



Cochrane
Library

Cochrane Database of Systematic Reviews

Potential harms of interventions for spinal metastatic disease (Protocol)

Carrwik C, Murakami H, Willander J, Robinson Y

Carrwik C, Murakami H, Willander J, Robinson Y.
Potential harms of interventions for spinal metastatic disease.
Cochrane Database of Systematic Reviews 2017, Issue 7. Art. No.: CD012724.
DOI: 10.1002/14651858.CD012724.

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
BACKGROUND	1
OBJECTIVES	2
METHODS	3
ACKNOWLEDGEMENTS	6
REFERENCES	6
ADDITIONAL TABLES	7
APPENDICES	12
CONTRIBUTIONS OF AUTHORS	14
DECLARATIONS OF INTEREST	15
SOURCES OF SUPPORT	15

Potential harms of interventions for spinal metastatic disease

Christian Carrwik¹, Hideki Murakami², Johan Willander³, Yohan Robinson¹

¹Department of Surgical Sciences, Uppsala University Hospital, Uppsala, Sweden. ²Department of Orthopaedic Surgery, Graduate School of Medical Science, Kanazawa University, Kanazawa, Japan. ³Department of Psychology, Gävle University, Uppsala, Sweden

Contact address: Yohan Robinson, Department of Surgical Sciences, Uppsala University Hospital, Uppsala, Sweden. yohan.robinson@surgsci.uu.se.

Editorial group: Cochrane Back and Neck Group.

Publication status and date: New, published in Issue 7, 2017.

Citation: Carrwik C, Murakami H, Willander J, Robinson Y. Potential harms of interventions for spinal metastatic disease. *Cochrane Database of Systematic Reviews* 2017, Issue 7. Art. No.: CD012724. DOI: 10.1002/14651858.CD012724.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

The primary objective of this review is to compare the potential harms of treatment for spinal metastatic disease for the following treatments:

1. Surgical intervention.
2. Surgical intervention with radiation therapy.
3. Radiation therapy alone.

Our secondary objectives are:

1. comparing the harms of different surgical methods;
2. comparing the harms between different radiation protocols.

BACKGROUND

Spinal metastatic disease is a common complication of several types of cancer. It is estimated that two thirds of cancer patients develop skeletal metastasis and the spine is the most common site (Maccauro 2011). The metastasis might cause pain and neurological symptoms, but can be asymptomatic during the remainder of the patient's life and thus never detected (Maccauro 2011).

Metastatic epidural spinal cord compression (MESCC) is a common neurological complication of spinal metastasis. The frequency among cancer patients is probably under-reported and dif-

ficult to calculate, but autopsy studies and register studies among specified populations suggest an incidence of MESCC in cancer patients of about 5% (Barron 1959; Spencer 2014). As cord compression often causes progressive neurological deficits, a rapid diagnosis and an individualized treatment decision is crucial to avoid treatment delay. Treatment of the metastasis rarely cures the patient from the cancer and the possible harms of the treatment may affect quality of life during the often short expected survival time.

Description of the condition

Almost any type of systemic cancer can cause spinal metastasis and MESCC. Prostate, breast and lung tumours are the most frequent origins of MESCC (Constans 1983). The tumours spread hematogenously and grow in the vertebrae. This can lead to gradual or acute damage to the spinal cord, either due to mechanical compression, secondary vascular damage, or pathological fracture. Pain and loss of motor function are the two most common symptoms (Helweg-Larsen 1994). The median survival time of patients with MESCC is estimated to be 3 to 6 months (Helweg-Larsen 2000).

Description of the intervention

There are multiple surgical and non-surgical methods to treat spinal metastasis. As soon as neurological symptoms are present, the first line of treatment is corticosteroid therapy (Ribas 2012). This can be combined with radiation therapy or different surgical techniques, or both. For the purpose of this review, the interventions studied will be surgery with or without radiation therapy. When it comes to surgical interventions, several techniques are described in the literature. In early studies, laminectomy alone was the standard surgical procedure. Bone and tumour mass at the level of compression and one level above and below were removed (Young 1980). Today, decompression followed by mechanical stabilization with implants is the method used in recent studies and clinical practice. By adding the instrumentation, the stability of the spine will increase and thus reduce pain and risk for neurological deterioration. In short, the aim of the surgery is to address symptoms that are refractory to non-operative care (Kaloostian 2014).

While the surgical techniques have evolved in recent years, radiotherapy (RT) is still the most commonly used modality for definitive treatment of MESCC. Radiotherapy can shrink the tumour and reduce the pressure on the spinal cord, reducing pain and neurological symptoms. Patients not treated with primary surgery usually receive RT (Loblaw 2012).

How the intervention might work

For patients with spinal metastatic disease without cord compression, the aim is to reduce pain and maintain spinal stability. If MESCC occurs, the aim is to reduce the compression of the spinal cord. The possible positive effects of this include preservation and restoration of neurological function, spinal stability, reduced pain and local tumour control (Laufer 2012).

Why it is important to do this review

The treatment of spinal metastasis is still a matter of debate and new surgical methods are gaining popularity. As the patients have short life expectancy, it is of paramount importance to avoid complications and hospitalisation affecting the remainder of their lives. One Cochrane review focused on the results of MESCC treatment, where harms were investigated as a secondary outcome, but only six randomized controlled trials (RCTs) met the inclusion criteria (George 2008). In a recent update, the authors found one more RCT to include in the review (George 2015). Still, only two of the RCTs include surgical treatment and one of them is from 1980, when the preferred surgical technique (decompression only) was not the same as today.

While the review by George and colleagues sheds light on the adverse effects of different radiation protocols, there is no comparison between the adverse effects caused by different surgical methods. As opposed to the review by George and colleagues, the focus of our review will be entirely on harms. Furthermore, we aim to find more data as we will include not only RCTs.

Studies evaluating adverse effects of spine surgery are often retrospective and adverse effects are not always included as primary outcomes. It is suggested that the morbidity rate after spinal surgery of any kind is under-reported (Dea 2014). This highlights the importance of synthesizing the evidence on harms to find the optimal treatment for these patients. While many of these patients will need surgical intervention to stop progression of their symptoms, we believe that clinicians and patients need more information on the potential harms in order to make informed decisions and select the best treatment.

In addition to the patient's suffering, complications after treatment for spinal metastasis will also have financial implications. The exact cost for an adverse effect depends on many factors, including the healthcare system, and it is hard to estimate. A study at an academic hospital in the USA among patients who underwent spinal surgery (including but not limited to MESCC) suggests that the direct cost of a wound infection is over USD 4000 while instrumentation malpositioning bears a direct cost of nearly USD 7000. The majority of the patients included in the study suffered some kind of adverse event, indicating that surgical intervention is associated with high risks (Whitmore 2012).

OBJECTIVES

The primary objective of this review is to compare the potential harms of treatment for spinal metastatic disease for the following treatments:

1. Surgical intervention.
2. Surgical intervention with radiation therapy.
3. Radiation therapy alone.

Our secondary objectives are:

1. comparing the harms of different surgical methods;
2. comparing the harms between different radiation protocols.

METHODS

Criteria for considering studies for this review

Types of studies

We will include RCTs, observational studies and case series. We will exclude editorials, letters, addresses, conference abstracts and narrative reviews. We expect to find studies where data on adverse effects (AEs) are not available, even after contact with the authors. Those studies will not be included in the analysis but we will list the excluded studies in the 'Characteristics of excluded studies' table.

Types of participants

Patients aged 18 years or older treated for extradural spine metastasis of a primary tumour not originating from the spine. As primary tumours of the spine represent a different entity when it comes to epidemiology, treatment and prognosis, they are not covered in this study.

Types of interventions

Surgical interventions, radiotherapy or combinations of both (Fehlings 2014). The surgical interventions studied will be cement augmentation (Berenson 2011), posterior decompression, posterior decompression and fusion, intralesional anterior corpectomy and en-bloc spondylectomy (Tomita 1994). Interventions of radiotherapy will be conventional radiation treatment with any fractionation or dose. As this review focuses on potential harms of specific interventions, no control groups (placebo, no treatment) will be used.

Types of outcome measures

The review will focus on adverse effects (AE) of an intervention. An AE is defined in the *Cochrane Handbook for Systematic Reviews of Interventions* (chapter 14) as "an adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility" (Higgins 2011).

Adverse effects of surgery

A validated system for describing and grading adverse events connected to spine surgery, Spine Adverse Events Severity System Version 2 (SAVES V-2), lists 38 possible adverse events. Each adverse event can be graded according to severity, which produces a high possible amount of comparable outcomes. The system is developed for general spine surgery including a variety of conditions and not only for metastatic spine surgery (Rampersaud 2010). For the purpose of this review, the authors have defined and grouped adverse effects of particular interest for the population included in this review.

Intra-operative adverse effects

These include blood loss of more than two liters, iatrogenic dural tear, nerve root injury, hardware malpositioning requiring revision and cardiac events. Other possible AEs not listed here but occurring during surgery (before the wound is closed) will belong to this group.

Post-operative adverse effects

These include delirium, deep vein thrombosis, pulmonary embolism, construct failure (with or without loss of correction), and neurological deterioration of one motor grade or more in ASIA motor scale. Other possible AEs occurring after surgery (except for infections) will be in this group.

Infection

These include deep and superficial surgical site infection, urinary tract infection, pneumonia and systemic infection.

Adverse effects of radiotherapy

The adverse effects of radiotherapy (RT) can be measured by different methods. The Common Terminology Criteria for Adverse Events (CTCAE) 4.03 is the measuring method recommended by the US Cancer Institute and is commonly used (National Cancer Institute 2009). The scale includes other AEs than those directly related to RT. The Acute Radiation Morbidity Scoring Criteria (ARMSC) launched in 1995 includes only AEs connected to radiation, but was replaced by the CTCAE in 2000 (Cox 1995; National Cancer Institute 2009).

In this review, we will focus on early AEs linked to RT. 'Early' in this case means that the AE occurs within three months after the last treatment.

Primary outcomes

We will pursue the incidence of AEs after surgery of any kind as listed above and the cumulated number of AEs suffered for each

patient, as reported within two weeks after surgery. Regarding AEs after radiation therapy, primary outcomes will be the incidence of AEs with a severity grade from 3 to 5 (severe to death) within three months after treatment as defined in CTCAE 4.03.

Secondary outcomes

For AEs after surgery, the incidence of AEs in each of the categories (rather than the cumulative incidence) will be pursued. Secondary outcomes for patients treated with RT will be the incidence of AEs with severity grade from 1 to 2 (mild to moderate) as defined in CTCAE 4.03.

Search methods for identification of studies

Electronic searches

A senior librarian at the Biomedical Library, Uppsala University will conduct the searches. We intend to use EndNote and Rayyan as data management software and we have access to Covidence. We will search the following databases from inception to current.

- Cochrane Central Register of Controlled Trials (CENTRAL, *the Cochrane Library*; latest issue);
- MEDLINE (Ovid);
- Embase (Elsevier);
- Science Citation Index (Web of Science);
- Latin American and Caribbean Health Sciences Literature (LILACS);
- ClinicalTrials.gov;
- World Health Organization (WHO) International Clinical Trials Registry (ICTRP).

The draft search strategy for MEDLINE can be found in [Appendix 1](#).

Searching other resources

The team content experts will identify other sources not covered by the electronic searches, for instance conference proceedings. The reference lists from recent review articles on the subject and all retrieved articles will be checked for other studies not captured by our search.

Data collection and analysis

Selection of studies

Two independent authors (YR and HM) will review all titles and abstracts found in the search. They will first screen articles based on title and abstract. We will then download those selected and

two independent authors will review the full text. Before starting the selection, we will perform multiple pilot tests of the selection criteria to ensure that all reviewers have the same standard for selecting articles.

The authors will be required to reach consensus on whether to include or exclude every single article. If they disagree, they will first be asked to reach consensus through discussion. If consensus can't be reached, they will consult a third author (CC) for judgement. Members of the team may not review articles they have authored, co-authored or consulted on. A third author will make a random check on a number of included, as well as excluded, articles to ensure the quality level of selection.

Studies will be considered for inclusion regardless of the original language. If the language is outside the linguistic competence of the team and its close collaborators, authors will seek assistance from Cochrane.

Data extraction and management

Two authors (YR and HM) will extract data independently, using standardized extraction forms. Data extracted will include study type, study population, intervention type and reported adverse effects. If requested data are not available in a study eligible for inclusion, we will try to contact the authors via e-mail and request the data. If authors disagree on the extracted data, they will reach consensus through discussion. They will consult a third author if consensus cannot be reached after discussion.

Assessment of risk of bias in included studies

We will use two different tools for assessing the risk of bias in the studies included. Assessment of bias for RCTs will be made using the tools described in [Table 1](#) and [Table 2](#) ([Furlan 2015](#)). For non-RCTs, we will use the ROBINS-I tool, developed by the Cochrane Methods Bias Group and Cochrane Non-randomized Studies for Interventions Group ([Cochrane Bias Methods Group 2016](#); [Sterne 2016](#)). Rather than calculating a score of each assessment, the authors will make an overall assessment of the bias with the tools and the considerations will be explained in the 'Risk of bias table in the final review. Titles of journals, names of authors or institutions will not be masked at any stage. If two authors (YR and HM) disagree on the level of bias, they will consult a third author (CC). If one of the review authors is credited as author or co-author of a study, this author will not be involved in the bias assessment for their work.

Measures of treatment effect

The review will cover harms and will report incidence, difference, relative risk, and odds ratio of adverse events of the given intervention.

Unit of analysis issues

Unit of analysis issues may arise, as the study populations can be exposed to several interventions and each patient can suffer from several AEs. As stated in the outcome section of this protocol, we will analyse the data both with the patient as unit of analysis (number of patients who suffer an AE for each intervention) and the AE as the unit of analysis (cumulated number of AEs for a specific intervention). We do not expect to find any cluster-randomised trials.

Dealing with missing data

If relevant data are missing, we will attempt to contact the author of the study to obtain further information. In the case of no response from the author, we will not do any data imputation. We will only do data transformation from percentages to absolute numbers if these are necessary to enter in meta-analyses. If necessary, we will use figures to extrapolate numbers such as means and standard deviations.

Assessment of heterogeneity

As the included patients suffer from different types of primary tumours, heterogeneity is expected to some extent. The surgical procedures are, to our knowledge, similar worldwide. Age and general medical condition will most probably affect the rate of AEs, as will the follow-up time. For surgical AEs, we anticipate finding the relevant AEs within a two-week follow-up, while the follow-up time for early AEs after radiation is up to three months.

Assessment of reporting biases

Studies included will be assessed for possible outcome reporting bias by at least two authors (YR and HM) Where readily available, the protocol for each study will be compared with the reported outcomes in the publication. To detect possible reporting bias within a study, the outcomes reported from each study will be listed in a matrix as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*. If an outcome reported by the majority of studies is missing in a study, we will conduct a more thorough search for possible selective outcome reporting bias in that particular study. We will use ClinicalTrials.gov, [WHO ICTRP](http://www.who.int/ictcp), and Scopus (Elsevier) to look for links to study protocols. If the original protocol is not available, we will assess if the outcomes listed in the trial registration are reported in the publication.

Most likely, we will not be able to do a meta-analysis due to an expected low number of high-quality studies. For assessing publication bias, we will do an eyeball test and plot the studies in a funnel plot. If we find at least five studies to include in a meta-analysis, the Egger test will be used to assess publication bias ([Egger 2001](#)).

Data synthesis

To assess whether the included studies are homogenous enough to pool, we will use the tools suggested by [Verbeek 2012](#) which emphasize similarities rather than differences between studies. Using this method, factors including control group, participants and follow-up time will be assessed for heterogeneity by two authors (YR and HM) independently and a third author (CC) will be consulted if no agreement is reached.

For dichotomous outcomes, the relative risk (RR) will be analysed. Uncertainty will be expressed with 95% confidence intervals (95% CI). If we find homogenous data in the included RCTs, the data may be pooled and meta-analysed using the Review Manager 5 ([Review Manager 2014](#)) software. A χ^2 test less than 0.05 will indicate a significant statistical heterogeneity.

Given the low known number of RCTs on the subject, we expect to include non-RCTs. Data from these studies may be pooled, unless at least two authors find the study populations to be too clinically heterogeneous or a high risk of bias is estimated using the tools described in [Table 1](#) and [Table 2](#).

Assessment of the quality of evidence will be made using the GRADE approach, as recommended in *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)) and adapted in the updated CBN method guidelines ([Furlan 2015](#)). The quality of evidence for each outcome will be graded from high to low according to the GRADE system ([Appendix 2](#)).

We will use [GRADEpro GDT 2015](#) to import data from RevMan 5 to create 'Summary of findings' tables. The tables will provide outcome-specific information regarding the quality of evidence from the included studies. If we include RCTs and find data eligible for pooling as described above, the evidence will be downgraded from 'high quality' by one level if we find serious study limitations including, but not limited by, risk of bias. For very serious limitations the downgrade will be two steps. For non-RCTs, the level of evidence will start at low and the criteria for downgrading will be the same.

The following outcomes will be in the 'Summary of findings' tables as drafted in [Table 3](#); [Table 4](#); and [Table 5](#)

- Incidence of AE after surgery at two weeks post-operatively.
- Cumulated number of AEs after surgery at two weeks postoperatively.
- Incidence of AEs with severity grade 3 to 5 within three months after radiation therapy.
- Incidence of AEs divided into intra-operative AEs, post-operative AEs, and infections at two weeks postoperatively.
- Incidence of AEs with severity grade 1 to 2 within three months after radiation therapy.

Subgroup analysis and investigation of heterogeneity

Based on our previous knowledge on the subject, we do not expect to find enough high-quality data to justify any a priori definition of a potential subgroup analysis. However, if there are sufficient

data after the data extraction, we plan to do a subgroup analysis of the two types expected to be the most common (breast, prostate) and the AEs after intervention in those particular populations.

Sensitivity analysis

A sensitivity analysis will be performed in order to vary the assumptions used in a possible meta-analysis, and also through single elimination of the studies in order to assess for significance. We plan to exclude studies without well-defined populations and

interventions. Interventions by radiotherapy should be defined regarding dose, fractioning and length of treatment. Regarding surgical interventions, we expect approach, type of decompression and type of instrumentation to be described.

ACKNOWLEDGEMENTS

We acknowledge chief librarian Ulla Jakobsson for helping us with the search strategy.

REFERENCES

Additional references

Barron 1959

Barron KD, Hirano A, Araki S, Terry RD. Experiences with metastatic neoplasms involving the spinal cord. *Neurology* 1959;**9**(2):91–106.

Berenson 2011

Berenson J, Pflugmacher R, Jarzem P, Zonder J, Schechtman K, Tillman JB, et al. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. *Lancet Oncology* 2011;**12**(3):225–35.

Cochrane Bias Methods Group 2016

Cochrane Bias Methods Group. ROBINS-I tool. sites.google.com/site/riskofbiastool/welcome/home (accessed 24 April 2017).

Constans 1983

Constans JP, de Divitiis E, Donzelli R, Spaziante R, Meder JF, Haye C. Spinal metastases with neurological manifestations Review of 600 cases. *Journal of Neurosurgery* 1983;**59**(1):111–8.

Cox 1995

Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *International Journal of Radiation Oncology, Biology, Physics* 1995;**31**(5):1341–6.

Dea 2014

Dea N, Versteeg A, Fisher C, Kelly A, Hartig D, Boyd M, et al. Adverse events in emergency oncological spine surgery: a prospective analysis. *Journal of Neurosurgery. Spine* 2014;**12**(978):S78.

Egger 2001

Egger M, Davey Smith G, Altman DG. *Systematic Reviews in Health Care: Meta-analysis in Context*. Second Edition. London: BMJ Books, 2001.

Fehlings 2014

Fehlings MG, Nater A, Holmer H. Cost-effectiveness of Surgery in the Management of Metastatic Epidural Spinal Cord Compression. *Spine* 2014;**39**(22S):S99–S105.

Furlan 2015

Furlan AD, Malmivaara A, Chou R, Maher CG, Deyo RA, Schoene M, et al. 2015 Updated Method Guideline for Systematic Reviews in the Cochrane Back and Neck Group. *Spine (Philadelphia, Pa. : 1986)* 2015;**40**(21):1660–73.

George 2008

George R, Jeba J, Ramkumar G, Chacko AG, Leng M, Tharyan P. Interventions for the treatment of metastatic extradural spinal cord compression in adults. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD006716.pub2]

George 2015

George R, Jeba J, Ramkumar G, Chacko AG, Tharyan P. Interventions for the treatment of metastatic extradural spinal cord compression in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 9. [DOI: 10.1002/14651858.CD006716.pub3]

GRADEpro GDT 2015 [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro GDT. Version accessed 30 June 2017. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Helweg-Larsen 1994

Helweg-Larsen S, Sorensen PS. Symptoms and signs in metastatic spinal cord compression: a study of progression from first symptom until diagnosis in 153 patients. *European Journal of Cancer* 1994;**30A**(3):396–8.

Helweg-Larsen 2000

Helweg-Larsen S, Sorensen PS, Kreiner S. Prognostic factors in metastatic spinal cord compression: a prospective study using multivariate analysis of variables influencing survival and gait function in 153 patients. *International Journal of Radiation Oncology, Biology, Physics* 2000;**46**(5):1163–9.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Kaloostian 2014

Kaloostian PE, Yurter A, Zadnik PL, Sciubba DM, Gokaslan ZL. Current paradigms for metastatic spinal disease: an evidence-based review. *Annals of Surgical Oncology* 2014;**21**(1):248–62.

Laufer 2012

Laufer I, Sciubba DM, Madera M, Bydon A, Witham TJ, Gokaslan ZL, et al. Surgical management of metastatic spinal tumors. *Cancer Control* 2012;**19**(2):122–8.

Loblaw 2012

Loblaw D A, Mitera G, Ford M, Laperriere N J. A 2011 updated systematic review and clinical practice guideline for the management of malignant extradural spinal cord compression. *International Journal of Radiation Oncology, Biology, Physics* 2012;**84**(2):312–7.

Maccauro 2011

Maccauro G, Spinelli MS, Mauro S, Perisano C, Graci C, Rosa MA. Physiopathology of Spine Metastasis. www.hindawi.com/journals/ijso/2011/107969/ (accessed 24 April 2017).

Mueller 2007

Mueller PS, Montori VM, Bassler D, Koenig BA, Guyatt GH. Ethical issues in stopping randomized trials early because of apparent benefit. *Annals of Internal Medicine* 2007;**146**(12):878–81.

National Cancer Institute 2009

National Cancer Institute. Common Terminology Criteria for Adverse Events v4.0. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (accessed 24 April 2017).

Rampersaud 2010

Rampersaud YR, Neary MA, White K. Spine adverse events severity system: content validation and interobserver reliability assessment. *Spine* 2010;**35**(7):790–5.

Review Manager 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Ribas 2012

Ribas ES, Schiff D. Spinal cord compression. *Current Treatment Options in Neurology* 2012;**14**(4):391–401.

Spencer 2014

Spencer BA, Shim JJ, Hershman DL, Zacharia BE, Lim EA, Benson MC, et al. Metastatic epidural spinal cord compression among elderly patients with advanced prostate cancer. *Supportive Care in Cancer* 2014;**22**(6):1549–55.

Sterne 2016

Sterne JAC, Hernán MA, Reeves BC, Savovič J, Berkman ND, Viswanathan M, etc. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. *BMJ* 2016;**355**:i4919.

Tomita 1994

Tomita K, Kawahara N, Baba H, Tsuchiya H, Nagata S, Toribatake Y. Total en bloc spondylectomy for solitary spinal metastases. *International Orthopaedics* 1994;**18**(5):291–8.

Verbeek 2012

Verbeek J, Ruotsalainen J, Hoving JL. Synthesizing study results in a systematic review. *Scandinavian Journal of Work, Environment & Health* 2012 May;**38**(3):282–90.

Whitmore 2012

Whitmore RG, Stephen J, Stein SC, Campbell PG, Yadla S, Harrop JS, et al. Patient comorbidities and complications after spinal surgery: a societal-based cost analysis. *Spine (Philadelphia, Pa. : 1986)* 2012;**37**(12):1065–71.

Young 1980

Young RF, Post EM, King GA. Treatment of spinal epidural metastases - Randomized prospective comparison of laminectomy and radiotherapy. *Journal of Neurosurgery* 1980;**53**(6):741–8.

* Indicates the major publication for the study

ADDITIONAL TABLES**Table 1. Sources of risk of bias**

Bias domain	Source of bias	Possible answers
Selection	(1) Was the method of randomization adequate?	Yes/no/unsure
Selection	(2) Was the treatment allocation concealed?	Yes/no/unsure
Performance	(3) Was the patient blinded to the intervention?	Yes/no/unsure

Table 1. Sources of risk of bias (Continued)

Performance	(4) Was the care provider blinded to the intervention?	Yes/no/unsure
Detection	(5) Was the outcome assessor blinded to the intervention?	Yes/no/unsure
Attrition	(6) Was the drop-out rate described and acceptable?	Yes/no/unsure
Attrition	(7) Were all randomized participants analyzed in the group to which they were allocated?	Yes/no/unsure
Reporting	(8) Are reports of the study free of suggestion of selective outcome reporting?	Yes/no/unsure
Selection	(9) Were the groups similar at baseline regarding the most important prognostic indicators?	Yes/no/unsure
Performance	(10) Were cointerventions avoided or similar?	Yes/no/unsure
Performance	(11) Was the compliance acceptable in all groups?	Yes/no/unsure
Detection	(12) Was the timing of the outcome assessment similar in all groups?	Yes/no/unsure
Other	(13) Are other sources of potential bias unlikely?	Yes/no/unsure

from [Furlan 2015](#)

Table 2. Criteria for a judgment of 'yes' for the sources of risk of bias

1	A random (unpredictable) assignment sequence. Examples of adequate methods are coin toss (for studies with 2 groups), rolling a dice (for studies with 2 or more groups), drawing of balls of different colours, drawing of ballots with the study group labels from a dark bag, computer-generated random sequence, preordered sealed envelopes, sequentially-ordered vials, telephone call to a central office, and preordered list of treatment assignments. Examples of inadequate methods are: alternation, birth date, social insurance/security number, date in which they are invited to participate in the study, and hospital registration number
2	Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient
3	Index and control groups are indistinguishable for the patients or if the success of blinding was tested among the patients and it was successful.
4	Index and control groups are indistinguishable for the care providers or if the success of blinding was tested among the care providers and it was successful.

Table 2. Criteria for a judgment of 'yes' for the sources of risk of bias (Continued)

5	<p>Adequacy of blinding should be assessed for each primary outcome separately. This item should be scored "yes" if the success of blinding was tested among the outcome assessors and it was successful or:</p> <ul style="list-style-type: none"> - for patient-reported outcomes in which the patient is the outcome assessor (e.g., pain, disability): the blinding procedure is adequate for outcome assessors if participant blinding is scored "yes" - for outcome criteria assessed during scheduled visit and that supposes a contact between participants and outcome assessors (e.g., clinical examination): the blinding procedure is adequate if patients are blinded, and the treatment or adverse effects of the treatment cannot be noticed during clinical examination - for outcome criteria that do not suppose a contact with participants (e.g., radiography, magnetic resonance imaging): the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed when assessing the main outcome - for outcome criteria that are clinical or therapeutic events that will be determined by the interaction between patients and care providers (e.g., cointerventions, hospitalization length, treatment failure), in which the care provider is the outcome assessor: the blinding procedure is adequate for outcome assessors if item "4" (caregivers) is scored "yes" - for outcome criteria that are assessed from data of the medical forms: the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed on the extracted data
6	<p>The number of participants who were included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and drop-outs does not exceed 20% for short-term follow-up and 30% for long-term follow-up and does not lead to substantial bias a "yes" is scored. (N.B. these percentages are arbitrary, not supported by literature)</p>
7	<p>All randomized patients are reported/analyzed in the group they were allocated to by randomization for the most important moments of effect measurement (minus missing values) irrespective of noncompliance and cointerventions.</p>
8	<p>All the results from all prespecified outcomes have been adequately reported in the published report of the trial. This information is either obtained by comparing the protocol and the report, or in the absence of the protocol, assessing that the published report includes enough information to make this judgment</p>
9	<p>Groups have to be similar at baseline regarding demographic factors, duration and severity of complaints, percentage of patients with neurological symptoms, and value of main outcome measure(s)</p>
10	<p>If there were no cointerventions or they were similar between the index and control groups</p>
11	<p>The reviewer determines if the compliance with the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s). For example, physiotherapy treatment is usually administered for several sessions; therefore it is necessary to assess how many sessions each patient attended. For single-session interventions (e.g., surgery), this item is irrelevant.</p>
12	<p>Timing of outcome assessment should be identical for all intervention groups and for all primary outcome measures.</p>
13	<p>Other types of biases. For example:</p> <ul style="list-style-type: none"> - When the outcome measures were not valid. There should be evidence from a previous or present scientific study that the primary outcome can be considered valid in the context of the present. - Industry-sponsored trials. The conflict of interest (COI) statement should explicitly state that the researchers have had full possession of the trial process from planning to reporting without funders with potential COI

Table 2. Criteria for a judgment of 'yes' for the sources of risk of bias (Continued)

having any possibility to interfere in the process. If, for example, the statistical analyses have been done by a funder with a potential COI, usually "unsure" is scored.
--

from [Furlan 2015](#)

Table 3. Summary of findings, surgery alone

Adverse effects after surgical intervention only			
Patient or population: Patients aged 18 years or older treated for extradural spine metastasis not originating from the spine Settings: Hospital Intervention: Surgery without radiation therapy Comparison: None			
Outcomes	Outcome type	Outcome measure	Comments
Incidence of AE after surgery	continuous	%	two weeks post-operatively
Cumulated number of AEs after surgery	continuous	number	two weeks post-operatively
Incidence of intra-operative AEs	continuous	%	before closure of the wound
Incidence of postoperative AEs (excluding infections)	continuous	%	two weeks post-operatively
Incidence of infections	continuous	%	two weeks post-operatively
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.			

Table 4. Summary of findings, surgery plus radiation

Adverse effects after surgery and radiation
Patient or population: Patients aged 18 years or older treated for extradural spine metastasis not originating from the spine Settings: Hospital Intervention: Surgery in combination with radiotherapy Comparison: None

Table 4. Summary of findings, surgery plus radiation (Continued)

Outcomes	Outcome type	Outcome measure	Comments
Incidence of AE after surgery and radiation	continuous	%	two weeks post-operatively
Cumulated number of AEs after surgery	continuous	number	two weeks post-operatively
Incidence of AEs with severity grade 3 to 5	continuous	%	three months after radiation therapy
Incidence of intra-operative AEs	continuous	%	before wound closure
Incidence of postoperative AEs (excluding infections)	continuous	%	two weeks post-operatively
Incidence of infections	continuous	%	two weeks post-operatively
Incidence of AEs with severity grade 1 to 2	continuous	%	three months after radiation therapy
<p>GRADE Working Group grades of evidence</p> <p>High quality: Further research is very unlikely to change our confidence in the estimate of effect.</p> <p>Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</p> <p>Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</p> <p>Very low quality: We are very uncertain about the estimate.</p>			

Table 5. Summary of findings, radiation alone

Adverse effects after radiation			
<p>Patient or population: Patients aged 18 years or older treated for extradural spine metastasis not originating from the spine</p> <p>Settings: Hospital</p> <p>Intervention: Radiotherapy without surgery</p> <p>Comparison: None</p>			
Outcomes	Outcome type	Outcome measure	Comments
Incidence of AEs with severity grade 3 to 5	continuous	%	three months after radiation therapy
Incidence of AEs with severity grade 1 to 2	continuous	%	three months after radiation therapy

Table 5. Summary of findings, radiation alone (Continued)

<p>GRADE Working Group grades of evidence</p> <p>High quality: Further research is very unlikely to change our confidence in the estimate of effect.</p> <p>Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</p> <p>Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</p> <p>Very low quality: We are very uncertain about the estimate.</p>
--

APPENDICES

Appendix I. MEDLINE search strategy

- 1 (metasta* ADJ3 spinal ADJ3 cord ADJ3 compression).tw.
- 2 (malignan* ADJ3 spinal ADJ3 cord ADJ3 compression).tw.
- 3 (metasta* ADJ3 spinal ADJ3 disease).tw.
- 4 exp Spinal cord compression
- 5 exp Neoplasm metastasis
- 6 exp Spinal neoplasms/sc
- 7 secondary.fs.
- 8 mescc.tw.
- 9 mscc.tw.
- 10 spinal metastas*.tw.
- 11 exp Spinal cord neoplasms/sc
- 12 radiation.tw.
- 13 rt.tw.
- 14 (radiation ADJ2 therap*).tw.
- 15 exp Radiotherapy
- 16 radiotherapy.fs.
- 17 exp Cementation
- 18 exp Cementoplasty
- 19 (cement ADJ3 augmentation).tw.
- 20 decompress*.tw.
- 21 exp Decompression OR exp Decompression, surgical
- 22 corpectom*.tw.
- 23 exp Discectomy
- 24 vertebrectom*.tw.
- 25 exp Spine/su
- 26 (en-bloc ADJ3 spondylectomy)
- 27 exp Spinal fusion
- 28 exp Spinal neoplasms/sc AND exp Spinal neoplasms/su
- 29 exp Spinal cord neoplasms/sc AND exp Spinal cord neoplasms/su
- 30 exp Spinal neoplasms/sc AND exp Spinal neoplasms/rt
- 31 exp Spinal cord neoplasms/sc AND exp Spinal cord neoplasms/rt
- 32 5 OR 6 OR 7

33 4 AND 32
 34 1 OR 2 OR 3 OR 6 OR 8 OR 9 OR 10 OR 11
 35 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27
 36 33 OR 34
 37 36 AND 35
 38 37 OR 28 OR 29 OR 30 OR 31
 39 adverse effect*.tw.
 40 ae.fs.
 41 side effect*.tw.
 42 harm*.tw.
 43 co.fs.
 44 complication*.tw.
 45 ((adverse OR unexpected OR undesirable) ADJ3 (outcome OR reaction OR effect* OR event*))
 45 radiation effects.fs.
 46 exp Radiation effects
 47 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46
 48 38 AND 47

Appendix 2. The GRADE approach to evidence synthesis

The quality of evidence will be categorized as follows:

- High (⊙ ⊙ ⊙ ⊙): further research is very unlikely to change the confidence in the estimate of effect.
- Moderate (⊙ ⊙ ⊙ ○): further research is likely to have an important impact in the confidence in the estimate of effect.
- Low (⊙ ⊙ ○ ○): further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very Low (⊙ ○ ○ ○): any estimate of effect is very uncertain.

The evidence available to answer each sub-question will be graded on the domains in the following manner:

1. Risk of bias

Limitations in the study design and implementation may bias the estimates of the treatment effect. Our confidence in the estimate of the effect and in the following recommendation decreases if studies suffer from major limitations. We will examine all studies on five types of biases:

- a) Selection (random sequence generation, allocation concealment, group similarities at baseline)
- b) Performance (blinding of participants, blinding of healthcare providers)
- c) Attrition (dropouts and intention-to-treat analysis)
- d) Measurement (blinding of the outcome assessors and timing of outcome assessment)
- e) Reporting bias (selective reporting)

2. Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. Widely differing estimates of the **treatment effect** (i.e. heterogeneity or variability in results) across studies suggest true differences in underlying treatment effect. Inconsistency may arise from differences in: **populations** (e.g. drugs may have larger relative effects in sicker populations), **interventions** (e.g. larger effects with higher drug doses), or **outcomes** (e.g. diminishing treatment effect with time).

The quality of evidence will be downgraded as follows:

- by one level: when the heterogeneity or variability in results is large.
- by two levels: when the heterogeneity or variability in results is large AND there was inconsistency arising from populations, interventions, or outcomes.

3. Indirectness

Indirect population, intervention, comparator, or outcome: the question being addressed in this systematic review is different from the available evidence regarding the population, intervention, comparator, or an outcome in the included randomised trial.

The quality of evidence will be downgraded as follows:

- by one level: when there is indirectness in only one area
- by two levels: when there is indirectness in two or more areas

4. Imprecision

Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect. In this case we judge the quality of the evidence lower than it otherwise would because of resulting uncertainty in the results. Each outcome is considered separately.

For dichotomous outcomes

We will consider imprecision for either of the following two reasons:

1. There is only one study. When there is more than one study, the total number of events is less than 300 (a threshold rule-of-thumb value) (Mueller 2007).
2. 95% confidence interval around the pooled or best estimate of effect includes both 1) no effect and 2) appreciable benefit or appreciable harm. The threshold for 'appreciable benefit' or 'appreciable harm' is a relative risk reduction (RRR) or relative risk increase (RRI) greater than 25%.

The quality of the evidence will be downgraded as follows:

- by one level: when there is imprecision due to (1) or (2)
- by two levels: when there is imprecision due to (1) and (2)

For continuous outcomes

We will consider imprecision for either of the following two reasons:

1. There is only one study. When there is more than one study, total population size is less than 400 (a threshold rule-of-thumb value; using the usual α and β , and an effect size of 0.2 SD, representing a small effect)
2. 95% confidence interval includes no effect and the upper or lower confidence limit crosses an effect size (standardized mean difference) of 0.5 in either direction.

The quality of the evidence will be downgraded as follows:

- by one level: when there is imprecision due to (1) or (2)
- by two levels: when there is imprecision due to (1) and (2)

5. Publication bias

Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies. The quality of evidence will be downgraded as follows:

- by one level: when the funnel plot suggests publication bias

CONTRIBUTIONS OF AUTHORS

The protocol was drafted by Christian Carrwik and Yohan Robinson.

DECLARATIONS OF INTEREST

Christian Carrwik was previously a shareholder of AstraZeneca and Elekta and has been cleared by the funding arbiter. Yohan Robinson received paid compensation for educational lectures for Medtronic and DePuy Synthes and has been cleared by the funding arbiter. Hideki Murakami and Johan Willander have no conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Uppsala University, Department of surgical sciences, Sweden.
Salaries

External sources

- No sources of support supplied