National Institute for Health and Care Excellence

Final

Spinal metastases and metastatic spinal cord compression

[I] Evidence reviews for analgesic interventions

NICE guideline number NG234

Evidence reviews underpinning recommendations 1.7.1 to 1.7.11 in the NICE guideline

September 2023

Final

These evidence reviews were developed by NICE

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ISBN: 978-1-4731-5319-6

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Analgesic interventions

Review question

How effective are analgesic interventions in managing pain related to spinal metastases, direct malignant infiltration of the spine with or without spinal cord compression?

Introduction

Patients with metastatic spinal disease often have accompanying pain, particularly if there is also spinal cord compression. This may be due to dural or neural compression, or the effects of tumour on the spinal bone.

In some patients, vertebral pain may be aggravated by spinal movement. This pain may be due to weakening of the bone, is commonly referred to as mechanical pain and is often treated by supporting the spine with external orthoses or by invasive interventions such as surgery.

In others pain is due to tumour expansion within the vertebral body and might not be affected by posture or movement. This is commonly referred to as non-mechanical pain and is usually treated using non-invasive methods (analgesics, radiotherapy, bone-targeted drugs including bisphosphonates, and denosumab and sometimes chemotherapy).

This review aimed to compare the effectiveness of pharmacological treatments, acupuncture, electrotherapy and physical exercise for pain due to spinal metastases or direct malignant infiltration of the spine.

Summary of the protocol

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

Table 1: Summary of the protocol (PICO table)

Population	• Adults with suspected or confirmed:
	  ○ metastatic spinal disease
	  ○ direct malignant infiltration of the spine.
	• Adults with suspected or confirmed spinal cord or nerve root compression because of:
	  ○ metastatic spinal disease
	  ○ direct malignant infiltration of the spine.

Intervention	Analgesic interventions for management of pain in patients with spinal metastases/ direct infiltration with or without spinal cord compression:
	• Pharmacological treatment (oral/sublingual, rectal, intra-muscular, transdermal, intravenous, subcutaneous, epidural or intrathecal routes of administration)
	  ○ Paracetamol
	  ○ Non-steroidal anti-inflammatory drugs
	  ○ Opioid analgesics
	  ○ Muscle relaxants
	  ○ Antidepressants
	  ○ SSRIs
	  ○ SNRIs such as duloxetine
	  ○ Tri-cyclic antidepressants such as amitriptyline
	  ○ Anti-convulsants
	  ○ Gabapentinoids such as gabapentin and pregabalin

	○ Other anticonvulsants • Acupuncture • Electrotherapy such as: ○ transcutaneous electrical nerve simulation (TENS) ○ percutaneous electrical nerve simulation (PENS) • Physical activity
Comparison	• Placebo/nothing • Each other, for example: ○ Opioids versus neurogenic agents ○ Paracetamol/NSAIDs versus opioids • Analgesia strategies, for example: ○ WHO pain ladder ○ Patient controlled analgesia versus other strategy • Combinations of interventions • Analgesia versus dexamethasone
Outcome	**Critical** • Pain ○ Change in pain score ○ Time to achieve pain relief • Health-related quality of life • Patient satisfaction **Important** • Treatment related adverse events (specific to class of treatment, for example, opioids) • Mobility and ambulatory status

NSAID: Non-Steroidal Anti-Inflammatory Drugs; SNRI: Serotonin-Norepinephrine Reuptake Inhibitor; SSRI: Selective Serotonin Reuptake Inhibitors; WHO: World Health Organization.

For further details see the review protocol in appendix A.

Methods and process

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

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

Effectiveness evidence

Included studies

Four studies were included in this review, reporting results from 2 randomised controlled trials (Rief 2014a, Rief 2014b, Rief 2014c, Sprave 2019).

The included studies are summarised in Table 2.

Two randomised controlled trials compared resistance training of vertebral muscles to passive respiratory exercises. Rief 2014a, b, c included patients assessed as having stable spinal metastases (breast, lung, melanoma, prostate, and renal cancer patients). Sprave 2019 compared the two interventions in patients assessed as having unstable spinal metastases (breast, lung, and prostate cancer patients). Classification of stability was made on the basis of Taneichi scores.

Both trials were from Germany (Rief 2014a, b, c, and Sprave 2019).

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

Excluded studies

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

Summary of included studies

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

Table 2: Summary of included studies.

Study	Population	Intervention	Comparison	Outcomes
Rief 2014a, b, c Randomised controlled trial Germany	N=60 Breast, lung, melanoma, prostate, and renal cancer patients with *stable* vertebral body metastases. Age, mean, years (SD): Exercise group 61.3 (10.1); control group 64.1 (10.9), p = 0.304. Sex: female n=27, male n=33.	Differentiated resistance training Duration of around 30 minutes. Muscle exercise component kept as simple as possible due to the differences between patients for example in relation to general health, pain, tumour stage.	Physical 'respiratory' measure/ breathing exercises Duration of around 15 minutes. Physical therapy in the form of respiration exercises and 'hot roll' treatments (hot towel rolls with essential oils pressed onto the thorax) over a period of two weeks.	• Pain • Health-related quality of life • Patient satisfaction • Mobility and ambulatory status • Adverse events
Sprave 2019 Randomised controlled trial Germany	N=60 Breast, lung, and prostate cancer patients with *unstable* spinal metastases Age, mean, years (SD): IPMT: 62.1 (8.8) MR: 61.1(8.5) Sex: female n=31, male n=25.	Isometric paravertebral muscle-training exercises (IPMT) Duration of around 15 minutes, to be completed once daily during palliative radiotherapy (starting on first day of radiotherapy). Comprised of isometric exercises performed (without a corset) in four positions: 'all fours (each extremity stretched separately), 'plank', 'swimming' (toes kept on the floor), and upright with an elastic band tightened in front of the trunk.	Muscle relaxation (MR) Duration of around 15 minutes, to be completed once daily during palliative radiotherapy. Comprised of progressive muscle relaxation for the face, arms, abdomen, and legs. The back was excluded to avoid training effects on the paravertebral muscles. Initially performed with 1:1 supervision and could voluntarily be continued following completion of radiotherapy (supported by an audio	• Pain • Health-related quality of life

Study	Population	Intervention	Comparison	Outcomes
		Initially performed with 1:1 supervision by exercise physiologists or physiotherapists. Following radiotherapy completion, patients were instructed to continue the same exercises three times a week (corroborated by a daily log) at home for another three months.	CD).	

CD: compact disc; SD: standard deviation

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

Summary of the evidence

See the evidence profiles in appendix F.

Resistance training versus passive respiratory exercises

Resistance training was associated with important reduction in some pain measures (pain as measured on a Visual Analog Scale at 3 months and 6 months; pain related to functional interference, pain characteristics and psychological aspects of pain all measured in subscales of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Bone Metastases Module [EORTC QLQ-BM] at 6 months) and important improvement in some measures of mobility (as measured by chair-stand test scores at 3 months) and health related quality of life (measured with the emotional distress subscale of a German quality of life related to cancer questionnaire [FBK]) over passive respiratory exercises, however this was the case for only a small number of outcomes. The majority of outcomes showed no evidence of an important difference (the majority of subscales related to pain of the EORTC QLQ-BM at different time points and the majority of subscales of the Visual Analog Scale at varying time points and the majority of subscale of the FBK at various follow-up times) showing no important differences.

Only 2 studies were found relating to this comparison. The outcomes were rated as very low to moderate quality due to a serious risk of bias in the evidence contributing to the outcomes (missing outcome data and high levels of loss to follow-up), and very serious to serious levels of imprecision in the effect estimates.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

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

Excluded studies

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

Summary of included economic evidence

No economic studies were identified which were applicable to this review question.

Economic model

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

The committee's discussion and interpretation of the evidence

The outcomes that matter most

The focus of this review was analgesic interventions so pain was prioritised as a critical outcome for decision making. Health related quality of life was also a critical outcome due to the adverse impact chronic pain has on quality of life. Patient satisfaction was selected as a critical outcome because treatments may differ in their acceptability – for example some effective analgesics might not be acceptable if they cause intolerable side effects or are administered in an uncomfortable way.

Treatment related adverse events was an important outcome because there are well known adverse effects of different analgesic classes which may impact their acceptability or even require treatment themselves. Mobility and ambulatory status was an important outcome because reduction in pain may enable a person to resume walking or achieve postures that were previously painful.

The quality of the evidence

The quality of the evidence was assessed using GRADE and ranged from very low to high, with most of the evidence being of low or moderate quality.

The majority of outcomes were downgraded due to the risk of bias in the designs of the contributing studies, and serious or very serious imprecision in the effect estimates, as only 2 small studies were identified for inclusion.

No evidence was identified in relation to the following interventions or comparisons: paracetamol, non-steroidal anti-inflammatory drugs, opioid analgesics, muscle relaxants, antidepressants, anticonvulsants, acupuncture, electrotherapy, analgesia strategies, analgesia versus dexamethasone.

As a result of the limited evidence in relation to pain management, the committee reviewed the recommendations from the previous version of the guideline to determine their relevance to current practice and to clarify and update these where necessary based on their experience and expertise.

Benefits and harms

Individualised pain assessment and management plan

Based on experience the committee noted that spinal metastases, direct malignant infiltration of the spine or MSCC can lead to significant pain and usually pain is the deciding factor why

people seek help. Within coordination of services there is a lot of urgent action to take and the committee discussed that it can lead to clinicians losing sight of the urgency of the person's pain management. To address this they made a recommendation that pain relief is provided promptly.

The committee agreed that individualised assessments of pain are essential to effective pain management. Based on their own experiences they noted that in current practice pain assessments do not always take a person-centred approach, and that there is a tendency to rely too heavily on pain scales. They decided that it is important to get information about characteristics of the pain, whether it has progressed and what impact it had on the person's life. This would mean that a treatment plan can be tailored to the person. The committee agreed that the recommendation they made would address the situation that clinicians do not always appreciate the effect that the pain is having over a person's daily life, and that people often do not feel as though their experiences are being taken seriously.

The committee also agreed on the importance of ensuring that decisions about pain management are made on a shared basis and that people should be able to openly discuss treatment options, any previous strategies tried, their concerns, and any expectations that they may have. Based on their own experiences, the committee felt that this would further encourage a person-centred approach to pain management. Based on their experience of clinical practice they noted that there were commonalities in what people want to discuss. The treatments that are planned can be complex and multi-faceted so the committee decided that the reasons for the suggested plan should be explained so that the person can make an informed choice. It was discussed that the perception and impact of pain varies between people, and they acknowledged that it can have a psychological impact, for example people may feel angry or depressed and this may also impact on their family life. To encourage clinicians not to lose sight of the emotional aspects of pain they recommended that this could also feature in their discussions.

Pharmacological analgesic options can be associated with side effects depending on type and dosage (for example drowsiness particularly related to opioids) and people would want information that is clearly tailored to them so that they know what they can expect. It was discussed that some people have their own individual coping strategies (which can range widely) that they may want to discuss and the committee agreed that if these strategies worked for the person previously they should not be discouraged from using this.

Although some evidence supported the use of resistance training, it did not show consistent benefits across all pain and mobility outcomes. The committee noted that this evidence showed that physical therapy can have a positive impact on levels of pain and so they listed it as one of the treatment options. It was agreed, based on experience that there are some situations where a body part is unstable, pain can develop and that some ways of immobilising these parts may reduce pain. The committee therefore included this in the list of possible options to discuss with people.

There was no evidence for psychological therapies but the committee drew on knowledge from other painful conditions, for example they discussed that CBT is used for chronic pain, to suggest that psychological therapies could be a treatment option to discuss. They noted that this would not have to be provided by a clinical psychologist but could be provided by an appropriately trained health or care professional.

The committee also noted that many of the primary treatments for this condition, such as systemic anticancer treatments, corticosteroids, radiotherapy or invasive treatments would also decrease the level of pain so they cross referred to the relevant other sections of the guideline. Some of these treatments were reviewed in other sections of this guideline and have supporting evidence (corticosteroids, radiotherapy and invasive treatments) and some were reviewed in the previous version of the guideline (bisphosphonates and denosumab) and the recommendations have been retained. Anticancer treatments were not in the scope of this guideline, but the committee agreed that reduction of pain is a benefit of this therapy.

The committee noted that persistent, progressive or changes in pain could be a sign that the condition has worsened or that further analgesic treatment is required.

To avoid someone suffering unnecessarily and to prevent worsening health the committee also recommended that the person is informed about when and how to seek further help if needed. They agreed that this is a shared decision making process and referred to the NICE guideline on shared decision making. Based on experience they also noted that there are side effects to medication which may mean that people do not adhere to a pharmacological treatment regimen, so they also cross referenced the NICE guideline on medicines adherence.

The committee agreed that it is important to assess regularly whether the treatment adequately relieves pain and so they recommended that it should be reviewed after starting or whenever a treatment is changed. Based on experience the committee discussed that there are services that are particularly specialised in managing pain and depending on the pain assessment and the impact the pain has on a person's life, they decided that a referral could be made at any stage, including at initial presentation. That committee noted that this will ensure that any pain that is difficult to manage is getting specialist attention if and when needed.

Analgesic medication

Based on their own experiences, the committee emphasised the importance of a clear discussion about the risk of adverse events when taking pain medication, noting that these do not always take place. It was agreed that this can sometimes leave people unaware of the effects that treatment could have on their quality of life and can cause difficulties in relation to adherence and ongoing pain management.

No evidence was identified in relation to specific analgesic strategies, however the committee agreed to make recommendations on this issue based on their knowledge of the WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents (see the 'other factors the committee took into account' section below). They noted that WHO guidance no longer recommends use of the 'three-step pain ladder' and instead specifies that both non-opioids *and* opioids may be used, depending on the severity of the person's pain. They agreed that this is consistent with current practice. Whilst no specific evidence was identified the committee decided to make this a strong recommendation so that pain is managed quickly whilst the person is awaiting investigations or treatment for spinal metastases or MSCC. The committee agreed that the choice of medicine should be based on the individualised pain assessment and agreed in the pain management plan.

The committee also discussed that people's responses to pain treatment vary and that it is important not to leave people on a treatment that may not be working or may require a different dosage to achieve effective pain relief. To avoid inadequate pain relief, they recommended that dosage, titration and tolerability are discussed at each review.

Similarly, no evidence was identified in relation to the use of neuropathic pain relief. The committee therefore agreed based on their own expertise that these can be provided if the pain has neuropathic features or if opioid analgesics have been ineffective. They noted that these should be prescribed in line with the NICE guideline on neuropathic pain in adults: pharmacological management in non-specialist settings.

The committee emphasised the importance of pain relief in palliative cancer care, as well as the need to ensure that controlled drugs are always used safely and appropriately, however they noted the existence of other guidelines dedicated to these topics and agreed that it was appropriate to signpost to these (see the 'other factors the committee took into account' section below).

This topic was not prioritised for a research recommendation because even though there was little research much is known from general medical knowledge and expertise about pain management options. The committee therefore thought that other topics would have a higher priority for future research.

Bisphosphonates

The recommendations on bisphosphonate treatment in the 2008 guideline were retained and the evidence for this will be reviewed in a later update to take into account upcoming patent changes. The committee agreed that the recommendations are consistent with current practice and that retaining them would benefit patients and would not be a safety concern.

Denosumab

Even though the evidence for bisphosphonates and denosumab was not reviewed for this guideline, the committee agreed to cross refer to the related NICE technological appraisal guidance on denosumab because it can be used as an option instead of bisphosphonates for people with bone metastases from breast cancer and from solid tumours other than prostate.

Cost effectiveness and resource use

No economic evidence was identified for this topic from the systematic search of previously published evidence. The committee considered cost effectiveness based on their own experience and knowledge.

Recommendations around assessments and having discussions with the person are current practice and would not have any additional resource impact. Suggesting points for discussion will help clinicians to individualise care which will in turn improve people's satisfaction with services and the care that they receive.

Recommendations referring people to specialist pain centres when needed will lead to an increase in appointments at these centres. These centres are already established, and complex cases are already being referred for people with MSCC. Therefore, any increase in cost is expected to be small.

Whilst the recommendations suggest a wide range of options, some more costly than others, the committee agreed that the population that each option would apply to is relatively small and that most of the options are already in use. More optimised management of pain by tailoring it to the individual and reviewing it, will reduce the use of less effective and inappropriate interventions, reduce future healthcare contacts due to better managed pain and lead to improvements in quality of life.

Other factors the committee took into account

The committee discussed that the WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents (2018) and the European Society for Medical Oncology's guideline on management of cancer pain in adult patients (2018), as well as related NICE guidelines (the NICE guideline on neuropathic pain in adults: pharmacological management, the NICE guideline on palliative care for adults: strong opioids for pain relief and the NICE guideline on controlled drugs) are consistent with the recommendations they made.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.7.1 to 1.7.11.

References – included studies

Effectiveness

Rief 2014a

Rief H, Akbar M, Keller M, et al. Quality of life and fatigue of patients with spinal bone metastases under combined treatment with resistance training and radiation therapy - a randomized pilot trial. Radiation Oncology, 9, 151, 2014

Rief 2014b

Rief H, Omlor G, Akbar M, et al. Feasibility of isometric spinal muscle training in patients with bone metastases under radiation therapy - first results of a randomized pilot trial. BMC Cancer, 14, 67, 2014

Rief 2014c

Rief H, Welzel T, Omlor G, et al. Pain response of resistance training of the paravertebral musculature under radiotherapy in patients with spinal bone metastases - a randomized trial. BMC Cancer, 14, 485, 2014

Sprave 2019

Sprave T, Rosenberger F, Verma V, et al. Paravertebral muscle training in patients with unstable spinal metastases receiving palliative radiotherapy: An exploratory randomized feasibility trial. Cancers, 11, 1771, 2019

Appendices

Appendix A Review protocols

Review protocol for review question: How effective are analgesic interventions in managing pain related to spinal metastases, direct malignant infiltration of the spine with or without associated spinal cord compression?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022303729
1.	Review title	Analgesic interventions in managing pain related to spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression
2.	Review question	How effective are analgesic interventions in managing pain related to spinal metastases, direct malignant infiltration of the spine with or without associated spinal cord compression?
3.	Objective	To establish the effectiveness of analgesic interventions in managing pain related to spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Cumulative Index to Nursing and Allied Health Literature (CINAHL) • Embase • Epistemonikos • International Health Technology Assessment (IHTA) database • MEDLINE & MEDLINE In-Process Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews

ID	Field	Content
		With the agreement of the guideline committee the searches will be re-run between 6-8 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Analgesic interventions in managing pain related to spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression

6.	Population	**Inclusion**:
		• Adults with suspected or confirmed:
		  ○ metastatic spinal disease
		  ○ direct malignant infiltration of the spine.
		• Adults with suspected or confirmed spinal cord or nerve root compression because of:
		  ○ metastatic spinal disease
		  ○ direct malignant infiltration of the spine.
		
		Exclusion:
		• Adults with spinal cord compression because of primary tumours of the spinal cord, meninges or nerve roots.
		• Adults with spinal cord compression because of non-malignant causes.
		• Adults with primary bone tumours of the spinal column.
		• Children and young people under the age of 18.

7.	Interventions	Analgesic interventions for management of pain in patients with spinal metastases/ direct infiltration with or without spinal cord compression:
		
		• **Pharmacological treatment** (oral/sublingual, rectal, intra-muscular, transdermal, intravenous, sub-cutaneous, epidural or intrathecal routes of administration)
		  ○ Paracetamol
		  ○ Non-steroidal anti-inflammatory drugs (NSAIDs)
		  ○ Opioid analgesics
		  ○ Muscle relaxants
		  ○ Antidepressants
		  ○ SSRIs
		  ○ SNRIs such as duloxetine

ID	Field	Content
		○ Tri-cyclic antidepressants such as amitriptyline ○ Anticonvulsants ○ Gabapentinoids such as gabapentin and pregabalin ○ Other anticonvulsants • **Acupuncture** • **Electrotherapy such as:** ○ transcutaneous electrical nerve simulation (TENS) ○ percutaneous electrical nerve simulation (PENS) • **Physical activity**
8.	Comparators	• Placebo/nothing • Each other, for example: ○ Opioids versus neurogenic agents ○ Paracetamol/NSAIDs versus opioids • Analgesia strategies, for example: ○ WHO pain ladder ○ Patient controlled analgesia versus other strategy • Combinations of interventions • Analgesia versus dexamethasone
9.	Types of study to be included	Experimental studies (where the investigator assigned intervention or control) including: • Randomised controlled trials • Non-randomised controlled trials • Comparative observational studies • Systematic reviews/meta-analyses of controlled trials.
10.	Other exclusion criteria	**Inclusion**: • Full text papers • Observational studies should adjust for baseline differences between patients in different intervention groups in their analyses **Exclusion**: • Conference abstracts • Papers that do not include methodological details will not be included as they do not provide suffi-

ID	Field	Content
		cient information to evaluate risk of bias/study quality. • Non-English language articles For NMA: Active interventions that are not part of the decision problem will not be considered in the analysis, unless they act as the sole connectors of the interventions of interest in the network.
11.	Context	Metastatic spinal cord compression in adults: risk assessment, diagnosis and management (2008) NICE guideline will be updated by this review question
12.	Primary outcomes (critical outcomes)	• Pain ○ Change in pain score ○ Time to achieve pain relief • Health-related quality of life • Patient satisfaction
13.	Secondary outcomes (important outcomes)	• Treatment related adverse events (specific to class of treatment, for example, opioids) • Mobility and ambulatory status
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. The full set of records will not be dual screened because the population, interventions and relevant study designs are relatively clear and should be readily identified from titles and abstracts. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics,

ID	Field	Content
		inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Risk of bias of individual studies will be assessed using the preferred checklist as described in Appendix H of Developing NICE guidelines: the manual • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs • The non-randomised study design appropriate checklist. For example Cochrane ROBINS-I tool for non-randomised controlled trials and cohort studies; the EPOC RoB tool for controlled before and after studies. The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. <u>Data Synthesis</u> Where possible, pairwise meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios for dichotomous outcomes. Peto odds ratio will be used for outcomes with zero events Mean differences or standardised mean differences will be calculated for continuous outcomes. If sufficient RCTs are available forming a network of relevant interventions, network meta-analysis will be done using MetaInsight V3 (Owen, RK, Bradbury, N, Xin, Y, Cooper, N, Sutton, A. MetaInsight: An interactive web-based tool for analyzing, interrogating, and visualizing network meta-analyses using R-shiny and netmeta. Res Syn Meth. 2019; 10: 569-581) <u>Heterogeneity</u> Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. In the case of serious or very serious unexplained heterogeneity (remaining after pre-specified subgroup and stratified analyses) meta-analysis will be done using a random effects model. <u>Minimal important differences (MIDs)</u>

ID	Field	Content	

		Default MIDs will be used for risk ratios and continuous outcomes only, unless the committee pre-specifies published or other MIDs for specific outcomes
		• For risk ratios: 0.8 and 1.25.
		• For continuous outcomes:
		  ○ MID is calculated by ranking the studies in order of SD in the control arms. The MID is calculated as +/- 0.5 times median SD.
		  ○ For studies that have been pooled using SMD (meta-analysed): +0.5 and -0.5 in the SMD scale are used as MID boundaries.
		
		<u>Validity</u>
		The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/	

17.	Analysis of sub-groups	Evidence will be stratified by • Severity of pain (for example, mild versus severe pain) Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: • Presumed neuropathic pain versus other presumed type of pain • Subgroups listed in the equality impact assessment form: age, race, sex & socioeconomic status Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic

ID	Field	Content	
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date		
22.	Anticipated completion date		
23.	Stage of review at time of this submission	**Review stage**	**Started** / **Completed**
		Preliminary searches	☑ / ☑
		Piloting of the study selection process	☑ / ☑
		Formal screening of search results against eligibility criteria	☑ / ☑
		Data extraction	☑ / ☑
		Risk of bias (quality) assessment	☑ / ☑
		Data analysis	☑ / ☑
24.	Named contact	**5a. Named contact** NICE **5b Named contact e-mail** metastaticspinal@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)	
25.	Review team members	NICE Technical Team	
26.	Funding sources/sponsor	This systematic review is being completed by NICE.	
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with	

ID	Field	Content	
		NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10185	
29.	Other registration details	Not applicable	
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=303729	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Pain; analgesia; MSCC	
33.	Details of existing review of same topic by same authors	Not applicable	
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information		
36.	Details of final publication	www.nice.org.uk	
	Relevant papers	Wiffen (2017) Opioids for cancer pain - an overview of Cochrane reviews	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CINAHL: Cumulative Index to Nursing and Allied Health Literature; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimally important difference; MSCC: metastatic spinal cord compression; NHS: National health service; NICE: National Institute for Health and Care Excel-

lence; NSAIDs: Non-steroidal anti-inflammatory drugs; PENS: percutaneous electrical nerve simulation; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation; SNRI: Serotonin–norepinephrine reuptake inhibitor; SSRI: Selective serotonin reuptake inhibitor; TENS: transcutaneous electrical nerve simulation

Appendix B Literature search strategies (clinical / economic)

Literature search strategies for review question: How effective are analgesic interventions in managing pain related to spinal metastases, direct malignant infiltration of the spine with or without associated spinal cord compression?

Database: Medline – OVID interface

#	Searches
1	Spinal Cord Compression/
2	((spine or spinal or vertebr*) and (metast* or oligometastas*)).tw.
3	(mescc or mscc).tw.
4	((cauda equina or cervical* or cervicothoracic or cord* or coccyx or duralsac* or dural sac* or intervertebr* or lumbar or lumbosac* or lumbo sac* or medulla* or orthothoracic or sacral or sacrum or spinal or spine* or thecal sac* or thoracic or vertebr* or epidural or extradural or extra dural or ((axon* or neuron* or nerve*) adj2 root)) and (collaps* or compress* or pinch* or press*) and (adeno* or cancer* or carcinoma* or chordoma* or intraepithelial* or intra epithelial* or malignan* or metast* or neoplas* or oligometast* or tumo?r*)).tw.
5	or/1-4
6	paracetamol/
7	(Paracetamol or acetamidophenol or acetaminophen*).ti,ab.
8	exp Anti-Inflammatory Agents, Non-Steroidal/
9	(((nonsteroid* or non steroid*) adj (antiinflammator* or anti inflammator* or antirheumatic* or anti rheumatic*)) or NSAID*).tw.
10	(aspirin or acetylsalicylic acid or celecoxib or diclofenac or etoricoxib or ibuprofen or indomethacin or mefenamic acid or naproxen).tw.
11	exp Analgesics, Opioid/
12	(Alfentanil or Alphaprodine or Buprenorphine or (Buprenorphine adj3 Naloxone) or Butorphanol or Codeine or Dextromoramide or Dextropropoxyphene or Dihydromorphine or Diphenoxylate or Enkephalin or Enkephalin or Ethylketocyclazocine or Ethylmorphine or Etorphine or Fentanyl or Heroin or Hydrocodone or Hydromorphone or Levorphanol or Meperidine or Meptazinol or Methadone or Methadyl Acetate or Morphine or Nalbuphine or Opiate Alkaloid? or Opium or Oxycodone or Oxymorphone or Pentazocine or Phenazocine or Phenoperidine or Pirinitramide or Promedol or Remifentanil or Sufentanil or Tapentadol or Tilidine or Tramadol).mp.
13	exp Muscle Relaxants, Central/
14	(Baclofen or Carisoprodol or Chlormezanone or Chlorphenesin or Chlorzoxazone or Dantrolene or Diazepam or Medazepam or Mephenesin or Meprobamate or Methocarbamol or Orphenadrine or Quinine or Tolperisone or Xylazine or Zoxazolamine).mp.
15	exp Antidepressive Agents/
16	(Aripiprazole or Benactyzine or Clorgyline or Deanol or Desvenlafaxine or Duloxetine or Iproniazid or Isocarboxazid or Levomilnacipran or Lithium or Mirtazapine or Moclobemide or Nialamide or Phenelzine or Pizotyline or Quetiapine or Reboxetine or Rolipram or Selegiline or Sertraline or Tranylcypromine or Vilazodone or Vortioxetine).mp.
17	exp "Serotonin and Noradrenaline Reuptake Inhibitors"/
18	(Amoxapine or Citalopram or Clomipramine or Fenfluramine or Fluoxetine or Fluvoxamine or Norfenfluramine or Olanzapine or Paroxetine or Sertraline or Trazodone or Vilazodone or Vortioxetine or Zimeldine).mp.
19	exp Serotonin Uptake Inhibitors/
20	(Desvenlafaxine or Duloxetine or Levomilnacipran or Milnacipran or Venlafaxine).mp.
21	exp Antidepressive Agents, Tricyclic/
22	(Amitriptyline or Amoxapine or Clomipramine or Desipramine or Dothiepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nortriptyline or Opipramol or Protriptyline or Trimipramine).mp.
23	(Amoxapine or Citalopram or Clomipramine or Fenfluramine or Fluoxetine or Fluvoxamine or Norfenfluramine or Olanzapine or Paroxetine or Sertraline or Trazodone or Vilazodone or Vortioxetine or Zimeldine).mp.
24	exp Anticonvulsants/
25	(anti convuls* or anticonvuls* or anti epilep* or antiepilep*).ti,ab.
26	(acetazolamide or bromide? or cannobidiol or carbamazepi?e or tegretol or chlormethiazole or clobazam or clonazepam or clorazepate dipotassium or diazepam or dimethadione or estazolam or ethosuximide or felbamate or flunarizine or gabapentin* or neurontin or gamma aminobutyric acid* or lacosamide or lamotrigine or lamictal or levetiracetam or keppra or lorazepam or magnesium sulfate or medazepam or mephenytoin or mephobarbital or meprobamate or nitrazepam or oxcarbazepine or trileptal or paraldehyde or phenobarbital or phenytoin or dilantin or pregabalin or lyrica or primidone or riluzole or thiopental or tiagabine or gabitril or tiletamine or topiramate or topamax or trimethadione or valproate or valproic acid or vigabatrin or zonisamide).ti,ab.
27	exp acupuncture/ or accupressure/
28	(acu point* or acupoint* or acupressur* or acupunctur* or electroacupunct* or needle therap*).tw.
29	exp electric stimulation therapy/ or Electromagnetic Fields/
30	((electr* adj2 (field* or simulat* or therap* or treatment*)) or pens or tens).tw.
31	PHYSICAL THERAPY MODALITIES/
32	exp EXERCISE THERAPY/
33	(kinesiotherap* or physiotherap* or physical therap*).ti,ab.
34	(or/6-33) or ((Drug or Pharmacol*) adj3 (intervention* or therap* or treat*)).tw.
35	exp ANIMALS, LABORATORY/ or exp ANIMAL EXPERIMENTATION/ or exp MODELS, ANIMAL/ or exp RODENTIA/ or (rat or rats or mouse or mice).ti.
36	LETTER/ or EDITORIAL/ or NEWS/ or exp HISTORICAL ARTICLE/ or ANECDOTES AS TOPIC/ or COMMENT/ or

#	Searches
	CASE REPORT/ or (letter or comment*).ti.
37	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
38	36 not 37
39	35 or 38
40	(5 and 34) not 39
41	limit 40 to english language
42	exp spinal cord neoplasms/ or Spinal Neoplasms/
43	((spine or spinal or vertebr*) adj2 (adeno* or cancer* or carcinoma* or intraepithelial* or intra epithelial* or malignan* or neoplas* or tumo?r*)).tw.
44	((spine or spinal or vertebr*) and (metast* or oligometast*)).tw.
45	spinal cord compression/
46	((cauda equina or cervical* or cervicothoracic or cord* or coccyx or duralsac* or dural sac* or intervertebr* or lumbar or lumbosac* or lumbo sac* or medulla* or orthothoracic or sacral or sacrum or spinal or spine* or thecal sac* or thoracic or vertebr* or epidural or extradural or extra dural or ((axon* or neuron* or nerve*) adj2 root)) and (collaps* or compress* or pinch* or press*) and (adeno* or cancer* or carcinoma* or chordoma* or intraepithelial* or intra epithelial* or malignan* or metast* or neoplas* or oligometast* or tumo?r*)).tw.
47	(myelopath* or myeloradiculopath* or radiculopath*).tw,hw. or (radicular adj2 (disorder* or syndrome*)).tw.
48	(mescc or mscc).tw.
49	or/42-48
50	(34 and 49) not 39
51	limit 50 to english language

Health economic search strategy

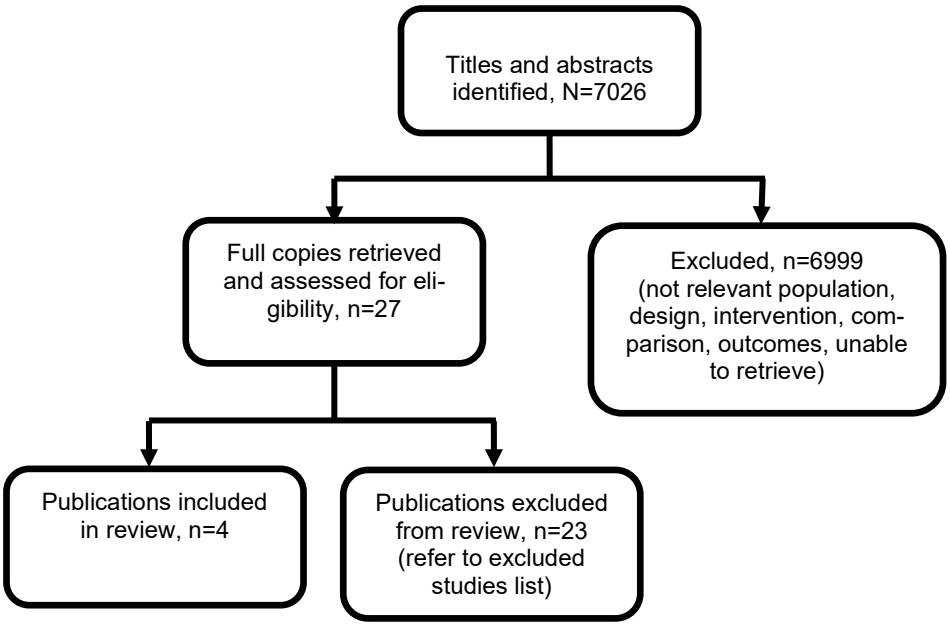
Database: Medline – OVID interface

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

Appendix C Effectiveness evidence study selection

Study selection for: How effective are analgesic interventions in managing pain related to spinal metastases, direct malignant infiltration of the spine with or without associated spinal cord compression?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: How effective are analgesic interventions in managing pain related to spinal metastases, direct malignant infiltration of the spine with or without associated spinal cord compression?

Table 4: Evidence tables

Rief, 2014 a, b, c
Rief H, Akbar M, Keller M, et al. Quality of life and fatigue of patients with spinal bone metastases under combined treatment with resistance training and radiation therapy - a randomized pilot trial. Radiation Oncology, 9, 151, 2014

Study details

Country/ies where study was carried out	Germany.
Study type	Randomised controlled trial (RCT) 1:1 randomisation ratio.
Study dates	September 2011 - March 2013.
Inclusion criteria	Patients with a histologically confirmed tumor diagnosis and also solitary or multiple bone metastases of the thoracic or lumbar segments of the vertebral column or of the sacral region • 18 to 80 years of age • Karnofsky performance score ≥ 70 • Written declaration of informed consent • Already initiated bisphosphonate therapy. • 'Stable' vertebral body metastasis (assessed as 'stable' by both a specialist for radiology and a specialist for orthopedic surgery. Assessments based on Taneichi scores).
Exclusion criteria	• Significant neurological or psychiatric disorder • Diagnosed vertebral-body instability or involvement of the cervical spine
Patient characteristics	Age, mean, years (SD): Exercise group 61.3 (10.1); control group 64.1 (10.9), p = 0.304. Sex: female n=27, male n=33. Karnofsky-index, median (range): Exercise group 80 (70–100); control group 80 (70–100), *p* = 1.000. Primary site: Lung cancer – Exercise group n=12; control n=8, *p* = 0.320. Breast cancer – Exercise group n=5; control group n=6, *p* = 0.542. Prostate cancer – Exercise group n=5; control group n=9, *p* = 0.156. Melanoma – Exercise group n=1; control group n=1, *p* = 1.000.

	Renal cancer – Exercise group n=1; control group 2, *p* = 0.875. Other – Exercise group n=6; control group n=4, *p* = 0.325. Localization metastases, *p* = 0.717: Thoracic – Exercise group n=17; control group n=14. Lumbar – Exercise group n= 9; control group n=13. Thoracic and lumbar – Exercise group n=2; control group n=2. Sacrum – Exercise group n= 2 6.7 1 3.3 Number metastases, *p* = 0.257: Mean (range) – Exercise group 1.4 (2–4); control group 1.7 (1–5). Solitary – Exercise group n=22; control group n=18. Multiple – Exercise group n=8; control group n=12. Type of metastases, *p* = 0.961: Mixed – Exercise group n=2; control group 2, *p* = 1.000. Osteoblast – Exercise group n= 9; control group 10, *p* = 0.956. Osteolytic – Exercise group n=19; control group n=18, *p* = 0.0932. Distant metastases at baseline: Visceral – Exercise group n=12; control group 5, *p* = 0.045. Brain – Exercise group n=3; control group n=3, *p* = 1.000. Lung – Exercise group n=7; control group n=4, *p* = 0.320. Tissue – Exercise group n= 8; control group n=6, *p* = 0.542. Hormonotherapy – Exercise group n=10; control group n=16, *p* = 0.118. Immunotherapy – Exercise group n=7; control group n=5, *p* = 0.519. Chemotherapy – Exercise group n= 25; control group n=20, *p* = 0.136. Pathological fracture at baseline: Exercise group n=6; control group n=9, *p* = 0.379. Neurological deficit: Exercise group n= 0; control group n=2, *p* = 0.150. Orthopaedic corset at baseline: Exercise group n=7; control group n=5, *p* = 0.519. Radiotherapy dose completed (Gy), *p* = 0.136: Single dose (median, range) - exercise group 3 (2–4); control group 3 (2–4), *p* = 1.000 Cumulative dose (median, range) – exercise group 30 (30–40); control group 30 (30–40), *p* = 1.000.
Intervention(s)/control	Intervention group - differentiated resistance training:

	Duration of around 30 minutes. Muscle exercise component kept as simple as possible due to the differences between patients such as general health, pain, tumour stage. Three different exercises enacted to ensure an even isometric training of the muscles along the entire vertebral column as the site of bone metastases varied between patients. During the two-week period of radiotherapy, patients in the resistance training group performed exercises under the guidance of a physiotherapist. The patients were then requested to carry out the defined training program in their home setting three times a week and to document the exercises themselves. No implements were required for home training, and the exercises were designed to be easily completed at the patient's home. Training schedules were verified at the t2 follow-up. Differentiated isometric exercise of the autochthonous muscles: Exercises in the 'all fours' position, the 'gluteus arch position' and the supine position. Control group - physical "respiratory" measure/breathing exercises: Duration of around 15 minutes. Physical therapy in the form of respiration exercises and ventro-thoracic application 'hot roll' treatments) over a period of two weeks. 'Hot roll' treatment was administered by a therapist who pours hot water or essential oils onto a rolled up towel and presses the towel into the patients thorax (who is either sitting or lying on their back). This provides a warming effect in the area. The therapist unfolds the rolled towel, dabbing the patient's skin with each warm layer in the process. The patient is asked to comment on their comfort at regular intervals to ensure that the skin is not overheated; the patient should be as relaxed as possible at all times and asked to inhale deeply to benefit from the respiratory-therapeutic effect of the essential oils. Interventions started on the same day with radiotherapy and were performed on each of the treatment days (Monday until Friday) over a two-week period, independent of the number of radiotherapy fractions. After completion of radiotherapy schedule or, respectively, after two weeks, patients in the training group were guided to continue exercises, which were demonstrated to them by their therapist in the one-on-one situation, on their own at home for a further twelve weeks. The training exercises were documented. The patients in the control group did not carry out any further measures at home after the two week therapy period. After virtual simulation was performed to plan the radiation schedule, radiotherapy was carried out over a dorsal photon field of the 6MV energy range. Primary target volume (PTV) covered the specific vertebral body affected as well as the ones immediately above and below. In Arm A, 24 patients (80%) were treated with 10 × 3 Gy, three patients (10%) with 14 × 2.5 Gy, and three patients (10%) with 20 × 2 Gy. In Arm B, the RT protocols for 28 patients (93.4%) were 10 × 3 Gy, for one patient (3.3%) 14 × 2.5 Gy, and for one patient (3.3%) 20 × 2 Gy. The median single dose was 3 Gy (range 2–3 Gy), the median total dose 30 Gy (range 20–35 Gy). The single and total doses were decided separately for each patient, depending on the histology, the patient's general state of health, and on the current staging and the corresponding prognosis.
Duration of follow-up	**2014a** *Rief H, Akbar M, Keller M, et al. Quality of life and fatigue of patients with spinal bone metastases under combined treatment with resistance training and radiation therapy - a randomized pilot trial. Radiation Oncology, 9, 151, 2014* - mean follow-up = 6.3 months for both groups.

	2014b *Rief H, Omlor G, Akbar M, et al. Feasibility of isometric spinal muscle training in patients with bone metastases under radiation therapy - first results of a randomized pilot trial. BMC Cancer, 14, 67, 2014* - median follow-up = 3.3 months for both groups (range 2.8 — 4.0) **2014c** *Rief H, Welzel T, Omlor G, et al. Pain response of resistance training of the paravertebral musculature under radiotherapy in patients with spinal bone metastases - a randomized trial. BMC Cancer, 14, 485, 2014* – median follow-up = 6.3 months for both groups.
Sources of funding	Not reported.
Sample size	N=60 randomised (intervention group n=30; control group n=30). n=48 completed 12-week follow-up assessments (intervention group n=25; control group n=23). n=36 completed 24-week follow-up assessments (intervention group n=18; control group n=18).
Other information	Results reported from: **2014a** *Rief H, Akbar M, Keller M, et al. Quality of life and fatigue of patients with spinal bone metastases under combined treatment with resistance training and radiation therapy - a randomized pilot trial. Radiation Oncology, 9, 151, 2014* **2014b** *Rief H, Omlor G, Akbar M, et al. Feasibility of isometric spinal muscle training in patients with bone metastases under radiation therapy - first results of a randomized pilot trial. BMC Cancer, 14, 67, 2014* **2014c** *Rief H, Welzel T, Omlor G, et al. Pain response of resistance training of the paravertebral musculature under radiotherapy in patients with spinal bone metastases - a randomized trial. BMC Cancer, 14, 485, 2014*

Outcomes

Outcome	Resistance training, n=30	Passive respiratory exercises, n=30
Pain – functional interference at 3 months, mean (SD) scores on EORTC QLQ-BM 22 (range 0-100, lower scores are better):	35.33 (20.35)	44.7 (30.38)
Pain – functional interference at 6 months, mean (SD) scores on EORTC QLQ-BM 22 (range 0-100, lower scores are better)	29.86 (20.77)	48.38 (30.12)
Pain – neuropathic pain scores, mean (SD) at completion of radiotherapy (measured using VAS, range 0 – 1, lower scores are better)	0.1 (0.3)	0.2 (0.4)
Pain – neuropathic pain scores, mean (SD) at 3 months (measured using VAS, range 0 – 1, lower scores are better)	0.2 (0.4)	0.2 (0.4)
Pain – neuropathic pain scores, mean (SD) at 6 months (measured using VAS, range 0 – 1, lower scores are better)	0.2 (0.4)	0.2 (0.4)
Pain - pain characteristics at 3 months, mean (SD) scores on EORTC QLQ-BM 22, range 0-100, lower scores are better)	25.78 (17.78)	41.92 (35.62)
Pain - pain characteristics at 6 months, mean (SD) scores on EORTC QLQ-BM 22, range 0-100, lower	25.31 (19.73)	45.06 (36.65)

Outcome	Resistance training, n=30	Passive respiratory exercises, n=30
scores are better)		
Pain - pain response, VAS, 0 - 10 (3 months) - responders = partial or complete response	17	11
Pain - pain response, VAS, 0 - 100 (3 months) - responders = partial or complete response	15	10
Pain - pain response, VAS, 0 - 100 (6 months) - responders = partial or complete response	16	6
Pain - pain scores at 3 months (measured using VAS (range 0-10, lower scores are better)	1.9 (1.4)	3.8 (2.3)
Pain - pain scores, VAS (3 months; range 0-100, lower scores are better)	15.8 (12.1)	40.7 (21.7)
Pain - pain scores, VAS (6 months; range 0-100, lower scores are better)	16.7 (14.8)	50.3 (22.8)
Pain - painful sites at 3 months (measured using EORTC QLQ-BM 22, range 0-100, lower scores are better)	29.6 (19.73)	35.76 (27.1)
Pain - painful sites at 6 months (measured using EORTC QLQ-BM 22, range 0-100, lower scores are better)	22.22 (13.14)	35.93 (32.67)
Patient satisfaction - withdrawal from/refusal to take part in programme	0/30	0/30
Treatment related adverse events - adverse events (any, 6 months)	0/18	0/18
Pain - psychosocial aspects at 3 months (measured using EORTC QLQ-BM 22, range 0 to 100, lower scores are better)	45.56 (19.71)	54.55 (20.9)
Pain - psychosocial aspects at 6 months (measured using EORTC QLQ-BM 22, range 0 to 100, lower scores are better)	41.05 (19.65)	50.93 (20.55)
Health-related quality of life - emotional distress at 3 months (measured using FBK-R10, range 0 – 50, lower scores are better)	18.84 (9.2)	22.41 (11.8)
Health- related quality of life - emotional distress at 6 months (measured using FBK-R10, range 0 – 50, lower scores are better)	23.8 (20.2)	33.3 (24.6)
Health-related quality of life - emotional fatigue at 3 months (measured using EORTC QLQ-FA, range 0-100, lower scores are better)	33.67 (25.63)	43.18 (34.85)

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
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Some concerns. Missing outcome data.
Overall bias and Directness	Overall Directness	Directly applicable

Sprave, 2019
Sprave T, Rosenberger F, Verma V, et al. Paravertebral muscle training in patients with unstable spinal metastases receiving palliative radiotherapy: An exploratory randomized feasibility trial. Cancers, 11, 1771, 2019

Study details	
Country/ies where study was carried out	Germany
Study type	Randomised controlled trial (RCT)
Study dates	December 2016 to November 2018
Inclusion criteria	• Aged 18–80 years • Histologically confirmed cancer • Unstable metastases of the thoracolumbar segments. Unstable spine metastases defined using CT and/or MRI (assessed as 'unstable' by both a specialist for radiology and a specialist for orthopaedic surgery. Assessments based on Taneichi scores). • Karnofsky performance score > 70 • Indication for palliative radiotherapy/unsuitable for surgical intervention/refused surgery • Already initiated bisphosphonates or anti-RANKL therapy (required to be delivered if patient not already receiving one of these agents. • Ability to provide written informed consent.
Exclusion criteria	• Previous radiotherapy or surgery to the given irradiation site • Spinal cord compression according to Bilsky score • Myeloma/lymphoma histology • Involvement of cervical spine • Inability/refusal to complete the given exercise regimen.
Patient characteris-tics	Age, years, mean (SD): IPMT: 62.1 (8.8) MR: 61.1(8.5) Age, mean, years (SD): IPMT: 62.1 (8.8) MR: 61.1(8.5) Sex: female n=31, male n=25. SINS score (mean, SD): IPMT: 12.0 (2.5) MR: 10.3 (2.2)
Intervention(s)/control	Intervention: IPMT (Isometric paravertebral muscle-training) exercises, n=30 Duration of around 15 minutes, to be completed once daily during palliative radiotherapy (starting on first day of radiotherapy). Comprised of isometric exercises performed (without a corset) in four positions: ‘all fours (each extremity stretched separately), ‘plank’, ‘swimming’ (toes kept on the floor), and upright with an elastic band tightened in front of the trunk. The holding time for each position was 20 seconds initially and increased from session to session when feasible.

	Initially performed with 1:1 supervised (exercise physiologists or physical therapists). Following radiotherapy completion, patients were instructed to continue the same exercises three times a week (corroborated by a daily log) at home for another three months. <u>Control: Muscle relaxation, n=30</u> Duration of around 15 minutes, to be completed once daily during palliative radiotherapy. Comprised of progressive muscle relaxation for the face, arms, abdomen, and legs. The back was excluded to avoid training effects on the para-vertebral muscles. Initially performed with 1:1 supervision and could voluntarily be continued following completion of radiotherapy (corroborated by an audio CD).
Duration of follow-up	6 months
Sources of funding	None.
Sample size	n=60 IPMT n=30 MR n=30

Study arms: Isometric Paravertebral Muscle Training (IPMT, n=30); muscle relaxation (n=30)
Study timepoints: 0 months/completion of radiotherapy; 3 months; 6 months

Outcomes

Outcome	IPMT, 0-month, N = 27	Muscle relaxation, 0-month, N = 29	IPMT, 3-month, N = 14	Muscle relaxation, 3-month, N = 18	IPMT, 6-month, N = 8	Muscle relaxation, 6-month, N = 11
Pain response (measured using Visual Analog Scale), mean (SD)	30.6 (19.7)	29.1 (24.8)	25.4 (15.5)	28.3 (26.6)	24.3 (18.1)	25 (26.1)
Painful sites (measured using EORTC QLQ-BM 22 questionnaire), mean (SD)	58.5 (17.5)	50.4 (18.1)	52.4 (20.8)	52.2 (18.6)	42.9 (23.3)	51.2 (21.5)
Physical fatigue EORTC QLQ-FA 13 questionnaire, mean (SD)	14.7 (23.7)	*empty data*	16.7 (28.5)	*empty data*	*empty data*	*empty data*
Painful sites - Pain characteristics EORTC QLQ-BM 22 questionnaire, mean (SD)	29.5 (19.5)	20.7 (20.3)	27.6 (19.9)	22.2 (13.9)	32.4 (18.4)	17.8 (14.1)
Painful sites - Functional interference EORTC QLQ-BM 22 questionnaire, mean (SD)	44.9 (28.4)	36 (32.6)	30.2 (28.7)	29.5 (28.3)	22.2 (22.2)	23.5 (26.3)
Painful sites - Psychosocial aspects	44.6 (24.6)	36.2 (22.6)	37.8 (29.3)	28.5 (18.7)	28.6 (26.8)	31.9 (19.8)

Outcome	IPMT, 0-month, N = 27	Muscle relaxation, 0-month, N = 29	IPMT, 3-month, N = 14	Muscle relaxation, 3-month, N = 18	IPMT, 6-month, N = 8	Muscle relaxation, 6-month, N = 11
EORTC QLQ-BM 22 questionnaire, mean (SD)						
Physical fatigue - Emotional fatigue EORTC QLQ-FA 13 questionnaire, mean (SD)	60 (25.1)	52 (28.6)	45.2 (31)	50 (28.7)	45.2 (34.6)	46.3 (30.1)
Physical fatigue - Cognitive fatigue EORTC QLQ-FA 13 questionnaire, mean (SD)	39.7 (30)	29.9 (28.3)	27.4 (23.7)	31.5 (30.2)	31 (39.9)	30.6 (30.3)
Physical fatigue - Interference with daily life EORTC QLQ-FA 13 questionnaire, mean (SD)	17.3 (18.7)	13 (16.8)	16.7 (16.2)	13 (18.4)	23.8 (37.1)	13.6 (12.1)
Physical fatigue - Social sequelae EORTC QLQ-FA 13 questionnaire, mean (SD)	50.7 (37.4)	41.4 (29.1)	50 (36.4)	28.9 (30.8)	42.9 (41.8)	29.6 (35.1)
Emotional distress QSC -R10 questionnaire, mean (SD)	19.7 (8.5)	15.7 (8.6)	19.7 (9.3)	13.8 (9.4)	*empty data*	*empty data*

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 *(Missing outcome data, high attrition)*
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	Some concerns

Section	Question	Answer
		(High attrition)
Overall bias and Directness	Overall Directness	Directly applicable

Appendix E Forest plots

Forest plots for review question: How effective are analgesic interventions in managing pain related to spinal metastases, direct malignant infiltration of the spine with or without associated spinal cord compression?

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

Figure 2: Resistance training versus passive respiratory exercises: Pain - functional interference EORTC QLQ-BM 22 (3 months)

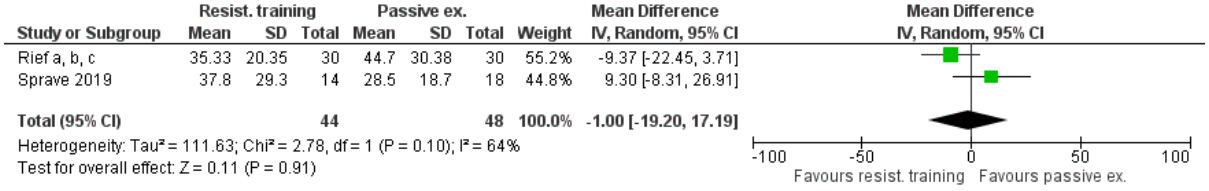


Figure 3: Resistance training versus passive respiratory exercises: Pain - functional interference EORTC QLQ-BM 22 (6 months)

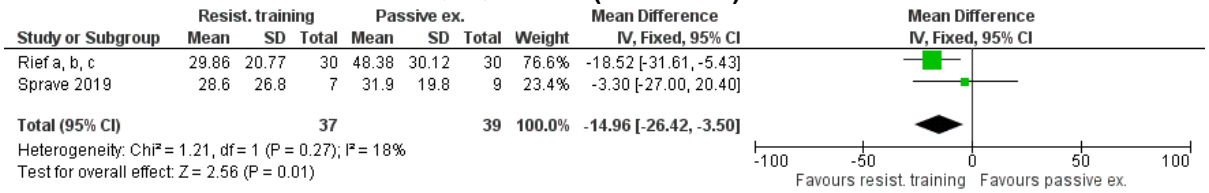


Figure 4: Resistance training versus passive respiratory exercises: Pain – pain characteristics EORTC QLQ-BM 22 (3 months)

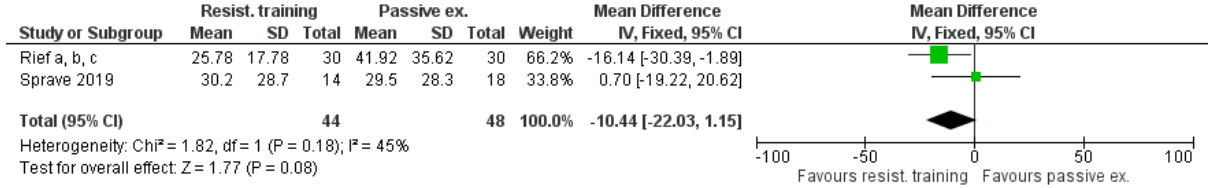


Figure 5: Resistance training versus passive respiratory exercises: Pain – pain characteristics EORTC QLQ-BM 22 (6 months)

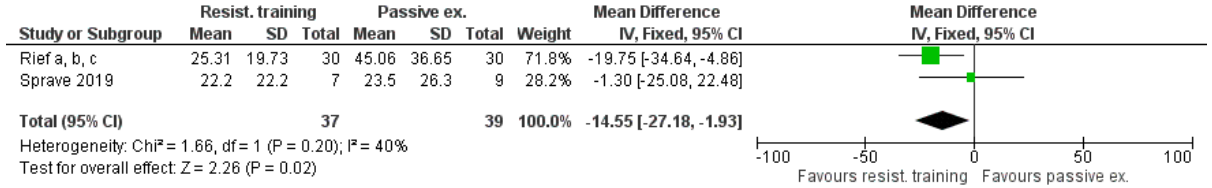


Figure 6: Resistance training versus passive respiratory exercises: Pain – pain visual analogue score (VAS; 3 months)

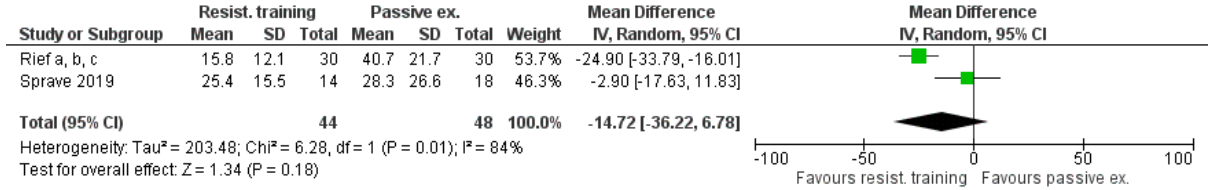


Figure 7: Resistance training versus passive respiratory exercises: Pain – pain visual analogue score (VAS; 6 months)

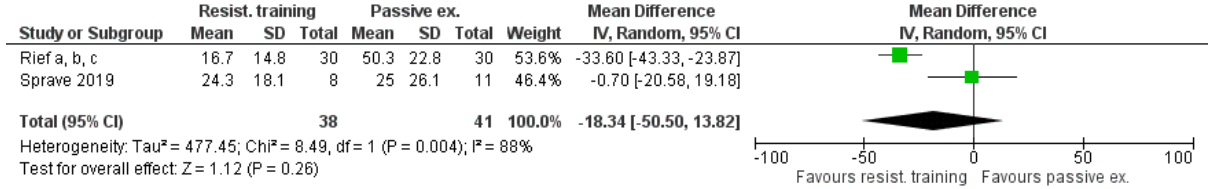


Figure 8: Resistance training versus passive respiratory exercises: Pain – painful sites EORTC QLQ-BM 22 (3 months)

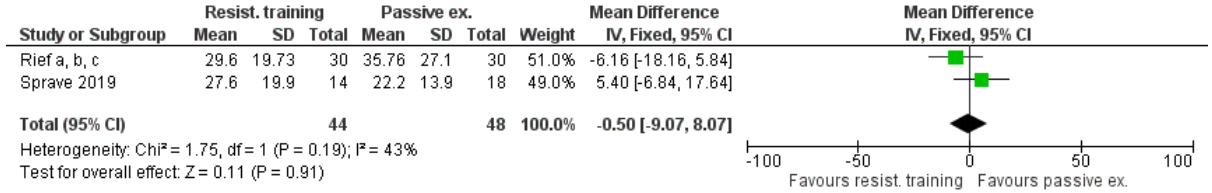


Figure 9: Resistance training versus passive respiratory exercises: Pain – painful sites EORTC QLQ-BM 22 (6 months)

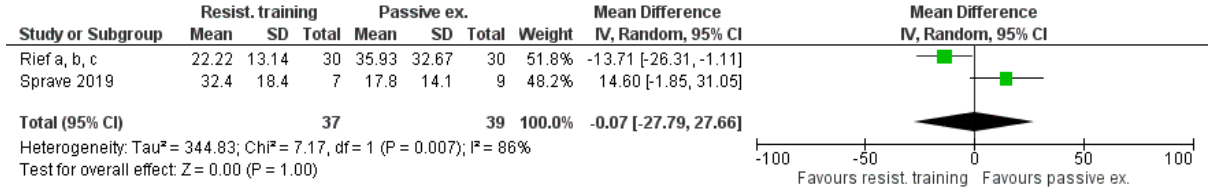


Figure 10: Resistance training versus passive respiratory exercises: Pain – psycho-social aspects EORTC QLQ-BM 22 (3 months)

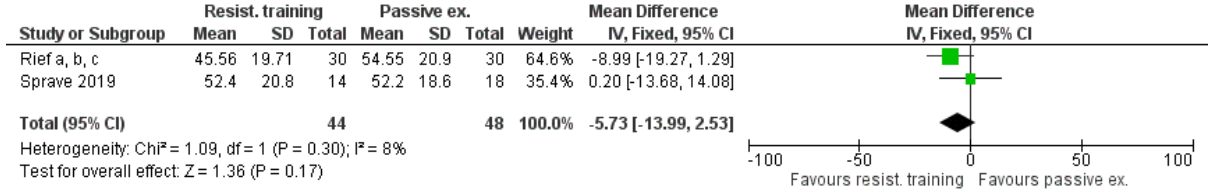


Figure 11: Resistance training versus passive respiratory exercises: Pain – psycho-social aspects EORTC QLQ-BM 22 (6 months)

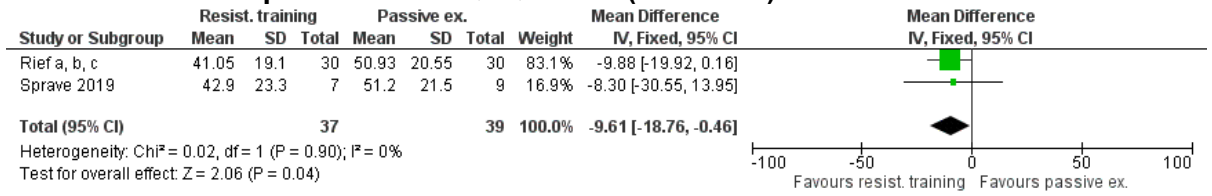


Figure 12: Resistance training versus passive respiratory exercises: Health-related quality of life - emotional distress, FBK -R10 (3 months)

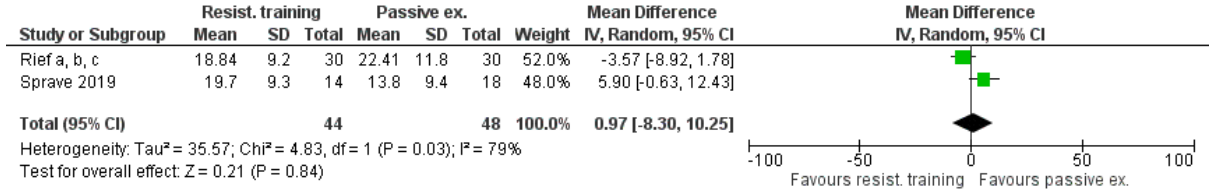
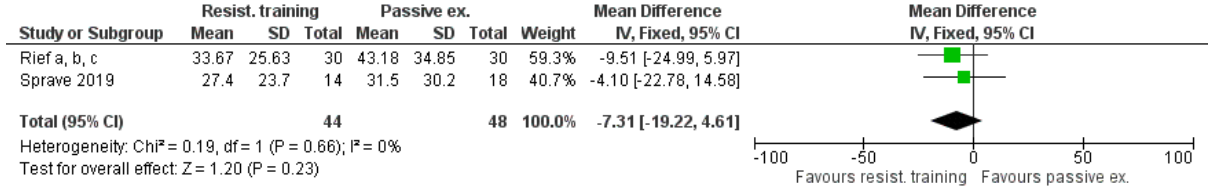


Figure 13: Resistance training versus passive respiratory exercises: Health-related quality of life - emotional fatigue, EORTC QLQ-FA (3 months)



Appendix F GRADE tables

GRADE tables for review question: How effective are analgesic interventions in managing pain related to spinal metastases, direct malignant infiltration of the spine with or without associated spinal cord compression?

Table 5: Evidence profile for comparison between resistance training and passive respiratory exercises

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance training	passive respiratory exercises	Relative (95% CI)	Absolute (95% CI)		
Pain - functional interference at 0 months (measured using EORTC QLQ-BM 22, range 0-100, lower scores are better)												
1 (Sprave 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26	29	Not estimable	MD 8.4 higher (4.13 lower to 20.93 higher)	LOW	CRITICAL
Pain - functional interference at 3 months (measured using EORTC QLQ-BM 22, range 0-100, lower scores are better)												
2 (Rief 2014, Sprave 2019)	randomised trials	serious[1]	serious[6]	no serious indirectness	very serious[3]	none	44	48	Not estimable	MD 1.00 lower (19.20 lower to 17.79 higher)	VERY LOW	CRITICAL
Pain - functional interference at 6 months (measured using EORTC QLQ-BM 22, range 0-100, lower scores are better)												
2 (Rief 2014, Sprave 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	37	39	Not estimable	MD 14.96 lower (26.42 lower to 3.5 lower)	LOW	CRITICAL
Pain – neuropathic pain scores at completion of radiotherapy (measured using VAS, range 0 – 1, lower scores are better)												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance training	passive respiratory exercises	Relative (95% CI)	Absolute (95% CI)		
1 (Rief 2014)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	Not estimable	MD 0.1 lower (0.28 lower to 0.08 higher)	LOW	CRITICAL
Pain – neuropathic pain scores at 3 months (measured using VAS, range 0 – 1, lower scores are better)												
1 (Rief 2014)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	30	Not estimable	MD 0 (0.2 lower to 0.2 higher)	MODERATE	CRITICAL
Pain – neuropathic pain scores at 6 months (measured using VAS, range 0 – 1, lower scores are better)												
1 (Rief 2014)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	30	Not estimable	MD 0 (0.2 lower to 0.2 higher)	MODERATE	CRITICAL
Pain - pain characteristics at 0 months (measured using EORTC QLQ-BM 22, range 0-100, lower scores are better)												
1 (Sprave 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	26	29	Not estimable	MD 8.9 higher (7.22 lower to 25.02 higher)	MODERATE	CRITICAL
Pain - pain characteristics at 3 months (measured using EORTC QLQ-BM 22, range 0-100, lower scores are better)												
2 (Rief 2014, Sprave 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	44	48	Not estimable	MD 10.44 lower (22.03 lower to 1.15 higher)	MODERATE	CRITICAL
Pain - pain characteristics at 6 months (measured using EORTC QLQ-BM 22, range 0-100, lower scores are better)												
2 (Rief	randomised	serious[1]	no serious	no serious	no serious im-	none	37	39	Not esti-	MD	MODERATE	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance training	passive respiratory exercises	Relative (95% CI)	Absolute (95% CI)		
2014, Sprave 2019)	trials		inconsistency	indirectness	precision				mable	14.55 lower (27.18 lower to 1.93 lower)		
Pain - pain response, VAS, 0 - 100 (3 months) - partial or complete response												
1 (Rief 2014)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	17/30 (56.7%)	11/30 (36.7%)	RR 1.55 (0.88 to 2.72)	202 more per 1,000 (from 44 fewer to 631 more)	LOW	CRITICAL
Pain - pain response, VAS, 0 - 100 (6 months) - partial or complete response												
1 (Rief 2014)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	16/30 (53.3%)	6/30 (20%)	RR 2.67 (1.21 to 5.88)	334 more per 1,000 (from 42 more to 976 more)	LOW	CRITICAL
Pain - pain scores at 3 months (measured using VAS (range 0-10, lower scores are better)												
1 (Rief 2014)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	Not estimable	MD 1.9 lower (2.86 lower to 0.94 lower)	LOW	CRITICAL
Pain - pain scores, VAS (at completion of radiotherapy; range 0-100, lower scores are better)												
1 (Rief 2014)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	Not estimable	MD 9.5 lower (20.89 lower to 1.89 higher)	LOW	CRITICAL
Pain - pain scores, VAS (at completion of radiotherapy; range 0-100, lower better)												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance training	passive respiratory exercises	Relative (95% CI)	Absolute (95% CI)		
1 (Sprave 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	27	29	Not estimable	MD 1.5 higher (10.19 lower to 13.19 higher)	MODERATE	CRITICAL
Pain - pain scores, VAS (3 months; range 0-100, lower scores are better)												
2 (Rief 2014, Sprave 2019)	randomised trials	serious[1]	serious[6]	no serious indirectness	serious[2]	none	44	48	Not estimable	MD 14.72 lower (36.22 lower to 6.78 higher)	VERY LOW	CRITICAL
Pain - pain scores, VAS (6 months; range 0-100, lower scores are better)												
2 (Rief 2014, Sprave 2019)	randomised trials	serious[1]	serious[6]	no serious indirectness	serious[2]	none	38	41	Not estimable	MD 18.34 lower (50.50 lower to 13.82 higher)	VERY LOW	CRITICAL
Pain - painful sites at 3 months (measured using EORTC QLQ-BM 22, range 0-100, lower scores are better)												
2 (Rief 2014, Sprave 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	44	48	Not estimable	MD 0.5 lower (9.07 lower to 8.07 higher)	MODERATE	CRITICAL
Pain - painful sites at 0 months (measured using EORTC QLQ-BM 22, range 0-100, lower scores are better)												
1 (Sprave 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	26	29	Not estimable	MD 8.8 higher (1.72 lower to 19.32	MODERATE	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance training	passive respiratory exercises	Relative (95% CI)	Absolute (95% CI)		
										higher)		
Pain - painful sites at 6 months (measured using EORTC QLQ-BM 22, range 0-100, lower scores are better)												
2 (Rief 2014, Sprave 2019)	randomised trials	serious[1]	serious[6]	no serious indirectness	serious[2]	none	37	39	Not estimable	MD 0.07 lower (27.79 lower to 27.66 higher)	LOW	CRITICAL
Health-related quality of life - cognitive fatigue at 0 months (measured using EORTC QLQ-FA (range 0 to 100, lower scores are better)												
1 (Sprave 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25	29	Not estimable	MD 4.3 higher (5.25 lower to 13.85 higher)	MODERATE	IMPORTANT
Health-related quality of life - cognitive fatigue at 3 months (measured using EORTC QLQ-FA (range 0 to 100, lower scores are better)												
1 (Sprave 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14	18	Not estimable	MD 3.7 higher (8.31 lower to 15.71 higher)	MODERATE	CRITICAL
Health-related quality of life - cognitive fatigue at 6 months (measured using EORTC QLQ-FA (range 0 to 100, lower scores are better)												
1 (Sprave 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7	9	Not estimable	MD 10.2 higher (18.4 lower to 38.8 higher)	LOW	CRITICAL
Health-related quality of life - fatigue - interference with daily life at 0 months (measured using EORTC QLQ-FA, range 0 to 100, lower scores are better)												
1 (Sprave 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25	29	Not estimable	MD 9.3 higher (8.79 lower to	MODERATE	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance training	passive respiratory exercises	Relative (95% CI)	Absolute (95% CI)		
										27.39 higher)		
Health-related quality of life - fatigue - interference with daily life at 3 months (measured using EORTC QLQ-FA, range 0 to 100, lower scores are better)												
1 (Sprave 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14	18	Not estimable	MD 21.1 higher (2.69 lower to 44.89 higher)	MODERATE	CRITICAL
Health-related quality of life - fatigue - interference with daily life at 6 months (measured using EORTC QLQ-FA, range 0 to 100, lower scores are better)												
1 (Sprave 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	7	9	Not estimable	MD 13.3 higher (25.23 lower to 51.83 higher)	VERY LOW	CRITICAL
Health-related quality of life - physical fatigue at 0 months (measured using EORTC QLQ-FA (range 0 to 100, lower scores are better)												
1 (Sprave 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25	29	Not estimable	MD 8 higher (6.4 lower to 22.4 higher)	MODERATE	CRITICAL
Health-related quality of life - physical fatigue at 3 months (measured using EORTC QLQ-FA (range 0 to 100, lower scores are better)												
1 (Sprave 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	14	18	Not estimable	MD 4.8 lower (25.76 lower to 16.16 higher)	VERY LOW	CRITICAL
Health-related quality of life - physical fatigue at 6 months (measured using EORTC QLQ-FA (range 0 to 100, lower scores are better)												
1 (Sprave 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	7	9	Not estimable	MD 1.1 lower (33.41 lower to	VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance training	passive respiratory exercises	Relative (95% CI)	Absolute (95% CI)		
										31.21 higher)		
Patient satisfaction - withdrawal from/refusal to take part in programme												
1 (Rief 2014)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	0/30 (0.0%)	0/30 (0.0%)	RD 0.00 (-0.06 to 0.06)	0 fewer per 1,000 (from 60 fewer to 60 more)	VERY LOW	CRITICAL
Treatment related adverse events - adverse events (any, 6 months)												
1 (Rief 2014)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	0/18 (0.0%)	0/18 (0.0%)	RD 0.0 (-0.1 to 0.1)	0 fewer per 1,000 (from 10 fewer to 10 more)	VERY LOW	IMPORTANT
Mobility and ambulatory status - chair-stand test scores at 3 months (number of repetitions within 30 seconds)												
1 (Rief 2014)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	30	Not estimable	MD 4 higher (2.66 higher to 5.34 higher)	MODERATE	IMPORTANT
Pain - psychosocial aspects at 0 months (measured using EORTC QLQ-BM 22, range 0 to 100, lower scores are better)												
1 (Sprave 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26	29	Not estimable	MD 8.1 higher (1.32 lower to 17.52 higher)	LOW	CRITICAL
Pain - psychosocial aspects at 3 months (measured using EORTC QLQ-BM 22, range 0 to 100, lower scores are better)												
2 (Rief 2014, Sprave 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	44	48	Not estimable	MD 5.73 lower (13.99 lower to 2.53	LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance training	passive respiratory exercises	Relative (95% CI)	Absolute (95% CI)		
										higher)		
Pain - psychosocial aspects at 6 months (measured using EORTC QLQ-BM 22, range 0 to 100, lower scores are better)												
2 (Rief 2014, Sprave 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	37	39	Not estimable	MD 9.61 lower (18.76 lower to 0.46 lower)	LOW	CRITICAL
Health-related quality of life - emotional distress at completion of radiotherapy (measured using FBK-R10, range 0 – 50, lower scores are better)												
1 (Sprave 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26	28	Not estimable	MD 4 higher (0.56 lower to 8.56 higher)	LOW	CRITICAL
Health-related quality of life - emotional distress at 3 months (measured using FBK-R10, range 0 – 50, lower scores are better)												
2 (Rief 2014, Sprave 2019)	randomised trials	serious[1]	serious[6]	no serious indirectness	very serious[4]	none	44	48	Not estimable	MD 0.97 higher (8.30 lower to 10.25 higher)	VERY LOW	CRITICAL
Health-related quality of life - emotional distress at 6 months (measured using FBK-R10, range 0 – 50, lower scores are better)												
1 (Rief 2014)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	Not estimable	MD 9.51 lower (15.03 lower to 3.99 lower)	LOW	CRITICAL
Health-related quality of life - emotional fatigue at 0 months (measured using EORTC QLQ-FA, range 0-100, lower scores are better)												
1 (Sprave 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25	29	Not estimable	MD 9.8 higher (5.83 lower to	LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance training	passive respiratory exercises	Relative (95% CI)	Absolute (95% CI)		
										25.43 higher)		
Health-related quality of life - emotional fatigue at 3 months (measured using EORTC QLQ-FA, range 0-100, lower scores are better)												
2 (Rief 2014, Sprave 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	44	48	Not estimable	MD 7.31 lower (19.22 lower to 4.61 higher)	LOW	CRITICAL
Health-related quality of life - emotional fatigue at 6 months (measured using EORTC QLQ-FA, range 0-100, lower scores are better)												
1 (Sprave 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	7	9	Not estimable	MD 0.4 higher (35.17 lower to 35.97 higher)	VERY LOW	CRITICAL

CI: confidence interval; EORTC QLQ-BM: European Organization for Research and Treatment of Cancer – Quality of Life - Group Bone Metastases Module; EORTC-QLQ-FA: European Organization for Research and Treatment of Cancer – Quality of Life – Fatigue Module; FBK: Fragebogen zur Belastung von Krebskranken (German questionnaire on quality of life related to cancer); QSC-R10: Questionnaire on Distress in Cancer Patients -short form; MD: mean difference; RR: risk ratio; VAS: Visual Analogue Scale

1. Serious risk of bias in the evidence contributing to the outcomes as per RoB2.
2. 95% CI crosses 1 MID (0.5x control group SD, for EORTC QLQ-BM 22 functional interference ±12.89; for VAS 0-1 neuropathic pain scores ±0.2; for VAS 0-10 pain scale ±1.35; for VAS 0-100 pain scale 13.45; for EORTC QLQ-BM 22 painful sites ±11.20; for EORTC QLQ-FA cognitive fatigue ±14.15; for chair-stand test ±1; for EORTC QLQ-BM 22 pain - psychosocial aspects ±9.49; for FBK-R10 emotional distress ±5.33; for EORTC QLQ-FA emotional fatigue ±14.65).
3. 95% CI crosses 1 MID (0.8 or 1.25).
4. 95% CI crosses 2 MIDs (0.5x control group SD, for EORTC QLQ-BM 22 functional interference ±12.89; for EORTC QLQ-BM 22 psychosocial aspects ±9.05; for EORTC QLQ-FA interference with daily life ±14.5; for EORTC QLQ-FA physical fatigue ±14.45; for EORTC QLQ-FA emotional fatigue ±14.15; for FBK-R10 emotional distress ±5.33).
5. Sample size <100
6. Serious heterogeneity unexplained by subgroup analysis

Appendix G Economic evidence study selection

Study selection for: How effective are analgesic interventions in managing pain related to spinal metastases, direct malignant infiltration of the spine with or without associated spinal cord compression?

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

Appendix H Economic evidence tables

Economic evidence tables for review question: How effective are analgesic interventions in managing pain related to spinal metastases, direct malignant infiltration of the spine with or without associated spinal cord compression?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: How effective are analgesic interventions in managing pain related to spinal metastases, direct malignant infiltration of the spine with or without associated spinal cord compression?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: How effective are analgesic interventions in managing pain related to spinal metastases, direct malignant infiltration of the spine with or without associated spinal cord compression?

Excluded effectiveness studies

Table 6: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Anonymous. (2006) Best treatment approaches for malignant spinal cord compression. Journal of Supportive Oncology 4(2): 62-63	Publication type does not match review protocol - conference abstract
Body, J-J (2004) Reducing skeletal complications and bone pain with intravenous ibandronate for metastatic bone disease. European journal of cancer, supplement 2(5): 5-8	Population does not match review protocol
Cao, Q, Huang, D, Xu, H et al. (2014) Pregabalin combined with intrathecal sufentanil infusion for breakthrough pain in patients with bone metastases. Zhong nan da xue xue bao. Yi xue ban [Journal of Central South University. Medical sciences] 39(4): 384-388	Other protocol criteria – not available in English
Comlek, S. (2021) Treatment methods for bone metastasis-induced pain. Turk Onkoloji Dergisi 36(suppl1): 73-78	Study design does not match protocol - guidance
Ding, Q G (2015) Clinical study of acupuncture at Mingmen and Guanyuan acupionts combined with analgesic on the treatment of lumbar spinal metastatic carcinoma pains. Chinese medicine modern distance education of china [zhong guo zhong yi yao xian dai yuan cheng jiao yu] 13(7): 65-66	Other protocol criteria – not available in English
Eisenach, J.C., DuPen, S., Dubois, M. et al. (1995) Epidural clonidine analgesia for intractable cancer pain. Pain 61(3): 391-399	Other protocol criteria - duplicate publication
Eisenach, James C, DuPen, Stuart, Dubois, Michel et al. (1995) Epidural clonidine analgesia for intractable cancer pain. The Epidural Clonidine Study Group. Pain 61(3): 391-399	Population does not match review protocol
Fanous, S.N., Saleh, E.G., Abd Elghafar, E.M. et al. (2021) Randomized controlled trials between dorsal root ganglion thermal radiofrequency, pulsed radiofrequency and steroids for the management of intractable metastatic back pain in thoracic vertebral body. British Journal of Pain 15(3): 270-281	Intervention does not match review protocol
Galvao, D.A.; Taaffe, D.R.; Spry, N.; Cormie, P.; Joseph, D.; Chambers, S.K.; Chee, R.; Peddle-McIntyre, C.J.; Hart, N.H.; Baumann, F.T.; Denham, J.; Baker, M.; Newton, R.U.; Exercise Preserves Physical Function in Prostate Cancer Patients with Bone Metastases; Medicine and science in sports and exercise; 2018; vol. 50 (no. 3); 393-399	Outcomes do not match review protocol
Hart, N.H., Galvao, D.A., Saunders, C. et al. (2018) Mechanical suppression of osteolytic bone metastases in advanced breast	Other protocol criteria – study

Study	Reason for exclusion
cancer patients: A randomised controlled study protocol evaluating safety, feasibility and preliminary efficacy of exercise as a targeted medicine. Trials 19(1): 695	protocol
Hart, N.H., Newton, R.U., Spry, N.A. et al. (2017) Can exercise suppress tumour growth in advanced prostate cancer patients with sclerotic bone metastases? A randomised, controlled study protocol examining feasibility, safety and efficacy. BMJ Open 7(5): e014458	Other protocol criteria – study protocol
Jain, P and Chatterjee A, Randomized Placebo-Controlled Trial Evaluating the Analgesic Effect of Salmon Calcitonin in Refractory Bone Metastasis Pain. Indian Journal of Palliative Care 26, 4-8, 2020	Intervention does not match review protocol
Kaloostian, P.E., Yurter, A., Etame, A.B. et al. (2014) Palliative strategies for the management of primary and metastatic spinal tumors. Cancer Control 21(2): 140-143	Study design does not match review protocol - expert review/narrative. Checked for relevant studies
Paniagua-Collado, Maria and Cauli, Omar (2018) Non-pharmacological interventions in patients with spinal cord compression: a systematic review. Journal of neuro-oncology 136(3): 423-434	Study design - systematic review without pooled results/quantitative data, checked for relevant studies
Payton, S (2013) Prostate cancer: abiraterone benefit extends to bone-related symptoms. Nature reviews urology 10(1): 1	Population does not match review protocol
Peng, L, Min, S, Zejun, Z et al. (2015) Spinal cord stimulation for cancer-related pain in adults. Cochrane Database of Systematic Reviews	Population does not match review protocol
Rief, H., Bruckner, T., Schlampp, I. et al. (2016) Resistance training concomitant to radiotherapy of spinal bone metastases - survival and prognostic factors of a randomized trial. Radiation Oncology 11(1): 97	Outcomes do not match review protocol
Rief, H., Jensen, A.D., Bruckner, T. et al. (2011) Isometric muscle training of the spine musculature in patients with spinal bony metastases under radiation therapy. BMC Cancer 11: 482	Other protocol criteria – study protocol
Rief, H., Petersen, L.C., Omlor, G. et al. (2014) The effect of resistance training during radiotherapy on spinal bone metastases in cancer patients - A randomized trial. Radiotherapy and Oncology 112(1): 133-139	Outcomes do not match review protocol
Rosenberger, F., Sprave, T., Rief, H. et al. (2020) Safety and feasibility of paravertebral muscle training in patients with unstable spinal metastases undergoing palliative radiotherapy. Oncology Research and Treatment 43(supplement1): 190	Publication type does not match review protocol - conference abstract
Vayne-Bossert, P., Afsharimani, B., Good, P. et al. (2016) Interventional options for the management of refractory cancer pain-what is the evidence?. Supportive Care in Cancer 24(3): 1429-1438	Study design does not match review protocol - expert review/narrative. Checked for relevant studies
von Moos, R, Body, JJ, Egerdie, B et al. (2016) Pain and analgesic use associated with skeletal-related events in patients with advanced cancer and bone metastases. Supportive care in cancer 24(3): 1327-1337	Intervention does not match review protocol – evaluates denosumab/zoledronic acid
Welte, S.E., Wiskemann, J., Scharhag-Rosenberger, F. et al. (2017) Differentiated resistance training of the paravertebral muscles in patients with unstable spinal bone metastasis under concomitant radiotherapy: Study protocol for a randomized pilot trial.	Other protocol criteria – study protocol

Study	Reason for exclusion
Trials 18(1): 155	

Excluded economic studies

No economic evidence was identified for this review. See supplement 2 for further information.

Appendix K Research recommendations

Research recommendations for review question: How effective are analgesic interventions in managing pain related to spinal metastases, direct malignant infiltration of the spine with or without associated spinal cord compression?

No research recommendations were made for this review question.