36.9 (31.2)	39.2 (28.5)	37.1 (26.8)	38.9 (26.1)
Psychosocial aspects (QOL) Mean (SD)	45.6 (28.7)	39.2 (28.5)	58.5 (23.3)	52.8 (17.8)

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

intended interventions (effect of assignment to intervention)		
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High. SABR: 19 patients (70%) analysed (ITT basis) at follow-up; 3DCRT 23 patients (82%) analysed (ITT basis) at follow-up).
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably yes. For patient-reported outcomes.
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns. Subjective or patient reported outcomes could have been influenced by knowledge of the intervention received.
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High. Risk of bias due to missing outcome data, and potential for bias in patient reported outcomes.
Overall bias and Directness	Overall Directness	Directly applicable

Sprave, 2018e (NCT- 02358720)

Sprave T, Verma V, Forster R, et al, Randomized phase II trial evaluating pain response in patients with spinal metastases following stereotactic body radiotherapy versus three-dimensional conformal radiotherapy. Radiotherapy and Oncology 128, 274-282, 2018

Study details

Country/ies where	Germany

study was carried out	
Study type	Randomised controlled trial (RCT) Randomised, single-institutional, non-blinded, phase II explorative trial
Study dates	November 2014 to March 2017
Inclusion criteria	• Aged 18 to 80 years • Karnofsky performance score >70 • ability to provide written informed consent • a maximum of 2 irradiated vertebral bodies per region • a maximum of 2 different vertebral regions affected • tumour distance >3 mm to the spinal cord. Additional inclusion criteria (https://clinicaltrials.gov/ct2/show/NCT02358720) • Patients with a histologically confirmed tumour diagnosis, with secondary diagnosed solitary/multiple spinal bone metastases • indication for radiotherapy of the spinal bone metastases.
Exclusion criteria	• Patients with significant neurological or psychiatric disorders precluding informed consent • previous radiotherapy to the given irradiation site • contraindications for MRI • multiple myeloma or lymphoma histology, or involvement of the cervical spine. "The prerequisite for participation in the study was the exclusion of spinal cord compression, along with a sufficient distance (>3 mm) between the metastasized vertebral body and spinal cord on MRI" (p. 275).
Patient characteristics	Age, mean, years (SD): Stereotactic ablative body RT 61 (8.2); conventional RT 63.9 (10.8). Sex: female n=27, male n=28. Type of malignancy, primary tumour: Lung: SABR: 9 (33.3%); 3DCRT: 10 (35.7%); Breast: SABR: 7 (26.3%); 3DCRT: 10 (35.7%); Renal: SABR: 2 (7.4%); 3DCRT: 2 (7.1%); Other: SABR: 9 (33.3%); 3DCRT: 6 (21.4%) Level of compression: Patients did not have spinal cord compression at baseline Location of metastasis in spine, treatment site: Thoracic: SABR: 14 (51.9%); 3DCRT: 19 (67.9%); Lumbar: SABR: 13 (48.1%); 3DCRT: 8 (28.6%) *(Distant metastases at baseline: Visceral: SABR: 12 (44.4%); 3DCRT: 14 (51.9%); Lung: SABR: 11 (40.7%); 3DCRT: 4 (14.8%); Brain: SABR: 7 (25.9%); 3DCRT: 3 (11.1%); Tissue: SABR: 5 (18.5%); 3DCRT: 4 (14.8%))* Evidence of bony instability / vertebral collapse on MRI: Not reported Mobility (ambulant or not): Not reported.
Intervention(s)/control	**High dose single fraction stereotactic ablative body radiotherapy SABR versus 3DCRT** **High dose single-fraction stereotactic ablative body radiation therapy (24 Gy to the 80% isodose line) (SABR):** treatment was delivered using one

	of three possible techniques (VMAT with 6 MV flattering filter free (FFF) beams delivered at a dose rate of 1400 MU/min; TomoTherapy involving image guidance comprising pre-treatment megavoltage CT, followed by delivery of 12 Gy, followed by repeat megavoltage CT, and delivery of the remaining 12 Gy; step-and-shoot IMRT with flattened 6 MV photons). **Conventionally-fractionated 3D-conformal radiotherapy (30 Gy in 10 fractions) (3DCRT):** irradiation of the involved vertebral body as well those immediately above and below at a total dose of 30 Gy in 10 fractions, mostly delivered with 3 or 4 anteroposterior/posteroanterior beams. In addition, use of basic pain medications and other concurrent medications were permitted. Neuropathic pain use, opioid analgesic usage and any non-opioid analgesics were also permitted.
Duration of follow-up	3 and 6 months.
Sources of funding	Tschira Foundation.
Sample size	N=60 (SABR: n=30; 3DCRT: n=30)
Other information	Results also reported from: Sprave, T., Verma, V., Forster, R. et al. (2018) Quality of Life Following Stereotactic Body Radiotherapy Versus Three-Dimensional Conformal Radiotherapy for Vertebral Metastases: Secondary Analysis of an Exploratory Phase II Randomized Trial. Anticancer Research 38: 4961-4968. Sprave, T., Verma, V., Forster, R. et al. (2018) Local response and pathologic fractures following stereotactic body radiotherapy versus three-dimensional conformal radiotherapy for spinal metastases - a randomized controlled trial. BMC Cancer 18: 859. **Medication at baseline:** Sleeping medication: SABR: 1 (3.7%); 3DCRT: 1 (3.6%) Psychiatric medication: SABR: 3 (11.1%); 3DCRT: 5 (17.9%) Opiate: SABR: 11 (40.7%); 3DCRT: 10 (35.7%) NSAID: SABR: 15 (55.6%); 3DCRT: 15 (53.6%)

Study arms: stereotactic ablative body radiotherapy (SABR, n=30) versus 3-dimensional conformal radiotherapy (3DCRT, n=30)

Outcomes

Outcome	SABR, 3 month, N = 23	SABR, 6 month, N = 19	3DCRT, 3 month, N = 23	3DCRT, 6 month, N = 20
Painful sites Mean (SD)	31.6 (18.6)	23.2 (20.2)	25.5 (21.3)	27.7 (19.7)
Pain characteristics Mean (SD)	26.6 (25)	31.6 (18.2)	25.5 (21.3)	27.8 (27.8)

Outcome	SABR, 3 month, N = 23	SABR, 6 month, N = 19	3DCRT, 3 month, N = 23	3DCRT, 6 month, N = 20
Functional interference Mean (SD)	29.7 (24.6)	38.2 (19.6)	29.9 (19.5)	34.8 (19.8)
Psychosocial aspects (QOL) Mean (SD)	50.2 (26.3)	44.7 (27.6)	52.9 (21.9)	46.4 (21)
Bone density (Hounsfield Units) Median (IQR)	231 (196 to 420)	336.5 (215 to 481)	310 (234 to 428)	363.5 (218.5 to 463.5)
Pathological fractures No of events	n = 23; % = 47.8	n = 18; % = 61.1	n = 23; % = 21.7	n = 20; % = 30
Complete response No of events	n = 10; % = 43.5	n = 10; % = 52.6	n = 4; % = 17.4	n = 2; % = 10
Partial response No of events	n = 6; % = 26.1	n = 4; % = 21.1	n = 7; % = 30.43	n = 5; % = 25
Pain progression No of events	n = 2; % = 8.7	n = 2; % = 10.5	n = 0; % = 0	n = 0; % = 0
Intermediate pain No of events	n = 5; % = 21.7	n = 3; % = 15.8	n = 12; % = 52.2	n = 13; % = 65
Neuropathic pain Mean (SD)	0 (0)	0.1 (0.2)	0 (0.2)	0.1 (0.2)

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns. No information provided regarding allocation concealment.
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns. Three patients in the IMRT group and 2 patients in the 3DCRT interrupted/did not complete the treatment owing to systemic neoplastic progression and declining performance status. No information about whether participants were aware of their assigned intervention during the trial. No information about whether carers and those delivering the intervention were aware of participants assigned intervention during the trial.
Domain 2b: Risk of bias due to deviations from the	Risk of bias judgement for deviations	Low

intended interventions (effect of adhering to intervention)	from the intended interventions (effect of adhering to intervention)	
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High. IMRT: 17/30 (57%) patients; 3DCRT: 12/30 (40%) patients analysed on ITT basis.
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably yes. For patient reported outcomes.
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns. Patient reported outcomes could have been influenced by knowledge of the intervention received.
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low. Trial registered at ClinicalTrials.gov (NCT02832830).
Overall bias and Directness	Risk of bias judgement	High. Potential risk of bias in relation to allocation concealment, deviations from the intended interventions, missing outcome data and patient reported outcomes.
Overall bias and Directness	Overall Directness	Directly applicable

Steenland, 1999 (Dutch Bone Metastasis trial)

Steenland E, Leer J, van Houwelingen H, et al. The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. Radiotherapy and Oncology, 52, 101-109, 1999

Study details

Country/ies where study was carried out	The Netherlands
Study type	Randomised controlled trial (RCT)
Study dates	March 1996 to September 1998

Inclusion criteria	• Patients with painful bone metastases from a solid tumour; pain score of at least 2 on an 11-point scale from 0 (no pain at all) to 10 (worst imaginable pain) at time of admission to the radiotherapy department • the painful bone metastases had to be treatable in one target volume • patients with favourable prognosis, that is patients with breast cancer with no visceral metastases in a long term complete remission (more than 1 year) due to first line systemic treatment and patients with a diagnosis of prostate cancer, a Karnofsky index of 60% or more, who had not been treated by hormonal treatment were eligible for inclusion to answer the question whether patients with a longer life expectancy would also benefit from a single dose of irradiation.
Exclusion criteria	• Patients with painful bone metastases that had previously been irradiated, or a pathological fracture that needed surgical fixation or a spinal cord compression • patients with metastases of malignant melanoma or renal cell carcinoma (considered to express a different biological behaviour) • patients with metastases in the cervical spine (it was believed that large fractions might lead to a radiation induced myelopathy).
Patient characteristics	Age, mean, years (SD): single frac-tion 65 (SD not reported); multiple fraction 65 (SD not reported). Sex: female n=533, male n=624. Type of malignancy, primary tumour: Breast: 4 Gy x 6: 38%; 8 Gy x 1: 40%; Prostate: 4 Gy x 6: 24%; 8 Gy x 1: 22%; Lung: 4 Gy x 6: 25%; 8 Gy x 1: 25%; Other: 4 Gy x 6: 13%; 8 Gy x 1: 13% Level of compression: Not reported Location of metastasis in spine, treatment site: Thoracic/lumbar spine: 4 Gy x 6: 30%; 8 Gy x 1: 29% (Pelvis: 4 Gy x 6: 39%; 8 Gy x 1: 34%; Femur: 4 Gy x 6: 11%; 8 Gy x 1: 9%; Ribs: 4 Gy x 6: 8%; 8 Gy x 1: 9%; Humerus: 4 Gy x 6: 5%; 8 Gy x 1: 6%; Other: 4 Gy x 6: 7%; 8 Gy x 1: 13% Other metastases: Lung: 4 Gy x 6: 5%; 8 Gy x 1: 4%; Liver: 4 Gy x 6: 5%; 8 Gy x 1: 5%; Bone (non-painful): 4 Gy x 6: 67%; 8 Gy x 1: 68%; Lymph nodes: 4 Gy x 6: 8%; 8 Gy x 1: 10%; Other: 4 Gy x 6: 15%; 8 Gy x 1: 13% Evidence of bony instability / vertebral collapse on MRI: Not reported Mobility (ambulant or not): Not reported
Intervention(s)/control	Single dose of 8 Gy *versus* 24 Gy in 6 fractions. No guidelines or restrictions were formulated with respect to the radiation technique.
Duration of follow-up	• Self-assessment questionnaires relating to pain at treatment site, analgesics consumption, quality of life and side effects were completed by patients every week up to 3 months and then every 4 weeks up to 2 years • the number of fractions and total dosage given, the need for reirradiation, the occurrence of spinal cord compression and/or fractures along with data on systemic treatment were collected at three-monthly intervals.

	Data collection stopped when completion of questionnaires became too strenuous for patients or at death.
Sources of funding	Health Care Insurance Board.
Sample size	N=1157 (N=578 in the 4 Gy x 6 group and N=579 in the 8 Gy x 1 group)* 25% patients completed less than 4 of 14 questionnaires; 37% of patients stopped completing questionnaires due to death, 13% stopped due to closure of the study, and 50% mostly due to ill health. At 1 year after randomisation, N=98 in the 4 Gy x 6 group and N=107 in the 8 Gy x 1 group. *N=1171 patients originally randomised, but n=14 patients retrospectively did not meet the inclusion criteria: 6 because of the presence of multiple painful bone metastases that could not be encompassed in one volume; 3 because of previous irradiation; 3 because of the occurrence of fractures that needed surgical fixation at time of randomisation and 2 because of diagnoses that appeared to be non-Hodgkin lymphoma and osteoporosis respectively.
Other information	Outcome data analysed on an intention-to-treat basis. Baseline characteristics were reported for non-randomised patients. Reasons for non-randomisation included: no informed consent (22%), pain score less than 2 (8%), no solid tumour (1%), no single target volume possible (24%), fractured bones that needed surgery (8%), spinal cord compression (13%), previous irradiation (8%), cervical bone metastases (6%), melanoma or renal cell carcinoma (6%), and for some institutes favourable diagnosis of breast cancer (3%) or prostate cancer (1%).

Study arms: 8 Gy x 1 (n=585) versus 4 Gy x 6 (n=586)

Outcomes

Outcome	**8 Gy x 1, 4 month, n=165**	**4 Gy x 6, 4 month, n=177**
Number of fractures (number of patients with event)	n=4	n=1

Critical appraisal – Cochrane RoB 2

Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns. *No difference in baseline characteristics with the exception of the number of males and females.*
Domain 2a: Risk of bias due to deviations from the intended interventions	Risk of bias for deviations from the intended interventions (effect of	Some concerns. *No information about whether participants were aware of their assigned intervention during the trial. No information about whether carers and those de-*

Section	Question	Answer
(effect of assignment to intervention)	assignment to intervention)	*livering the intervention were aware of participants assigned intervention during the trial.*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns. *No information about adherence or non-protocol interventions.*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High. *At 1 year after randomisation: N=205 patients remained (4 Gy x 6: N=98; 8 Gy x 1: N=107). Missingness could depend on outcome values and may not be balanced between groups.*
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably yes. *For patient-reported outcomes.*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns. *Patient reported outcomes could have been influenced by knowledge of the intervention received.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns. *Unclear whether there was a pre-specified trial protocol.*
Overall bias and Directness	Risk of bias judgement	High. Potential risk of bias relating to adherence to interventions, as well as missing outcome data and reporting of results.
Overall bias and Directness	Overall Directness	Directly applicable

Appendix E Forest plots

Forest plots for review question: How effective is radiotherapy, including both fractionated and unfractionated radiotherapy, for the management of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Comparison 1: Spinal metastases patients - single fraction radiotherapy versus multiple fraction radiotherapy

Figure 2: Overall survival

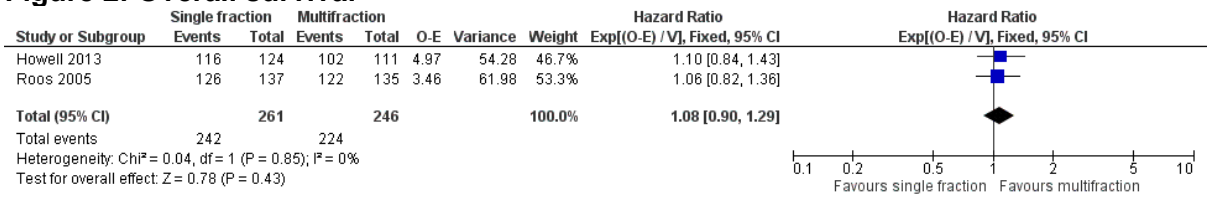


Figure 3: Pain: Complete or partial pain response (follow-up 1 to 3 months)

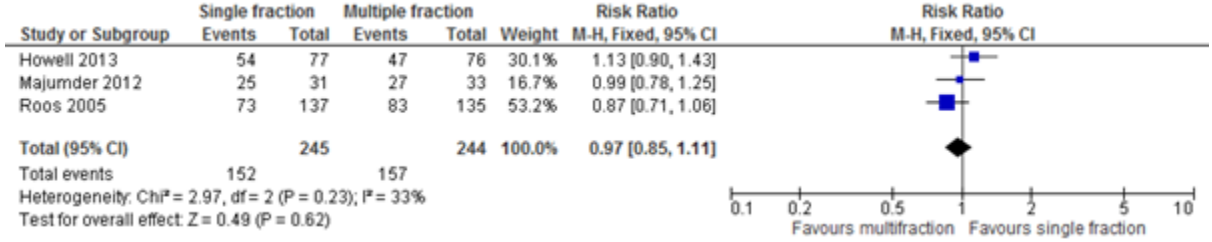


Figure 4: Treatment related morbidity: Grade 2 to 4 adverse events

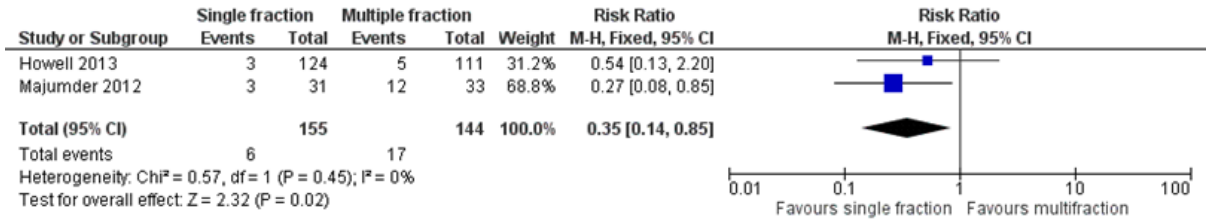
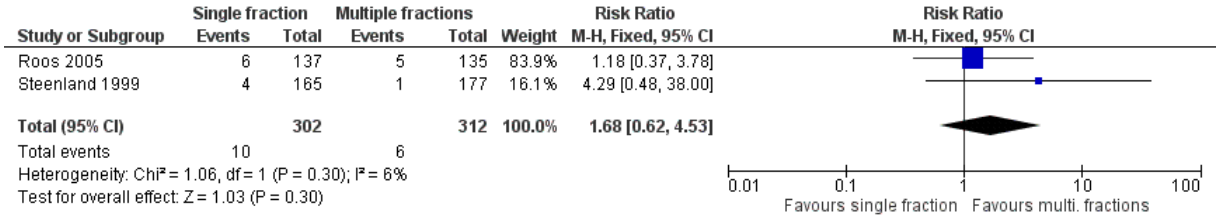


Figure 5: Spinal stability: Fractures (median follow-up 11 months)



Comparison 2: Patients with metastatic spinal cord compression - single fraction radiotherapy versus multiple (or short) fraction radiotherapy

Figure 6: Neurological and functional status: Ability to walk after treatment

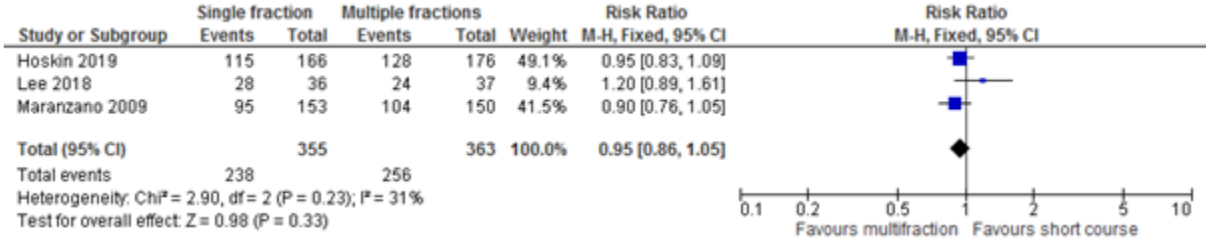


Figure 7: Neurological and functional status: Normal bowel function after treatment

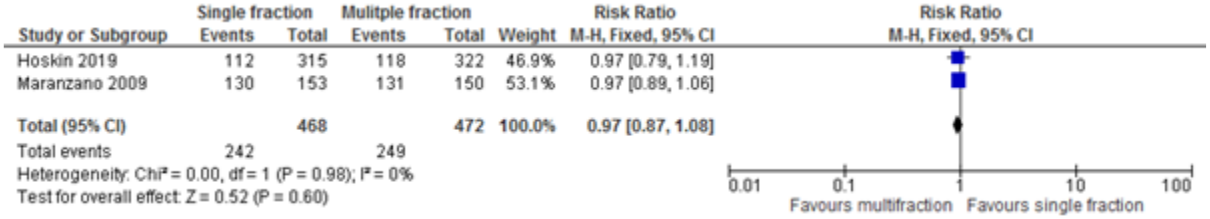


Figure 8: Overall survival

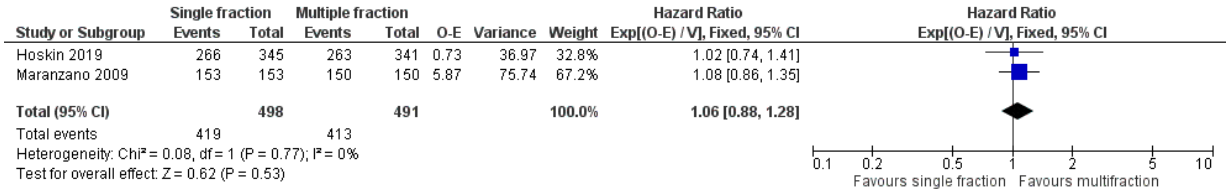
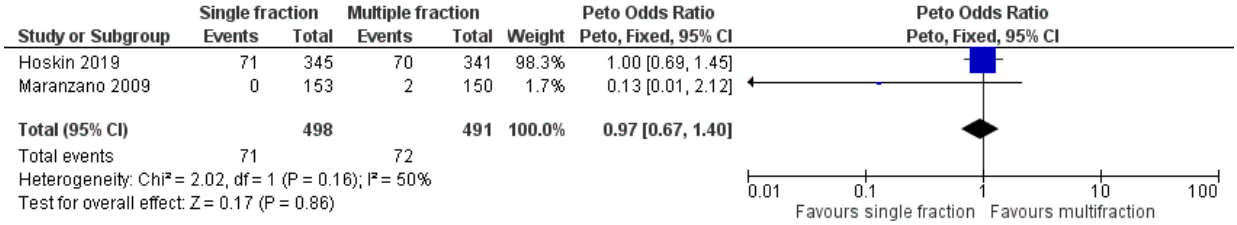


Figure 9: Treatment related morbidity: Grade 3 or 4 adverse events



Comparison 4: Spinal metastases patients – Stereotactic ablative body radiotherapy versus conventional radiotherapy

Figure 10: Pain: complete or partial pain response (6 months follow-up)

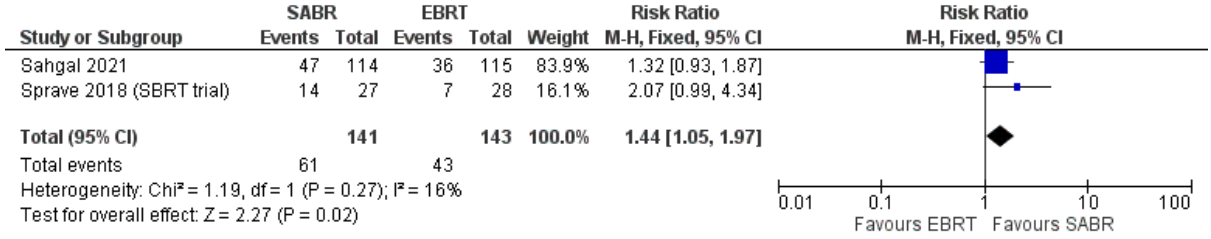
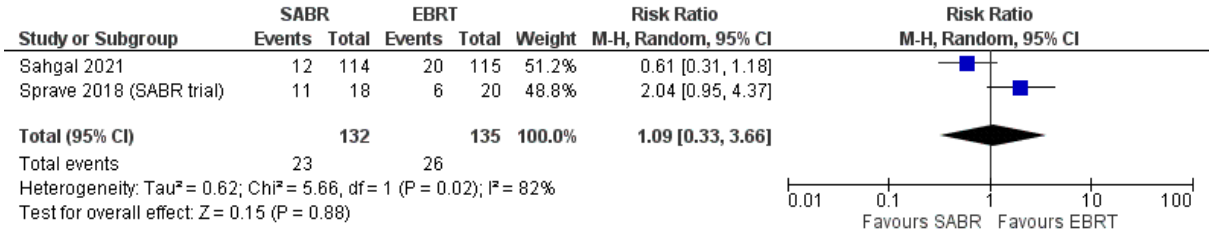


Figure 11: Spinal stability: vertebral compression fracture of any grade - 6 months



Appendix F GRADE tables

GRADE tables for review question: How effective is radiotherapy, including both fractionated and unfractionated radiotherapy, for the management of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Table 6: Evidence profile for comparison 1: Spinal metastases patients - single fraction radiotherapy versus multiple fraction radiotherapy

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single fraction RT	Multiple fraction RT	Relative (95% CI)	Absolute		
Overall survival (event is death from any cause; median follow-up 11 months)												
2[6]	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	242/261 (92.7%)	224/246 (91.1%)	HR 1.08 (0.9 to 1.29)	16 more per 1000 (from 24 fewer to 45 more)	VERY LOW	CRITICAL
Pain - complete or partial pain response (follow-up 1 to 3 months)												
3[7]	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	152/245 (62%)	157/244 (64.3%)	RR 0.97 (0.85 to 1.11)	19 fewer per 1000 (from 97 fewer to 71 more)	VERY LOW	CRITICAL
Treatment related morbidity - grade 2 to 4 adverse events												
2[8]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	6/155 (3.9%)	17/144 (11.8%)	RR 0.35 (0.14 to 0.85)	77 fewer per 1000 (from 18 fewer to 102 fewer)	VERY LOW	IMPORTANT
Treatment related morbidity - moderate or severe flare effect												
1 (Roos 2005)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	12/137 (8.8%)	4/135 (3%)	RR 2.96 (0.98 to 8.94)	58 more per 1000 (from 1 fewer to 235 more)	LOW	IMPORTANT
Treatment related morbidity - treatment discontinuation due to adverse events												
1 (Majumder 2012)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	0/31 (0%)	0/33 (0%)	Not estimable	0 fewer per 1000 (from 60 fewer to 60 more)	LOW	IMPORTANT
Spinal stability - cord compression (median follow-up 11 months)												
1 (Roos 2005)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[5]	none	9/137 (6.6%)	8/135 (5.9%)	RR 1.11 (0.44 to 2.79)	7 more per 1000 (from 33 fewer to 106 more)	VERY LOW	IMPORTANT

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single fraction RT	Multiple fraction RT	Relative (95% CI)	Absolute		
Spinal stability - fractures (median follow-up 11 months)												
2[9]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[5]	none	10/302 (3.3%)	6/312 (1.9%)	RR 1.68 (0.62 to 4.53)	13 more per 1000 (from 7 fewer to 68 more)	VERY LOW	IMPORTANT

CI: confidence interval; HR: hazard ratio; RR: risk ratio; RT: radiotherapy
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2.
[2] Population is indirect due to inclusion of patients with non-spinal metastases in TROG 96-05 trial (Roos 2005).
[3] 95% CI crosses 1 MID
[4] Absolute effect range crosses 2 MIDs (10 more per 1000 and 10 fewer per 1000)
[5] 95% CI crosses 2 MIDs
[6] Howell 2013, Roos 2005
[7] Howell 2013, Majumder 2012, Roos 2005
[8] Howell 2013, Majumder 2012
[9] Roos 2005, Steenland 1999

Table 7: Evidence profile for comparison 2: Patients with metastatic spinal cord compression - single fraction radiotherapy versus multiple (or short) fraction radiotherapy

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single fraction RT	Multiple (or short) fraction RT	Relative (95% CI)	Absolute		
Health related quality of life - EORTC QLQ-C30 Global health (standardised mean differences at 2 months between groups, adjusted for baseline values, range 0 –100, higher scores are better)												
1 (Hoskin 2019)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	345	341	not estimable	SMD 0.13 lower (1-sided 97.5% CI 0.38 lower to ∞ higher)[6]	MODERATE	CRITICAL
Health related quality of life - EORTC QLQ-C30 Physical functioning (standardised mean differences at 2 months between groups, adjusted for baseline values, range 0 – 100, higher scores are better)												
1 (Hoskin 2019)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	345	341	not estimable	SMD 0.12 lower (1-sided 97.5% CI 0.35 lower to ∞ higher)[6]	MODERATE	CRITICAL
Health related quality of life - EORTC QLQ-C30 Emotional functioning (standardised mean differences at 2 months between groups, adjusted for baseline values, range 0 – 100, higher scores are better)												
1 (Hoskin 2019)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	345	341	not estimable	SMD 0.18 lower (1-sided 97.5% CI 0.41	MODERATE	CRITICAL

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single fraction RT	Multiple (or short) fraction RT	Relative (95% CI)	Absolute		
										lower to ∞ higher)[6]		
Neurological and functional status - ability to walk after treatment												
3[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	238/355 (67%)	256/363 (70.5%)	RR 0.95 (0.86 to 1.05)	35 fewer per 1000 (from 99 fewer to 35 more)	HIGH	CRITICAL
Neurological and functional status - normal bladder function												
1 (Hoskin 2019)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	184/316 (58.2%)	211/322 (65.5%)	RR 0.89 (0.79 to 1.00)	72 fewer per 1000 (from 138 fewer to 0 more)	MODERATE	CRITICAL
Neurological and functional status - normal bowel function after treatment												
2[5]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	242/468 (51.7%)	249/472 (52.8%)	RR 0.97 (0.87 to 1.08)	16 fewer per 1000 (from 69 fewer to 42 more)	HIGH	CRITICAL
Overall survival (event is death from any cause)												
2[5]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	419/494 (84.8%)	413/495 (83.4%)	HR 1.06 (0.88 to 1.28)	not estimable	MODERATE	CRITICAL
Pain - complete or partial pain response												
1 (Maranzano 2009)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	80/153 (52.3%)	80/150 (53.3%)	RR 0.98 (0.79 to 1.21)	11 fewer per 1000 (from 112 fewer to 112 more)	MODERATE	CRITICAL
Pain - pain score (standardised mean difference between groups at 8 week follow-up)												
1 (Hoskin 2019)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	345	341	not estimable	SMD 0.12 higher (1-sided 97.5% CI ∞ lower to 0.38 higher)[6]	MODERATE	CRITICAL
Treatment related morbidity: Grade 3 or 4 adverse events												
2[5]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	71/498 (14.3%)	72/491 (14.7%)	RR 0.97 (0.73 to 1.3)	4 fewer per 1000 (from 40 fewer to 44 more)	LOW	IMPORTANT

CI: confidence interval; HR: hazard ratio; RR: risk ratio; RT: radiotherapy; SMD: standardised mean difference

[1] 95% CI crosses 1 MID (for EORTC QLQ-C30 1-sided MID was -0.28; pain score 1-sided MID was +0.28)
[2] 95% CI crosses 2 MIDs
[4] Hoskin 2019, Lee 2018, Maranzano 2009
[5] Hoskin 2019, Maranzano 2009
[6] Results reported as SMD with 1-sided 97.5% CI

Table 8: Evidence profile for comparison 3: Spinal metastases patients – Image guided intensity modulated radiotherapy versus conventional radiotherapy

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IMRT	3D-CRT	Relative (95% CI)	Absolute		
Health related quality of life - EORTC QLQ-BM 22 Functional interference (at 6 months follow-up, range 0 – 100, higher scores are better)												
1 (Sprave 2018a)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	17	12	Not estimable	MD 0.3 higher (19.74 lower to 20.34 higher)	VERY LOW	CRITICAL
Health related quality of life - EORTC QLQ-BM 22 Psychosocial aspects (at 6 months follow-up, range 0 – 100, lower scores are better)												
1 (Sprave 2018a)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	17	12	Not estimable	MD 13.6 lower (30.48 lower to 3.28 higher)	VERY LOW	CRITICAL
Overall survival (mean follow-up 6 months)												
1 (Sprave 2018a)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	14/30 (46.7%)	7/30 (23.3%)	HR 2.02 (0.81 to 5)	MSH: Please insert content in this cell. -	VERY LOW	CRITICAL
Pain - complete or partial pain response (follow-up 3 months)												
1 (Sprave 2018a)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	14/20 (70%)	9/19 (47.4%)	RR 1.48 (0.85 to 2.57)	227 more per 1000 (from 71 fewer to 744 more)	VERY LOW	CRITICAL
Treatment related morbidity - grade 3 to 4 adverse events (follow-up 3 months)												
1 (Sprave 2018a)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	1/30 (3.3%)	4/30 (13.3%)	RR 0.25 (0.03 to 2.11)	100 fewer per 1000 (from 129 fewer to 148 more)	VERY LOW	IMPORTANT
Spinal stability - pathologic fractures (follow-up 3 months)												
1 (Sprave 2018a)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	3/20 (15%)	2/19 (10.5%)	RR 1.42 (0.27 to 7.61)	44 more per 1000 (from 77 fewer to 696 more)	VERY LOW	IMPORTANT

3DCRT: three dimensional conventional radiotherapy; CI: confidence interval; HR: hazard ratio; IMRT: image guided intensity modulated radiotherapy; MD: mean difference; RR: risk ratio; RT: radiotherapy.

[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2.
[2] 95% CI crosses 2 MIDs (0.5x control group SD, for HRQOL: EORTC QLQ-BM 22 Functional Interference ±14.9).
[3] 95% CI crosses 1 MID (0.5x control group SD, for HRQOL: EORTC QLQ-BM 22 Psychosocial aspects ±9).
[4] 95% CI crosses 1 MID
[5] 95% CI crosses 2 MIDs

Table 9: Evidence profile for comparison 4: Spinal metastases patients – Stereotactic ablative body radiotherapy versus conventional radiotherapy

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SABR	EBRT or 3D-CRT	Relative (95% CI)	Absolute		
Health related quality of life - EORTC QLQ-BM 22 Functional interference (at 6 months follow-up, range 0 – 100, higher scores are better)												
1 (Sprave 2018d)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19	20	Not estimable	MD 3.4 higher (8.97 lower to 15.77 higher)	VERY LOW	CRITICAL
Health related quality of life - EORTC QLQ-BM 22 Global quality of life, change from baseline to 6 months (range 0 – 100, higher scores are better)												
1 (Sahgal 2021)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	115	114	Not estimable	MD 5.10 higher (2.67 lower to 12.87 higher)	LOW	CRITICAL
Health related quality of life - EORTC QLQ-BM 22 Psychosocial aspects (at 6 months follow-up, range 0 – 100, lower scores are better)												
1 (Sprave 2018d)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	19	20	Not estimable	MD 1.7 lower (17.15 lower to 13.75 higher)	VERY LOW	CRITICAL
Overall survival												
1 (Sprave 2018d)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	15/27 (55.6%)	15/28 (53.6%)	HR 1 (0.49 to 2.05)	not estimable	VERY LOW	CRITICAL
Pain - complete or partial pain response (6 months follow-up)												
2[7]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	61/141 (43.3%)	43/143 (30.1%)	RR 1.44 (1.05 to 1.97)	132 more per 1000 (from 15 more to 292 more)	VERY LOW	CRITICAL
Treatment related morbidity - grade 3 adverse event (6 months follow-up)												
1 (Sahgal 2021)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	5/115 (4.3%)	5/114 (4.4%)	RR 0.99 (0.29 to 3.33)	0 fewer per 1000 (from 31 fewer to 102 more)	VERY LOW	IMPORTANT
Spinal stability - vertebral compression fracture of any grade (6 months follow-up)												
2[7]	randomised trials	very serious[1]	very serious[6]	no serious indirectness	very serious[4]	none	23/132 (17.4%)	26/135 (19.3%)	RR 1.09 (0.33 to 3.66)	17 more per 1000 (from 129 fewer to 512 more)	VERY LOW	IMPORTANT

3DCRT: three dimensional conventional radiotherapy; CI: confidence interval; EBRT: external beam radiotherapy; HR: hazard ratio; IMRT: image guided intensity modulated radiotherapy; MD: mean difference; RR: risk ratio; RT: radiotherapy.

[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2.
[2] 95% CI crosses 1 MID (0.5x control group SD, for HRQOL: EORTC QLQ-BM 22 Functional interference ±12.2).
[3] 95% CI crosses 2 MIDs (0.5x control group SD, for HRQOL: EORTC QLQ-BM 22 Psychosocial aspects ±11.8).
[4] 95% CI crosses 2 MIDs
[5] 95% CI crosses 1 MID
[6] Very serious heterogeneity unexplained by subgroup analysis

[7] Sahgal 2021, Sprave 2018d

Table 10: Evidence profile for comparison 5: Patients with metastatic spinal cord compression - short course radiotherapy versus split course radiotherapy

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course RT	Split course RT	Relative (95% CI)	Absolute		
Neurological and functional status - ability to walk after treatment												
1 (Maranzano 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	97/142 (68.3%)	95/134 (70.9%)	RR 0.96 (0.82 to 1.13)	28 fewer per 1000 (from 128 fewer to 92 more)	HIGH	CRITICAL
Neurological and functional status - normal sphincter control after treatment												
1 (Maranzano 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	128/142 (90.1%)	119/134 (88.8%)	RR 1.02 (0.94 to 1.1)	18 more per 1000 (from 53 fewer to 89 more)	HIGH	CRITICAL
Pain - complete or partial pain response after treatment												
1 (Maranzano 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	80/142 (56.3%)	79/134 (59%)	RR 0.96 (0.78 to 1.17)	24 fewer per 1000 (from 130 fewer to 100 more)	MODERATE	CRITICAL
Treatment related morbidity - grade 3 or more adverse events												
1 (Maranzano 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	3/142 (2.1%)	5/134 (3.7%)	RR 0.57 (0.14 to 2.32)	16 fewer per 1000 (from 32 fewer to 49 more)	LOW	IMPORTANT
Spinal stability - in field recurrence												
1 (Maranzano 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	5/142 (3.5%)	0/134 (0%)	POR 7.19 (1.23 to 42.06)	40 more per 1000 (from 0 more to 70 more)	MODERATE	IMPORTANT

CI: confidence interval; POR: Peto odds ratio; RR: risk ratio

[1] 95% CI crosses 1 MID
[2] 95% CI crosses 2 MIDs

Table 11: Evidence profile for comparison 6: Patients with metastatic spinal cord compression – short course radiotherapy versus long course radiotherapy

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course RT	Long course RT	Relative (95% CI)	Absolute		
Neurological and functional status - ambulatory status (1 month follow-up)												
1 (Rades 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	56/78 (71.8%)	57/77 (74%)	RR 0.97 (0.80 to 1.18)	22 fewer per 1000 (from 148 fewer to 133 more)	HIGH	CRITICAL
Neurological and functional status - motor deficits improved or stable (1 month follow-up)												
1 (Rades 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	68/78 (87.2%)	69/77 (89.6%)	RR 0.97 (0.87 to 1.09)	27 fewer per 1000 (from 116 fewer to 81 more)	HIGH	CRITICAL
Overall survival (6 months follow-up)												
1 (Rades 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	9/101 (8.9%)	9/102 (8.8%)	HR 1.21 (0.48 to 3.06)	18 more per 1000 (from 45 fewer to 158 more)	LOW	CRITICAL
Pain - complete or partial pain response (1 month follow-up)												
1 (Rades 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	36/101 (35.6%)	40/102 (39.2%)	RR 0.91 (0.64 to 1.3)	35 fewer per 1000 (from 141 fewer to 118 more)	LOW	CRITICAL
Treatment related morbidity - grade 3 or 4 acute toxicity												
1 (Rades 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	0/101 (0%)	0/102 (0%)	RD 0.00	0 fewer per 1000 (from 20 fewer to 20 more)	MODERATE	IMPORTANT

CI: confidence interval; HR: hazard ratio; RD: risk difference; RR: risk ratio; RT: radiotherapy.

[1] 95% CI crosses 2 MIDs
[2] Sample size < 300

Table 12: Evidence profile for comparison 7: Patients with metastatic spinal cord compression – surgery + radiotherapy versus radiotherapy only

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery + RT	RT only	Relative (95% CI)	Absolute		
Neurological and functional status - ambulant after treatment - all patients												

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery + RT	RT only	Relative (95% CI)	Absolute		
1 (Patchell 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	42/50 (84%)	29/51 (56.9%)	RR 1.48 (1.13 to 1.93)	273 more per 1000 (from 74 more to 529 more)	MODERATE	CRITICAL
Neurological and functional status - ambulant after treatment – patients ambulatory at study entry												
1 (Patchell 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	32/34 (94.1%)	26/35 (74.3%)	RR 1.27 (1.02 to 1.57)	201 more per 1000 (from 15 more to 423 more)	MODERATE	CRITICAL
Neurological and functional status - ambulant after treatment - patients non ambulatory at study entry												
1 (Patchell 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	10/16 (62.5%)	3/16 (18.8%)	RR 3.33 (1.12 to 9.9)	437 more per 1000 (from 23 more to 1000 more)	MODERATE	CRITICAL
Neurological and functional status - maintenance of continence (time to incontinence)												
1 (Patchell 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50	51	HR 2.13 (1.15 to 4.00)	Median 149 days longer	MODERATE	CRITICAL
Neurological and functional status - maintenance of muscle strength (time ASIA score was maintained)												
1 (Patchell 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	51	HR 3.57 (1.64 to 7.69)	Median 494 days longer	HIGH	CRITICAL
Neurological and functional status - maintenance of functional ability (time Frankel score was maintained)												
1 (Patchell 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	51	HR 4.17 (1.85 to 9.09)	Median 494 days longer	HIGH	CRITICAL
Pain - median [IQR] daily equivalent dose of morphine, mg												
1 (Patchell 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	50	51	Not estimable	Median 4.4 mg lower	MODERATE	CRITICAL
Treatment related morbidity - 30 day mortality												
1 (Patchell 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	3/50 (6%)	7/51 (13.7%)	RR 0.44 (0.12 to 1.6)	77 fewer per 1000 (from 121 fewer to 82 more)	LOW	IMPORTANT

CI: confidence interval; RR: risk ratio; RT: radiotherapy.
[1] 95% CI crosses 1 MID
[2] 95% CI crosses 2 MIDs
[3] Sample size < 300

Appendix G Economic evidence study selection

Study selection for: How effective is radiotherapy, including both fractionated and unfractionated radiotherapy, for the management of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information

Appendix H Economic evidence tables

Economic evidence tables for review question: How effective is radiotherapy, including both fractionated and unfractionated radiotherapy, for the management of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Table 13: Economic evidence tables

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Author and year: Turner 2018 **Country:** UK **Type of economic analysis:** Cost utility **Source of funding:** National Institute for Health Research Biomedical Research Centre	**Intervention**: Surgery and radiotherapy (RT) **Comparator:** Radiotherapy alone	**Population characteristic:** 130 consecutive patients who required surgery and RT for symptomatic spinal metastases from any cancer at a NHS spinal tertiary referral centre between 2009 and 2015 **Mean age**:60.6 years Male: 51.5% Paralysed: 30.4% The comparator group (RT alone) were modelled on the above cohort and values from Patchel (2005) **Modelling approach:** Prospectively collected costs and quality of	**Mean cost per participant (SD)** Intervention: £42,904(£24,768) Comparator: £55,743 (£43,646) Difference: -£12,839 (SD £37,896) **Mean outcome per participant (SD):** Intervention: 0.64 QALYs (0.41) Comparator: 0.32 QALYs (0.45)	**ICERs:** Surgery and RT dominant less costly but more effective **Sensitivity analysis:** Surgery and RT remained less costly and more effective when costs from the 2008 NICE guideline manual were used instead of reimbursement costs and under different QALY assumptions for the hypothetical group (linear decline of QoL until death, QOL maintained at pre-operative levels) No probabilistic sensitivity analyses were undertaken.	**Perspective:** UK NHS & PSS **Currency**: Pounds sterling (£) **Cost year:** 2016 **Time horizon:** Lifetime **Discounting**: 3.5% per annum both costs and QALYs **Applicability**: Directly Applicable **Limitations**: Potentially serious limitations **Other comments:** Groups not randomised. Patients recruited post 2008 where CG75 recommended surgery and radiotherapy for eligible people. RT arm was based on modelling using values

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		life from consecutive patients. Hypothetical comparator adjusting results based on one trial. **Source of baseline data:** Collected prospectively from people in the study **Source of effectiveness data:** Hypothetical comparator cohort adjusted using Patchell 2015. Quality of life using the EQ-5D questionnaire at pre- and post-operatively and at 3,6 and 12 months and every 12 months until death and scored using the UK population value set. Source of cost data: Tariff reimbursement extracted from hospital database			from Patchell 2005

Appendix I Economic model

Economic model for review question: How effective is radiotherapy, including both fractionated and unfractionated radiotherapy, for the management of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: How effective is radiotherapy, including both fractionated and unfractionated radiotherapy, for the management of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Excluded effectiveness studies

Table 14: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
(2013) Xofigo (radium-223 dichloride; Bayer HealthCare Pharmaceuticals Inc.) for treatment of bone metastases in castration-resistant prostate cancer. Lansdale, PA: HAYES, Inc	Publication type does not match review protocol – conference abstract
(2011) Robotically assisted stereotactic radiosurgery (SRS) for spinal and extracranial head and neck indications. Lansdale, PA: HAYES, Inc	Publication type does not match review protocol – conference abstract
Amouzegar-Hashemi, F, Behrouzi, H, Kazemian, A et al. (2008) Single versus multiple fractions of palliative radiotherapy for bone metastases: a randomized clinical trial in Iranian patients. Current oncology (toronto, ont.) 15(3): 36-39	Population does not match review protocol
Bakar, D., Tanenbaum, J. E., Phan, K. et al. (2016) Decompression surgery for spinal metastases: a systematic review. Neurosurgical Focus 41: e2	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Barrie, U., Elguindy, M., Pernik, M. et al. (2020) Intramedullary Spinal Metastatic Renal Cell Carcinoma: Systematic Review of Disease Presentation, Treatment, and Prognosis with Case Illustration. World Neurosurgery 134: 584-593	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Bilsky, M. H.; Laufer, I.; Burch, S. (2009) Shifting paradigms in the treatment of metastatic spine disease. Spine 34: S101-7	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Broder, M. S., Gutierrez, B., Cherepanov, D. et al. (2015) Burden of skeletal-related events in prostate cancer: unmet need in pain improvement. Supportive Care in Cancer 23(1): 237-247	Population does not match review protocol
Cellini, F., Manfrida, S., Deodato, F. et al. (2019) Pain REduction with bone metastases STereotactic radiotherapy (PREST): A phase III randomized multicentric trial. Trials 20(1)	Publication type does not match review protocol – study protocol
Chang, J. H., Shin, J. H., Yamada, Y. J. et al. (2016) Stereotactic Body Radiotherapy for Spinal Metastases: What are the Risks and How Do We Minimize Them?. Spine 41suppl20: S238-S245	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Chen, B., Xiao, S., Tong, X. et al. (2015) Comparison of the Therapeutic Efficacy of Surgery with or without Adjuvant Radiotherapy	Study design does not match protocol criteria - systematic

Study	Reason for exclusion
versus Radiotherapy Alone for Metastatic Spinal Cord Compression: A Meta-Analysis. World Neurosurgery 83(6): 1066-1073	review without pooled results/quantitative data, checked for relevant studies
Chi, J. H., Gokaslan, Z., McCormick, P. et al. (2009) Selecting treatment for patients with malignant epidural spinal cord compression-does age matter? Results from a randomized clinical trial. Spine 34(5): 431-435	Other protocol criteria - post-hoc analysis of Patchell 2005 trial
Chow, E., Harris, K., Fan, G. et al. (2007) Palliative radiotherapy trials for bone metastases: a systematic review. Journal of Clinical Oncology 25: 1423-36	Population does not match review protocol
Chow, E., Hoskin, P. J., Wu, J. et al. (2006) A phase III international randomised trial comparing single with multiple fractions for re-irradiation of painful bone metastases: National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) SC 20. Clinical Oncology 18(2): 125-128	Population does not match review protocol
Chow, E., van der Linden, Y. M., Roos, D. et al. (2014) Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial. Lancet Oncology 15: 164-71	Population does not match review protocol
Chow, E., Zeng, L., Salvo, N. et al. (2012) Update on the systematic review of palliative radiotherapy trials for bone metastases. Clinical Oncology (Royal College of Radiologists) 24: 112-24	Population does not match review protocol
Dhamija, B.; Batheja, D.; Balain, B. S. (2021) A systematic review of MIS and open decompression surgery for spinal metastases in the last two decades. Journal of Clinical Orthopaedics & Trauma 22: 101596	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Donovan, E. K., Sienna, J., Mitera, G. et al. (2019) Single versus multifraction radiotherapy for spinal cord compression: A systematic review and meta-analysis. Radiotherapy & Oncology 134: 55-66	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Dy, S. M., Asch, S. M., Naeim, A. et al. (2008) Evidence-based standards for cancer pain management. Journal of Clinical Oncology 26(23): 3879-3885	Population does not match review protocol
Falkmer, U., Jarhult, J., Wersall, P. et al. (2003) A systematic overview of radiation therapy effects in skeletal metastases. Acta Oncologica 42(5-6): 620-633	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Feyer, P., Sautter-Bihl, M. L., Budachs, W. et al. (2010) DEGRO practical guidelines for palliative radiotherapy of breast cancer patients: Brain metastases and leptomeningeal carcinomatosis. Strahlentherapie und Onkologie 186(2): 63-69	Population does not match review protocol
Garcia-Torralba, E., Spada, F., Lim, K. H. J. et al. (2021) Knowns and unknowns of bone metastases in patients with neuroendocrine neoplasms: A systematic review and meta-analysis. Cancer Treatment Reviews 94 (no pagination)	Population does not match review protocol

Study	Reason for exclusion
George, R, Sundararaj, JJ, Govindaraj, R et al. (2015) Interventions for the treatment of metastatic extradural spinal cord compression in adults. Cochrane Database of Systematic Reviews	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Gerszten, P. C.; Mendel, E.; Yamada, Y. (2009) Radiotherapy and radiosurgery for metastatic spine disease: what are the options, indications, and outcomes?. Spine 34: S78-92	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Ghia, A. J., Chang, E. L., Bishop, A. J. et al. (2016) Single-fraction versus multifraction spinal stereotactic radiosurgery for spinal metastases from renal cell carcinoma: secondary analysis of Phase I/II trials. Journal of Neurosurgery Spine 24: 829-36	Study design - phase I or II trials - patients not randomly allocated to treatment
Glicksman, R. M., Tjong, M. C., Neves-Junior, W. F. P. et al. (2020) Stereotactic Ablative Radiotherapy for the Management of Spinal Metastases: A Review. JAMA Oncology 6: 567-577	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Gong, Y., Xu, L., Zhuang, H. et al. (2019) Efficacy and safety of different fractions in stereotactic body radiotherapy for spinal metastases: A systematic review. Cancer Medicine 8: 6176-6184	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Goodwin, C. R., Sankey, E. W., Liu, A. et al. (2016) A systematic review of clinical outcomes for patients diagnosed with skin cancer spinal metastases. Journal of Neurosurgery: Spine 24(5): 837-849	Intervention does not match review protocol
Hamouda, W. E.; Roshdy, W.; Teema, M. (2007) Single versus conventional fractionated radiotherapy in the palliation of painful bone metastases. The gulf journal of oncology 1: 35-41	Population does not match review protocol
Hernandez-Duran, S., Hanft, S., Komotar, R. J. et al. (2016) The role of stereotactic radiosurgery in the treatment of intramedullary spinal cord neoplasms: a systematic literature review. Neurosurgical Review 39(2): 175-183	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Holt, T., Hoskin, P., Maranzano, E. et al. (2012) Malignant epidural spinal cord compression: the role of external beam radiotherapy. Current Opinion in Supportive & Palliative Care 6: 103-8	Study design does not match review protocol – expert review/narrative
Howell, DD, James, JL, Hartsell, WF et al. (2009) Randomized trial of short-course versus long-course radiotherapy for palliation of painful vertebral bone metastases: a retrospective analysis of RTOG 97-14. Journal of clinical oncology 27(15sparti): 488	Publication type does not match review protocol – conference abstract
Husain, Z. A., Sahgal, A., De Salles, A. et al. (2017) Stereotactic body radiotherapy for de novo spinal metastases: systematic review. Journal of Neurosurgery Spine 27: 295-302	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Jeremic, B. (2001) Single fraction external beam radiation therapy in the treatment of localized metastatic bone pain. A review. Journal of Pain and Symptom Management 22(6): 1048-1058	Population does not match review protocol

Study	Reason for exclusion
Jeremic, B, Shibamoto, Y, Acimovic, L et al. (1998) A randomized trial of three single-dose radiation therapy regimens in the treatment of metastatic bone pain. International journal of radiation oncology, biology, physics 42(1): 161-167	Population does not match review protocol
Kim, J. M., Losina, E., Bono, C. M. et al. (2012) Clinical outcome of metastatic spinal cord compression treated with surgical excision +/- radiation versus radiation therapy alone: a systematic review of literature. Spine 37: 78-84	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Klimo Jr, P., Thompson, C. J., Kestle, J. R. W. et al. (2005) A meta-analysis of surgery versus conventional radiotherapy for the treatment of metastatic spinal epidural disease. Neuro-Oncology 7(1): 64-76	Intervention and comparator do not match review protocol
Kumar, N., Madhu, S., Bohra, H. et al. (2020) Is there an optimal timing between radiotherapy and surgery to reduce wound complications in metastatic spine disease? A systematic review. European Spine Journal 29: 3080-3115	Outcomes do not match review protocol
Lee, C. H., Kwon, J. W., Lee, J. et al. (2014) Direct decompressive surgery followed by radiotherapy versus radiotherapy alone for metastatic epidural spinal cord compression: a meta-analysis. Spine 39: E587-92	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Leer, JWH; Steenland, E; van Houwelingen, H (1999) Pain control for bone metastases. European journal of cancer 35(abstract462): 129	Publication type does not match review protocol – conference abstract
Loblaw, D. A. and Laperriere, N. J. (1998) Emergency treatment of malignant extradural spinal cord compression: An evidence-based guideline. Journal of Clinical Oncology 16(4): 1613-1624	Publication type does not match review protocol – duplicate publication - updated version available
Loblaw, D. A., Mitera, G., Ford, M. et al. (2012) A 2011 updated systematic review and clinical practice guideline for the management of malignant extradural spinal cord compression. International Journal of Radiation Oncology, Biology, Physics 84: 312-7	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Loblaw, D. A., Perry, J., Chambers, A. et al. (2005) Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. Journal of Clinical Oncology 23: 2028-37	Publication type does not match review protocol – duplicate publication - updated version available
Lohre, E. T.; Lund, J.; Kaasa, S. (2012) Radiation therapy in malignant spinal cord compression: what is the current knowledge on fractionation schedules? A systematic literature review. BMJ supportive & palliative care 2(1): 51-56	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Lutz, S., Balboni, T., Jones, J. et al. (2017) Palliative radiation therapy for bone metastases: Update of an ASTRO Evidence-Based Guideline. Practical Radiation Oncology 7: 4-12	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies

Study	Reason for exclusion
Ma, Y., He, S., Liu, T. et al. (2017) Quality of Life of Patients with Spinal Metastasis from Cancer of Unknown Primary Origin: A Longitudinal Study of Surgical Management Combined with Postoperative Radiation Therapy. Journal of Bone & Joint Surgery - American Volume 99: 1629-1639	Study design does not match review protocol – non-randomised study
Maranzano, E., Trippa, F., Casale, M. et al. (2011) Reirradiation of metastatic spinal cord compression: definitive results of two randomized trials. Radiotherapy & Oncology 98: 234-7	Study design does not match review protocol - post-hoc analysis (patients not randomised to re-treatment with radiotherapy)
Migliorini, F., Eschweiler, J., Trivellas, A. et al. (2021) Better pain control with 8-gray single fraction palliative radiotherapy for skeletal metastases: a Bayesian network meta-analysis. Clinical and Experimental Metastasis 38(2): 197-208	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Moller, T. (1996) Skeletal metastases. Acta oncologica (Stockholm, Sweden) 35suppl7: 125-136	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Moulding, H. D. and Bilsky, M. H. (2010) Metastases to the craniovertebral junction. Neurosurgery 66(SUPPL. 3): A113-A118	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Myrehaug, S., Sahgal, A., Hayashi, M. et al. (2017) Reirradiation spine stereotactic body radiation therapy for spinal metastases: systematic review. Journal of Neurosurgery Spine 27: 428-435	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Niewald, M., Tkocz, H. J., Abel, U. et al. (1996) Rapid course radiation therapy vs. more standard treatment: a randomized trial for bone metastases. International Journal of Radiation Oncology, Biology, Physics 36: 1085-9	Population does not match review protocol - data for spinal metastases group not reported
Ozsaran, Z, Yalman, D, Anacak, Y et al. (2001) Palliative radiotherapy in bone metastases: results of a randomized trial comparing three fractionation schedules. Journal of B.U.ON. 6(1): 43-48	Population does not match review protocol
Pontoriero, A., Lillo, S., Caravatta, L. et al. (2021) Cumulative dose, toxicity, and outcomes of spinal metastases re-irradiation: Systematic review on behalf of the Re-Irradiation Working Group of the Italian Association of Radiotherapy and Clinical Oncology (AIRO). Strahlentherapie und Onkologie 197: 369-384	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Qu, S., Meng, H. L., Liang, Z. G. et al. (2015) Comparison of short-course radiotherapy versus long-course radiotherapy for treatment of metastatic spinal cord compression: A systematic review and meta-analysis. Medicine (United States) 94(43)	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Quraishi, N. A., Giannoulis, K. E., Edwards, K. L. et al. (2012) Management of metastatic sacral tumours. European Spine Journal 21: 1984-93	Study design does not match protocol criteria - systematic

Study	Reason for exclusion
	review without pooled results/quantitative data, checked for relevant studies
Rades, D. (2010) Dose-fractionation schedules for radiotherapy of bone metastases. Breast Care 5(5): 339-344	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Rades, D., Cacicedo, J., Conde-Moreno, A. J. et al. (2021) Comparison of 5 x 5 Gy and 10 x 3 Gy for metastatic spinal cord compression using data from three prospective trials. Radiation Oncology 16: 7	Patients were not randomly allocated to treatment groups
Rich, S. E., Chow, R., Raman, S. et al. (2018) Update of the systematic review of palliative radiation therapy fractionation for bone metastases. Radiotherapy & Oncology 126: 547-557	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Roos, D. E., O'Brien, P. C., Smith, J. G. et al. (2000) A role for radiotherapy in neuropathic bone pain: preliminary response rates from a prospective trial (Trans-tasman radiation oncology group, TROG 96.05). International Journal of Radiation Oncology, Biology, Physics 46: 975-81	Other protocol criteria - data from preliminary analysis reported in Roos 2005 which has been included in this review
Roos, D. E., Davis, S. R., Turner, S. L. et al. (2003) Quality assurance experience with the randomized neuropathic bone pain trial (Trans-Tasman Radiation Oncology Group, 96.05). Radiotherapy & Oncology 67: 207-12	Population does not match review protocol - data for spinal metastases group not reported
Roque i Figuls, M., Martinez-Zapata, M. J., Scott-Brown, M. et al. (2017) Radioisotopes for metastatic bone pain. Cochrane Database of Systematic Reviews 2017(3)	Publication type does not match review protocol – duplicate publication - withdrawn version of a Cochrane review
Sahgal, A., Myrehaug, S. D., Siva, S. et al. (2020) CCTG SC.24/TROG 17.06: A Randomized Phase II/III Study Comparing 24Gy in 2 Stereotactic Body Radiotherapy (SABR) Fractions Versus 20Gy in 5 Conventional Palliative Radiotherapy (CRT) Fractions for Patients with Painful Spinal Metastases. International journal of radiation oncology, biology, physics 108(5): 1397-1398	Publication type does not match review protocol – conference abstract
Sande, T. A., Ruenes, R., Lund, J. A. et al. (2009) Long-term follow-up of cancer patients receiving radiotherapy for bone metastases: results from a randomised multicentre trial. Radiotherapy & Oncology 91: 261-6	Population does not match review protocol
Sapkaroski, D.; Osborne, C.; Knight, K. A. (2015) A review of stereotactic body radiotherapy - is volumetric modulated arc therapy the answer?. Journal of Medical Radiation Sciences 62(2): 142-151	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Sharma, R., Sagoo, N. S., Haider, A. S. et al. (2021) Iodine-125 radioactive seed brachytherapy as a treatment for spine and bone metastases: A systematic review and meta-analysis. Surgical Oncology 38 (no pagination)	Study design does not match protocol criteria - systematic

Study	Reason for exclusion
	review without pooled results/quantitative data, checked for relevant studies
Singh, R., Lehrer, E. J., Dahshan, B. et al. (2020) Single fraction radiosurgery, fractionated radiosurgery, and conventional radiotherapy for spinal oligometastasis (SAFFRON): A systematic review and meta-analysis. Radiotherapy & Oncology 146: 76-89	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Smith, B. W., Joseph, J. R., Saadeh, Y. S. et al. (2018) Radiosurgery for Treatment of Renal Cell Metastases to Spine: A Systematic Review of the Literature. World Neurosurgery 109: e502-e509	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Sohn, S. and Chung, C. K. (2012) The role of stereotactic radiosurgery in metastasis to the spine. Journal of Korean Neurosurgical Society 51: 1-7	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Soltys, S. G., Grimm, J., Milano, M. T. et al. (2021) Stereotactic Body Radiation Therapy for Spinal Metastases: Tumor Control Probability Analyses and Recommended Reporting Standards. International Journal of Radiation Oncology, Biology, Physics 110: 112-123	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Souchon, R., Wenz, F., Sedlmayer, F. et al. (2009) DEGRO practice guidelines for palliative radiotherapy of metastatic breast cancer: bone metastases and metastatic spinal cord compression (MSCC). Strahlentherapie und Onkologie 185: 417-24	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Stebbing, J. and Ngan, S. (2010) Breast cancer (metastatic). BMJ clinical evidence	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Suppli, MH, Munck Af Rosenschold, P, Dahl, B et al. (2020) Premature Termination of a Randomized Controlled Trial on Image-Guided Stereotactic Body Radiotherapy of Metastatic Spinal Cord Compression. Oncologist 25(3): 210-e422	Outcomes do not match review protocol – no outcomes reported (trial was closed prematurely)
Sze, W. M., Shelley, M., Held, I. et al. (2004) Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy - a systematic review of the randomised trials. Cochrane Database of Systematic Reviews: cd004721	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Thirion, P. G., Dunne, M. T., Kelly, P. J. et al. (2020) Non-inferiority randomised phase 3 trial comparing two radiation schedules (single vs. five fractions) in malignant spinal cord compression. British Journal of Cancer 122: 1315-1323	Other protocol criteria - secondary publication of ICORG 05-03 trial (Lee 2018), but no additional relevant outcome data reported that match the protocol for this review
Trilling, G. M., Cho, H., Ugas, M. A. et al. (2012) Spinal metastasis in head and neck cancer. Head and Neck Oncology 4(1)	Study design does not match protocol criteria - systematic

Study	Reason for exclusion
	review without pooled results/quantitative data, checked for relevant studies
van der Linden, YM, Dijkstra, SP, Vonk, EJ et al. (2005) Prediction of survival in patients with metastases in the spinal column: results based on a randomized trial of radiotherapy. Cancer 103(2): 320-328	Intervention does not match review protocol
Van Der Linden, YM, Steenland, E, Post, WJ et al. (2002) Single-dose irradiation of painful bone metastases is as effective as multiple fractions. Outcome of the Dutch Bone Metastasis Study. Nederlands tijdschrift voor geneeskunde 146(35): 1645-1650	Other protocol criteria – not available in English
Verbiest, A., De Meerleer, G., Albersen, M. et al. (2018) Non-surgical ablative treatment of distant extracranial metastases for renal cell carcinoma: A systematic review. Kidney Cancer 2(1): 57-67	Intervention does not match review protocol
Westhoff, P. G., de Graeff, A., Monninkhof, E. M. et al. (2018) Effectiveness and toxicity of conventional radiotherapy treatment for painful spinal metastases: a detailed course of side effects after opposing fields versus a single posterior field technique. Journal of Radiation Oncology 7: 17-26	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Wild, A. T. and Yamada, Y. (2017) Treatment Options in Oligometastatic Disease: Stereotactic Body Radiation Therapy - Focus on Colorectal Cancer. Visceral Medicine 33: 54-61	Publication type does not match review protocol – expert review/narrative
Wowra, B, Zausinger, S, Muacevic, A et al. (2009) Radiosurgery for spinal malignant tumors. Deutsches Aerzteblatt International 106(7): 106-112	Study design does not match review protocol – expert review/narrative
Yang, J., Yan, J., Zeng, M. et al. (2020) Bone metastases of gastrointestinal stromal tumor: A review of published literature. Cancer Management and Research 12: 1411-1417	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Yao, A., Sarkiss, C. A., Ladner, T. R. et al. (2017) Contemporary spinal oncology treatment paradigms and outcomes for metastatic tumors to the spine: A systematic review of breast, prostate, renal, and lung metastases. Journal of Clinical Neuroscience 41: 11-23	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies
Young, RF; Post, EM; King, GA (1980) Treatment of spinal epidural metastases. Randomized prospective comparison of laminectomy and radiotherapy. Journal of neurosurgery 53(6): 741-748	Publication date before cut-off in review protocol
Zuckerman, S. L., Lim, J., Yamada, Y. et al. (2018) Brachytherapy in Spinal Tumors: A Systematic Review. World Neurosurgery 118: e235-e244	Study design does not match protocol criteria - systematic review without pooled results/quantitative data, checked for relevant studies

Excluded economic studies

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information

Appendix K Research recommendations – full details

Research recommendations for review question: How effective is radiotherapy, including both fractionated and unfractionated radiotherapy, for the management of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

K.1.1 Research recommendation

How effective is postoperative SABR compared to postoperative standard RT in the treatment of MSCC?

K.1.2 Why this is important

There is evidence that SABR technology is more effective than conventional RT (EBRT or 3D-CRT) in reducing pain in people with painful spinal bone metastases (without spinal cord compression). However, no evidence was identified about the use of SABR for people with cord compression. Extending the evidence base to this group of people would potentially provide the opportunity for further treatment options for people with MSCC.

K.1.3 Rationale for research recommendation

Table 15: Research recommendation rationale

Importance to 'patients' or the population	MSCC is an acute medical emergency and treatment for this is a priority with timely effective treatment having the potential to reduce pain and increase survival and quality of life.
Relevance to NICE guidance	The relative absence of evidence regarding this topic currently restricts NICE guidance from making specific recommendations about SABR for the treatment of MSCC. The outcome of this research would allow such recommendations to be developed and become part of NICE guidance
Relevance to the NHS	More timely and effective cancer treatment is relevant to the NHS because it can improve survival and quality of life.
National priorities	Priority 3.62 of the NHS Long Term plan: "Safer and more precise treatments including advanced radiotherapy techniques and immunotherapies will continue to support improvements in survival rates. We will complete the £130 million upgrade of radiotherapy machines across England and commission the NHS new state-of-the-art Proton Beam facilities in London and Reforms to the specialised commissioning payments for radiotherapy hypofractionation will be introduced to support further equipment upgrades. Faster, smarter and effective radiotherapy, supported by greater networking of specialised expertise, will mean more patients are offered curative treatment, with fewer side effects and shorter treatment times. Starting with ovarian cancer, we will ensure greater access to specialist expertise and knowledge in the treatment of cancers where there are fewer or more risky treatment options."
Current evidence base	The systematic review did not identify evidence specifically for MSCC whilst there was evidence that this technology showed some

	effectiveness in reducing pain in people with painful spinal bone metastases.
Equality considerations	Even though this technology is available in some centres (because it is used in the treatment of cancers for other remits), it is not currently used for the treatment of MSCC. There may therefore be geographical inequalities related to this.
Feasibility	Time pressures are great with MSCC treatment with it being an oncologic emergency, with SABR being a technically demanding and time-consuming process, this will prove a logistical challenge to implement in an emergency situation. Such events tend to happen over weekends when staff availability could be a major practical issue also in the context of SABR being a resource intense process Numbers of people with MSCC are relatively low compared to the overall number of people with cancer and recruitment may therefore be difficult. However, otherwise it would be feasible to carry out such research - multicentre or multinational study likely to be needed.

MSCC: metastatic spinal cord compression; SABR: stereotactic ablative body radiation

K.1.4 Modified PICO table

Table 16: Research recommendation modified PICO table

Population	People with MSCC. (Including those with radiographical MSCC without neurological symptoms)
Intervention	SABR combined with surgery
Comparator	EBRT combined with surgery

Outcomes	• Health related quality of life
	• Neurological and functional status including:
	  ○ Bowel & bladder function
	  ○ Mobility or ambulatory status
	• Overall survival
	• Pain

Study design	RCT or observational study
Timeframe	9 months
Additional information	Observational studies will need to adjust for baseline differences in patient groups such as: site of primary cancer, number of MSCC sites, location of spinal metastases, ambulatory status and performance status

EBRT: external beam radiotherapy; MSCC: metastatic spinal cord compression; SABR: stereotactic ablative body radiation