

Interventions for the treatment of metastatic extradural spinal cord compression in adults (Review)

George R, Jeba J, Ramkumar G, Chacko AG, Leng M, Tharyan P



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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	2
OBJECTIVES	3
METHODS	4
RESULTS	6
DISCUSSION	12
AUTHORS' CONCLUSIONS	14
ACKNOWLEDGEMENTS	14
REFERENCES	15
CHARACTERISTICS OF STUDIES	16
DATA AND ANALYSES	27
Analysis 1.1. Comparison 1 Radiotherapy 8 fractions versus 2 fractions, Outcome 1 Ambulation (short term).	29
Analysis 1.2. Comparison 1 Radiotherapy 8 fractions versus 2 fractions, Outcome 2 Reduction in analgesic use.	30
Analysis 1.3. Comparison 1 Radiotherapy 8 fractions versus 2 fractions, Outcome 3 Urinary continence (short term).	30
Analysis 1.4. Comparison 1 Radiotherapy 8 fractions versus 2 fractions, Outcome 4 Gastrointestinal adverse effects.	31
Analysis 2.1. Comparison 2 Laminectomy plus radiotherapy versus radiotherapy alone, Outcome 1 Ambulation (short term).	32
Analysis 2.2. Comparison 2 Laminectomy plus radiotherapy versus radiotherapy alone, Outcome 2 Ambulation (intermediate term).	33
Analysis 2.3. Comparison 2 Laminectomy plus radiotherapy versus radiotherapy alone, Outcome 3 Survival.	33
Analysis 2.4. Comparison 2 Laminectomy plus radiotherapy versus radiotherapy alone, Outcome 4 Reduction in analgesic use.	34
Analysis 2.5. Comparison 2 Laminectomy plus radiotherapy versus radiotherapy alone, Outcome 5 Urinary continence (short term).	34
Analysis 2.6. Comparison 2 Laminectomy plus radiotherapy versus radiotherapy alone, Outcome 6 Urinary continence (intermediate term).	35
Analysis 3.1. Comparison 3 Decompressive surgery plus radiotherapy versus radiotherapy alone, Outcome 1 Ambulation (short term).	36
Analysis 3.2. Comparison 3 Decompressive surgery plus radiotherapy versus radiotherapy alone, Outcome 2 Survival (short term).	37
Analysis 4.1. Comparison 4 High dose versus no or moderate dose corticosteroids, Outcome 1 Overall ambulation (short term).	37
Analysis 4.2. Comparison 4 High dose versus no or moderate dose corticosteroids, Outcome 2 Participants maintaining or regaining ambulation (short term).	38
Analysis 4.3. Comparison 4 High dose versus no or moderate dose corticosteroids, Outcome 3 Survival (long term).	39
Analysis 4.4. Comparison 4 High dose versus no or moderate dose corticosteroids, Outcome 4 Pain reduction.	39
Analysis 4.5. Comparison 4 High dose versus no or moderate dose corticosteroids, Outcome 5 Urinary continence (short term).	40
Analysis 4.6. Comparison 4 High dose versus no or moderate dose corticosteroids, Outcome 6 Serious drug related adverse effects.	40
APPENDICES	41
WHAT'S NEW	44
HISTORY	44
CONTRIBUTIONS OF AUTHORS	45
DECLARATIONS OF INTEREST	45
SOURCES OF SUPPORT	45
INDEX TERMS	45

[Intervention Review]

Interventions for the treatment of metastatic extradural spinal cord compression in adults

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ABSTRACT

Background

Metastatic epidural spinal cord compression (MESCC) is often treated with radiotherapy and corticosteroids. Recent reports suggest benefit from decompressive surgery.

Objectives

To determine effectiveness and adverse effects of radiotherapy, surgery and corticosteroids in MESCC.

Search strategy

CENTRAL, MEDLINE, EMBASE, CINAHL, LILACS and CANCERLIT were searched; last search ran July 2008

Selection criteria

We selected randomized controlled trials (RCTs) of radiotherapy, surgery and corticosteroids in adults with MESCC.

Data collection and analysis

Three review authors independently assessed quality of included studies and extracted data. We calculated risk ratios (RR) and numbers needed to treat to benefit (NNT) with 95% confidence intervals (CI) and assessed heterogeneity.

Main results

We identified six trials (n = 544). One trial (n = 276) compared radiotherapy 30 Gray in eight fractions with 16 Gray in two fractions and showed no difference. Overall ambulatory rates were 71% versus 68%, (RR 1.02, CI 0.90 to 1.15); 91% versus 89% of ambulant patients maintained ambulation (RR 1.02, CI 0.93 to 1.12); 28% versus 29% of non-ambulant patients regained ambulation (RR 0.98, CI 0.51 to 1.88). In one trial (n = 101) decompressive surgery had significantly better outcomes than radiotherapy in selected patients. Overall ambulatory rates were 84% versus 57% (RR 0.67, CI 0.53 to 0.86, NNT 3.70 CI 2.38 to 7.69); 94% versus 74% maintained ambulation (RR 0.79, CI 0.64 to 0.98, NNT 5.00 CI 2.78 to 33.33); 63% versus 19% regained ambulation (RR 0.30, CI

0.10 to 0.89; NNT 2.27 CI 1.35 to 7.69). Median survival was 126 days versus 100 days. Laminectomy offered no advantage (n = 29, 1 trial). Three trials provided insufficient evidence about the role of corticosteroids (n = 105, Overall ambulation RR 0.91, CI 0.68 to 1.23). Serious adverse effects were significantly higher in high dose corticosteroid arms (n = 77, two RCTs, RR 0.12, CI 0.02 to 0.97).

Authors' conclusions

Patients with stable spines retaining the ability to walk may be treated with radiotherapy. One trial indicates that short course radiotherapy suffices in patients with unfavourable histologies or predicted survival of less than six months. There is some evidence of benefit from decompressive surgery in ambulant patients with poor prognostic factors for radiotherapy; and in non-ambulant patients with a single area of compression, paraplegia < 48 hours, non-radiosensitive tumours and a predicted survival of more than three months. High dose corticosteroids carry a significant risk of serious adverse effects.

PLAIN LANGUAGE SUMMARY

Interventions for the treatment of metastatic extradural spinal cord compression

Cancer that spreads to the spine can compress the spinal cord and nearby spinal structures. If this is not treated, it can lead to pain, disability (including paraplegia) and incontinence. Radiotherapy, steroids and different surgical techniques have been used to reduce the pressure on the spinal cord. It is important to select patients carefully for the different types of treatments as the prognosis and outcome vary greatly depending on the type of cancer and the stage of the illness. This review included trials of radiotherapy, surgery, and steroids to assess if these treatments helped improve walking ability. One study showed that in some common cancers, or where survival was expected to be short, two radiotherapy treatments a week apart were as effective as longer courses of radiation treatment. Another trial showed that with decompressive surgery before radiotherapy compared to radiotherapy alone, more patients maintained the ability to walk and more patients regained their ability to walk. Survival in the radiotherapy alone group was 100 days versus 126 days in those who had surgery first. An older trial reported no additional benefit with the surgical procedure of laminectomy before radiotherapy. It is difficult to give definite recommendations based on these few trials which included a relatively small number of patients, and had different selection criteria. Radiotherapy will be required in the majority of patients, with better results seen in those who have not lost walking ability. Carefully selected patients with a single site of cord compression, who are fit for surgery and have not been paraplegic for more than 48 hours may be considered for decompressive surgery before radiotherapy. High doses of steroids (96 to 100 mg of dexamethasone) significantly increased the risk of serious side effects as compared to moderate doses of 10 to 16 mg dexamethasone or placebo.

BACKGROUND

Metastatic extradural spinal cord compression (MESCC), left untreated leads to pain, progressive motor and sensory loss, including possible paraplegia and quadriplegia, bowel and bladder dysfunction, and can have a devastating impact on patients and their families (Loblaw 1998). It has been defined as “the compression of the dural sac and its contents, spinal cord or cauda equina, or both, by an extradural tumour mass. The minimum radiologic evidence for cord compression is indentation of the theca, at the level of clinical features” (Laperriere 1996; Loblaw 1998). In this definition, and frequently in clinical practice, the term metastatic spinal cord compression refers to compression of the cord itself,

or of the cauda equina more distally within the spinal canal.

Up to 40% of all cancer patients develop spinal metastases (Wong 1990). Ten to twenty per cent of these may produce symptomatic cord compression (Klimo 2004; Schaberg 1985). A population based study in Canada estimated that at least 2.5% of all people with cancer experienced one or more episodes of spinal cord compression in the five years preceding death. The cumulative five-year incidence for different primary sites were: myeloma 8%; prostate 7%; nasopharynx 6.5%; lung 6%; breast 5.5%; kidney 5%; cervix 2.5%; head and neck 0.9%; colorectum 0.8% and stomach 0.6% (Loblaw 2003).

Corticosteroids and radiotherapy are widely used treatments for MESCC. Bony compression and spinal instability have been considered as poor prognostic factors for treatment with radiation. Combined results from prospective non-randomized studies of radiotherapy for MESCC revealed that ambulatory rates after radiotherapy in people without bony compression were 93.8% in those who were ambulatory before treatment; and 62.8%, in those who needed assistance for ambulation prior to treatment. The rates for ambulation were 38% and 12.5% in people who were paraparetic and paraplegic respectively, prior to treatment (Loblaw 2005). Reviews of non-randomized studies also indicate that although a wide range of radiotherapy schedules have been used, none are clearly superior (Falkmer 2003; Loblaw 2005). Combined results from retrospective studies indicating better local tumour control associated with longer courses of radiotherapy (Rades 2006) have not been confirmed in a prospective, non-randomized evaluation of different radiation schedules - 40 Gray (Gy; a unit of radiation dosage) in twenty fractions was not superior to 30 Gy in ten fractions (Rades 2004).

Corticosteroids have demonstrated neurological improvement in rat experimental models of epidural tumours (Ushio 1977), and in human studies (Sorensen 1994). This benefit is probably mediated through their anti-inflammatory and anti-oedema effects. While results in rat experiments, studying high versus low dose dexamethasone are conflicting (Delattre 1988; Delattre 1989), in a case control study 14% of patients receiving 96 mg per day of dexamethasone developed serious adverse events, as compared to 0% of those receiving 16 mg per day (Heimdal 1992). In clinical practice corticosteroid doses vary widely and it is unclear if higher doses offer a therapeutic benefit.

Early surgical studies on laminectomy had been abandoned as they did not show benefit over radiotherapy alone (Young 1980). More recently encouraging results have been seen with immediate decompressive surgery (Klimo 2005). With the development of new techniques in surgery, alternate radiotherapy schedules, advances in imaging, and the recognition of important prognostic factors, there is controversy over what is the most appropriate treatment.

Until recently there have been very few randomized controlled trials (RCTs) on spinal cord compression. A comprehensive review of papers published up to 2004, (Loblaw 2005) recommended early detection, with magnetic resonance imaging (MRI) as the preferred imaging modality; and measures to avoid delays in treatment. The Loblaw 2005 review found that no radiotherapy regimen demonstrated clear superiority; and drew attention to the evolving role of surgery.

In the absence of RCTs, Klimo 2005 undertook a meta-analysis of non-randomized single arm radiotherapy and surgical case series. Overall ambulatory success rates for surgery and radiation were 85% and 64% respectively. People who had recently lost the ability to walk were more than twice as likely to regain mobility with

surgery compared to radiotherapy. Since the publication of the reviews by Klimo 2005 and Loblaw 2005, the results of trials comparing surgery versus radiotherapy, or different schedules of radiotherapy have become available (Maranzano 2005; Patchell 2005).

People with bone metastases and spinal cord compression are not a homogenous population. In a randomized trial on bone metastases without cord compression (Van der Linden 2005), the median survival was three, nine and eighteen months in poor, intermediate and good prognostic groups respectively. This prognostic grouping was based on three criteria namely 1) the performance scores reflecting global assessment of functioning and symptoms; 2) the site of primary tumour, where for example breast cancer had a better prognosis than lung cancer; and 3) the presence or absence of visceral metastases in organs such as the lung, liver or brain (Van der Linden 2005). Survival also depends on the speed at which the primary tumour metastasizes. In a prospective study, the time interval between the diagnosis of cancer and the development of cord compression was found to predict survival (Helweg-Larsen 2000). The strongest predictors in this study for ambulation were the pre-treatment ambulatory status and primary tumour histology. Other prognostic factors identified in prospective studies include myelographic block; early detection and treatment; and rapidity of neurological deterioration (Maranzano 1991; Rades 2004; Wang 2004).

For this Cochrane review we reviewed the relative benefits and harms of surgery, radiotherapy, corticosteroids, and where reported we noted the prognostic factors that predict survival and ambulatory outcomes. This information if available would be important to discriminate between people who clearly benefit from combined modalities of treatment, those who do well with single modalities of treatment alone, and those with poor prognosis and limited survival who should be spared complex or prolonged courses of treatment.

OBJECTIVES

Our primary objective was to compare the efficacy and harm of treating extradural spinal cord compression for the following:

1. different schedules of radiation therapy;
2. surgery with or without radiation therapy versus radiation therapy alone;
3. the administration of high dose corticosteroids (more than 32 mg of dexamethasone equivalent), versus moderate dose (less than 32 mg), or no corticosteroids; with or without surgery/radiotherapy.

Our secondary objectives were:

1. to compare the adverse effects of surgery, radiotherapy and corticosteroids for metastatic spinal cord compression;

2. to ascertain if the clinical benefit, if any, was influenced by neurological and oncological factors such as ambulatory status, primary tumour type, duration of cord compression and the presence of visceral metastases, spinal instability or bony collapse.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs of surgery, radiotherapy or corticosteroids for spinal cord compression. Studies published in any language were eligible if they fulfilled the inclusion criteria.

Types of participants

People with clinical or radiological evidence of extradural spinal cord compression or cauda equina compression caused by metastatic cancer, or both. We reviewed trials involving adults (aged eighteen years or more), but would have included reports with younger people where the majority (> 90%) of participants were adults. We included trials with participants who were ambulatory, or with paresis and paraplegia. We excluded trials for primary tumours of the spinal cord.

Types of interventions

- Radiation treatment using any dose or fractionation schedule.
- Surgery (e.g. laminectomy, decompressive surgery, corpectomy) with or without radiotherapy versus radiotherapy alone.
- High dose corticosteroids versus moderate dose or no corticosteroids with or without surgery/radiotherapy.

Types of outcome measures

Primary outcomes

1. Ambulation

- Overall ambulatory rates
- Proportion of patients maintaining ambulation
- Proportion of non-ambulant patients regaining ambulation

Secondary outcomes

2. Survival

3. Pain relief

- Validated pain scales
- Use of concomitant analgesics

4. Urinary incontinence

- Overall proportion of patients with bladder control
- Percentage of patients maintaining bladder control (absence of urinary catheter)
- Percentage of patients regaining bladder control (absence of urinary catheter)

5. Adverse effects as reported for:

- Radiotherapy
- Surgery
- Corticosteroids

6. Quality of life (participant or caregiver rated)

7. Characteristics of participants who benefit from treatment

8. Participant and caregiver satisfaction

All outcomes were subgrouped as short term (less than four months), medium term (four months to a year) and long term (more than one year).

Search methods for identification of studies

We identified relevant trials using the following electronic databases which were searched in July 2008 (except where stated otherwise):

1. The Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*. This provides access to specialized registers and handsearched journals;
2. MEDLINE
3. EMBASE
4. CINAHL
5. LILACS (April 2007)
6. CANCER LIT (April 2007)

The search strategy was linked to phases 1 and 2 of the Cochrane highly sensitive search strategy for identifying reports of RCTs as published in Appendix 5b of the Cochrane Handbook for Systematic Reviews of Interventions, Version 4.2.6 (Higgins 2006). The search strategy devised for MEDLINE and adapted for the other databases searched can be seen in Appendix 1. The search strategies for CANCER LIT, LILACS, CINAHL, EMBASE and CENTRAL are listed in Appendix 2.

We also searched the references of identified trials for other trials. We contacted the first author of identified trials for unpublished trials. We searched trials registers (www.clinicaltrials.gov; www.trialscentral.org; www.controlled-trials.com; www.nrr.nhs.uk) for ongoing trials.

Data collection and analysis

Study selection

Two review authors (RG and JJ) independently reviewed the abstracts of articles identified using the above search strategy. Review authors read full reports for all references deemed by either assessor to meet the inclusion criteria. Differences regarding trial selection, methodological quality or data extraction were resolved by mutual discussion or through consultation with another review author (PT).

Assessment of methodological quality

We independently assessed methodological quality of selected RCTs by:

- considering the randomization process,
- the presence or not of adequate randomization concealment,
- the description of follow up and the reporting of losses of included patients as described in The Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2006).

Studies were scored A if a method of randomization and allocation concealment were reported that minimized the chance of selection bias. If insufficient information was available they were scored B, and studies where allocation was not concealed at the point of enrolment were scored C.

Data extraction and management

Four review authors (JJ, RKG, RG and ML) extracted data. Discrepancies in the results were resolved by discussion or by clarification with another review author (PT). We used a standardized form to extract the following information:

Participant characteristics

The number of participants in the trial; age; gender; their performance and ambulatory status; the investigative techniques and definitions used to diagnose cord compression; the types of primary tumours and the presence or absence of visceral metastases; the duration and rapidity of onset of cord compression; the spinal level and the presence of spinal instability or vertebral collapse.

Intervention details

The year, country and setting in which the trial was conducted; surgical procedures used; radiotherapy doses and schedules; names, and doses of corticosteroids; the provision of rehabilitation services; the timing of these interventions in relation to the development of cord compression and the usage of opioids or other analgesics.

Outcome data

Short term, intermediate and long term ambulatory and survival rates; the definition of ambulation used in the study; urinary sphincter function; the proportion of participants with pain relief or reduced analgesic use; the adverse effects of interventions; quality of life as assessed by any validated scale and participant satisfaction.

Data synthesis

If binary outcomes (proportions) were used, we calculated risk ratios (RR) and confidence intervals (CI) for each outcome. In addition we calculated absolute measures, number needed to treat to benefit (NNT) and we undertook analyses on an intention-to-treat basis where such data were available.

We had planned to include data from trials where more than 20% of people were lost to follow-up in a sensitivity analysis. Had there been continuous data for our outcomes of interest we would have reported these as presented in the original studies without making any assumptions about those lost to follow-up. For continuous outcomes we had planned to calculate pooled weighted mean differences (WMD) and CIs for outcomes using similar measures. If dissimilar measures were used for similar outcomes from trials (such as quality of life scales that measured similar domains) data from these would have been combined using pooled standardized mean difference (SMD) and CIs.

Where possible we reported endpoint data, and if both endpoint and change data were available for the same outcomes, then we reported only the former.

Heterogeneity

After considering the likelihood of clinical heterogeneity based on comparisons of the included studies, we supplemented the graphical display of results with the Mantel-Haenszel Chi-squared test

of heterogeneity to check whether differences in results were due to chance alone. Since this test has a low power to detect heterogeneity, a significance level of less than 0.10 was interpreted as evidence of heterogeneity. In addition, we quantified inconsistency across studies and its impact on the meta-analysis by examining the value of I-squared (I^2) to estimate the percentage of variability due to heterogeneity rather than chance alone. We interpreted an I^2 value of 50% or greater as indicating substantial levels of heterogeneity (Deeks 2005; Higgins 2003). If heterogeneity was detected but not quantified as contributing substantially to variation in data, all data would have been pooled and interpreted using the random-effects model. If inconsistency was substantial, we would have undertaken a sensitivity analysis to detect the presence or absence of these data. If this had altered the results significantly, data from the responsible studies would not have been pooled, the results would have been presented separately and reasons for heterogeneity explored.

Subgroup analysis

If data were available we would have conducted subgroup analyses according to the following categories:

1. ambulant versus non-ambulant patients
2. the presence or absence of unfavourable radiological features such as bony instability, or vertebral collapse
3. primary tumour type
4. presence or absence of visceral metastases
5. screening versus no screening for cord compression

The trials identified reported results separately only for ambulant versus non-ambulant participants and the results of these subgroups are reported as the proportions maintaining and regaining ambulation.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

1. Excluded studies

The literature search yielded 1255 citations (CENTRAL 114, MEDLINE 845, EMBASE 226, CINAHL 24, LILACS 22, CASCERLIT 24) of which we selected seven for further scrutiny of the full report. We excluded one report (Aviles 2002) because although the abstract described it as randomized, on reviewing the full paper we found it to be a retrospective rather than a prospective randomized comparison. Full details of the excluded study can be seen in the [Characteristics of excluded studies](#) table.

2. Ongoing trials

The two ongoing trials (ISRCTN97555949 and ICORG 05-03) are listed in the [Characteristics of ongoing studies](#) table.

3. Included studies

We selected a total of six trials for inclusion for this review which are summarized below. Please see the '[Characteristics of included studies](#)' table for more details.

3.1 Trials comparing different radiotherapy doses and schedules

Maranzano 2005

A randomized controlled multicentric trial from Italy with adequate allocation concealment. The participants had poor prognosis - unfavourable primaries; or poor neurologic and performance status despite favourable histology. Eighty five per cent of participants referred for radiotherapy had very poor prognostic features. Fifteen per cent of participants who had favourable histologies (lymphoma, seminoma, myeloma, breast or prostate) and good neurologic status were excluded, as additionally, were those with indications for surgery such as no histologic proof of malignancy, vertebral collapse impinging on the cord or nerve roots or previous irradiation in the same area. Three hundred patients were randomized to 'short course radiotherapy', 16 Gray in two fractions; or 'split course radiotherapy', 30 Gray in eight fractions. All patients received dexamethasone 8 mg twice daily, tapered after completion of radiotherapy.

Outcomes measured were ambulation, survival, analgesic use and urinary continence.

The authors' analysis excluded 8% of participants (seven lost to follow-up and seventeen deaths that occurred within the first ten days).

3.2 Trials comparing laminectomy with postoperative radiotherapy with radiotherapy alone

Young 1980

This was the first randomized trial on MESCC and was conducted in two centres in the United States of America. Twenty nine participants with haematologic and solid tumours, and a myelographic diagnosis of cord compression were randomized to laminectomy and postoperative radiotherapy or radiotherapy alone. Concealment of allocation was unclear, although all patients randomized, were analyzed. The outcomes measured were; ambulation, survival, pain relief and urinary continence. Complete myelographic block was more common in the surgery group and was thought to be a confounding factor. The authors emphasized the need to stratify patients by clinically significant prognostic factors in future studies.

3.3 Trials comparing direct decompressive surgery and postoperative radiotherapy with radiotherapy alone

[Patchell 2005](#)

This was a randomized controlled multicentric trial with adequate concealment and intention-to-treat analysis conducted in the United States of America. The trial recruited participants with (MRI) diagnosis of a single area of MESCC, an expected survival of at least three months, and non-radiosensitive primaries. Participants should not have been paraplegic for greater than 48 hours. Over one third of participants had spinal instability or pathologic spine fractures. One hundred and one participants were randomized to surgical decompression and postoperative radiotherapy; (with stabilization if instability was present) or radiotherapy alone, 30 Gray in ten fractions. All patients were given high dose dexamethasone 100 mg initially, tapered until completion of radiotherapy. Ten patients from the radiotherapy arm crossed over to surgery because of deteriorating neurology. The outcomes assessed were ambulation, urinary continence, use of opioid analgesics and corticosteroids, change in Frankel functional scale scores and American Spinal Injury Association (ASIA) motor scores. After ten years, the study was stopped with 50% recruitment because results in the surgical arm were superior.

3.4 Trials evaluating corticosteroids

Three trials ([Graham 2006](#); [Sorensen 1994](#); [Vecht 1989](#)) with participant numbers ranging from twenty to fifty seven assessed the role of corticosteroids in patients receiving radiotherapy for MESCC. [Sorensen 1994](#) and [Graham 2006](#) excluded haematologic malignancies. [Graham 2006](#) and [Vecht 1989](#) compared high dose boluses of dexamethasone of 96 mg to 100 mg, with moderate doses of 10 mg to 16 mg. Steroid doses were then tapered. [Sorensen 1994](#) compared a single dose of 100 mg dexamethasone with saline placebo. [Graham 2006](#) administered omeprazole and nystatin prophylactically to all participants. All three trials reported ambulatory outcomes. [Vecht 1989](#) did not report adverse

effects. [Graham 2006](#) described their report as a “pilot feasibility trial”.

Risk of bias in included studies

The details of quality assessment are in the '[Characteristics of included studies](#)' table.

1. Selection bias (Randomization and allocation concealment)

All included studies were randomized, of which four ([Graham 2006](#); [Maranzano 2005](#); [Patchell 2005](#); [Vecht 1989](#)) reported an adequate method of allocation concealment. The concealment of treatment allocation was unclear in two studies.

2. Performance bias (blinding of participants, researchers and outcome assessment)

Because of the nature of the studies, blinding of clinicians and participants was not practical for the radiotherapy and surgical trials. Among the three corticosteroid studies, [Vecht 1989](#) was double blinded, [Sorensen 1994](#) had observers blinded and [Graham 2006](#) had neither participants nor observers blinded.

3. Attrition bias (loss of participants to follow up)

Two studies had dropouts which comprised less than 10% of participants ([Maranzano 2005](#); [Vecht 1989](#)).

Effects of interventions

Meta-analysis was possible only for the corticosteroid comparisons. All other results described are from single trials. Please see [Table 1](#) for details.

Table 1. Detailed results

Parameters	Results
Different radiotherapy schedules (Eight versus two fractions)	
Overall ambulatory rates (short term)	95/134 (71%) versus 97/142 (68%) RR 1.02; (95% CI 0.90 to 1.15) (n = 276).
Pretreatment ambulant participants maintaining ambulation (short term)	83/91 (91%) versus 83/93 (89%) RR 1.02; (95% CI 0.93 to 1.12) (n = 184).
Pretreatment non-ambulant participants regaining ambulation (short term)	12/43 (28%) versus 14/49 (29%) RR 0.98; (95% CI 0.51 to 1.88) (n = 92)

Table 1. Detailed results (Continued)

Median duration of ambulation	3.5 months in both arms (excluding 17 early deaths)
Survival	Four months in both arms (excluding 17 early deaths), five months in pretreatment ambulant participants and three months in pretreatment non-ambulant participants.
Pain relief (short term)	61/126 (48%) versus 52/136 (38%) RR 1.24; (95% CI 0.94 to 1.64) (n = 262)
Urinary continence (short term)	118/134 (89%) versus 128/142 (90%) RR 0.97; (95% CI 0.93 to 1.02) (n = 275)
Participants maintaining urinary continence (short term)	116/120 (97%) versus 126/126 (100%) RR 0.97; (95% CI 0.93 to 1.00) (n = 246)
Participants regaining urinary continence (short term)	2/13 (15%) versus 2/16 (13%) RR 1.23; (95% CI 0.20 to 7.58) (n = 29)
Adverse effects (early)	Grade three acute gastrointestinal mucositis attributable to radiation - 5/134 (4%) versus 3/142 (2%) RR 1.77; (95% CI 0.43 to 7.25) 6/276 participants had Grade three vomiting; the incidence was similar in both the arms. Grade three nausea was present in 5/276 participants (n = 276).
Adverse effects (late)	No documented late radiation myelopathy or serious adverse effects
Outcomes not reported	Survival rates, quality of life, participant and caregiver satisfaction.
Laminectomy plus radiotherapy versus radiotherapy alone	
Overall ambulatory rates (short term)	7 /16 (44%) versus 7/13 (54%) RR 1.20; (95% CI 0.59 to 2.43) (n = 29)
Pretreatment ambulant participants maintaining ambulation (short term)	3/6 (50%) versus 5/5 (100%) RR 1.83; (95% CI 0.84 to 4.00) (n = 11)
Pretreatment non-ambulant participants regaining ambulation (short term)	4/10 (40%) versus 2/8 (25%) RR 0.63; (95% CI 0.15 to 2.59) (n = 18)
Overall ambulatory rates (intermediate term)	6/9 (67%) versus 5/6 (83%) RR 1.25; (95% CI 0.70 to 2.24) (n = 15)
Survival (short term)	16/16 (100%) versus 10/13 (76%) RR 0.77; (95% CI 0.56 to 1.06) (n = 29)
Survival (Intermediate term)	9/16 (56%) versus 6/13 (46%) RR 0.82; (95% CI 0.40 to 1.70) (n = 29)

Table 1. Detailed results (Continued)

Pain relief	8/14 (57%) versus 6/12 (50%) RR 0.88; (95% CI 0.42 to 1.81) (n = 26)
Overall urinary continence (short term)	7/16 (44%) versus 7/13 (54%) 95% CI RR 0.94; (95% CI 0.50 to 1.77) (n = 29)
Proportion of participants maintaining urinary continence (short term)	6/8 (75%) versus 6/10 (60%) RR 0.80; (95% CI 0.42 to 1.52) (n = 18)
Proportion of participants regaining urinary continence (short term)	1/8 (13%) versus 1/3 (33%) RR 2.67; (95% CI 0.23 to 30.40) (n = 11)
Overall urinary continence (intermediate term)	6/9 (67%) versus 6/6 (100%) RR 1.43; (95% CI 0.87 to 2.35) (n = 15)
Adverse effects	There were no surgery or radiotherapy related complications
Outcomes not reported	Quality of life, participant and caregiver satisfaction.
Direct decompressive surgery with radiotherapy versus radiotherapy	
Overall ambulatory rates (short term)	29/51 (57%) versus 42/50 (84%), RR 0.67; (95% CI 0.53 to 0.86) (n = 101), NNTB 3.70 (95% CI 2.38 to 7.69)
Proportion of pretreatment ambulant participants maintaining ambulation (short term)	26/35 (74%) versus 32/34 (94%) RR 0.79; (95% CI 0.64 to 0.98) (n = 69), NNTB 5.00 (95% CI 2.78 to 33.33)
Proportion of pretreatment non-ambulant participants regaining ambulation (short term)	3/16 (19%) versus 10/16 (63%) RR 0.30; (95% CI 0.10 to 0.89) (n = 32), NNTB 2.27 (95% CI 1.35 to 7.69)
Median duration of ambulation	The median duration of ambulation was 13 days versus 122 days, (those maintaining ambulation 54 days versus 153 days and regaining ambulation was 0 versus 59 days)
Survival (short term)	44/51 (86%) versus 47/50 (94%) RR 0.92; (95% CI 0.81 to 1.05) (n = 101)
Median survival	100 days versus 126 days
Outcomes not reported	Quality of life, participant and care giver satisfaction were not assessed. Participant rated pain relief, adverse effects and dichotomous data for analgesic reduction and urinary continence
High dose corticosteroids versus no or moderate dose corticosteroids	
Overall ambulatory rates (short term)	RR 0.91; (95% CI 0.68 to 1.23) (n = 105, three trials)

Table 1. Detailed results (Continued)

Proportion of pretreatment ambulant participants maintaining ambulation (short term)	17/17 (100%) versus 17/19 (90%) RR 0.90; (95% CI 0.75 to 1.08) (n = 36, one trial)
Proportion of pretreatment non-ambulant participants regaining ambulation (short term)	5/10 (50%) versus 2/11 (18%) RR 0.36; (95% CI 0.09 to 1.47) (n = 21, one trial)
Survival (long term)	5/10 (50%) versus 2/11 (18%) RR 0.36; (95% CI 0.09 to 1.47) (n = 21, one trial)
Pain relief	11/14 (79%) versus 10/11 (91%) RR 1.16; (95% CI 0.83 to 1.61) (n = 25, one trial)
Urinary continence	12/19 (63%) versus 8/15 (53%) RR 0.84; (95% CI 0.47 to 1.52) (n = 34, one trial)
Adverse effects	High dose corticosteroids versus no or moderate dose corticosteroids RR 0.12; (95% CI 0.02 to 0.97) (n = 77, two trials) High dose versus no corticosteroids RR 0.10; (95% CI 0.01 to 1.78) (n = 57, one trial) High dose versus moderate dose corticosteroids RR 0.17; (95% CI 0.01 to 3.08) (n = 20, one trial)
Outcomes not reported	Quality of life, participant rated and care giver satisfaction. Intermediate term outcomes from Sorensen 1994 could not be calculated as survival rates were not available.

1. Different radiotherapy schedules

The treatment arms of 'short course radiotherapy' and 'split course radiotherapy' in [Maranzano 2005](#) will be referred to as two fractions and eight fractions. There were no statistically significant differences between the two arms for any of the outcomes we analyzed.

1.1 Ambulation

Overall ambulatory rates were 71% for eight fractions versus 68% for two fractions (RR 1.02; 95% CI 0.90 to 1.15 n = 276). There were 91% versus 89% of patients who maintained ambulation (RR 1.02; 95% CI 0.93 to 1.12; n = 184). There were 28% versus 29% who regained ambulation (RR 0.98; 95% CI 0.51 to 1.88 n = 92). The median duration of ambulation, (excluding 17 early deaths) was 3.5 months in both arms.

1.2 Other outcomes

The median survival was four months in both study arms (excluding 17 early deaths), five months in pre-treatment ambulant participants and three months in pre-treatment non-ambulant participants. The proportion of participants with reduction in the use of analgesics was not significantly different - 48% versus 38% for eight versus two fractions. The overall proportion of participants with urinary continence was 89% versus 90% for two versus eight fractions.

1.3 Adverse effects

Early

Grade three acute gastrointestinal mucositis attributable to radiation was reported in 4% of patients who had eight fractions of radiotherapy and in 2% of those who had two fractions of radiotherapy. 6/276 participants had Grade three vomiting; the incidence was similar in both the arms. Grade three nausea was present in 5/276 participants.

Late

There was no documented late radiation myelopathy or serious adverse effects.

1.4 Outcomes not reported

Survival rates, quality of life, participant and caregiver satisfaction were not reported.

2. Laminectomy plus radiotherapy versus radiotherapy alone

The results for laminectomy plus radiotherapy versus radiotherapy alone are summarized below (also see [Table 1](#)) and were not significantly different for any of the primary or secondary outcomes ([Young 1980](#)).

2.1 Ambulation

Overall ambulatory rates for laminectomy versus radiotherapy were 44% and 54% immediately after treatment and 67% versus 83% in those alive at four months. Fifty percent of laminectomy patients versus 100% of radiotherapy patients maintained ambulation while 40% of surgical patients and 25% of radiotherapy patients regained ambulation.

2.2 Other outcomes

Short term and intermediate term results for survival, pain relief and urinary continence were not significantly different between the two arms ([Table 1](#)).

2.3 Adverse effects

There were no surgery or radiotherapy related complications.

2.4 Outcomes not reported

Quality of life, participant and caregiver satisfaction were not assessed.

3. Direct decompressive surgery with radiotherapy versus radiotherapy

3.1 Ambulation

The overall ambulatory rates and the proportion of participants maintaining or regaining ambulation were significantly better in the surgery plus radiotherapy group ([Patchell 2005](#)). At completion of treatment overall ambulatory rates were 84% versus 57%. (RR 0.67; 95% CI 0.53 to 0.86 n = 101). The NNT was 3.70 (95% CI 2.38 to 7.69). 94% versus 74% maintained ambulation

(RR 0.79; 95% CI 0.64 to 0.98; n = 69), with a NNT of 5 (95% CI 2.78 to 33.33). Sixty three percent versus 19% regained ambulation; (RR 0.30; 95% CI 0.10 to 0.89; n = 32), with a NNT of 2.27 (95% CI 1.35 to 7.69). The median duration of ambulation was 122 days versus 13 days, for maintaining ambulation 153 days versus 54 days and for regaining ambulation 59 versus 0 days in the surgery and radiotherapy arms respectively.

3.2 Other outcomes

94% of patients in the surgery arm and 86% of those in the radiotherapy arm were alive at one month (RR 0.92; CI 0.81 to 1.05). The median survival was 126 days for surgery plus radiotherapy versus 100 days for radiotherapy alone.

3.3 Outcomes not reported

Quality of life, participant and care giver satisfaction were not assessed. Participant rated pain relief, adverse effects and dichotomous data for analgesic reduction and urinary continence were not reported.

4. High dose corticosteroids versus no or moderate dose corticosteroids

4.1 Ambulation

The three small trials ([Graham 2006](#); [Sorensen 1994](#); [Vecht 1989](#)) did not show significant benefit for high dose corticosteroids (RR 0.91; 95% CI 0.68 to 1.23, n = 105, three trials).

4.2 Other outcomes

Trials showed no difference between high dose versus moderate or no corticosteroids for two-year survival (11% versus 10%, RR 0.90, 0.20 to 4.09, n = 57, one trial); pain relief (79% versus 91%, RR 1.16, 95% CI 0.83 to 1.61, n = 25 one trial); or urinary continence (63% versus 53%, RR 0.84, 95% CI 0.47 to 1.52, n = 34, one trial). Please see [Table 1](#) for details.

4.3 Adverse effects

There was a significant increase in the incidence of serious drug related adverse effects such as perforated gastric ulcer, psychoses and deaths due to infection in patients who received high dose corticosteroids. Seventeen percent of this group developed serious adverse effects as compared to 0% of patients who received moderate or low dose corticosteroids (RR 0.12; 95% CI 0.02 to 0.97; n = 77, two trials)

4.4 Outcomes not reported

Quality of life, participant rated and care giver satisfaction was not reported in any of the three corticosteroid trials.

DISCUSSION

Although MESCC is a common and distressing problem in many cancers, there are few RCTs to inform optimal treatment. We found six eligible trials with a total of 544 participants. We had planned to evaluate radiotherapy schedules, surgical interventions and adjunctive therapies. However, 'high versus moderate/low dose corticosteroids' was the only comparison for which there was more than one published trial to allow meta-analysis. Pre-planned subgroup analysis was possible only for ambulant versus non-ambulant patients and has been reported separately as the proportions of patients maintaining or regaining ambulation respectively.

Differences in inclusion criteria

Within these six trials, there were differences in inclusion criteria. [Maranzano 2005](#) recruited patients with a poor prognosis while [Patchell 2005](#) required an estimated survival of at least three months. [Maranzano 2005](#) excluded patients with spinal instability but such patients comprised over a third of the [Patchell 2005](#) population. While some trials excluded radiosensitive tumours ([Graham 2006](#); [Patchell 2005](#); [Sorensen 1994](#)) others included haematologic and germ cell tumours ([Maranzano 2005](#); [Vecht 1989](#); [Young 1980](#)). [Patchell 2005](#) excluded patients with cauda equina lesions.

Differences in the definition of ambulation

Although ambulation was the primary outcome in all six trials there were differences in definition. [Patchell 2005](#) reported a participant as ambulant if he or she was able to take at least two steps with each foot either unassisted or with use of a cane or walker at completion of radiotherapy. In [Maranzano 2005](#), participants who were walking with or without support at one month were called ambulant. The three corticosteroid studies measured ambulation at different time points. It is important that ambulation be defined in a way that is meaningful and worthwhile for patients considering the intervention.

Radiotherapy doses and schedules

Radiotherapy is the most widely used treatment for cord compression, and was part of the treatment protocol in all the six trials reviewed but only [Maranzano 2005](#) compared different radiotherapy fractionation schedules.

This trial demonstrated that in patients with unfavourable histology or an estimated poor survival, there was no difference in outcomes between patients receiving 16 Gray in two fractions and 30 Gray in eight fractions. Eighty five per cent of people referred for radiotherapy met poor prognostic criteria. With 91% versus 89% of ambulant patients maintaining ambulation, a documented in-field recurrence rate of 3.3%, a median survival of four months, and minimal toxicity, such short courses of radiotherapy appear justified in poor prognostic patients who constitute a significant proportion of the MESCC population.

The results in non-ambulant patients were similar to other radiotherapy reports with 28% to 29% of non-ambulant patients regaining ambulation.

There were no trials comparing radiotherapy doses, schedules or techniques in patients with a good prognosis and no conclusions can be drawn regarding the optimal radiotherapy dose for such patients.

Surgery with or without radiation therapy versus radiation therapy alone

There were two trials assessing surgical interventions.

Laminectomy

[Young 1980](#) compared outcomes in 16 patients undergoing laminectomy followed by radiation, with 13 patients treated with radiation alone. In the short term they found no significant difference in the outcome between the two groups. Laminectomy for a ventrally located tumour is undesirable as direct decompression of the cord through removal of the compressive element is not achieved. Moreover, removal of the laminae and posterior ligaments of the spine in the setting of vertebral body disease quite often further destabilizes the spine ([Klimo 2005](#)). Thus the results of this study should not be used to assess the role of surgery in metastatic spine disease.

Direct decompressive surgical resection

Progress in spine surgery, particularly with regard to sophisticated instrumentation and ventral approaches through the neck, thorax and abdomen, provides an opportunity for direct decompression of the cord and fixation. Utilizing these techniques, [Patchell 2005](#) performed a prospective randomized trial in 101 participants with spinal cord compression due to metastatic disease. Surgery was tailored to the location of the compression, that is, a ventral approach was employed for vertebral body disease, a lateral approach for predominantly laterally located compression and a posterior approach when the posterior elements were primarily involved. When required the spines were fixed using bone grafts and instrumentation.

Median survivals were short in both treatment arms although statistically significantly longer in the surgery group at 126 days versus 100 days for radiotherapy alone.

With ambulation as a primary endpoint, [Patchell 2005](#) reports that 63% of non-ambulant patients regained the ability to walk with surgery and radiotherapy as compared with only 19% in those receiving radiotherapy alone. A potential source of bias in [Patchell 2005](#) was that 18 of 51 participants receiving radiotherapy alone had spinal instability; precluding them from being mobilized early. Radiotherapy does not relieve compression caused by bone fragments; nor does it correct deformities such as vertebral collapse ([Klimo 2005](#); [Wise 1999](#)).

[Patchell 2005](#) does not provide the results in patients with unstable spines treated with radiotherapy alone, but unstable spines were a predictor for poor outcome in the study population as a whole. Twenty per cent of ambulant patients randomized to the radiotherapy arm crossed over to surgery on the occurrence of neurological deterioration and lost the ability to walk. Thirty per cent of them regained the ability to walk, but the complication rate was higher in this group. [Patchell 2005](#) therefore justifies the use of surgery as the first line of therapy even in ambulant patients. [Patchell 2005](#) acknowledges the restrictive selection criteria used in the trial and concedes that the results do not apply to the entire MESCC population. We feel that the case for direct decompressive surgery in patients with good neurological function and stable spines is not convincing based on current evidence. We suggest that in a patient with localized cord compression the clinician needs to consider the following questions:

1. Are there prognostic features to suggest that the patient would have poor ambulatory outcomes with radiotherapy?
2. Will the patient survive long enough to benefit from a major surgery?

In RCTs and prospective cohort studies, poor baseline neurological status and unstable spines ([Maranzano 2005](#); [Patchell 2005](#)), complete myelographic block ([Maranzano 1991](#)), and rapid progression of motor deficits ([Rades 2000](#)) have been factors predicting poor ambulatory and neurological outcomes. RCTs have shown that the factors that favour longer survival are the ambulatory status, and favourable histologies such as breast and prostate primaries ([Maranzano 2005](#); [Patchell 2005](#)); while prospective cohort studies indicate that renal cancers, lymphomas, myelomas ([Bauer 1995](#); [Rades 2004](#)), solitary skeletal metastases ([Bauer 1995](#)), the absence of visceral or brain metastases ([Bauer 1995](#)) and a long interval between cancer diagnosis and MESCC ([Helweg-Larsen 2000](#)) are good prognostic factors for survival.

In an attempt to systematically use prognostic factors to aid clinical decision making some authors have used the regression coefficients and hazard ratios, albeit from non-randomized studies, to devise scoring systems ([Bauer 1995](#); [Tomita 2001](#)). Scoring systems developed for clinical use in the future should incorporate the information from RCTs.

In summary, non-ambulant patients (with the exclusion of those with radiosensitive tumours, paraplegia for over 48 hours, multiple sites of compression and an expected survival of less than three months) would benefit from decompressive surgery before radiotherapy. Radiotherapy alone may suffice for many ambulant patients with stable spines. Surgery may be offered as first-line therapy in those ambulant patients known to have factors that would predict a poor outcome with radiotherapy and with good predicted survivals.

Corticosteroids

Although corticosteroids have been used in the treatment of MESCC for many years, we found only three small trials inadequately powered to determine clinical benefit and optimal dosage. High dose corticosteroids were associated with serious drug related adverse effects ([Graham 2006](#); [Sorensen 1994](#)).

Considering the widespread clinical use of corticosteroids in MESCC, it is unlikely that a trial comparing corticosteroids to placebo will be undertaken in the future; but the serious adverse effects reported here should be noted with caution. Future studies comparing different doses of corticosteroids should be adequately powered to ascertain the balance between benefits and adverse effects with different doses of corticosteroids.

Adverse effects

One of our secondary objectives was to compare the adverse effects between different interventions but these were not always systematically recorded or graded. Serious adverse effects were low in both arms of the [Maranzano 2005](#) study. [Patchell 2005](#) reported more adverse effects in patients who had preoperative rather than postoperative radiotherapy but did not report the adverse effects in the trial as a whole. The one-month mortality was 6% versus 14% in the surgery versus RT alone arms. Serious gastrointestinal, infectious and central nervous system adverse effects were reported in 15% to 22% of participants receiving high dose corticosteroids.

Limitations of this review

Studies

We have tried to assess different comparisons in a heterogeneous population of adult patients with MESCC. Many of the trials included here have small numbers of participants making it difficult to draw precise or firm conclusions. Nor can our conclusions apply to all subgroups - patients with haematologic tumours, post-radiotherapy recurrences, or paraplegia longer than 48 hours constitute a very small proportion of participants. We found no trials assessing the value of interventions such as rehabilitation, supportive

care and patient education. Although we had not specified these search terms, our broad search strategy should have detected such RCTs.

Outcomes

Clinically significant outcomes such as survival rates, patient related pain relief and quality of life were often not reported. There were many variations in the definition and times of assessment of ambulatory outcomes.

Data

Not all reported data could be used for analysis, for example when mean values were reported without standard deviations.

AUTHORS' CONCLUSIONS

Implications for practice

- Radiotherapy is recommended as the primary treatment for ambulant patients with stable spines and for those who do not meet the recommendations for surgery listed below.
- Limited evidence suggests that short courses of radiotherapy suffice in patients with unfavourable histologies or a predicted survival of less than six months. There are no RCTs to draw conclusions regarding the optimal radiotherapy dose in good prognostic patients.
- Evidence from this review indicates that non-ambulant patients have only an 18% to 29% chance of regaining ambulation with radiotherapy.
- Patients who have lost motor function for less than 48 hours, have localized cord compression and an estimated survival of greater than three months, may benefit from decompressive surgery. Careful patient selection is crucial and should be performed by a multidisciplinary team.
- Ambulant patients with poor prognostic factors for radiotherapy (e.g. spinal instability, bony compression, rapidly progressive neurologic deficits) appear to be good candidates for decompressive surgery, provided good prognostic factors for survival are present.
- The extent of benefit from, and optimal dosage for corticosteroids is unclear. High dose corticosteroids carry a significant risk of adverse effects.

Implications for research

Trials should report results in accordance with the [CONSORT 2001](#) guidelines. Where appropriate, outcomes and endpoints should be patient and caregiver defined.

There is a need for further clarification of prognostic factors, and a first step towards that would ideally be an individual patient data meta-analysis of participants from the randomized and prospective studies to date. The hazard ratios of prognostic factors identified could guide the development of a prognostic score. Stratification by prognostic factors is important in RCTs comparing different interventions, which would need to be adequately powered to detect differences between subgroups.

Adequately powered, multinational RCTs are needed to:

- define appropriate radiotherapy schedules for good prognostic patients;
- clarify the role of decompressive surgery in different prognostic groups and health care settings;
- determine the optimal dosage and duration of corticosteroids.

Additionally, there is need for both qualitative and quantitative research into education, rehabilitation, screening and supportive care for patients with MESCC.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Graham 2006

Methods	<p>“Pilot randomized comparison”</p> <p>Study closed due to low recruitment</p> <p>Concealment of Allocation: yes, website randomization</p> <p>Generation of allocation sequence: computerized</p> <p>Blinding: no</p> <p>Attrition: 20%</p> <p>Intention-to-treat analysis: no</p>
Participants	<p>Australia, September 2001 to November 2003, multi-institutional</p> <p>Inclusion: MRI evidence, ECOG less than four, minimum survival two months, and minimum power 1/5.</p> <p>Exclusion: prior treatment for MESCC, lymphoma and myeloma, people undergoing surgery, central nervous system disease, multi-level MESCC, ongoing steroid medication, pregnancy, peptic ulcer or cardiac failure</p> <p>Age: 41 to 81 years</p> <p>Gender: males - 14, females - 6</p> <p>Ambulant pretreatment:</p> <p>High dose dexamethasone versus low dose dexamethasone: 6 versus 9</p> <p>Performance status: not stated</p> <p>Type of primary tumours:</p> <p>Breast , prostate - 11</p> <p>Others - 9</p> <p>Visceral metastasis: not stated</p> <p>Duration and rapidity of cord compression: not stated</p> <p>Spinal level:</p> <p>Cervical - 1</p> <p>Thoracic - 15</p> <p>Lumbar - 4</p> <p>Spinal instability: not stated</p>
Interventions	<p>High dose dexamethasone 96 intravenous on days 0 to 2; n = 9</p> <p>Low dose dexamethasone 16 intravenous on days 0 to 2; n = 11</p> <p>then weaned over 15 days in both arms</p> <p>Radiotherapy 30 Gray in 10 fractions in both arms</p> <p>Timing of intervention in relation to development of cord compression not stated</p> <p>Concomitant medications: omeprazole, trimethoprim if on urinary catheter, oral nystatin drops and laxatives</p>
Outcomes	<p>Outcomes of interest reported and used:</p> <p>Overall ambulation rate (at one month)</p> <p>Adverse events</p> <p>Outcomes reported but not used :</p> <p>Mean Functional Improvement score (FIS)</p> <p>Changes in Barthel score, Functional Independence Measure (FIM)</p>

Graham 2006 (Continued)

	Pain relief: Mean Visual analogue pain score (no SD provided) Median survival	
Notes	No provision for rehabilitation was reported Outcomes of interest not reported: Survival rates, reduction in analgesic use, urinary continence, quality of life, participant and caregiver satisfaction, characteristics of participants who benefit from treatment	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Maranzano 2005

Methods	Randomized controlled trial. Generation of allocation sequence: one to one randomization, central. Concealment of allocation: yes, by centralized registration. Blinding : no Attrition: seven loss to follow up. Intention-to-treat analysis : no	
Participants	Italy, February 1998 to November 2002, multicenter trial Inclusion: MRI or CT diagnosis, short life expectancy (less than or equals six months, as defined by unfavourable histologies or favourable histologies with poor performance status, motor or sphincter dysfunction). Exclusion: Diagnostic doubt, spinal instability, bony impingement, previous irradiation, favourable histology with life expectancy greater than or equals 6 months (15% of observed patients). Age: 30 to 89 years Gender: male - 191, female - 85 Pretreatment ambulant: Two fractions versus eight fractions: 93 versus 91 Performance status: Karnovsky performance status: ≤ 40 - 86, 50 to 70 - 143, 80 to 100 - 47 Type of primary tumours: Favourable histology (lymphoma, seminoma, myeloma, breast and prostate cancer) - 99 Unfavourable histology (lung, renal, gastrointestinal, head and neck carcinoma, melanoma, sarcoma) - 177 Visceral metastasis: unclear Duration and rapidity of cord compression: not stated Spinal level: Cervical - 8%, Thoracic - 50%, lumbar - 23%, sacral - 7%, cervicothoracic - 1%, thoracolumbar - 6%, lumbosacral - 2%	
Interventions	Two fractions: "Short course regimen" (8 Gray, 6-days rest, and then 8 Gray, to a total of 16 Gray in 1 week), n = 153 Eight fractions: "Split course regimen" (5 Gray x 3, 4 days rest, then 3 Gray x 5, to a total of 30 Gray in 2 weeks), n = 147 Timing of intervention in relation to development of cord compression not stated	

Maranzano 2005 (Continued)

	Concomitant medications: Dexamethasone: 8 mg twice daily tapered after completion of radiotherapy. Parenteral 5 hydroxytryptamine-3 receptor antagonist if radiation included upper abdomen.
Outcomes	Outcomes of interest reported and used : Ambulation (able to walk with or without support at one month after radiotherapy): overall ambulatory rate, proportion maintaining and regaining ambulation Reduction in analgesic use Urinary continence: overall, proportion maintaining and regaining continence Adverse effects: gastrointestinal and late spinal cord morbidity. Outcomes reported but not used: Percent probability of survival and median survival In-field recurrences
Notes	The author's analysis excluded 8% of participants (seven lost to follow up and seventeen deaths that occurred within the first ten days. Characteristics of participants who benefit from treatment: favourable histology Outcomes not reported: patient rated pain relief, survival rates, quality of life, participant and caregiver satisfaction Provision for rehabilitation not reported Intention-to-treat analysis was used for survival outcome

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Patchell 2005

Methods	Randomized trial Concealment of allocation: yes, computerized technique Generation of allocation sequence: yes, computerized permutation blocks Blinding: no Attrition: nil Intention-to-treat analysis: yes
Participants	United States of America, September 1992 to December 2002, multi-institutional Inclusion: MRI diagnosis, life expectancy greater than or equals three months, less than 48 hours total paraplegia, cervical or thoracic lesions Exclusion: total paraplegia more than 48 hours, multiple discrete compression, radiosensitive tumours (haematologic and germ cell tumours), previous irradiation, compression of only cauda equina or spinal roots, preexisting neurological problems Age: median 60 years Gender: males - 70, females - 31 Pretreatment ambulant: Surgery plus radiotherapy versus radiotherapy alone: 34 versus 35 Performance status: not stated Type of primary tumours: all except radiosensitive tumours (haematologic and germ cell tumours)

Patchell 2005 (Continued)

	<p>Visceral metastasis: not stated Duration of cord compression: Not less than 48 hours Rapidity of cord compression: not stated Spinal level: cervical - 13, upper thoracic - 38, lower thoracic - 50 Spinal instability: Surgery plus radiotherapy versus radiotherapy alone: 20 versus 18</p>
Interventions	<p>Surgery with radiotherapy: n = 50 Surgery- direct circumferential decompression with or without stabilization within 24 hours of randomization Radiotherapy- 3 Gray x 10, starting within 14 days of surgery Radiotherapy alone: n = 51 Radiotherapy - 3 Gray x 10 fractions Timing of intervention in relation to development of cord compression - Surgery plus radiotherapy versus radiotherapy alone: median time 10 versus 12 days Concomitant medications: Dexamethasone, both arms 100 mg immediate, 24 mg four times daily till start of radiotherapy or surgery then tapered.</p>
Outcomes	<p>Outcomes of interest reported and used : Ambulation (able to take at least two steps with each foot unassisted (four steps total), even if a cane or walker was needed, immediately after radiotherapy) Overall ambulatory rates, proportion maintaining and regaining ambulation. Survival (30 day mortality) Outcomes reported but not used: Median duration of ambulation Changes in Frankel functional scale scores, American Spinal Injury Association (ASIA) motor scores Median survival Median duration of maintenance of urinary continence Pain relief: mean daily morphine equivalent dose (without SD)</p>
Notes	<p>Eighteen participants with unstable spine were randomized to radiotherapy alone Ten participants crossed over from radiotherapy to surgery arm (due to decline in motor strength, and three regained ambulation) Stratification - treating institution, tumour type, ambulatory status, relative stability of the spine No provision for rehabilitation was reported. Characteristics of participants who benefit from treatment: stable spine, cervical spinal level, baseline neurology status, breast primary tumours Outcomes not reported: urinary continence and analgesic reduction as dichotomous data, quality of life, participant and caregiver satisfaction.</p>

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Sorensen 1994

Methods	<p>Randomized trial Generation of allocation sequence: method not stated Allocation concealment: unclear Blinding: single, observer blinded, method not stated Intention-to-treat analysis: yes</p>	
Participants	<p>Denmark, May 1987 to April 1989 Single institution. Inclusion: confirmation by myelogram, carcinoma Exclusion: lymphoma, surgery for cord compression, unstable vertebral lesions, previous treatment for epidural metastasis, carcinomatous meningitis, peptic ulcer, infection Age: 41 to 81 years Gender: males - 18, females 39 Pretreatment ambulant: High dose corticosteroids versus no corticosteroids: 17 versus 19 Performance status: not stated Type of primary tumours: all types except lymphoma Visceral metastasis: not stated Duration and rapidity of cord compression: not stated Spinal level: Cervical - 3 Thoracic - 33 Lumbar - 21</p>	
Interventions	<p>Dexamethasone 96 mg intravenous stat and per oral for 3 days and taper over 15 days - n = 27 No dexamethasone - n = 30 Radiotherapy in both arms - 28 Gray in 7 fractions Timing of intervention in relation to development of cord compression - not stated Concomitant medications: prophylactic medication in peptic ulcer and dyspepsia.</p>	
Outcomes	<p>Outcomes of interest reported and used: Ambulation (able to walk at three months) Overall, proportion maintaining and regaining. Survival Adverse effects Outcomes reported but not used: median survival</p>	
Notes	<p>No provision for rehabilitation was reported. Stratification by primary tumour and gait function. Outcomes of interest not reported: pain relief, urinary continence, quality of life, participant and caregiver satisfaction and characteristics of participants who benefit from treatment</p>	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Vecht 1989

Methods	Randomized trial Allocation concealment: yes Generation of allocation sequence: unclear Blinding: yes, by identical coded ampules, code broken by statistician Attrition: data for three participants not available Intention-to-treat analysis: no	
Participants	Netherlands, multi-institutional Inclusion: complete obstruction on myelogram, carcinoma or lymphoreticular malignancy Exclusion: not mentioned Age: 22 to 87 years Gender: males - 26, females - 11 Pretreatment ambulant: High dose versus moderate dose corticosteroids: 14 versus 7 Performance status: not stated Type of primary tumours: Carcinoma - 26 Lymphoreticular malignancy - 11 Visceral metastasis: not stated Duration and rapidity of cord compression: not stated Spinal level: not stated Spinal instability: not stated	
Interventions	Dexamethasone 100 mg (n = 22) versus 10 mg (n = 15) intravenous followed by 16 mg orally Radiotherapy in both arms: 3 Gray x 7 or 10 fractions Timing of intervention in relation to development of cord compression - not stated Concomitant medications: not stated	
Outcomes	Outcomes of interest reported and used: Ambulation (walking independently or with aid at one week): overall Urinary continence Patient rated pain relief Outcomes reported and not used: mean pain score	
Notes	No provision for rehabilitation was reported Stratification for carcinoma versus lymphoreticular malignancy. Outcomes of interest not reported: survival, quality of life, participant and caregiver satisfaction and characteristics of participants who benefit from treatment	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Young 1980

Methods	<p>Randomized prospective comparison</p> <p>Concealment of allocation: unclear</p> <p>Generation of allocation sequence: table of random numbers</p> <p>Blinding: no</p> <p>Attrition: nil</p> <p>Intention-to-treat analysis: yes</p>
Participants	<p>United States of America.</p> <p>Inclusion: myelogram showing extradural lesion or block that correlated with clinical presentation</p> <p>Exclusion: prior radiotherapy, unfit for surgery, more than one lesion, presence of only spinal or radicular pain.</p> <p>Age: 19 to 83 years</p> <p>Gender: not stated</p> <p>Pretreatment ambulant:</p> <p>Laminectomy plus radiotherapy versus radiotherapy alone: 6 versus 5</p> <p>Performance status: not stated</p> <p>Type of primary tumours: all types</p> <p>Visceral metastasis: not stated</p> <p>Duration and rapidity of cord compression: not stated</p> <p>Spinal level: not stated</p> <p>Spinal instability: not stated</p>
Interventions	<p>Laminectomy with radiotherapy: 30 Gray in ten fractions over 14 days, n = 16</p> <p>Radiotherapy alone: 30 Gray in ten fractions (4 Gray/day first 3 days, then 18 Gray in 7 fractions over 14 days), n = 13</p> <p>Timing of intervention in relation to development of cord compression - not stated</p> <p>Concomitant medications: Dexamethasone 12 mg stat followed by 4 mg four times daily till radiotherapy completion</p>
Outcomes	<p>Outcomes of interest reported and used:</p> <p>Ambulation (ability to take steps alone with or without a cane or walker at four months):</p> <p>Overall ambulatory rates, proportion maintaining ambulation and proportion regaining ambulation</p> <p>Survival</p> <p>Pain relief: Reduction in analgesic use</p> <p>Urinary continence : Overall, proportion maintaining and regaining continence</p> <p>Adverse effects</p> <p>Outcomes reported but not used:</p> <p>Mean survival</p>
Notes	<p>Radiotherapy alone: Mortality - 24% (due to underlying disease)</p> <p>No provision for rehabilitation was reported</p> <p>Outcomes of interest not reported: quality of life, participant and caregiver satisfaction and characteristics of patients who benefit the treatment</p>

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

MRI- magnetic resonance imaging
 CT- computed tomography
 ECOG- Eastern Co-operative Oncology Group
 SD - Standard Deviation

Characteristics of excluded studies *[ordered by study ID]*

Aviles 2002	Abstract described it as randomized, but on reviewing the full paper we found it to be a retrospective rather than a prospective randomized comparison
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Characteristics of ongoing studies *[ordered by study ID]*

ICORG 05-03

Trial name or title	A randomised phase III trial of two fractionation schemes in the treatment of malignant spinal cord compression
Methods	
Participants	<p>Inclusion:</p> <ol style="list-style-type: none"> 1. Diagnosis of spinal cord compression, confirmed on MRI 2. Histologically proven malignancy other than leukaemia, myeloma, germ cell tumours, or primary tumours of the spine or vertebral column 3. MRI of the entire spine performed 4. Karnofsky performance score greater or equal to 30 5. Age greater or equal to 18 years 6. Written informed consent <p>Exclusion:</p> <ol style="list-style-type: none"> 1. Previous treatment with radiotherapy to the involved area of the spinal cord such that further treatment exceeds spinal cord tolerance 2. Single bone metastasis with controlled primary site 3. Patients deemed suitable for neurosurgical intervention at the time of initial assessment (patients deemed medically inoperable are eligible) 4. Patients who have a medical or psychiatric condition, which in the opinion of the investigator/research team, contraindicates the patient's participation in this study
Interventions	<p>Radiotherapy (single or multiple fractions):</p> <p>Arm 1: 20 Gy/5 fractions daily for five consecutive days</p> <p>Arm 2: 10 Gy/1 fraction</p>
Outcomes	<p>Primary outcome measure(s):</p> <p>Change in motor functioning as measured by the change in physical functioning dimension of the EORTC QLQ-C30 version 3 quality of life questionnaire, over a four week period</p> <p>Secondary outcome measure(s):</p>

ICORG 05-03 (Continued)

	<ol style="list-style-type: none"> 1. Quality of life: assessed according to the EORTC QLQ-C30 version 3 quality of life questionnaire 2. Toxicity ? assessed at first follow-up, evaluated as per standard RTOG criteria 3. Mobility 4. Pain control <p>Median survival - calculated on the basis of time from date of randomisation to death.</p>
Starting date	February 2007
Contact information	<p>Dr Joe O’Sullivan Senior Lecturer and Consultant in Clinical Oncology The Northern Ireland Cancer Centre Belfast City Hospital Belfast BT9 7AB Northern Ireland Tel: +44 (0)28 90699204 joe.osullivan@Queens-Belfast.ac.uk</p>
Notes	

ISRCTN97555949

Trial name or title	A randomised feasibility study of single fraction radiotherapy compared to multi-fraction radiotherapy in patients with metastatic spinal cord compression
Methods	
Participants	<p>Inclusion: <ol style="list-style-type: none"> 1. Proven diagnosis of spinal cord compression on Magnetic Resonance Imaging (MRI) 2. Histologically or cytologically confirmed malignant disease 3. Life expectancy > 1 month 4. Age 18 years or older 5. Able to give informed consent 6. Willing and able to complete assessment forms <p>Exclusion : <ol style="list-style-type: none"> 1. Patients for whom surgery or chemotherapy treatment is more appropriate 2. Patient who are known to be pregnant </p> </p>
Interventions	<p>Radiotherapy (single or multiple fractions): Arm 1: 20 Gy/5 fractions daily for five consecutive days Arm 2: 8 Gy/1 fraction</p>
Outcomes	<p>Primary outcome measure(s) Patient accrual per centre over a 12 month period</p> <p>Secondary outcome measure(s) <ol style="list-style-type: none"> 1. Ambulatory status at 1, 4, 8 and 12 weeks from Day 1 of treatment compared to baseline 2. Bladder and bowel function at baseline compared to week 1, 4, 8 and 12 3. Acute side effects at week 1 and 4. assessed using Radiation Therapy Oncology Group (RTOG) scales 4. Quality of life at week 1, 4, 8 and 12, measured by the EORTC QLQ-C30 questionnaire 5. Further treatment </p>

ISRCTN97555949 (Continued)

	6. Overall survival at 3, 6 and 12 months 7. Total number of days spent in hospital 8. Preferred place of care 9. Number of patients who were eligible but not randomised and reasons for non-randomisation
Starting date	November 2007
Contact information	Prof Peter J Hoskin Marie Curie Research Wing Mount Vernon Hospital Rickmansworth Road Northwood Middlesex Northwood United Kingdom HA6 2RN
Notes	

DATA AND ANALYSES

Comparison 1. Radiotherapy 8 fractions versus 2 fractions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ambulation (short term)	1	276	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.90, 1.15]
1.1 Pretreatment ambulant subgroup - maintaining ambulation	1	184	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.93, 1.12]
1.2 Pretreatment non-ambulant subgroup - regaining ambulation	1	92	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.51, 1.88]
2 Reduction in analgesic use	1	262	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.96, 1.67]
3 Urinary continence (short term)	1	275	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.93, 1.02]
3.1 Proportion maintaining urinary continence	1	246	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.93, 1.00]
3.2 Proportion regaining urinary continence	1	29	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.20, 7.58]
4 Gastrointestinal adverse effects	1	276	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [0.43, 7.25]

Comparison 2. Laminectomy plus radiotherapy versus radiotherapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ambulation (short term)	1	29	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.59, 2.43]
1.1 Pretreatment ambulant subgroup - maintaining ambulation	1	11	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [0.84, 4.00]
1.2 Pretreatment non-ambulant subgroup - regaining ambulation	1	18	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.15, 2.59]
2 Ambulation (intermediate term)	1	15	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.70, 2.24]
3 Survival	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Short term survival	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.56, 1.06]
3.2 Intermediate term survival	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.40, 1.70]
4 Reduction in analgesic use	1	26	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.42, 1.81]
5 Urinary continence (short term)	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.50, 1.77]
5.1 Proportion maintaining urinary continence	1	18	Risk Ratio (M-H, Fixed, 95% CI)	0.8 [0.42, 1.52]
5.2 Proportion regaining urinary continence	1	11	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [0.23, 30.40]
6 Urinary continence (intermediate term)	1	15	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.87, 2.35]

Comparison 3. Decompressive surgery plus radiotherapy versus radiotherapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ambulation (short term)	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.53, 0.86]
1.1 Pretreatment ambulant subgroup - maintaining ambulation	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.64, 0.98]
1.2 Pretreatment non-ambulant subgroup regaining ambulation	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.3 [0.10, 0.89]
2 Survival (short term)	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.81, 1.05]

Comparison 4. High dose versus no or moderate dose corticosteroids

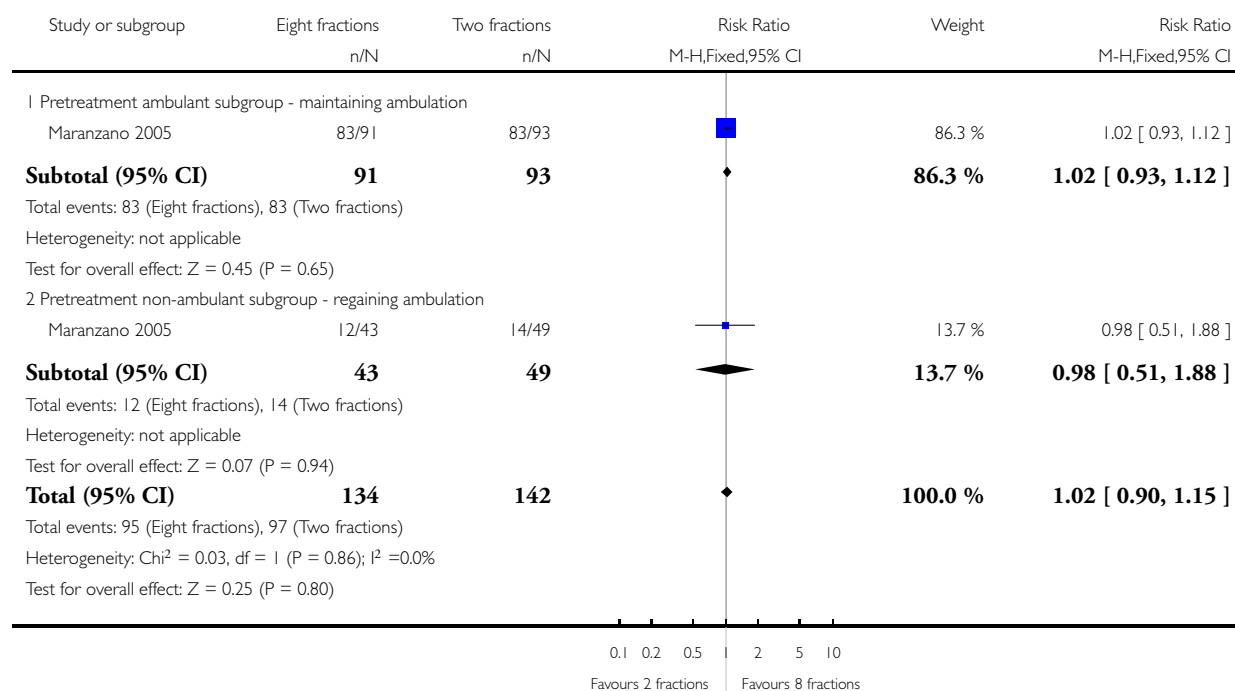
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall ambulation (short term)	3	105	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.68, 1.23]
1.1 High dose versus no corticosteroids	1	57	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.56, 1.08]
1.2 High versus moderate corticosteroids	2	48	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.68, 2.12]
2 Participants maintaining or regaining ambulation (short term)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Pretreatment ambulant subgroup - maintaining ambulation	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.9 [0.75, 1.08]
2.2 Pretreatment non-ambulant subgroup regaining ambulation	1	21	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.09, 1.47]
3 Survival (long term)	1	57	Risk Ratio (M-H, Fixed, 95% CI)	0.9 [0.20, 4.09]
4 Pain reduction	1	25	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.83, 1.61]
5 Urinary continence (short term)	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.47, 1.52]
6 Serious drug related adverse effects	2	77	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.02, 0.97]
6.1 High dose versus no corticosteroids	1	57	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 1.78]
6.2 High dose versus moderate dose corticosteroids	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.01, 3.08]

Analysis 1.1. Comparison 1 Radiotherapy 8 fractions versus 2 fractions, Outcome 1 Ambulation (short term).

Review: Interventions for the treatment of metastatic extradural spinal cord compression in adults

Comparison: 1 Radiotherapy 8 fractions versus 2 fractions

Outcome: 1 Ambulation (short term)

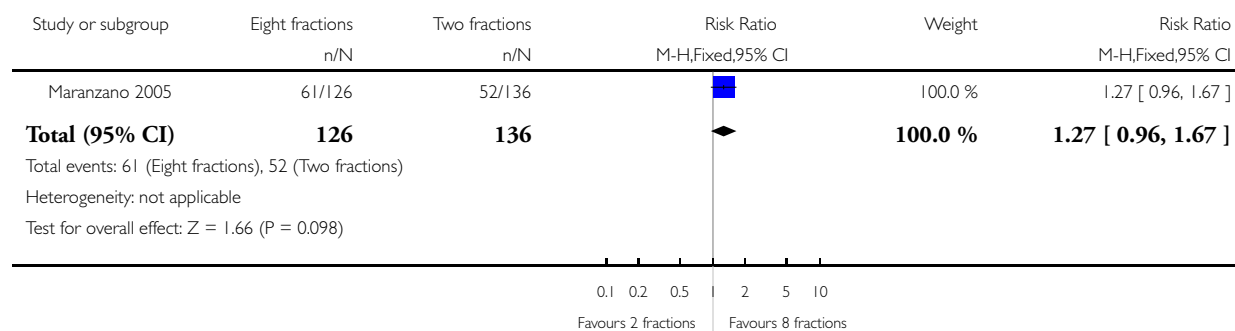


Analysis 1.2. Comparison 1 Radiotherapy 8 fractions versus 2 fractions, Outcome 2 Reduction in analgesic use.

Review: Interventions for the treatment of metastatic extradural spinal cord compression in adults

Comparison: 1 Radiotherapy 8 fractions versus 2 fractions

Outcome: 2 Reduction in analgesic use

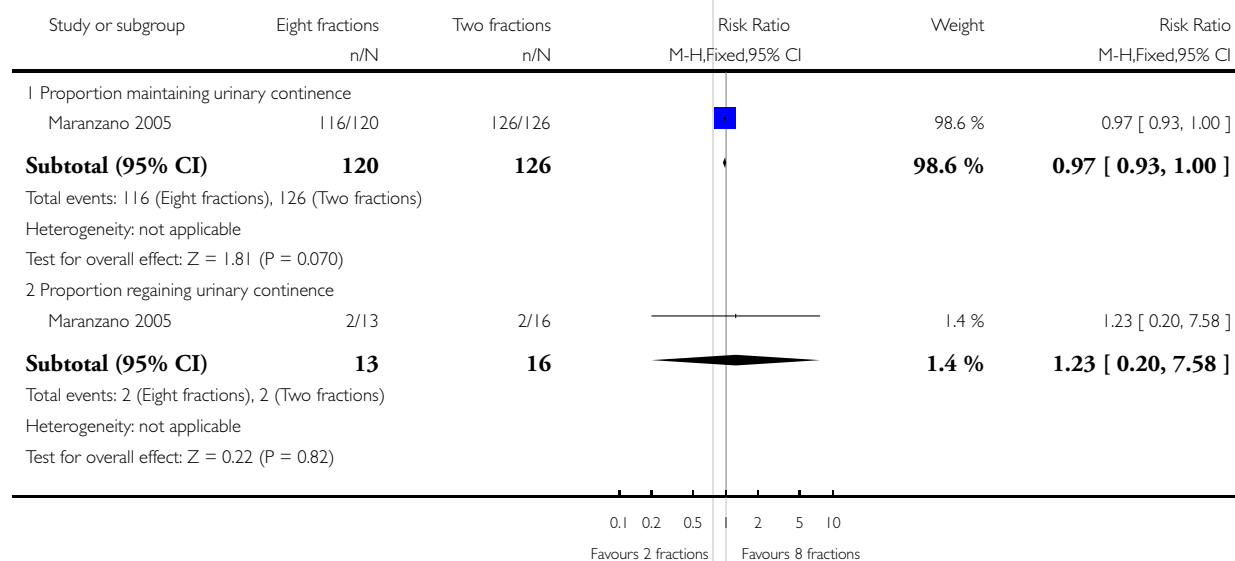


Analysis 1.3. Comparison 1 Radiotherapy 8 fractions versus 2 fractions, Outcome 3 Urinary continence (short term).

Review: Interventions for the treatment of metastatic extradural spinal cord compression in adults

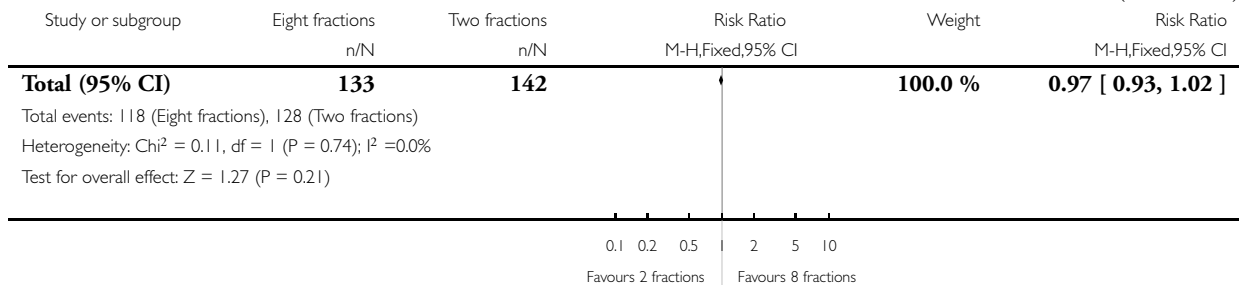
Comparison: 1 Radiotherapy 8 fractions versus 2 fractions

Outcome: 3 Urinary continence (short term)



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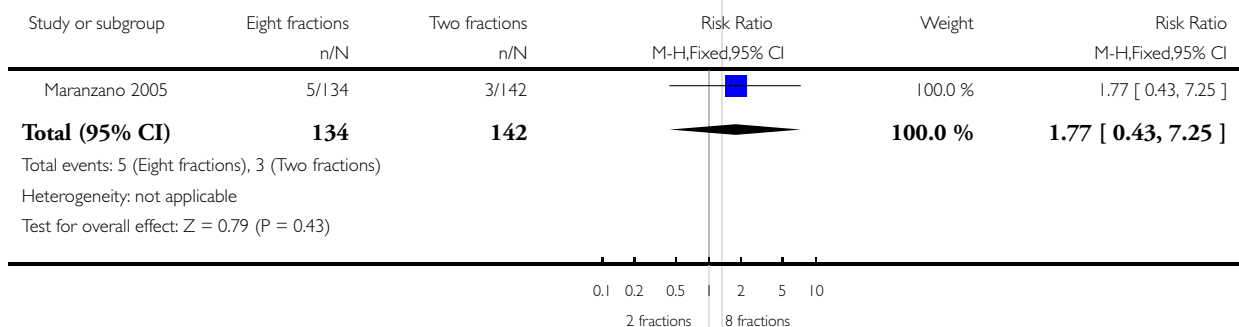


Analysis 1.4. Comparison 1 Radiotherapy 8 fractions versus 2 fractions, Outcome 4 Gastrointestinal adverse effects.

Review: Interventions for the treatment of metastatic extradural spinal cord compression in adults

Comparison: 1 Radiotherapy 8 fractions versus 2 fractions

Outcome: 4 Gastrointestinal adverse effects

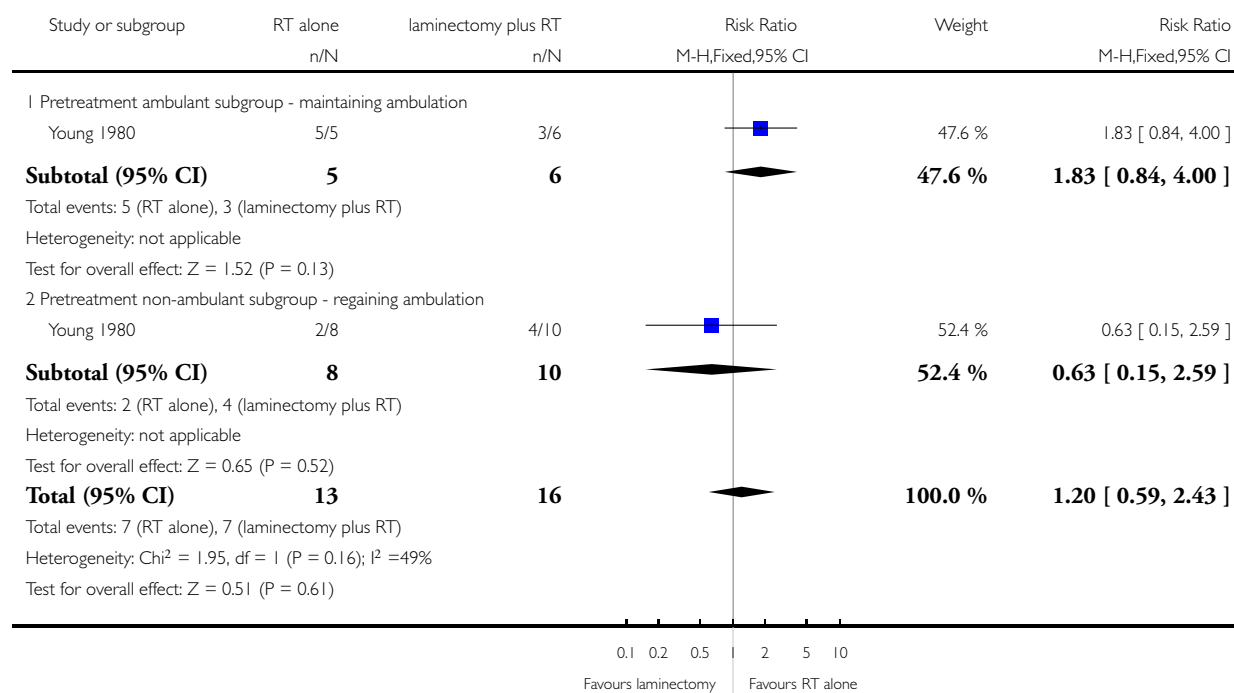


Analysis 2.1. Comparison 2 Laminectomy plus radiotherapy versus radiotherapy alone, Outcome 1 Ambulation (short term).

Review: Interventions for the treatment of metastatic extradural spinal cord compression in adults

Comparison: 2 Laminectomy plus radiotherapy versus radiotherapy alone

Outcome: 1 Ambulation (short term)

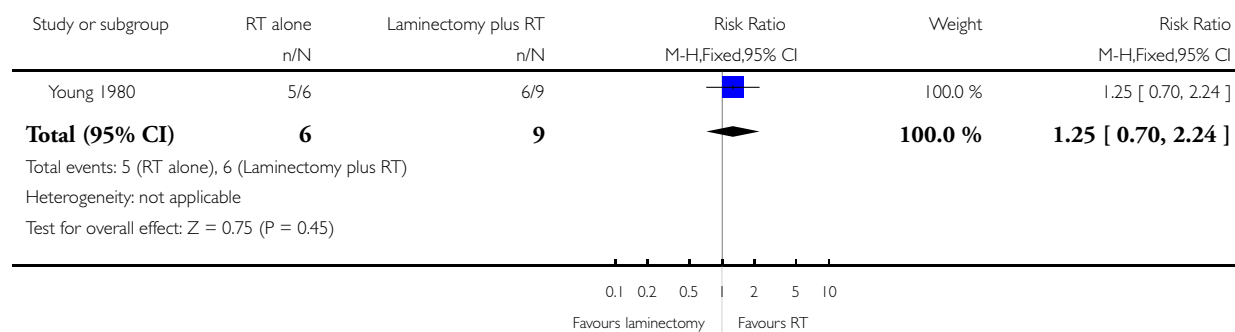


Analysis 2.2. Comparison 2 Laminectomy plus radiotherapy versus radiotherapy alone, Outcome 2 Ambulation (intermediate term).

Review: Interventions for the treatment of metastatic extradural spinal cord compression in adults

Comparison: 2 Laminectomy plus radiotherapy versus radiotherapy alone

Outcome: 2 Ambulation (intermediate term)

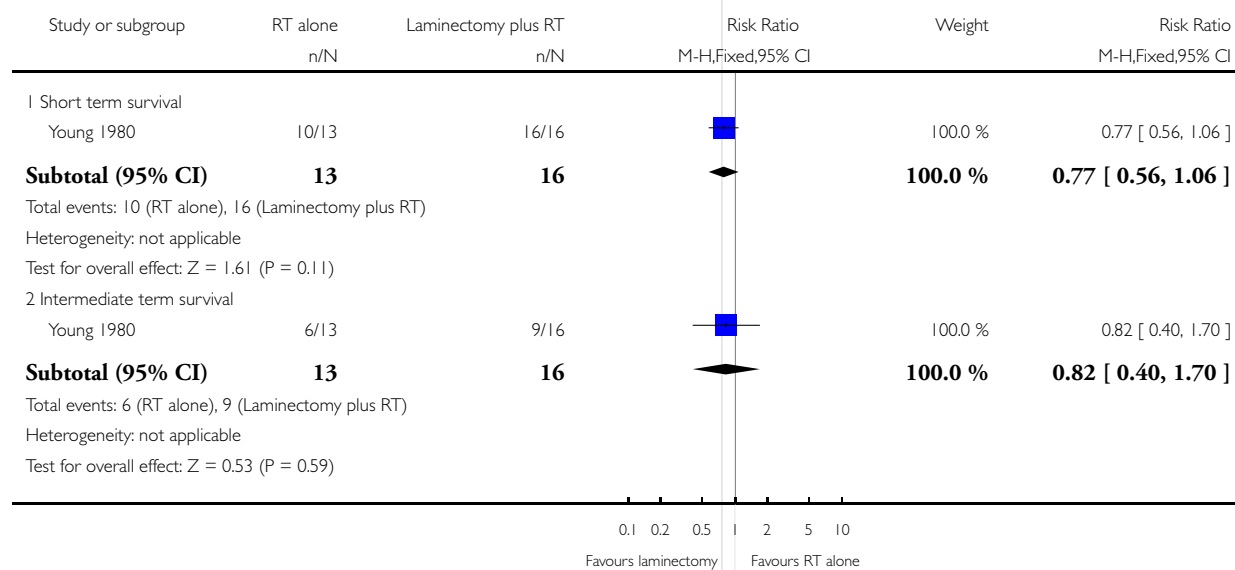


Analysis 2.3. Comparison 2 Laminectomy plus radiotherapy versus radiotherapy alone, Outcome 3 Survival.

Review: Interventions for the treatment of metastatic extradural spinal cord compression in adults

Comparison: 2 Laminectomy plus radiotherapy versus radiotherapy alone

Outcome: 3 Survival

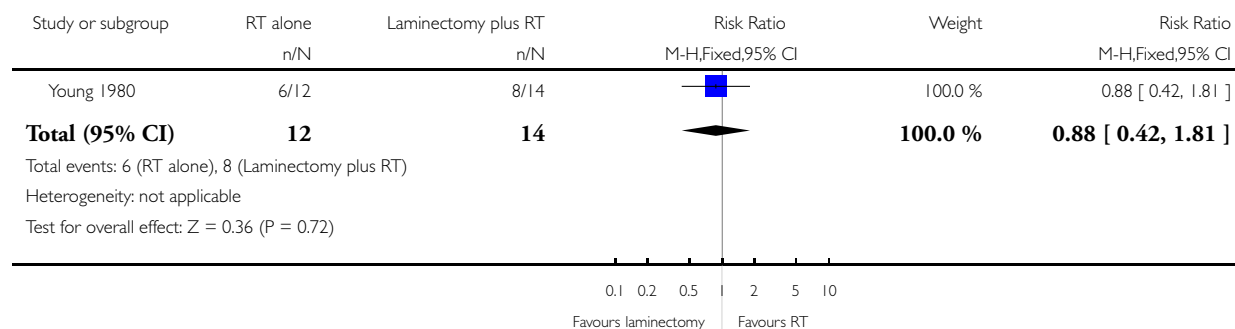


Analysis 2.4. Comparison 2 Laminectomy plus radiotherapy versus radiotherapy alone, Outcome 4 Reduction in analgesic use.

Review: Interventions for the treatment of metastatic extradural spinal cord compression in adults

Comparison: 2 Laminectomy plus radiotherapy versus radiotherapy alone

Outcome: 4 Reduction in analgesic use

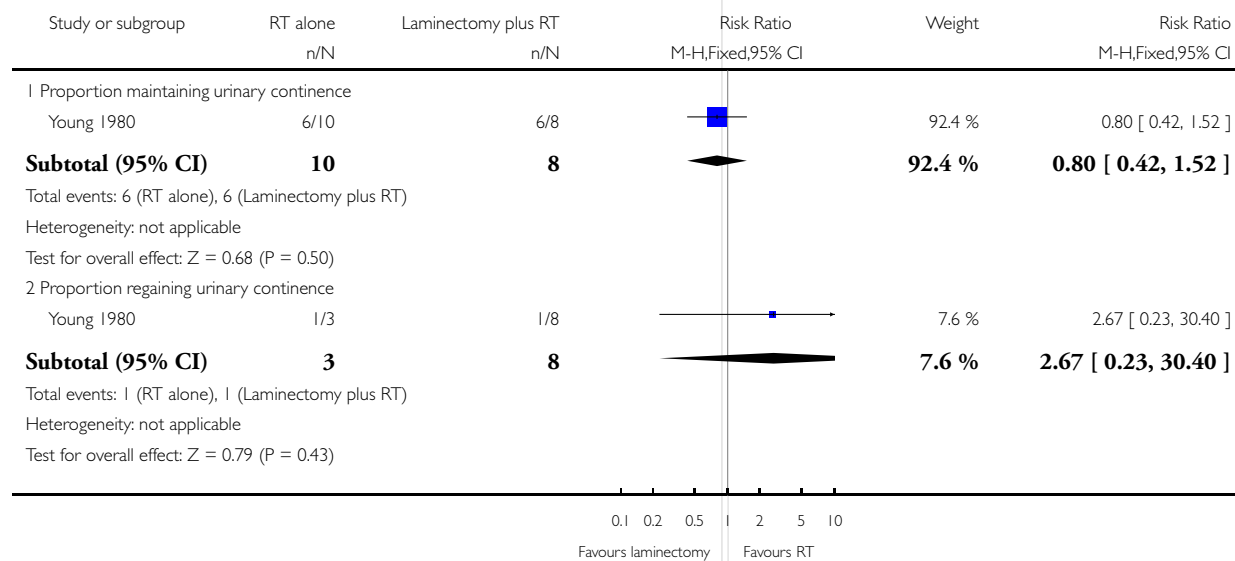


Analysis 2.5. Comparison 2 Laminectomy plus radiotherapy versus radiotherapy alone, Outcome 5 Urinary continence (short term).

Review: Interventions for the treatment of metastatic extradural spinal cord compression in adults

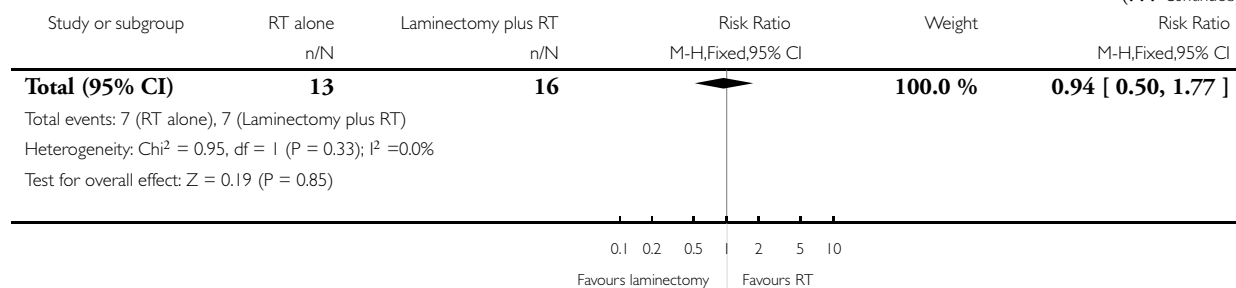
Comparison: 2 Laminectomy plus radiotherapy versus radiotherapy alone

Outcome: 5 Urinary continence (short term)



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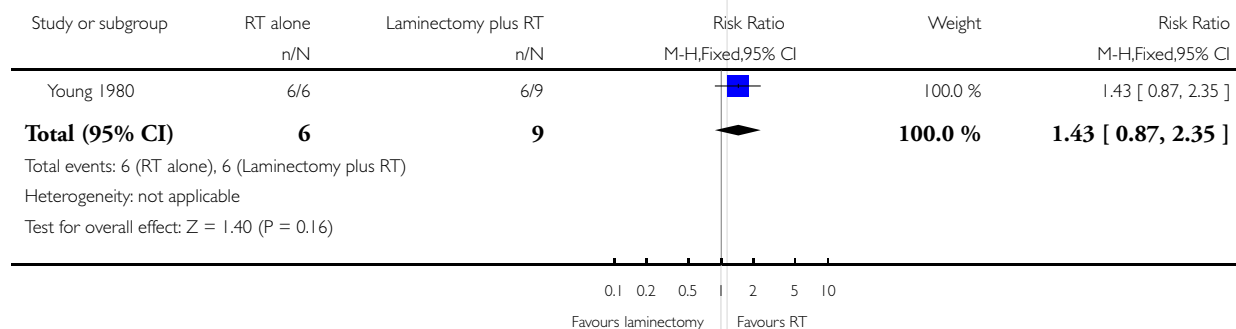


Analysis 2.6. Comparison 2 Laminectomy plus radiotherapy versus radiotherapy alone, Outcome 6 Urinary continence (intermediate term).

Review: Interventions for the treatment of metastatic extradural spinal cord compression in adults

Comparison: 2 Laminectomy plus radiotherapy versus radiotherapy alone

Outcome: 6 Urinary continence (intermediate term)

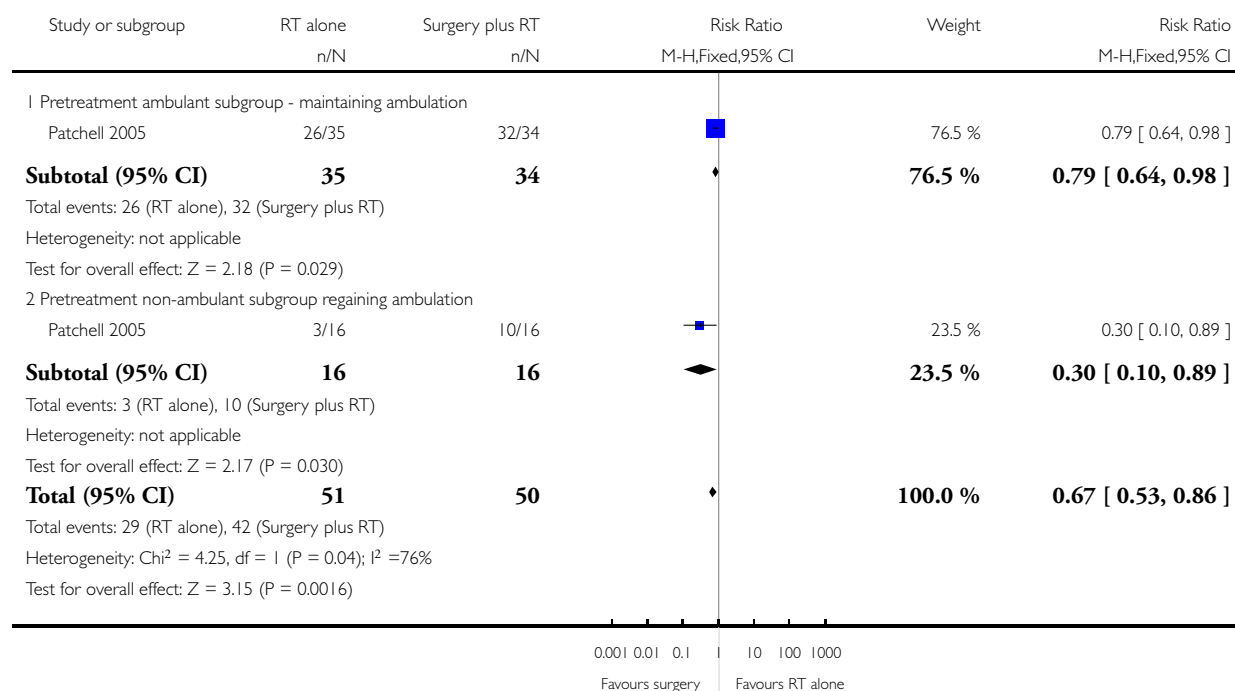


Analysis 3.1. Comparison 3 Decompressive surgery plus radiotherapy versus radiotherapy alone, Outcome 1 Ambulation (short term).

Review: Interventions for the treatment of metastatic extradural spinal cord compression in adults

Comparison: 3 Decompressive surgery plus radiotherapy versus radiotherapy alone

Outcome: 1 Ambulation (short term)

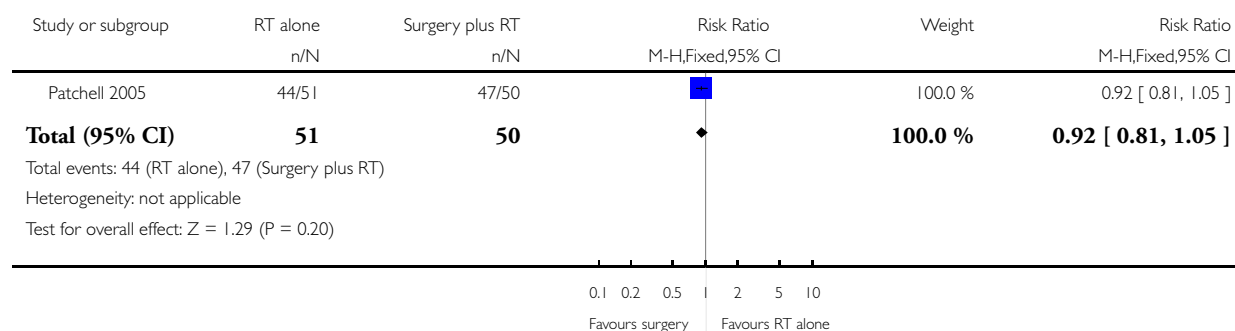


Analysis 3.2. Comparison 3 Decompressive surgery plus radiotherapy versus radiotherapy alone, Outcome 2 Survival (short term).

Review: Interventions for the treatment of metastatic extradural spinal cord compression in adults

Comparison: 3 Decompressive surgery plus radiotherapy versus radiotherapy alone

Outcome: 2 Survival (short term)

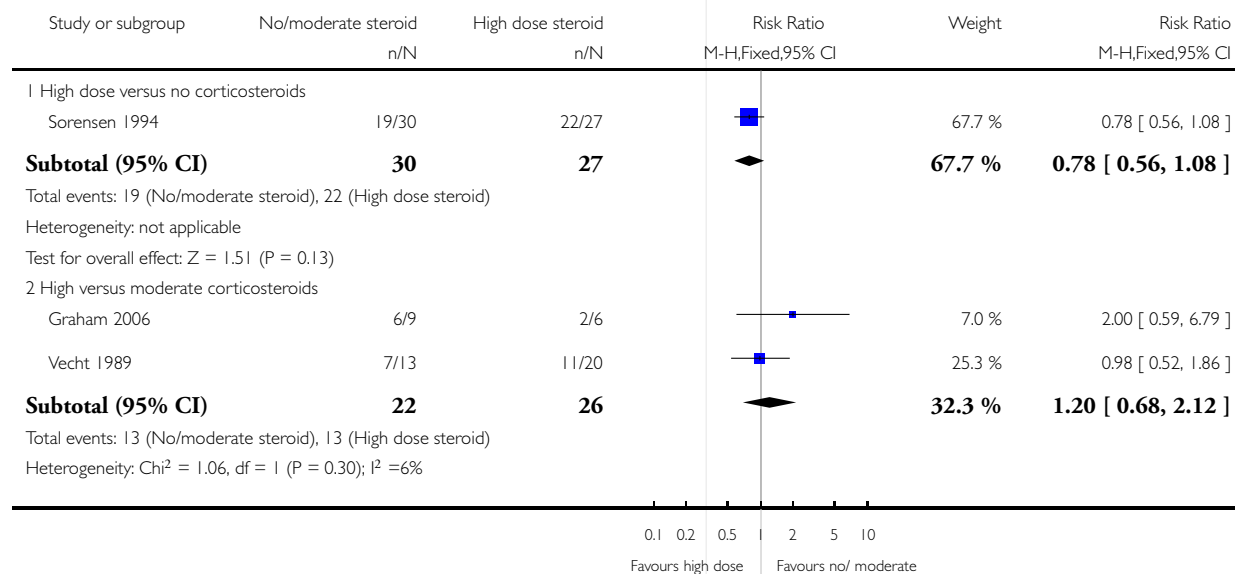


Analysis 4.1. Comparison 4 High dose versus no or moderate dose corticosteroids, Outcome 1 Overall ambulation (short term).

Review: Interventions for the treatment of metastatic extradural spinal cord compression in adults

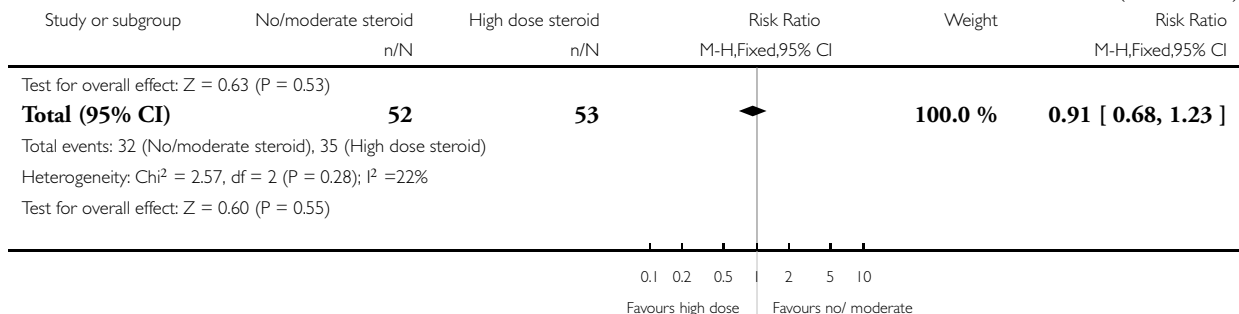
Comparison: 4 High dose versus no or moderate dose corticosteroids

Outcome: 1 Overall ambulation (short term)



(Continued . . .)

(... Continued)

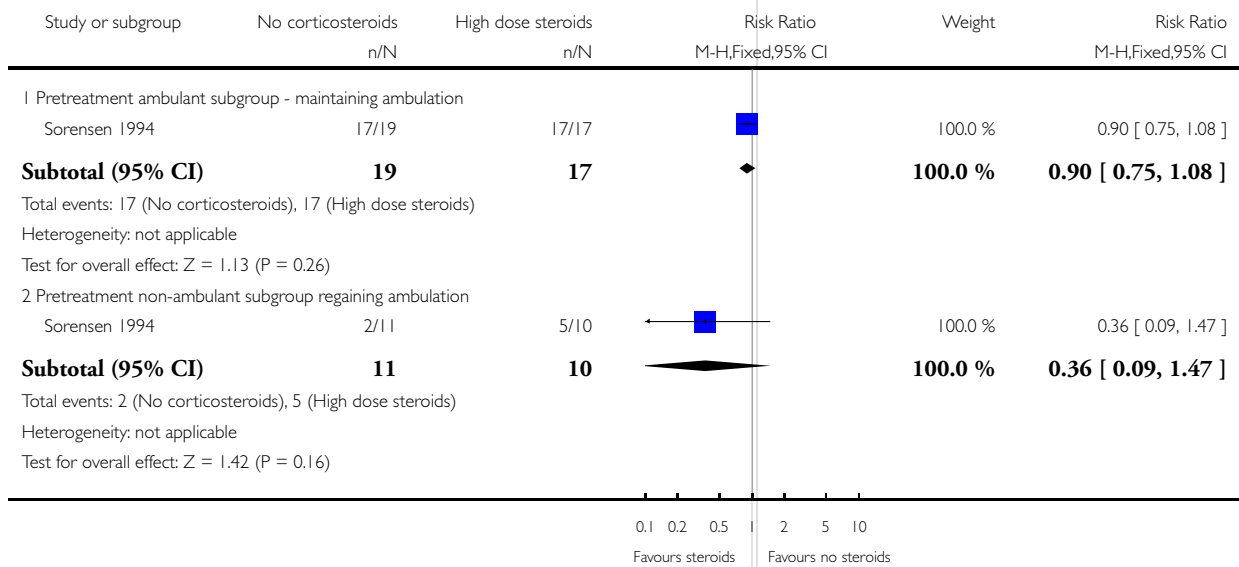


Analysis 4.2. Comparison 4 High dose versus no or moderate dose corticosteroids, Outcome 2 Participants maintaining or regaining ambulation (short term).

Review: Interventions for the treatment of metastatic extradural spinal cord compression in adults

Comparison: 4 High dose versus no or moderate dose corticosteroids

Outcome: 2 Participants maintaining or regaining ambulation (short term)

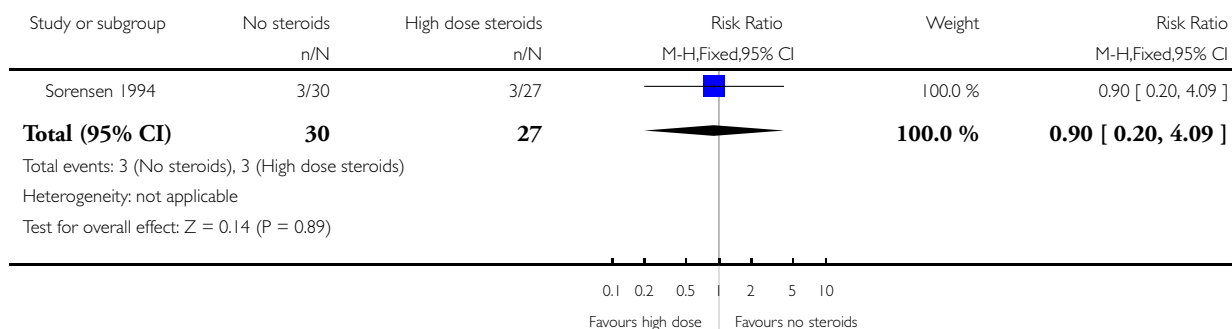


Analysis 4.3. Comparison 4 High dose versus no or moderate dose corticosteroids, Outcome 3 Survival (long term).

Review: Interventions for the treatment of metastatic extradural spinal cord compression in adults

Comparison: 4 High dose versus no or moderate dose corticosteroids

Outcome: 3 Survival (long term)

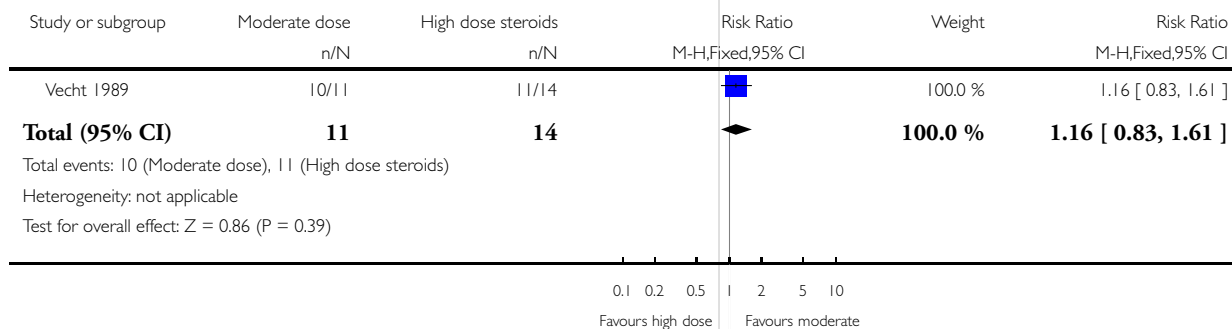


Analysis 4.4. Comparison 4 High dose versus no or moderate dose corticosteroids, Outcome 4 Pain reduction.

Review: Interventions for the treatment of metastatic extradural spinal cord compression in adults

Comparison: 4 High dose versus no or moderate dose corticosteroids

Outcome: 4 Pain reduction

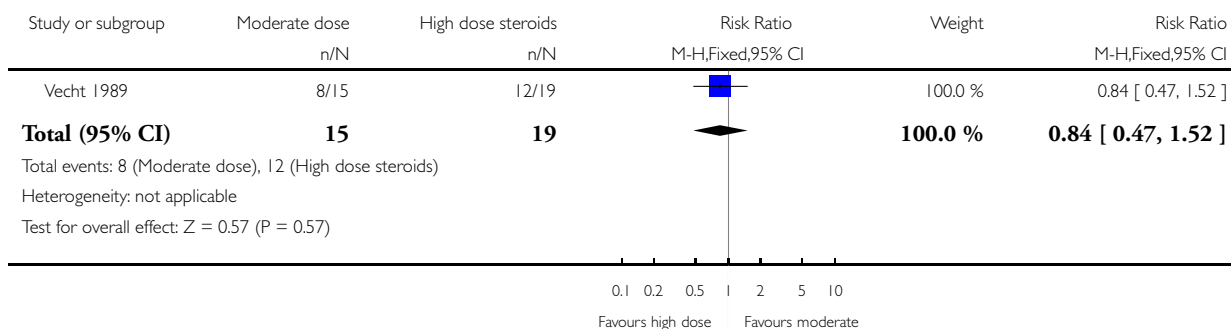


Analysis 4.5. Comparison 4 High dose versus no or moderate dose corticosteroids, Outcome 5 Urinary continence (short term).

Review: Interventions for the treatment of metastatic extradural spinal cord compression in adults

Comparison: 4 High dose versus no or moderate dose corticosteroids

Outcome: 5 Urinary continence (short term)

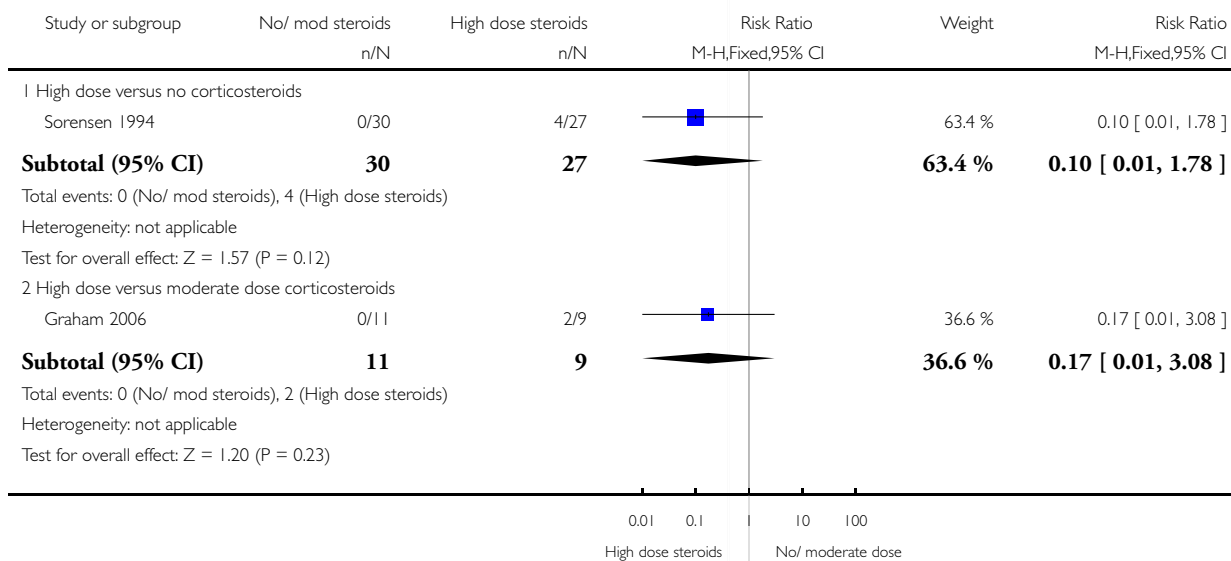


Analysis 4.6. Comparison 4 High dose versus no or moderate dose corticosteroids, Outcome 6 Serious drug related adverse effects.

Review: Interventions for the treatment of metastatic extradural spinal cord compression in adults


Comparison: 4 High dose versus no or moderate dose corticosteroids

Outcome: 6 Serious drug related adverse effects



(Continued . . .)

(. . . Continued)

Study or subgroup	No/ mod steroids	High dose steroids	Risk Ratio		Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI			M-H,Fixed,95% CI
Total (95% CI)	41	36			100.0 %	0.12 [0.02, 0.97]
Total events: 0 (No/ mod steroids), 6 (High dose steroids)						
Heterogeneity: Chi ² = 0.06, df = 1 (P = 0.81); I ² = 0.0%						
Test for overall effect: Z = 1.99 (P = 0.047)						
			0.01	0.1	10	100
			High dose steroids		No/ moderate dose	

APPENDICES

Appendix I. MEDLINE search strategy

1. SPINAL CORD COMPRESSION/
2. SPINAL CORD NEOPLASMS/
3. ((epidural or extradural or extra-dural or "spinal cord" or "dural sac" or "cauda equina" or "spinal column") AND (neoplasm\$ or cancer\$ or tumour\$ or tumor\$ or malignan\$ or metast\$) AND compress\$)
4. (neoplasm\$ or cancer\$ or tumour\$ or tumor\$ or malignan\$ or metast\$).mp. [mp=ti, ot, ab, nm, hw]
5. 1 AND 4
6. 2 OR 3 OR 5
7. RANDOMIZED CONTROLLED TRIAL.pt.
8. CONTROLLED CLINICAL TRIAL.pt.
9. RANDOMIZED CONTROLLED TRIALS.sh.
10. RANDOM ALLOCATION.sh.
11. DOUBLE BLIND METHOD.sh.
12. SINGLE BLIND METHOD.sh.
13. OR/7-12
14. (ANIMALS not HUMANS).sh.
15. 13 NOT 14
16. CLINICAL TRIAL.pt.
17. exp CLINICAL TRIALS/
18. (clin\$ adj25 trial\$).ti,ab.
19. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
20. placebos.sh.
21. placebo\$.ti,ab.
22. random\$.ti,ab.
23. research design.sh.
24. or/16-23
25. 24 not 14
26. 25 not 15
27. 15 or 25
28. 6 AND 27

Appendix 2. Additional search strategies

Database	Search strategy
EMBASE (1980 to July 2008)	<ol style="list-style-type: none"> 1. Spinal Cord Compression/ 2. exp Spinal Cord Tumor/ 3. ((epidural or extradural or extra-dural or "spinal cord" or "dural sac" or "cauda equina" or "spinal column") and (neoplasm\$ or cancer\$ or tumour\$ or tumor\$ or malignan\$ or metast\$) and compress\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 4. or/1-3 5. random\$.ti,ab. 6. factorial\$.ti,ab. 7. (crossover\$ or cross over\$ or cross-over\$).ti,ab. 8. placebo\$.ti,ab. 9. (doubl\$ adj blind\$).ti,ab. 10. (singl\$ adj blind\$).ti,ab. 11. assign\$.ti,ab. 12. allocat\$.ti,ab. 13. volunteer\$.ti,ab. 14. CROSSOVER PROCEDURE.sh. 15. DOUBLE-BLIND PROCEDURE.sh. 16. RANDOMIZED CONTROLLED TRIAL.sh. 17. SINGLE BLIND PROCEDURE.sh. 18. or/5-17 19. ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/ 20. HUMAN/ 21. 20 and 19 22. 19 not 21 23. 18 not 22 24. 4 and 23
CANCERLIT (PubMed cancer subset)	<p>("Spinal Cord Compression" OR "Spinal Cord neoplasm" OR (epidural OR extradural OR extra-dural OR "Spinal cord" OR "dural sac" OR "cauda equina" OR "spinal column") AND (neoplasm* OR Cancer* OR Tumour* OR Tumor* OR malignan* OR metast*) AND compression*)</p> <p>AND</p> <p>(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR random* [tw] NOT (animals [mh]))</p>
LILACS (1992 to April 2007)	<p>(Mh "Spinal Cord Compression" OR Tw"Spinal Cord neoplasm\$" OR (Tw epidural OR Tw extradural OR Tw extra-dural OR " Tw Spinal cord" OR " Tw dural sac" OR " Tw cauda equina" OR " Tw spinal column") AND (Tw neoplasm\$ OR Tw Cancer\$ OR Tw Tumour\$ OR Tw Tumor\$ OR Tw</p>

(Continued)

	<p>Malignan\$ OR Tw metast\$) AND Tw compression\$) [Words] and (Pt ENSAIO CONTROLADO ALEATORIO Or Pt ENSAIO CLINICO CONTROLADO OR Pt ENSAIO CLÍNICO OR Mh ENSAIOS CONTROLADOS ALEATORIOS Or Mh DISTRIBUICAO ALEATORIA Or Mh MÉTODO DUPLO-CEGO Or Mh MÉTODO SIMPLES-CEGO OR Ex E05.318.760.535\$ OR Mh PLACEBOS OR Mh RESEARCH DESIGN) AND NOT (Ct ANIMAL AND NOT (Ct HUMAN and Ct ANIMAL)) OR ((Tw clin\$ AND (Tw trial\$ OR Tw ensa\$ OR Tw estud\$ OR Tw experim\$ OR Tw investiga\$)) or ((Tw random\$ OR Tw randon\$ OR Tw casual\$ OR Tw acaso\$ OR Tw azar OR Tw aleator\$) and (Tw singl\$ OR Tw simple\$ OR Tw doubl\$ OR Tw doble\$ OR Tw duplo\$ OR Tw trebl\$ OR Tw trip\$) and (Tw blind\$ OR Tw cego\$ OR Tw ciego\$ OR Tw mask\$ OR Tw mascar\$)) OR Tw placebo\$ OR (Tw random\$ OR Tw randon\$ OR Tw casual\$ OR Tw acaso\$ OR Tw azar OR Tw aleator\$)) AND NOT (Pt ENSAIO CONTROLADO ALEATORIO Or Pt ENSAIO CLINICO CONTROLADO OR Pt ENSAIO CLÍNICO OR Mh ENSAIOS CONTROLADOS ALEATORIOS Or Mh DISTRIBUICAO ALEATORIA Or Mh MÉTODO DUPLO-CEGO Or Mh MÉTODO SIMPLES-CEGO OR Ex E05.318.760.535\$ OR Mh PLACEBOS OR Mh RESEARCH DESIGN) AND NOT (Ct ANIMAL AND NOT (Ct HUMAN and Ct ANIMAL)) OR ((Ct COMPARATIVE STUDY or Ex E05.337\$ or Mh FOLLOW-UP STUDIES or Mh PROSPECTIVE STUDIES or Tw control\$ OR Tw prospectiv\$ OR Tw volunt\$ OR Tw vol-unteer\$) and not (Ct ANIMAL AND NOT (Ct HUMAN and Ct ANIMAL)) and not (Pt ENSAIO CONTROLADO ALEATORIO Or Pt ENSAIO CLINICO CONTROLADO Or Mh ENSAIOS CONTROLADOS ALEATORIOS Or Mh DISTRIBUICAO ALEATORIA Or Mh MÉTODO DUPLO-CEGO Or Mh MÉTODO SIMPLES-CEGO) OR ((Pt ENSAIO CLÍNICO or Ex E05.318.760.535\$ or (Tw clin\$ AND (Tw trial\$ OR Tw ensa\$ OR Tw estud\$ OR Tw experim\$ OR Tw investiga\$)) OR ((Tw random\$ OR Tw randon\$ OR Tw casual\$ OR Tw acaso\$ OR Tw azar OR Tw aleator\$) and (Tw singl\$ OR Tw simple\$ OR Tw doubl\$ OR Tw doble\$ OR Tw duplo\$ OR Tw trebl\$ OR Tw trip\$) and (Tw blind\$ OR Tw cego\$ OR Tw ciego\$ OR Tw mask\$ OR Tw mascar\$)) or Mh PLACEBOS or Tw placebo\$ or (Tw random\$ OR Tw randon\$ OR Tw casual\$ OR Tw acaso\$ OR Tw azar OR Tw aleator\$) or Mh RESEARCH DESIGN)) and not ((Pt ENSAIO CONTROLADO ALEATORIO Or Pt ENSAIO CLINICO CONTROLADO Or Mh ENSAIOS CONTROLADOS ALEATORIOS Or Mh DISTRIBUICAO ALEATORIA Or Mh MÉTODO DUPLO-CEGO Or Mh MÉTODO SIMPLES-CEGO)) and not (Ct ANIMAL AND NOT (Ct HUMAN and Ct ANIMAL))) [Words]</p>
CINAHL (1982 to July 2008)	<ol style="list-style-type: none">1. spinal cord compression/ or spinal cord neoplasms/2. ((epidural or extradural or extra-dural or “spinal cord” or “dural sac” or “cauda equina” or “spinal column”) and (neoplasm\$ or cancer\$ or tumour\$ or tumor\$ or malignan\$ or metast\$) and compress\$).mp. [mp=title, subject heading word, abstract, instrumentation]3. or/1-24. Random Assignment/5. single-blind studies/

(Continued)

	<ol style="list-style-type: none">6. Double-Blind Studies/7. Triple-Blind Studies/8. Crossover Design/9. Factorial Design/10. (multicentre study or multicenter study or multi-centre study or multi-center study).mp. [mp=title, subject heading word, abstract, instrumentation]11. random\$.ti,ab.12. latin square.ti,ab.13. cross-over.mp. or crossover.ti,ab. [mp=title, subject heading word, abstract, instrumentation]14. Placebos/15. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.16. placebo\$.mp. [mp=title, subject heading word, abstract, instrumentation]17. Clinical Trials/18. (clin\$ adj25 trial\$).mp. [mp=title, subject heading word, abstract, instrumentation]19. or/4-1820. 3 and 19
CENTRAL (Issue 3, 2008 of <i>The Cochrane Library</i>)	<p>#1 "Spinal Cord Compression" (single term MeSH) #2 "Spinal Cord Neoplasms" (single term MeSH) #3 ((epidural OR extradural OR extra-dural OR "spinal cord" OR "dural sac" OR "cauda equina" OR "spinal column") AND (neoplasm* OR cancer* OR tumour* OR tumor* OR malignan* OR metast*)) AND compress*) #4 #1 OR #2 OR #3</p>

WHAT'S NEW

Last assessed as up-to-date: 6 August 2008.

9 November 2009	Amended	Contact details updated.
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HISTORY

Protocol first published: Issue 3, 2007

Review first published: Issue 4, 2008

CONTRIBUTIONS OF AUTHORS

Conceived review - RG, JJ

Devised search strategy - JJ, RG, RKG in collaboration with Sylvia Bickley

Wrote protocol - RG, JJ, PT

Reviewed protocol - ML, AGC

Assessed and selected trials - JJ, RG

Obtained reports - RKG, RG

Literature search - RKG, RG, JJ

Assessed quality - RKG, JJ, RG

Extracted data - JJ, RG, RKG, ML

Analyzed and interpreted data - JJ, RG, RKG, PT

Wrote review - RG, JJ, RKG, AGC, PT

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Christian Medical College, Vellore, India.
- South Asian Cochrane Network, India.

External sources

- Cairdeas International Palliative Care Trust, Aberdeen, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

*Decompression, Surgical; Adrenal Cortex Hormones [*therapeutic use]; Laminectomy; Radiotherapy; Randomized Controlled Trials as Topic; Spinal Cord Compression [etiology; *therapy]; Spinal Neoplasms [secondary; *therapy]; Walking

MeSH check words

Adult; Humans