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

Outcome	Single fraction radiotherapy, n=345	Multiple fraction radiotherapy, n=341
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
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.*

Section	Question	Answer
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
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 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. 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 study was carried out	India.
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)
Intervention(s)/control	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**

Outcome	Single fraction radiotherapy, n=153	Multiple fraction radiotherapy, n=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.
Intervention(s)/control	**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

Outcome	Surgery + radiotherapy, n=50	Radiotherapy alone n=51
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
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 antidepressant. 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

Section	Question	Answer
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 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	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

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
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
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)

Outcome	IMRT, 3 month, N = 20	IMRT, 6 month, N = 18	3DCRT, 3 month, N = 19	3DCRT, 6 month, N = 12
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 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	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 study was carried out	Germany
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)
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

Outcome	SABR, 3 month, N = 23	SABR, 6 month, N = 19	3DCRT, 3 month, N = 23	3DCRT, 6 month, N = 20
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 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. 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 (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns. *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 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.*

Section	Question	Answer
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