

Metastatic Spinal Cord Compression:

diagnosis and management of adults at risk of
and with metastatic spinal cord compression

Evidence Review

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Developed for NICE by the National Collaborating Centre for Cancer

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Chapter 2 - Service Configuration and Urgency of Treatment

2.2 MSCC co-ordinator and senior professional advice (SPA) - role and responsibilities

What is the most effective way of delivering care and co-ordinating services for patients with MSCC or suspected MSCC?

No evidence about the effectiveness of MDTs for MSCC patients exists. Other NICE service guidance provides a background and evidence about the effectiveness of MDTs in different settings. These include NICE Service Guidance on: Breast Cancer (2002); Colorectal cancer; Sarcoma (2006); Brain and other CNS tumours (2006) and Skin tumours including melanoma (2006). The NICE Supportive and Palliative Care guidance (2004) provides a general overview. Other evidence based guidelines have been identified as relevant and graded as moderate to high quality using the AGREE Tool. These guidelines include: West of Scotland Guidelines for Malignant Spinal Cord Compression produced (2007) and the SIGN Guidelines : Management with Stroke (2002): Specialised Units.

The guideline produced by the West of Scotland lacked the systematic approach promoted by the AGREE instrument (for guideline appraisal) but it is very practical and easily understood. It clearly explains that it has been developed with the support of clinical experts and that it is not truly evidence based. Some evidence is presented throughout, although it has not been systematically searched or appraised. SIGN guidelines are rated highly using the AGREE instrument.

A study by Lee *et al.* (2007) reported improvements in the quality of care for metastatic spinal cord compression over 6 months by ensuring that >90% of patients receive definitive treatment within 24 hours of radiological diagnosis. Interventions evaluated were derived from a process that identified gaps and delays in current practices and clinical pathways used for the acute management of patients presenting with MSCC. The interventions were then fed into a revised clinical pathway for patients to be managed. The study was affected by substantial bias but reported that the mean overall response time to start corticosteroids was statistically significantly reduced from baseline. The mean overall response time to start radiation or surgical therapy was not statistically significantly reduced. The mean overall response time to length of stay was statistically significantly reduced and the mean overall hospitalisation costs were reduced but it was not statistically significant.

References

Lee, K., Tsou, I., Wong, S., Yu, C., Ming, Z., Loh, Y., Shakespeare, T., Mukherjee, R. & Back, M. (2007) Metastatic spinal cord compression as an oncology emergency getting our act together. *International Journal for Quality in Health Care*, 19: 377-381

SIGN 64 Management with Stroke (2002): Specialised Units – for stroke patients were effective. <http://www.sign.ac.uk/pdf/sign64.pdf>

West of Scotland Malignant Spinal Cord Compression Guidelines (2007). Development Working Group on behalf of the West of Scotland Cancer Network.

Evidence Tables

<p>Lee, K., Tsou, I., Wong, S., Yu, C., Ming, Z., Loh, Y., Shakespeare, T., Mukherjee, R. & Back, M. (2007) Metastatic spinal cord compression as an oncology emergency getting our act together. <i>International Journal for Quality in Health Care</i>, 19: 377-381</p>
<p>Design: Before and After study - observational 2- Country: Singapore</p> <p>Aim: To improve the quality of care for metastatic spinal cord compression over 6 months by ensuring that >90% of patients receive definitive treatment within 24 hours of radiological diagnosis.</p>
<p>Inclusion criteria MSCC patients presenting to the Centre.</p>
<p>Exclusion criteria Not reported</p>
<p>Population 22 patients who presented with MSCC from July 2004 to May 2005 were managed using the revised clinical pathway and treatment protocol.</p> <p>A group of patients who were managed using current practices and clinical pathways n=17, were used as the comparative baseline measurement.</p>
<p>Interventions Interventions were derived from a process that identified gaps and delays in current practices and clinical pathways used for the acute management of patients presenting with MSCC. The interventions were then fed into a revised clinical pathway for patients to be managed. Interventions included:</p> <ol style="list-style-type: none">1. setting up a multidisciplinary acute cord crisis team,2. expediting the multidisciplinary reporting and referring processes3. formulating a standardised treatment protocol for the acute management of MSCC patients. <p>The main treatment modalities included: initial steroidal therapy and definitive (urgent) radiotherapy or surgery to be started within 24 h of diagnosis. The use of a validated surgical scoring instrument was introduced in the protocol for instant preoperative assessment of all patients to facilitate urgent surgical decisions.</p>
<p>Outcomes Individual patient parameters were recorded and tracked as before and compared with the baseline data set. The Mann–Whitney U-test was used to evaluate the median values for response time to start of steroids and radiotherapy or surgery, length of stay and hospital bill between the two cohorts of patients presenting before and after interventions were implemented.</p>
<p>Results The mean overall response time to start steroidal was statistically significantly reduced: From baseline 8.4 to 2.6 days (p<0,03)</p> <p>The mean overall response time to start radiation or surgical therapy was not statistically significantly reduced: from 9.9 to 3.9 days (p<0.223)</p>

The mean overall response time to length of stay was statistically significantly reduced:
From 23.8 to 14.7 days ($p < 0.036$)

The mean overall hospitalisation costs was reduced but it was not statistically significant:
From 13,723 to 8808 Singapore \$ ($p < 0.081$)

General comments

The limits of this study include the low number of patients involved, limited outcome measures and the lack of a multivariate analysis that could have been used to predict which factors affected an outcome, for example, the impact of neurological status on length of stay or use of rehabilitative services on hospitalisation costs or place of referral on time to start radiation or surgical therapy. The authors used surrogate measures such as length of stay and hospitalisation costs to indicate the severity of disease and care required which also bring uncertainty to the findings.

West of Scotland Malignant Spinal Cord Compression Guidelines.
Produced by West of Scotland Malignant Spinal Cord Compression Guidelines
Development Working Group on behalf of the West of Scotland Cancer Network.
2007

Design: Clinical Practice Guideline

Country: Scotland

Setting: National Health System

Population

MSCC patients

General comments –

The strengths and weakness of the guideline are described below using the AGREE tool to appraise the guideline.

*The AGREE tool identified the following areas that were **strong** for this guideline:*

1. The overall objectives of the guideline are specifically described.
2. The patients to whom the guideline is meant to apply are specifically described.
3. The guideline development group includes individuals from all the relevant professional groups.
4. The health benefits, side effects and risks are considered in formulating the recommendations.
5. The different options for diagnosis and/or treatment of the condition are clearly presented.
6. Key recommendations are easily identifiable.
7. The guideline is editorially independent from the funding body.

*The AGREE tool identified the following areas that were **weak** for this guideline:*

1. The clinical questions covered by the guideline are not specifically described.
2. The patients' views and preferences have been sought
3. The target users of the guideline are clearly defined.
4. The guideline was not piloted among target users.
5. Systematic methods are used to search for evidence.
6. The criteria for selecting the evidence are clearly described.
7. The methods used for formulating the recommendations are clearly described.
8. There is not an explicit link between the recommendations and the supporting evidence.
9. The guideline is externally reviewed by experts prior to publication.
10. The recommendations are specific and unambiguous.
11. A procedure for updating the guideline was not provided.
12. The guideline was not supported with tools for application.
13. The potential organisational barriers in applying the recommendations were not discussed.
14. The potential cost implications of applying the recommendations were not considered.
15. The guideline does not present key review criteria for monitoring and/or audit purposes.
16. Conflicts of interest of guideline development members were not recorded.

Although this guideline lacked the systematic approach promoted by the AGREE instrument (for guideline appraisal) it did provide a very practical and easily understood guideline. The West of Scotland guideline does not purport to be an evidence based

guideline, it clearly explains that it has been developed with the support of clinical experts. Some evidence is presented throughout the guideline, although it has not been systematically searched or appraised.

SIGN Guidelines:

Management with Stroke (2002) SIGN 64: Specialised Units – for stroke patients were effective. <http://www.sign.ac.uk/pdf/sign64.pdf>

Design: Clinical Practice Guideline

Country: Scotland

Setting: National Health System

General comments –

The strengths and weakness of SIGN guidelines (in general) are described below using the AGREE instrument to appraise the guideline.

*The AGREE tool identified the following areas that were **strong** for this guideline:*

1. The overall objectives of the guideline are specifically described.
2. The patients to whom the guideline is meant to apply are specifically described.
3. The guideline development group includes individuals from all the relevant professional groups.
4. The patients' views and preferences have been sought
5. The target users of the guideline are clearly defined.
6. Systematic methods are used to search for evidence.
7. The health benefits, side effects and risks are considered in formulating the recommendations
8. There is an explicit link between the recommendations and the supporting evidence
9. The guideline is externally reviewed by experts prior to publication
10. A procedure for updating the guideline was not provided
11. The recommendations are specific and unambiguous.
12. The different options for diagnosis and/or treatment of the condition are clearly presented.
13. The potential cost implications of applying the recommendations were considered
14. The guideline was supported with tools for application
15. The guideline is editorially independent from the funding body.
16. Conflicts of interest of guideline development members were not recorded.

*The AGREE tool identified the following areas that were **weak** for this guideline:*

1. The clinical questions are not covered by the guideline are not specifically described.
2. The guideline was not piloted among target users.
3. The criteria for selecting the evidence are not clearly described.
4. The methods used for formulating the recommendations are not clearly described.
5. Key recommendations are not easily identifiable.
6. The potential organisational barriers in applying the recommendations were not discussed.
7. The guideline does not present key review criteria for monitoring and/or audit purposes.

The guidelines developed by the SIGN are comprehensive evidence based documents. In general they lack some details as outlined above which would bring the guidelines up to a very high standard.

Chapter 3 - The Patient's Experience of MSCC

3.1 Introduction Supporting Patient Decisions

How effective are decision aids for patients with MSCC facing treatment decisions?

There is no evidence that involves patients with MSCC. However, the evidence that does exist provides a substantial platform for considering the use of decision aids in the healthcare and management of patients with MSCC (Estabrooks *et al.* 2001; Molenaar *et al.* 2000; O'Brien *et al.* 2002; O'Connor *et al.* 2003).

3.2 Emotional and family support

What is the most effective emotional and family support interventions for patients with MSCC?

The following NICE Guidelines addressed emotional and family support issues and cross reference to the following guidelines is required: NICE guideline CG23 Depression (2004, amended April 2007) and NICE Guideline Supportive And Palliative Care: The Manual (2004): Chapter 5: Psychological Support Service; Chapter 6: Social Support Services ; Chapter 10: Rehabilitation Services.

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Chapter 4 – Early Detection

4.3 Early Symptoms and Signs

In patients with cancer at risk of developing spinal cord compression, what symptoms and signs give early indications that malignant SCC is developing?

Short Summary

Overall the evidence available was of low quality. A systematic review (Loblaw *et al.* 2005) reported that symptoms for MSCC can include sensory changes, autonomic dysfunction, and back pain; however, because of the common incidence of back pain (those with and without MSCC) it was not predictive of MSCC. This review also reported that patients at high risk for MSCC (i.e. patients with known myeloma, breast, prostate, or kidney cancer) should be followed more actively and educated about the symptoms of MSCC, and impending cord compression. One study (Talcott *et al.* 1999) included in this systematic review, reported predictive risk factors for MSCC; these included: inability to walk, increased deep tendon reflexes, compression fractures on radiographs of spine, bone metastases present, bone metastases diagnosed more than 1 year earlier, and age less than 60 years. This study (Talcott *et al.* 1999) concluded that patients with none of the six risk factors had a 4% risk of MSCC compared with an 87% risk of MSCC in patients with five or more risk factors. Back pain failed to differentiate between patients with MSCC and patients without MSCC. Lu *et al.* (2005) determined independent clinical predictors (or potential risk factors) of MSCC, by using data from a cohort of cancer patients with suspected MSCC who underwent spine MRI. Four independent predictors of thecal sac compression (TSC) were identified and included: abnormal neurologic examination, middle or upper back pain, known vertebral metastases, metastatic disease at initial diagnosis. These predictors stratified patients experiencing episodes into subgroups with varying risks of TSC, ranging from 8% (no risk factors) to 81% (three or four risk factors).

The evidence confirms that the evaluation of cancer patients with suspected MSCC should be based upon clinical information that includes cancer-related history, symptom data, and the presence of pertinent neurologic signs.

PICO

Population Group	FACTORS (symptoms and signs)	Outcomes
patients with known diagnosis of cancer	<ul style="list-style-type: none"> ▪ Spinal pain ▪ Back pain ▪ Referred pain ▪ Radicular pain ▪ Radicular pain including valsalva manoeuvre (e.g. coughing, sneezing) exacerbations" ▪ Sensory symptoms/signs (including the Lhermitte sign) ▪ Motor symptoms/signs ▪ Sphincter involvement – incontinence ▪ Sudden paraparesis 	Quantify the predictive value (specificity / sensitivity) of the factors in determining that SCC is developing

	/paraplegia	
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This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary:

<p>Sensory Changes, Autonomic Dysfunction and Back Pain</p>				
<p>Loblaw <i>et al.</i> 2005 13 included studies reported factors associated with higher risks of symptomatic or sub-clinical MSCC.</p> <p>From included study six predictive risk factors for MSCC including :</p> <ul style="list-style-type: none"> • the inability to walk, • increased deep tendon reflexes, • compression fractures on radiographs of spine, • bone metastases present, • bone metastases diagnosed more than 1 year earlier, • age less than 60 years. <p>Authors concluded that patients with none of the six risk factors had a 4% risk of MSCC compared with an 87% risk of</p>	<p>Spinazze <i>et al.</i> 2005 This systematic review provided a narrative description of symptoms and risk factors but were not quantified.</p> <ul style="list-style-type: none"> • Progressive pain occurs frequently in patients with ESCC (epidural spinal cord compression). • Back pain at the level of the epidural metastasis can be followed by radicular pain. • Back pain may be elicited or worsened by vertebral compression, movement (especially flexion), or Valsalva manoeuvre. • The pain related to epidural metastases is exaggerated by lying down. • Radicular pain, associated with nerve root compression, gives an indication of the localisation of the lesion and it may radiate unilaterally or bilaterally to upper or lower limbs (in cervical or lumbar 	<p>Lu <i>et al.</i> 2005 Independent clinical predictors (or potential risk factors) of MSCC, were calculated</p> <p>4 independent predictors of thecal sac compression (TSC) were identified and included</p> <ol style="list-style-type: none"> 1. abnormal neurologic examination, 2. middle or upper back pain, 3. known vertebral metastases 4. metastatic disease at initial diagnosis <p>When patients were put into subgroups with varying risks of TSC, the study reported that 8% of patients had no risk factors to 81% of patients with three or four risk factors.</p>	<p>Harrison <i>et al.</i> 1985 The correlation of specific symptoms and signs with epidural spinal cord compression was reported.</p> <p>Breast cancer patients with suspected SCC who underwent myelography were included and the clinical features: absence of known - metastatic cancer, known bone or vertebral metastases, back pain, paresthesias, bowel or bladder dysfunction, and positive bone scan, positive spine radiograph) were shown to have a significantly association with a positive myelogram for SCC.</p>	<p>Rodichok <i>et al.</i> 1986 This study explored the feasibility of avoiding myelography in certain groups of patients by designing radiation therapy on the basis of clinical symptoms and the results of plain radiographs.</p> <p>Clinical recognition of radiculopathy was valuable in that it correlated with epidural disease in a larger proportion of patients (63%) than in those with local back pain only (44%).</p> <ul style="list-style-type: none"> • No additional clinical symptoms or signs were identified that would further enhanced the diagnostic yield. • No oncologic features were analysed, and the authors concluded that the majority of patients with cancer and back pain should undergo myelography.

<p>MSCC in patients with six or more risk factors.</p> <p>Back pain failed to differentiate between patients with MSCC and patients without MSCC.</p>	<p>lesions) or bilaterally around the chest or upper abdomen (in thoracic cord lesions). At the stage of radicular pain, depression of tendon reflexes, weakness and sensory changes may be found in the territory corresponding to the roots injured by epidural seeds.</p> <ul style="list-style-type: none"> • Referred pain could give a false localising sign. • Weakness is the second most common symptom, which develops in approximately 80% of patients. • Symptoms and signs of spinal cord dysfunction such as weakness, sensory disturbances, and bowel and bladder disorders, typically follow the pain. • The weakness can progress to paraplegia. • Sensory disturbances are present in 50% of patients at diagnosis • Paraparesis in the legs is also commonly reported. 			
<p>Lhermitte’s sign, Gait, Sphincter disturbances</p>				

Spinazze et al 2005

Lhermitte's sign, has occasionally been reported in patients with epidural metastases. Worsening of pre-existing stable bone pain, worsening of pain with Valsalva or recumbency, radicular-type pain and Lhermitte's sign should be regarded as warnings of epidural involvement at risk of ESCC.

Sphincter dysfunction (eg. impotence, urinary/faecal incontinence or retention with lumbar spinal compression,

Horner's syndrome with cervical or upper thoracic compression) occur late in 60% of patients and are associated with a poor prognosis.

Gait difficulties may also be caused by sensory ataxia presumably due to

posterior
column
compression.

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Evidence Tables

Systematic Reviews

REFERENCE	<p>Malignant Extradural Spinal Cord Compression: Diagnosis and Management D.A. Loblaw, N. Laperriere, J. Perry, A. Chambers, Cancer care Ontario Guidelines January 2004</p> <p>Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. Loblaw, D.A.; Perry, J.; Chambers, A.; Laperriere, N.J. Journal of Clinical Oncology 2005; 23: 9: 2028-2037</p>
Study design	Evidence-Based Clinical Guidelines / Systematic Review
Grade	2- (this is an overall representation of the level of evidence included for this question, because it is a review that included study designs that were not RCTs we normally would grade it down to a 4. The 2- gives you a better sense of the level of evidence included)
Setting/ Country	International evidence used
Objectives	<p>What are the clinical symptoms of malignant spinal cord compression (MSCC)?</p> <p>Inclusion Criteria : Observational and analytical studies investigating patients at risk for MSCC</p>
Patients (inclusions/exclusions)	<p>Target Population This evidence summary applies to adult patients with a <u>suspected or confirmed diagnosis of extradural malignant spinal cord compression.</u></p> <p>Patients with intramedullary or leptomeningeal cord compression are not considered in this report.</p> <p>Exclusion Criteria (for evidence included)</p> <ol style="list-style-type: none"> 1. Letters and editorials were not considered. 2. Papers published in a language other than English were not considered. 3. Papers describing a paediatric population were not considered, because the types of tumours that affect children differ from adults 4. Papers describing the majority of patients with intramedullary or leptomeningeal cord compression were not considered.
Interventions/ Comparisons/ Factors of interest	<ul style="list-style-type: none"> ▪ Spinal pain ▪ Back pain ▪ Referred pain ▪ Radicular pain ▪ Radicular pain including valsalva manoeuvre (e.g. coughing, sneezing) exacerbations" ▪ Sensory symptoms/signs (including the Lhermitte sign) ▪ Motor symptoms/signs ▪ Sphincter involvement – incontinence ▪ Sudden paraparesis /paraplegia
Outcomes	<ul style="list-style-type: none"> • Occurrence • Risk factors • Symptoms
Results	Thirteen studies were identified that reported the clinical symptoms of

MSCC (Helweg-Larsen 1994, Husband 98, Levack 2002, Mitera 2003, Rades 2002, Bayley et al 2001, Loblaw et al 1999, Loblaw et al 2000, Gilbert et al 1978, Bach et al 1990, Talcott et al 1999, Loblaw (abstract only) 2003).

A retrospective study of MSCC reported the cumulative incidence of MSCC varied widely by primary cancer site (Loblaw 1999). Patients in this study with myeloma, breast, prostate, or kidney cancer have the highest risk of developing cord compression in Ontario

A prospective study by Helweg-Larsen and Sorensen 1994 identified common symptoms of MSCC in 153 patients.

- Back pain was the most common complaint among all patients (88%).
- Patients with tumours localized in the lumbo-sacral area were more likely to report radicular pain (91%) than patients with tumours localized in the thoracic region (69%, $p=0.005$).
- Also motor weakness, sensory changes, and bladder dysfunction as frequent symptoms of patients with MSCC.

Bach 1990 and Gilbert 1978 reported a similar pattern of symptoms (back pain, weakness, bladder dysfunction, and sensory changes) at patient presentation.

From Talcott *et al* (1999), a predictive model, reported predictive risk factors for MSCC, these included: inability to walk, increased deep tendon reflexes, compression fractures on radiographs of spine, bone metastases present, bone metastases diagnosed more than 1 year earlier, and age less than 60 years. This study concluded that patients with none of the six risk factors had a 4% risk of MSCC compared with an 87% risk of MSCC in patients with five or more risk factors. Back pain failed to differentiate between patients with MSCC and patients without MSCC.

Using likelihood ratios calculated from Talcott's data (Talcott 1999), the histology-specific incidence data from a population-based study (Loblaw 1999) and Bayesian methodology, Loblaw (2000) estimated the lifetime incidence of MSCC for different groups of asymptomatic patients (i.e. no neurological symptoms) in Ontario according to their primary tumour site. The estimated lifetime risk of MSCC was 0.048% for asymptomatic patients with the following primary tumours: ovary, stomach, leukaemia, and pancreas, and the estimated lifetime risk of MSCC was 19.3% for asymptomatic patients with the following primary tumours: prostate, female breast, myeloma, and kidney.

Bayley *et al.* (2001) examined predictive factors of sub-clinical spinal cord compression, (i.e., cord compression or thecal sac indentation without neurologic abnormalities) in patients with metastatic prostate carcinoma. The study examined several potential predictors of MSCC including: presence of back pain, alkaline phosphatase levels, haemoglobin concentration, use of narcotic analgesics, bone scan extent of disease (EOD) score, and the duration of hormonal therapy prior to entering the study. From a univariate logistic regression: three predictors were significant: EOD score, duration of hormonal therapy, and haemoglobin concentration. From a multivariate logistic regression analysis, the EOD score and duration of hormonal therapy were predictive of sub-clinical cord compression ($p=0.02$ and $p=0.04$, respectively). Patients with extensive bone scan disease (>20 metastases) had a 32% risk of MSCC prior to

	<p>starting hormone therapy, and they were at a 44% risk of MSCC after 24 months of hormone therapy.</p> <p>Loblaw <i>et al.</i> [abstract] 2003 published an abstract of a retrospective review of 775 patients with 914 episodes of MSCC. Results indicated that pre-treatment motor functional status predicted post-treatment motor, sensory, and autonomic function and time to functional recovery. Findings showed that breast (25%), lung (21%), and prostate (18%) cancers were the most common cancers among patients with MSCC. In another publication, Loblaw <i>et al.</i> (2003) reviewed Ontario's population-based cancer registry from 1990 to 1995 to identify the incidence and treatment of MSCC in Ontario. The study reported that the cumulative incidence of MSCC was disease-specific, ranging from 0.22% in patients with pancreatic cancer to 7.91% in patients with myeloma. Myeloma, prostate, nasopharynx, breast, and kidney cancers had the highest cumulative incidence of MSCC.</p> <p>Levack <i>et al.</i> (2002) reported that these were the most common cancer sites among patients with MSCC in their prospective study. Of the 319 patients in the study, 248 patients reported symptoms. Ninety-four percent of these patients reported either spinal nerve root or localized back pain. However, Talcott (1999), reported that back pain failed to differentiate between those with and those without MSCC because back pain was nearly universal across the entire study population (patients with and without MSCC).</p> <p>Rades <i>et al.</i> (2002) examined the time to develop motor deficits before irradiation. 98 patients were included in the study (31 patients in the 1-7 days prior to irradiation; 31 patients in the 8-14 days prior to irradiation, and 36 patients in the >14 days prior to irradiation). Rades (2002) reported that the patients with the slowest development of motor deficits before irradiation (>14 days) had the best functional outcome compared to patients with faster development of motor deficits (<14 days) ($p < 0.01$). Loblaw Abstract 2003 also reported that a greater interval from cancer diagnosis to the cord compression independently predicted for improved survival. Each of these factors may reflect tumors of a less aggressive nature.</p> <p>Husband <i>et al.</i> (1998) conducted a study with 301 patients with MSCC, with approximately 70% of patients with loss of neurologic function between the onset of symptoms and the start of treatment. Delays were reported to be caused by lack of symptom recognition by the patient and diagnostic delay at the general practitioner or general hospital level. In the abstract by Loblaw <i>et al.</i> 2003, two thirds of the delay observed in 30 patients was attributed to delay in patients recognising the symptoms as indicating a potential problem. Patients who suspected it were related to their cancer had shorter delays.</p>
References included in the review	<p>Bach F, Larsen BH, Rohde K, et al (1990) Metastatic spinal cord compression: Occurrence, symptoms, clinical presentations and prognosis in 398 patients with spinal cord compression. <i>Acta Neurochir</i> 107:37-43</p> <p>Bayley A, Milosevic M, Blend R, et al (2001) A prospective study of factors predicting clinically occult spinal cord compression in patients with metastatic prostate cancer. <i>Cancer</i> 92:303-310</p> <p>Gilbert RW, Kim JH, Posner JB (1978) Epidural spinal cord compression from metastatic tumor: Diagnosis and treatment. <i>Ann Neurol</i> 3:40-51</p>

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Talcott JA, Stomper PC, Drislane FW, et al (1999) Assessing suspected spinal cord compression: A multidisciplinary outcomes analysis of 342 episodes. *Support Care Cancer* 7:31-38

Observational Studies

REFERENCE	Suspected spinal cord compression in cancer patients: a multidisciplinary risk assessment. Lu,C. Gonzalez, R.G. Jolesz, F.A. Wen,P.Y. Talcott,J.A. The Journal of Supportive Oncology 2005, 3: 4: 305-312
Study design	Prospective Cohort Study
Grade	2+
Setting/ Country	US
Objectives	To determine independent clinical predictors of SCC, a comprehensive data set of potential risk factors derived from a cohort of cancer patients with suspected SCC who underwent spine MRI was analysed.
Patients (inclusions/ exclusions)	Patients were eligible for the study if they met the following inclusion criteria: pathologically confirmed cancer diagnosis.
Interventions/ Comparisons/ Factors of interest	<p>Episodes of suspected SCC were recorded by regularly reviewing (every 2–3 days) the spine MRI scan scheduling records</p> <p>All patients were interviewed by telephone or in person. Information collected included: symptoms experienced before the spine MRI scan; information about patients' back pain (presence or absence, new discomfort (defined as starting or changing in quality within the previous 3 months), location (lower, middle/upper, or neck region), severity (scale of 1–10), pattern (progressive, stable, or improving), duration, activities that worsened or improved discomfort (lying, sitting, standing, straining/Valsalva manoeuvres), radiation of discomfort, and quality (dull/aching, sharp/stabbing, pressure/squeezing, warm/burning, other)); description of any weakness, difficulty walking, sensory loss, and bowel or bladder symptoms; identification of the symptom that occurred first; and to indicate whether they knew that they should contact their physician if any new or worsening back pain occurred.</p> <p>The authors contacted the physicians who ordered the MRIs and asked them uniform, focused questions concerning any abnormal neurological findings consistent with SCC (and not known to be pre-existent) that were noted on the subjects' most recent examinations prior to the spine MRI.</p> <p>The following signs were considered to be consistent with MSCC: increased deep tendon reflexes, abnormal plantar reflexes, decreased anal sphincter tone, bladder distension, objective weakness, and sensory loss.</p> <p>Authors also assessed the presence of spinal tenderness and inability to walk and noted any pertinent neurological signs that were not assessed during the examination.</p> <p>No attempt was made to blind the patient or the physician to the results of the MRI scan, although their knowledge of results was recorded.</p>
Outcomes	Clinically significant MSCC was defined as thecal sac compression (TSC)
Results	Clinically significant metastatic epidural cancer was defined as thecal sac compression (TSC).

A total of 167 eligible episodes of suspected SCC were identified and confirmed by physicians ordering the MRI scan, and 134 patients experiencing 136 (81%) of the suspected SCC episodes were recorded.

- The median age at the time of the spine MRI = 61.5 years (range, 30.9–84.8 years)
- The median time since the diagnosis of cancer = 1.3 years (range, 0.0–19.4 years)
- 48% of patients had metastatic cancer at the time of their initial cancer diagnosis,
- 31% were inpatients at the time of the spine MRI, 4% received prior spine radiotherapy.
- In over 60% of episodes, the underlying primary tumour involved the breasts, lungs, or prostate.
- Prior to spine MRI, 82% of episodes in patients with known metastatic and 56% of episodes were in patients with vertebral cancer. Among the 76 episodes in those with known vertebral metastases, 57 (75%) were based upon prior abnormal bone scans.
- Among the 92% of episodes in patients reporting back pain, 66% involved low back pain and 70% involved progressive pain
- The median severity was 8 (on a scale of 1 to 10) and duration of back pain was 42 days.
- Valsalva manoeuvre (16%) and lying supine (14%) worsened back pain, although lying supine improved symptoms in 55% of the episodes.
- Symptoms of difficulty walking (45%), weakness (24%), sensory loss (19%), and bowel or bladder incontinence (2%) were reported.

The presence of back pain ($P = 0.53$) was not associated significantly with TSC in this population. Authors point out that this finding is not surprising b/c back pain was present in the vast majority (92%) of episodes, limiting the discriminatory value of this variable, and 46% of episodes not involving back pain still featured TSC.

When a multivariable, logistic regression analysis was conducted, 4 independent predictors of TSC were identified:

1. abnormal neurological examination (where an abnormal neurological examination, was defined as the presence of at least one of weakness, sensory loss, increased deep tendon reflexes, abnormal plantar reflexes, and decreased anal sphincter tone or bladder distension), OR = 3.0 ((95% CI 1.6- 10.4) $P = 0.004$)
2. stage IV cancer at initial diagnosis, OR = 2.8 (95% CI 1.4- 7.7) $P = 0.006$
3. known vertebral metastases, OR = 2.8 (95% CI 1.4- 8.2) $P = 0.008$
4. middle or upper back pain, OR = 2.7 (95% CI 1.4- 9.1) $P = 0.010$

When divided into subgroups with varying risks of TSC ranging 8% of patients had no risk factors) to 81% of patients with three or four risk factors.

A subgroup of patient with normal neurological examinations was examined. A normal neurological examination was present in 100 episodes (out of a total of 136), including 30 among patients with TSC.

2 highly significant independent predictors of TSC were identified:

1. middle or upper back pain, OR = 4.5 (95%CI 1.7- 12.3), $P = 0.003$

	<p>2. stage IV cancer at initial diagnosis, OR = 3.9 (95%CI 1.5- 10.5) , P = 0.006 (known vertebral metastases, was significant at P = 0.066 (OR not reported))</p> <p>The two independent predictors (above) stratified episodes into subgroups with varying risks of TSC, ranging from 11% (no risk factors) to 69% (two risk factors).</p>
Comments	<p>These findings supported the results of prior studies, Talcott 1999 (included as part of the Loblaw Guidelines) and Lu 1998. (Lu C, Stomper PC, Drislane FW, et al. Suspected spinal cord compression in breast cancer patients: a multidisciplinary risk assessment. Breast Cancer Res Treat 1998;51:121–131 – not included in appraised evidence table b/c more up to date evidence by the same authors is available)</p> <p>Limitations to the study: 81% of patients were aware of spine MRI results at the time of the interview which could have influenced the patient reported symptoms, however, only one patient-reported symptom (middle or upper back pain) was in the final predictive model.</p> <p>Only < 5% physicians were blinded to the MRI results when they provided the neurologic examination data. Although physician bias could likely exaggerate the association between an abnormal neurologic examination and the outcome variable, the effect on the other predictors in the model likely is less.</p>

REFERENCE	Spinal cord compression in breast cancer Harrison,K.M.; Muss,H.B.; Ball,M.R.; McWhorter,M.; Case,D. Cancer 1985: 55: 12: 2839-2844
Study design	Retrospective cohort study
Grade	2-
Setting/ Country	US
Objectives	What is the correlation of specific symptoms and signs with ESCC?
Patients (inclusions/ exclusions)	78 breast cancer patients with suspected SCC who underwent myelography
Interventions/ Comparisons/ Factors of interest	Back pain, Radicular pain Paresthesias Extremity weakness Bladder/bowel dysfunction
Outcomes	Onset of ESCC
Results	Univariate analysis identified clinical features significantly associated with a positive myelogram, including oncologic features (absence of known metastatic cancer, known bone or vertebral metastases), neurologic features (back pain , paresthesias, bowel or bladder dysfunction), and radiographic features (positive bone scan, positive spine radiograph). Back pain, P <0.001 Radicular pain P = 0.06 Paresthesias P = 0.009 Extremity weakness P = 0.61 Bladder/bowel dysfunction P = 0.05
Comments	Authors did not perform multivariate analysis to identify independent predictors of SCC.

REFERENCE	Early detection and treatment of spinal epidural metastases: the role of myelography. Rodichok LD, Ruckdeschel JC, Harper GR, et al. Ann Neurol 1986;20:696–702.
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Rodichok LD, Ruckdeschel JC, Harper GR, et al.
Ann Neurol
1986;20:696–702.

REFERENCE	Early detection and treatment of spinal epidural metastases: the role of myelography. Rodichok LD, Ruckdeschel JC, Harper GR, et al. Ann Neurol 1986;20:696–702.
Study design	Prospective study
Grade	2+
Setting/ Country	US
Objectives	To explore the feasibility of avoiding myelography in certain groups of patients by designing radiation therapy on the basis of clinical symptoms and the results of plain radiographs.
Patients (inclusions/exclusions)	140 cancer patients with back pain who were evaluated with spine radiographs, bone scans, and myelograms
Interventions/ Comparisons/ Factors of interest	Back pain
Outcomes	Spinal epidural metastatic tumour
Results	<ul style="list-style-type: none"> • Brown-Sequard syndrome was present in all 3 patients with apparent radiation myelopathy but in only 1 patient with myelopathy caused by tumour. • Clinical recognition of radiculopathy was valuable in that it correlated with epidural disease in a larger proportion of patients (63%) than in those with local back pain only (44%). • No additional clinical symptoms or signs were identified that would further enhanced the diagnostic yield. • No oncologic features were analysed, and the authors concluded that the majority of patients with cancer and back pain should undergo myelography.

Narrative-Expert Review

REFERENCE	Epidural spinal cord compression Spinazze,S.; Caraceni,A.; Schrijvers,D. Critical Reviews in Oncology/Hematology 56 2005: 397–406
Study design	Systematic review (including all study designs)
Grade	4
Objectives	The review was developed using the START methodology. This methodology incorporates key EBM characteristics (which includes both clinical evidence and clinical expertise).
Patients	The Review provides evidence on the following issues: Incidence Aetiological and risk factors, pathophysiology Referral Recent reviews Diagnosis Signs and symptoms Instrumental diagnosis
Interventions/ Comparisons/ Factors of interest	Symptoms and risk factors were not quantified but were described as a narrative.
Outcomes	
Results	<ul style="list-style-type: none"> • Progressive pain occurs frequently in patients with ESCC (epidural spinal cord compression). • Back pain at the level of the epidural metastasis can be followed by radicular pain. • Back pain may be elicited or worsened by vertebral compression, movement (especially flexion), or Valsalva manoeuvre. • The pain related to epidural metastases is exaggerated by lying down. • Radicular pain, associated with nerve root compression, gives an indication of the localisation of the lesion and it may radiate unilaterally or bilaterally to upper or lower limbs (in cervical or lumbar lesions) or bilaterally around the chest or upper abdomen (in thoracic cord lesions). At the stage of radicular pain, depression of tendon reflexes, weakness and sensory changes may be found in the territory corresponding to the roots injured by epidural seeds. • Referred pain could give a false localising sign. • Weakness is the second most common symptom, which develops in approximately 80% of patients. • Symptoms and signs of spinal cord dysfunction such as weakness, sensory disturbances, and bowel and bladder disorders, typically follow the pain. • Gait difficulties may also be caused by sensory ataxia possibly due to posterior column compression.
Comments	This included this paper because it was based on EBM methods and it addressed nearly all the factors listed in our PICO table. However, in the section about signs and symptoms of Epidural SCC, the authors did not reference their clinical statements.

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Chapter 5 – Choice of Imaging

5.2 Imaging Modalities

Short Summary

From low quality studies, MRI was consistently found to provide superior diagnostic evaluation for MSCC across all studies included over all other imaging modalities. Studies consistently demonstrate moderate to high sensitivity (44-100%) and specificity (90-93%) of MRI in diagnosing spinal cord compression (Andreasson *et al.* 1990; Colletti *et al.* 1991; Colletti *et al.* 1996; Loblaw *et al.* 2005) and compression fractures (Jung *et al.* 2003).

PICO

Population Group	Intervention	Comparison	Outcomes
Population A: Patients with suspected metastatic spinal cord compression Population B: Patients with paraparesis or paraplegia	<ul style="list-style-type: none"> • CT (modern spiral) • MRI • CT myelography • CT Multi-detector MDCT also known as Multi-slice MSCT • PET-CT • Bone scintigraphy [This is for detecting mets rather than showing cord compression] 	With each other	<ul style="list-style-type: none"> • sensitivity • Specificity • cost

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

The studies included in this evidence summary evaluating MRI were all case series, either collected prospectively or retrospectively. These case series studies were small in number. Blinding of the reader (of the imaging results) occurred in nearly all studies. MRI was consistently used as the gold standard. When evaluating MRI, biopsy was not conducted consistently to confirm MRI findings. The ethical nature of conducting biopsy needs to be considered.

Evidence About Sensitivity And Specificity Of Imaging Modalities:

Imaging Modality	Sensitivity	Specificity
MRI	44 – 100% (Andreasson <i>et al.</i> 1990, Colletti <i>et al.</i> 1991, Colletti <i>et al.</i> 1996, Jung <i>et al.</i> 2003 (Compression Fractures), Loblaw <i>et al.</i> 2005)	90 – 93% (Andreasson <i>et al.</i> 1990, Colletti <i>et al.</i> 1991, Colletti <i>et al.</i> 1996, Jung <i>et al.</i> 2003 (Compression Fractures), Loblaw <i>et al.</i> 2005)
Bone Scintigraphy	19 – 100% (Levack <i>et al.</i> 2002, Andreasson <i>et al.</i> 1990, Colletti <i>et al.</i> 1991)	100% (Levack <i>et al.</i> 2002, Andreasson <i>et al.</i> 1990, Colletti <i>et al.</i> 1991)
CT	Lesion based: 68-78% Patient based: 50% (Metser <i>et al.</i> 2004)	Lesion based: 56% Patient based: 50% (Metser <i>et al.</i> 2004)

CT/Myelography	<p>All relevant studies identified by search (n=3) were dated 1991, 1992, 1995. This will not reflect a modern CT scan. Therefore results were not extracted and included in Evidence Table.</p> <p>No evidence for modern CT/Myelography was identified.</p>	
PET/CT	<p>Only one study was identified from the search, Metser <i>et al</i> 2004.</p> <p>The following was extracted from this study: 18F-FDG PET/CT performed on patients with malignant involvement of the spinal column has better specificity than does 18F-FDG PET alone. PET/CT enables precise localization of lesion level in the vertebral column and (essential for optimal treatment planning) identification of potentially neurologically significant soft-tissue abnormalities. (Metser <i>et al.</i>2004)</p>	

Evidence for a change in diagnosis or treatment:

- From one study, 48% symptomatic patients had a change in management based on the results of the MRI, compared with 32% asymptomatic patients. (Fuji *et al.* 1995)
- In 5.9% of another study sample a spinal MRI lead to a change of diagnosis from metastatic disease to spondylodiscitis. (Rades *et al.* 2001)
- MRI of the whole spine is recommended because the additional information may alter the management plan. MRI led to a change in the radiotherapy plan in around 50% of patients. (Husband *et al.* 2001 and Cook *et al.* 1998)

Evidence for effectiveness of T(1)-weighted sagittal images:

From one study (Kim *et al.* 2000);

- sensitivity of T1-weighted sagittal images alone for cord compression was 70% (97.6% CI = 59%-80%)
- specificity of T1-weighted sagittal images alone for cord compression was 97% (97.6% CI = 93-98%)

This study reported that for patients with symptoms of SCC an initial T(1)-weighted sagittal image of the whole spine was appropriate if a positive result was found then no further images would be required and treatment could commence. However, if patients with symptoms of SCC had a negative result with T(1)-weighted sagittal image, then further axial image need to be performed.

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Evidence Tables

Prospective case series

Metser, Lerman, Blank, Lievshitz, Bokstein & Even-Sapir . Malignant involvement of the spine: assessment by 18F-FDG PET/CT. J Nucl Med 45[2]. 2004.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: Israel,

Inclusion criteria

51 patients with malignant involvement of the spinal column:

Exclusion criteria -

Population

number of patients = 51, age range 25 to 83 years, mean age = 62 years.

Interventions

The aim was to assess the added value of CT to PET/CT studies in lesion detection and localisation of vertebral lesions. Special evaluation was described for the detection of SCC on the PET/CT images.

All patients received an IV of 18F-FDG.

CT (head to pelvic floor) was performed first on patients and immediately followed by PET (covering identical transverse field of view).

CT details: scanning was performed first, from the head to the pelvic floor, with 140 kV, 80 mA, a tubero-rotation time of 0.5 s, a pitch of 6, and a 5-mm section thickness, which matched the PET section thickness. Immediately after CT scanning, a PET emission scan was obtained that covered the identical transverse field of view. The acquisition time was 5 min per table position. PET image datasets were reconstructed iteratively using CT data for attenuation correction, and co-registered images were displayed on a workstation (eNTEGRA; ELGEMS).

The PET/CT data were separated into PET and CT image sets. Two specialists, evaluated a blinded and independent interpretation of the CT and PET images.

In a later session the radiologists interpreted the fused PET/CT images. PET/CT image interpretation was considered the gold standard.

Both PET and CT images were assessed using a standardised format, and have been described in detail in the paper.

Outcomes

The sensitivity and specificity of 18F-FDG - PET and CT for differentiation of malignant from benign bone lesions were assessed on both lesion-based and patient-based analyses and compared using the McNemar test. $P < 0.05$ was considered statistically significant.

Results

Overall, 51 patients with 253 lesions were assessed on PET alone, CT alone and fused PET/CT.

**Lesion
Detection:**

	Sensitivity	Specificity:
PET	96%	56%
CT	68%	56%
	PET identified a significantly greater number of malignant lesions than did CT (209 [96%] lesions, compared with 148 [68%] lesions, respectively [P <0.001, Chi squared = 51.25, 95% CI = 0.354-0.208]).	(P =not significant, Chi squared = 0.05).
Detection of osteoblastic metastases.	Sensitivity	
PET	88%	
CT	19%	
Detection of osteolytic metastases.	Sensitivity	
PET	100%	
CT	59%	
Detection of mixed metastases.	Sensitivity	
PET	100%	
CT	31%	

Patient Based analysis:	Sensitivity	Specificity:
PET	98%	50%
CT	74%	50%
	(P < 0.01, Chi Squared = 7.7, 95% CI= 0.08-0.39)	P = not significant

When interpretations of PET and PET/CT were compared for the presence of spinal metastases on a patient-based analysis, only 1 patient had evidence of a metastasis in the occipital condyle on PET/CT, and that finding was overlooked on the PET-alone Interpretation.

Location of metastases:

Of the 220 lesions that PET detected, 15% were incorrect in determining the level of metastases.

Incorrect localisation of abnormality within the vertebra by PET alone as compared with PET/CT was found for 40 (18%) of all vertebral lesions detected by PET. Most errors on PET (93%) were between posterior portions of the vertebral body and posterior elements.

Soft tissue Abnormalities at the Spinal Region:

79 of the 217 lesions detected in 17 of the 51 patients had either soft-tissue masses in the spinal column or vertebral metastases with an associated soft-tissue abnormality.

Of the 79 lesions, 25 were either :

epidural extension of tumour (n = 7),

neural foramen involvement of tumour (n = 7)

a combination of both (n=11).

Of the 18 epidural lesions:

8 had mild compression,

9 had moderate compression

1 had severe compression of the spinal cord or cauda equine.

Epidural or neural foramen involvement was validated by MRI, contrast-enhanced thin-section full-dose CT, biopsy, or resolution or progression of findings seen on follow-up PET/CT.

General comments

The limitations of this study are due to the retrospective study design, the heterogeneous patient population, and lack of histologic proof for most lesions.

Levack, P., et al & Scottish Cord Compression Study Group. 2002, "Don't wait for a sensory level--listen to the symptoms: a prospective audit of the delays in diagnosis of malignant cord compression", *Clinical Oncology (Royal College of Radiologists)*, vol. 14, no. 6, pp. 472-480.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: United Kingdom,

Inclusion criteria

The criterion for entry to the study was a definitive diagnosis of malignant cord compression by MRI of the spine.

MCC was defined on MRI as distortion of the cord or cauda equina, most commonly as a result of compression by tumour out with the cord (leptomeningeal, epidural or paraspinal tumour) or uncommonly within the cord (intraparenchymal tumour).

Exclusion criteria -

Population –

324 clinical episodes of compression were recorded in relation to 319 patients (203 male, 116 female). 89% of patients were over 50 years of age at diagnosis; the median age was 65

Interventions

To report details concerning the accuracy of imaging investigations carried out when diagnosing MSCC.

Accuracy for the following modalities were reported:

Plain films

MRI

Isotope Bone Scintigraphy

Once notified of diagnosis, the patient had a clinical history recorded (including pain and QoL). The functional status was measured using the Karnofsky Performance Status and Barthel Disability Index.

Pathological or histological confirmation of cancer along with treatment details (including the use of steroids, radiotherapy, chemotherapy and surgery) was checked from hospital records.

All imaging (x-rays, isotope scans, myelograms, MRI and CT scans) carried out in relation to the presenting episode of malignant cord compression, was collected. Attempts were made to obtain all imaging from the onset of symptoms and from all sources. The accuracy of diagnosing the level of cord compression was compared to the MRI.

Outcomes

Accuracy of detecting different levels of MSCC with different imaging modalities.

Follow up

Follow-up visits at one, 4, 7 and 10 months after the diagnosis of MCC. These visits took place either at home, in hospital or in a hospice.

Results

- 324 clinical episodes of SCC recorded (319 patients)
- 77% known to have cancer b/f imaging diagnosis of MSCC made, in 23% a diagnosis of MSCC was the presenting symptom.

Clinical Assessment in Hospital (as described from the paper)

- In 84% of all episodes (272/324), weakness was detected on clinical examination.
- In 58% (87/324), sensory abnormalities were found on examination, and in 169 of these (52% of all patients), a sensory level was noted.
- The clinical level of sensory abnormality corresponded poorly with the level of cord compression identified on MRI imaging, varying by up to 10 dermatomes below or above the compressive lesion. In those in which a sensory level and MRI level of compression could be compared (127 patients), the level was within three dermatomes (either above or below) in only 40% of cases. Therefore, considering the whole study population of 324 patients with MCC, a sensory level was of value in identifying the level of compression in only 16% of the MCC study group.

Accuracy of MSCC diagnosis:

Plain Films:

Using the plain film sign of significant vertebral collapse (50% or more loss of vertebral height), as an indicator of MCC, plain films were highly inaccurate in predicting the level of compression.

Vertebral collapse was seen in 60/187 (32%) of plain films, and in 39 of these the level of compression was confirmed on MRI.

Therefore in those patients who had plain films, the films obtained correctly predicted the subsequent level of compression in 21%.

Isotope Bone scintigraphy:

Isotope Bone scintigraphy correctly predicted the level of cord compression in 26/139 (19%) examinations.

MRI

MRI was equal to or superior to all other imaging modalities at detecting cord compression. MRI detected more collapsed vertebrae than plain films, and was equivalent to bone scintigraphy in the detection of metastatic disease in adjacent and non-adjacent vertebrae. (actual numbers were not provided)

Algra PR, Bloem JL, Tissing H, Falke TH, Arndt JW, Verboom LJ. Detection of vertebral metastases: comparison between MR imaging and bone scintigraphy. Radiographics 1991;11:219–32.

Design: Prospective case series (), evidence level: 3
Country: Netherlands

Inclusion criteria

71 patients with known malignant disease, biopsy proven skeletal mets.

Exclusion criteria -

Population

number of patients = 71, age range 14 to 83 years.

Interventions

Bone scintigraphy (BS)

MRI

2 observers for each modality were used and each were blind to other observer reports/findings.

the 4 observers had to score their certainty as to whether a vertebral body showed abnormal accumulation of radiotracer or abnormal signal (1 = certainly normal to 5=certainly abnormal)

Outcomes

sensitivity of MRI relative to bone scintigraphy in detecting vertebral metastases.

The rate of agreement b/n observers was statistically evaluated by means of weighted kappa formula.

Follow up -

Results

BS indicated 499 abnormal vertebrae

MRI indicated 818 abnormal vertebrae

This was equivalent to 49 patients.

For MRI:

40 patients had focal lytic lesion

10 had focal sclerotic lesions

17 had diffuse in homogenous images

4 had diffuse homogenous images

For 12 patients an additional biopsy was done on lesions that were positive for metastases with MRI and negative with BS. Histology confirmed the metastases.

In 14 patients MRI indicated clinically important results beyond that of BS results. This included information about the presence and extent of soft tissue extension and compressive myelopathy.

- For bone scintigraphy moderate agreement was calculated b/n observer readings. Kappa = 0.58
- For MRI strong agreement was calculated b/n observer readings. Kappa = 0.88.
- MRI showed relative distribution of metastases over spine similar to reports from BS.

-

General comments

Authors note that MRI is more sensitive than BS in detecting vertebrae mets most notably when mets show diffuse abnormal signal intensity on MRI.

This study does not provide enough data to calculate sensitivity or specificity. And the reports included in the paper do not describe a epidemiological sensitivity.

Andreasson, Petren-Mallmin, Strang, Nilsson, Nyman & Hemmingsson . Diagnostic methods in planning palliation of spinal metastases. Anticancer Res 10[3]. 1990.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: Sweden, setting: Secondary care

Inclusion criteria

30 patients with known different primaries.

Patients included if conventional radiography or scintigraphy detected spinal mets.

After inclusion all patients then received MRI followed by CT imaging. (within 6 weeks for comparative results)

Exclusion criteria -

Population

number of patients = 30, age range 37 to 80 years, median age = 59 years.

Interventions

MRI

conventional radiography

scintigraphy

computerised CT (Somatom DRH or DR2 - Siemens AG)

Outcomes

pathological lesions:

1. skeletal with suspect metastases
2. other, eg. soft tissue components or lesions with specific information about skeletal lesions such as spinal cord compromise.

Follow up -

Results

For 30 patients (156 lesions)

	Imaging Modality:		
	MRI	Scintigraphy	Conventional Radiography
Sensitivity (as specified in the study)	93%	77%	58%
Specificity	4%	100%	89%

For 28 out 30 patients (120 lesions)

	Imaging Modality:	
	MRI	CT
Sensitivity (as specified	92%	78%

in the study)		
Specificity (unable to calculate from study)	Reported as high (in study)	Reported as high (in study)

When comparing detection rates of skeletal lesions, Scintigraphy was significantly lower than MRI $p < 0.01$

Conventional radiography was significantly lower than for MRI ($p < 0.0001$) and scintigraphy ($p < 0.01$)

When detecting pathological lesions, MRI was significantly more sensitive than CT ($p < 0.01$)

-

General comments

This study provides some useful comparisons into the differences in detection rates of spinal mets and to some extent spinal cord compression, b/n imaging modalities (MRI, conventional radiography, scintigraphy and computerised CT (Somatom DRH or DR2 - Siemens AG)).

The sample number was small which limits the study.

Authors report that “even though scintigraphy has a lower sensitivity than MRI, it can be used prior to palliative radiotherapy for whole skeleton screening but it doesn't provide exact information about pathological lesions.”

CT can inform about stability of skeleton, is sensitive in detecting soft tissue components but detection rate for pathological lesions is lower than that of MRI.

MRI provides highest sensitivity compared to other modalities evaluated in this study and gives useful information about soft tissue components. For surgical cases, MRI is most informative.

Colletti, Dang, Deseran, Kerr, Boswell & Ralls . Spinal MR imaging in suspected metastases: Correlation with skeletal scintigraphy. Magn Reson.Imaging 9[3]. 1991.

Design: Prospective case series evidence level: 3
Country: US

Inclusion criteria

64 patients with spinal lesions (confirmed, by clinical follow-up, radiography, CT or myelography)

Exclusion criteria -

Population –

64 patients with spinal lesions (confirmed, by clinical follow-up, radiography, CT or myelography)

Interventions

Bone scintigraphy and magnetic resonance imaging were prospectively and retrospectively correlated in 64 patients with suspected spinal metastatic disease and possible spinal cord compression

Outcomes detection of spinal metastases.

Follow up -

Results

	Sensitivity from Prospective report	Sensitivity from Retrospective report
MRI	96%	100%
Bone Scintigraphy	77%	88%

-

General comments

This study confirms that bone scintigraphy is the modality of choice for global evaluation of skeletal metastatic disease. Authors note that patients with suspected spinal metastatic disease based on back pain or SCC will often benefit from spinal MRI. MRI is sensitive in detecting multiple lesions and indicating cord compression.

Retrospective case series

Colletti, Siegel, Woo, Young & Terk . The impact on treatment planning of MRI of the spine in patients suspected of vertebral metastasis: an efficacy study. Comput.Med Imaging Graph. 20[3]. 1996.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
County: United States, setting: Tertiary care

Inclusion criteria

100 sequential patients with known primary tumours and suspected spinal metastases were evaluated retrospectively and 30 prospectively. The most common tumour types were breast cancer (n=27), prostate cancer (n=17) and lung cancer (n=11).

Exclusion criteria -

Population

number of patients (in total) = 130, age range 19 to 85 years, mean age = 54 years.

Interventions

The aim of this study was to assess the efficacy of spinal MRI in influencing treatment choices in patients with suspected spinal metastatic disease.

MRI of the spine using a spin echo short TR, TE technique with sagittal and axial acquisitions

Outcomes

Change of therapy: discontinuation, initiation or change in radiotherapy ports or dose, chemotherapy, steroid usage or surgical intervention.

Follow up -

Results

108 patients had symptoms of spinal metastases, 22 were asymptomatic. 52/108 (48%) symptomatic patients had a change in management based on the results of the MRI, compared with 7/22 (32%) asymptomatic patients.

Fujii, Higashi, Owada, Okuno, Mizuno & Mizuno . Magnetic resonance imaging for the diagnosis of prostate cancer metastatic to bone. Br J Urol 75[1]. 1995.

Design: Retrospective case series (), evidence level: 3

Country: Japan

Inclusion criteria

36 patients with PC (histological proven) had an MRI and BS done 58 times.

Exclusion criteria -

Population –

36 patients with PC (histological proven) had an MRI and BS done 58 times.

Interventions

MRI

bone scan (BS)

Outcomes

Comparison b/n findings of BS and MRI in the diagnosis of bone metastases and suspected MSCC..

Follow up -

Results

From the 19 positive bone scans, MRI indicated a negative finding for metastasis in one.

Of 8 equivocal scans, 2 MR images were interpreted as positive and six as negative.

Of nine negative BSs, MRI was positive in one. Further MRI demonstrated additional metastatic lesions that were not shown by bone scintigraphy in six patients.

MRI clearly indicated the areas of spinal cord compression in five patients with spinal metastases and associated myelopathy.

-

General comments

Limitations of this study: results of the BS were done by radiologists who were aware of both MRI and clinical findings.

MRI was able to diagnose metastatic prostate cancer, especially when other radiographic examinations were inconclusive or spinal cord compression is suspected.

Jung, H. S., Jee, W. H., McCauley, T. R., Ha, K. Y., & Choi, K. H. 2003, "Discrimination of metastatic from acute osteoporotic compression spinal fractures with MR imaging", *Radiographics*, vol. 23, no. 1, pp. 179-187

Design: Retrospective case series (), evidence level: 3
Country: Korea (South), setting: Tertiary care

Inclusion criteria

The MR imaging findings in 27 patients with metastatic compression fractures and 55 patients with acute a traumatic osteoporotic compression fractures were compared.

mean age of patients with metastatic compression fractures = 57 years;
mean age of patients with acute osteoporotic compression fractures =69 years

Exclusion criteria -

Population , age range 35 to 92 years.

Interventions

This study evaluated whether MRI could discriminate between acute compression fractures of the spine due to osteoporosis and compression fractures of the spine due to metastatic disease.

Details of MRI techniques can be confirmed from paper - see AM.

Outcomes

MR imaging findings of metastatic and acute osteoporotic compression fractures. The final diagnosis was made on the basis of biopsy results or results of clinical and radiological follow-up for at least 1 year

Accuracy, sensitivity and specificity of MR imaging in differentiation of acute osteoporotic and metastatic compression fractures.

Univariate analysis with the Chi squared test and multivariate logistic regression analysis were performed to study possible associations between MR imaging findings and differentiation of metastatic from acute osteoporotic compression fractures.

Follow up -

Results

For metastatic compression fractures:

sensitivity = 100%

specificity = 93%

accuracy = 95%

Because this study focussed on vertebral compression fractures due to osteoporosis or spinal metastatic disease (as opposed to metastatic spinal cord compression) i have not provided the detailed table of results of association for each of the MRI findings with compression fractures due to osteoporosis or spinal metastatic disease - if this is required please inform AM and this detail will be provided.

In general terms, the statistical analysis indicated that :

a convex posterior border of the vertebral body, abnormal signal intensity of the pedicle or posterior element, an epidural mass, a focal para-spinal mass, and other spinal metastases were suggestive of metastatic compression fractures.

A low-signal-intensity band on T1- and T2-weighted images, spared normal bone marrow signal intensity of the vertebral body, retro-pulsion of a posterior bone fragment, and multiple compression fractures were suggestive of acute osteoporotic compression fractures.

General comments

Limitations of this study:

- The images were read by only one radiologists.
- All compression fractures were not confirmed with biopsy.
- Sample sizes in this study were small.
- The radiologists involved was not blind to the final diagnosis of compression fractures that were metastatic or osteoporotic.

The authors also point out further limitations including:

- The study did not include any cases of multiple myeloma, which would likely be more problematic for MR imaging diagnosis than metastasis.
- The lack of usefulness of T2-weighted images in the study might have been due to lack of fat suppression.

Rades, Bremer, Goehde, Joergensen & Karstens . Spondylodiscitis in patients with spinal cord compression: A possible pitfall in radiation oncology. Radiotherapy & Oncology 59[3]. 2001.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: Germany, setting: Tertiary care

Inclusion criteria

447 patients were referred for spinal irradiation b/c of metastatic disease (264 of these patients (59%) presented after regular hours).

170 patients had no spinal MRI and diagnosis was made on X-rays or CT scan. In these patients a spinal MRI was performed, to define the extension of SCC and the number of spinal lesions.

Exclusion criteria -

Population -

Interventions

To demonstrate that MRI can provide further diagnostic information in order to distinguish between SCC caused by spondylodiscitis and vertebral metastases.

Outcomes

Change in diagnosis from vertebral metastases to spondylodiscitis.

Follow up -

Results

In 10/170 (5.9%), a spinal MRI lead to a change of diagnosis from metastatic disease to spondylodiscitis.

- 6 patients were already known as cancer patients,
- 4 patients were presented with a diagnosis of cancer of unknown primary.

All ten patients complained about progressive spinal pain (duration between 5 days and 2 months) and neurological symptoms. Four patients even showed development of severe motor deficits (paraplegia) within 2±5 days, three of them additional sensory deficits and bladder dysfunction.

Diagnosis of bacterial spondylodiscitis was confirmed by surgery in 5 patients. In the other 5 patients biopsy revealed non-specific inflammatory changes as granulocytosis.

General comments

Systematic review of combined study designs

Loblaw DA; Perry J; Chambers A; Laperriere NJ. Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. J Clin Oncol 2005 Mar 20 ;23(9):2028-2037

Design: Systematic review of combined study designs, evidence level: 2-
Country: international

Inclusion criteria

All patients included in the review of the evidence for this question had suspected MSCC.

Inclusion of studies to answer this question:

RCTs comparing imaging modalities; phase II studies or retrospective reviews describing imaging modalities. All raters must be blinded from clinical information and the test.

Exclusion criteria -

Population -

Interventions

This review investigated the optimal approach for investigating suspected MSCC

CT (modern spiral, multi-detector, multi-slice)

MRI

Myelography

PET-CT

Bone scintigraphy

Outcomes

- Imaging test: Sensitivity and Specificity
- Complications of tests

Results

The reviews included, four case series (Husband *et al* 2001, Hagenau *et al* 1987, Carmody *et al* 1989, Loughrey *et al* 2000) and two retrospective studies (Cook *et al* 1998 and Li *et al* 1988) that described the optimal approach for investigating MSCC.

Study	Sensitivity		Specificity	
	MRI	Myelography	MRI	Myelography
Husband 2001	0.44	NR	0.98	NR
Carmody 1989	0.92	0.95	0.90	0.88
Li 1988	0.93	0.97	NR	NR
Hagenau 1987	0.83	0.71	0.96	1.00
NR= not				

The accuracy of MRI or myelography has been examined in four studies.

Loughrey *et al* 2000 and Cook *et al* 1998 evaluated the ability of MRI to identify MSCC. The results of both of the studies (one case series and one retrospective study) supported the use of whole-spine MRIs for patients with known malignancy and suspected MSCC.

MR imaging of the whole spine is recommended because the additional information may alter the management plan. MRI led to a change in the radiotherapy plan in around 50% of patients. (Husband 2001 and Cook 1998)

References of Included Studies:

Husband DJ, Grant KA, Romaniuk CS: MRI in the diagnosis and treatment of suspected malignant spinal cord compression. *Br J Radiol* 74:15-23, 2001

Hagenau C, Grosh W, Currie M, et al: Comparison of spinal magnetic resonance imaging and myelography in cancer patients. *J Clin Oncol* 5:1663-1669, 1987

Carmody RF, Yang PJ, Seeley GW, et al: Spinal cord compression due to metastatic disease: Diagnosis with MR imaging versus myelography. *Radiology* 173:225-229, 1989

Loughrey GJ, Collins CD, Todd SM, et al: Magnetic resonance imaging in the management of suspected spinal canal disease in patients with known malignancy. *Clin Radiol* 55: 849-855, 2000

Cook AM, Lau TN, Tomlinson MJ, et al: Magnetic resonance imaging of the whole spine in suspected malignant spinal cord compression: Impact on management. *Clin Oncol (R Coll Radiol)* 10:39-43, 1998

Li KC, Poon PY: Sensitivity and specificity of MRI in detecting malignant spinal cord compression and in distinguishing malignant from benign compression fractures of vertebrae. *Magn Reson Imaging* 6:547-556, 1988

Diagnostic study

Kim JK, Learch TJ, Colletti PM, et al. Diagnosis of vertebral metastasis, epidural metastasis, and malignant spinal cord compression: are T(1)-weighted sagittal images sufficient? Magn Reson Imaging 2000;18:819–824.

Design: Diagnostic study – retrospective case series, evidence level: -
Country: United States,

Inclusion criteria

57 consecutive patients examined over the last 2 years with clinically suspected malignant spinal cord compression including 94 imaging studies.

Exclusion criteria -

Population

number of patients = 57, age range 22 to 87 years, mean age = 49 years.

Interventions

This study investigated if T1-weighted sagittal images alone could provide sufficient information in cancer patients with clinically suspected evidence of metastasis. To do this, the study attempted to determine the level of agreement between T1- weighted sagittal images alone and T1- and T2-weighted axial and sagittal images with respect to the detection of vertebral metastasis, epidural metastasis, and malignant spinal cord compression with T1-weighted sagittal images alone versus T1- and T2-weighted axial and sagittal images.

All MRI specifications were reported – see AM for details.

Four radiologists independently and blindly reviewed randomized T1-weighted sagittal images alone and complete studies of the spine. The radiologists also blindly and independently evaluated the 11 gadolinium-enhanced studies concurrently with its complete study.

A standard protocol or "a complete study" for suspected spinal cord compression was T1- and T2-weighted sagittal images, and T1- and/or T2-weighted axial images of the spine.

The radiologists were told only that the patients had cancer.

In order to determine the sensitivity of T1-weighted sagittal images, a standard for comparison was necessary. This was achieved by the using the diagnosis from the complete image of a study to obtain an 'external' and an 'internal' standard for all three parameters. As reported by the authors: "If the two radiologists with the most experience agreed on the diagnosis, then this was used as the external standard for that case; but, if they disagreed on the diagnosis, then a third evaluation by a radiologist with 10 years of MRI experience, was used as the external standard for that particular case. This radiologist only participated in the determination of the external standard and was not one of the four radiologists evaluating both the complete studies and the T1-weighted sagittal images alone. Each individual radiologist's interpretation of the complete image was used as the internal standard for that particular case."

Outcomes

The parameters assessed were the presence of vertebral metastasis, epidural metastasis, and spinal cord compression. (SCC included in report)

On all three parameters, the number of cervical, thoracic and lumbar segments involved was recorded as one, two, or multiple.

The sensitivities, specificities, and corresponding 95%, 97.6%, or 99% confidence intervals (CI)

for the data

overall were calculated, for the performance based on the radiologists' experience, the spinal segment involved, and the patient's primary malignancy. A significance level of a $p = 0.05$ was selected.

The sensitivity and specificity was disregarded if the total number of cases was less than 21.

In order to measure agreement between the complete and T1-weighted sagittal studies for all 4 radiologists, and to measure the agreement of all 4 radiologists in the diagnosis using the complete studies and the sagittal studies alone, the chance corrected kappa statistic was calculated.

The concluding interpretations were:

when kappa = 0.75, it was excellent reproducibility,

when kappa $0.4 \leq k \leq 0.75$ it was good reproducibility,

when kappa $0 \leq k \leq 0.4$, it was marginal reproducibility

Follow up -

Results

This study found that a complete MRI study (T1-weighted and T2-weighted sagittal images and T1- and/or T2-weighted axial images) was superior to T1-weighted sagittal images alone in detecting epidural disease.

94 studies included:

22 cases (23%) of cord compression.

The sensitivity of T1-weighted sagittal images alone for cord compression was 70% (97.6% CI = 59%-80%), with the external standard.

The sensitivity of T(1)-weighted sagittal images alone to vertebral metastasis (87%) was statistically greater than cord compression (70%) ($p = 0.05$), and statistically greater than epidural metastasis (46%) ($p \leq 0.02$).

The specificity of T1-weighted sagittal images alone for cord compression was 97% (97.6% CI = 93-98%)

The specificity for cord compression (97%) was greater than the specificity for epidural metastasis (89%) ($p = 0.03$), and greater than the specificity for vertebral metastasis (83%) ($p \leq 0.02$)

The sensitivity and specificity of T1-weighted sagittal images alone, depending on the primary malignancy, were calculated. The most frequent malignancies were lung, breast, lymphoma, multiple myeloma, and prostate.

General comments

Limitations:

In order to assess the effectiveness of T1 weighted sagittal MRI this could have been conducted in a different, possibly more useful manner: such that a series of patients were diagnosed by an expert panel of radiologists, using all available MRI studies (T1+T2, axial, sagittal, gadolinium) and then compare this against the performance of T1 sagittal MRI only, possibly done by non-experts.

Instead, the actual study used an external standard as the reference which was not constant for all the cases included. The external standard was potentially different for each case. So in this respect it is very difficult to assess how useful this study really is. However, for this study it is the external standard that is the most relevant and will be used as the reference standard and the findings are reported in the results section.

An inadequate number of cases of cord compression and epidural metastasis in the cervical spine and among the individual primary malignancies in the study made it difficult to determine the sensitivity and specificity of T1-weighted sagittal images alone ((n<21) in some cells)

Health Economic Evaluation

During the compilation of the guideline, and before the health economic evidence for this topic was assessed, the GDG recommended MRI to be the imaging modality of choice for detecting MSCC. Therefore this topic was no longer considered to be a priority for health economic assessment.

5.3 MRI and early detection

Short Summary

The evidence presented for this clinical question is of low quality. There were no randomised comparative imaging studies only several small studies that reported the accuracy of imaging modalities. Most studies investigated metastatic spinal disease (and reported on MSCC if it was detected) (Andraesson *et al.* 1990, Colletti *et al.* 1991, Fuji *et al.* 1995, Kosuda *et al.* 1996, Sarpel *et al.* 1987, Godersky *et al.* 1987). A minority of studies investigated occult SCC specifically (Venkitaraman *et al.* 2007a, Bayley *et al.* 2001). Only one study examined what the outcome of detecting occult MSCC is with respect to neurological outcomes and survival (Venkitaraman *et al.* 2007b). There was no evidence for the benefit of serial imaging in asymptomatic patients.

For studies that investigated metastatic spinal disease: The sensitivity of MRI of detecting MSCC was 96% (Andraesson *et al.* 1990 and Colletti *et al.* 1991). The detection rate of SCC ranged from 26% (Fuji *et al.* 1995), 30% (Kosuda *et al.* 1996), 37.5% (Sarpel *et al.* 1987), 42% (Godersky *et al.* 1987).

From studies investigating occult SCC specifically: The detection rate of MSCC was 27.33% (Venkitaraman *et al.* 2007) and 32% (Bayley *et al.* 2001)

Outcome of Early Diagnosis: Only one study (Venkitaraman *et al.* 2007b) investigated the outcome of patients with metastatic prostate cancer with clinically occult MSCC identified with MRI and given early radiotherapy. This study reported that there was no statistical difference between subgroups of patients (Group A: patients who had radiological identified MSCC (rMSCC) and received radiotherapy, Group B: patients who did not have rMSCC but received radiotherapy for back pain, Group C: patients who did not have rMSCC or back pain and did not receive radiotherapy) either in neurologic deficit free interval or overall survival.

PICO

Population Group	Intervention	Comparison	Outcomes
Patients suspected of having bone metastases in the spine	<p>QUESTION A:</p> <ul style="list-style-type: none"> ▪MRI ▪PET ▪Skeletal survey (plain films) ▪Radioisotope bone scan ▪CT <p>QUESTION B:</p> <ul style="list-style-type: none"> ▪Serial imaging 	<ul style="list-style-type: none"> ▪No scanning ▪Interventions with each other 	<ul style="list-style-type: none"> ▪Identification patients at risk of developing MSCC ▪Improve clinical outcomes (prevention of established MSCC, mobility) ▪Sensitivity & specificity of imaging modalities ▪Sensitivity & specificity of developing cord compression

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary:

- The evidence presented for this clinical question is of low grade. There were no randomised comparative studies and several small studies that presented accuracy of imaging modalities compared to sensitivity or specificity of diagnosing MSCC.
- Most studies investigated metastatic spinal disease (and reported on MSCC if it was detected). Only a few studies investigated occult MSCC specifically
- Only one study examined what the outcome of detecting occult MSCC is with respect to neurological outcomes and survival
- Other studies were included that examined the accuracy of other imaging modalities

For studies investigating occult SCC specifically

- Bayley *et al.* 2001 reported clinically occult SAS/SC compression in 22/68 patients (32%). Risk of developing clinical spinal cord compression within 1 year of a negative screening MRI to be 3.2% and risk of developing clinical spinal cord compression within 2 years of a negative screening MRI to be 13.7%.
- Venkitaraman *et al.* 2007a reported occult SCC in 27% of patients

For Studies that investigated metastatic spinal disease

- The range of MSCC detection ranged from 26-42% (with MRI). (it is important to bear in mind the diverse sample populations of the individual studies which must be referred to in order to clarify the detection rate)
- Sensitivity of MRI of detecting MSCC = 96% (Andraesson *et al.* 1990 and Colletti *et al.* 1991)
- Detection rate of MSCC:
 - 26% (Fuji *et al.* 1995)
 - 30% (Kosuda *et al.* 1996)
 - 37.5% (Sarpel *et al.* 1987)
 - 42% [23% (5 of 22) of patients with back pain with no neurological abnormality had occult spinal cord compression] (Godersky *et al.* 1987)

Outcome of Early Detection:

Results from Venkitaraman *et al.* 2007b

MRI of the whole spine was carried out with the aim of detecting MSCC by metastatic involvement.

MRI findings were classified as:

- (1) 'Overt SCC', defined as involvement or compression of either the spinal cord or the cauda equine by an epidural or an intramedullary mass lesion,
- (2) 'Occult SCC', defined as metastatic disease causing impingement, indentation or loss of definition of the thecal sac
- (3) no SCC

For the purpose of statistical analysis, overt and occult SCC were considered together and were termed 'radiological spinal canal compromise' (rSCC).

The detection rate of rSCC by MRI of the spine and the clinical factors that could predict for rSCC were analysed.

• Analysis of patient subgroups showed:

Group A: patients who had rSCC and received radiotherapy = 39 patients

Group B: patients who did not have rSCC but received radiotherapy for back pain = 50

Group C: patients who did not have rSCC or back pain and did not receive radiotherapy = 59

- The number of patients who developed rSCC or functional neurologic deficit on follow-up was:
12 (30.7%) group A,
16 (32%) group B
11 (18.6%) group C.
- There was no statistical difference between the three subgroups of patients either in neurologic deficit free interval ($p = 0.13$) or overall survival ($p = 0.33$).
- The author's claim, "patients without pain and impending SCC appear to have a better neurologic outcome the other two groups (HR 0.44 (95% CI 0.19–1.01))"

Use of MRI

One study (Kienstra *et al* 2000) acknowledged that the treatment of spinal epidural metastases (SEM) was important in preventing neurological deficit due to SCC, and that because the use of MRI (which is used for diagnosis with limited in access and expensive) be omitted because of a low risk of SEM in a specific group of patients. The study calculated prediction of spinal metastatic disease (SMD) and especially SEM by means of a multivariate risk analysis of the parameters of the standard neurological evaluation as well as the risk implications of omitting MRI in patients with an estimated risk below different cutoff points.

- Spinal metastatic disease was diagnosed in 80 patients (47%); of these, 31 had SEM. A metastatic abnormality on plain films was the strongest independent predictor for SMD. Other important predictors were night pain, progressive pain, and Karnofsky score. Advanced age, exacerbation of pain during recumbency, and osteoporotic fracture imply a low risk of SMD. Night pain and the Karnofsky score proved to be the main predictors for SEM. A plain film showing an osteoporotic fracture strongly decreased the risk of SEM. The discriminating value of the multivariate analysis was too low, and too few patients can be excluded from undergoing MRI on the basis of the standard neurological checkup. To identify all the patients with SMD ($P < 0.01$), MRI would be excluded in only 7 patients. Identification of all patients with SEM ($P < 0.001$) reduced the number of MRIs by 21 at the expense of plain films of the whole spine for any patient.

Other Imaging Modalities:

- Soerdjbalie-Maikoe *et al* 2004 reported:
 - Mean survival after treatment of hormone refractory prostate cancer was 8.6 ± 10.6 months
 - SCC due to metastatic lesions to the vertebrae developed in 20 of 84 patients (24%) in 3 to 10 months after the bone scintigraphy. was performed and after hormone refractoriness established.
 - The bone scintigrams (which focussed on the extent of vertebral involvement – partial or total), significantly predicted SCC ($p < 0.0001$).

The study by Franken reported an risk overall: 50 patients whose PET study indicated a risk of MSCC, 35 were further evaluated with MRI or CT. Of these 35 patients 9 patients (26%) had spinal cord compression or nearby neurological structure confirmed and 8 of them received immediate treatment.

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Evidence Tables

Prospective case series

Bayley, Milosevic, Blend, Logue, Gospodarowicz, Boxen, Warde, McLean, Catton & Catton . A prospective study of factors predicting clinically occult spinal cord compression in patients with metastatic prostate carcinoma. Cancer 92[2], 303-310. 2001. United States.
Design Prospective case series (diagnosis, screening), evidence level: 3 County: Canada (federal state, Commonwealth Realm), setting: Tertiary care
Inclusion criteria Patients with vertebral bone metastases from prostate cancer and normal neurologic examination (no symptoms indicative of spinal cord compression), were accrued from outpatient radiation oncology clinics.
Exclusion criteria Previous spinal cord compression or a contraindication to MRI.
Population number of patients = 68, age range 50 to 84 years, median age = 71 years.
Interventions A bone scan was obtained in all patients within 1 week of study entry. MRI of the entire spine (sagittal T1-weighted, spin-echo sequence followed by a sagittal T2-weighted, fast spin-echo sequence).
Outcomes <ul style="list-style-type: none">• Subclinical spinal cord compression: visible subarachnoid space (SAS) or spinal cord (SC) compression, without neurologic abnormalities.• The risk of developing clinical spinal cord compression in the 2 years following a negative screening MRI was estimated using the Meier method.
Follow up -
Results <ul style="list-style-type: none">• Bone scans were negative for metastatic disease in 3/68 patients (4%).• 39/68 patients (57%) had received hormone therapy as their initial therapy. 64/68 patients (94%) were receiving continuous hormone treatment at the time of entry into the study, and 61 of these patients had hormone refractory tumours.• Vertebral metastases were identified by MRI in 65/68 patients (96%).• Clinically occult SAS/SC compression was identified in 22/68 patients (32%). In all cases compression was due to direct extension of metastatic tumour from the vertebral body.• 4 of the 46 patients (9%) with no evidence of SAS/SC compression on the screening MRI went on to develop clinically evident spinal cord compression.• Potential prognostic factors for spinal cord compression were examined using multivariate logistic regression. The extent of disease on bone scan and the duration of continuous hormonal therapy were independent predictors of SAS/SC compression.
Numeric results: <hr/> Risk of spinal cord compression <hr/>

Outcome: Risk of subclinical spinal cord compression	22/68
Outcome: Risk of developing clinical spinal cord compression within 1 year of a negative screening MRI	3.2 %
Outcome: Risk of developing clinical spinal cord compression within 2 years of a negative screening MRI	13.7%

General comments

Important outcomes (survival, quality of life etc.) are not reported. It is unclear how the initial vertebral bone metastases were discovered (before entry to the study).

It is assumed that MRI is the gold standard for the diagnosis of subclinical spinal cord compression, but it is not reported how many of those with sub clinical compression went on to develop symptoms. The management of these patients with clinically occult SAS/SC compression diagnosed by MRI was at the discretion of individual doctors, but patients usually received radiotherapy.

Kienstra GE, Terwee CB, Dekker FW, Canta LR, Borstlap AC, Tijssen CC, Bosch DA, Tijssen JG (2000) Prediction of spinal epidural metastases. Archives of Neurology 57, 690-695.

Design: prospective case series, 3
Setting: Holland

Inclusion criteria

Patients who presented with cancer with recently developed back pain, radiating pain, or both were prospectively evaluated.

Inclusion criteria for the study were a history of systemic cancer and recently developed back pain or radiating pain or radiating pain without local back pain. Also, patients who had synchronous back pain and primary tumor were included.

Exclusion criteria

Age younger than 20 years, location of the primary tumor in the central nervous system, history of SEM or vertebral metastases, spinal metastases in the results of bone scintigraphy, symptoms and signs of myelopathy without local back pain, contraindication for MRI, and refusal of the patient to undergo MRI.

Population

170 consecutive patients

Interventions

To identify the patients with back pain in whom MRI can safely be omitted because of a low risk of spinal metastatic disease (SMD) and especially spinal epidural mets (SEM).

Outcomes

In order to evaluate the risk of SMD and SEM, a logistic multivariate regression analysis was performed. The variables included the standardised neurological history, neurological examination, and finally included the variables of the plain films. Independent variables were also used.

Follow up

Results

Baseline characteristics.

The MRI results showed SMD in 80 patients (47%) and SEM in 31 (18%).

Risk functions.

The main risk factors for SMD in the univariate analysis were:

- metastatic abnormalities and metastatic fractures on plain films,
- prostate cancer,
- Karnofsky score

Patients with metastatic abnormalities on plain films had a 50-fold increased risk of SMD. The OR of the Karnofsky score was 0.95, which means that if the score increases 1 point the associate risk is multiplied by a factor 0.95. (A decrease of 10 points increases the OR to 1.65.)

The multivariate prediction model for SMD in 151 patients:

- Night pain and progressive pain in particular increased the risk of SMD,
- Advanced age and exacerbation of pain during recumbency decreased the risk of SMD.
- Among the variables of neurological examination, only vertebral pain on percussion proved to be a positive predictive factor for SMD.
- With the outcome of plain films, the prediction of SMD improved substantially. A metastatic abnormality on plain film was the strongest independent predictor of SMD.

For SEM, the main risk factors were:

- night pain;
- pain score of 7 to 10;
- pain exacerbated by Valsalva manoeuvre;
- specific neurological complaints, such as bladder dysfunction, numbness, gait disturbance (defined as walking with support), and paresthesias.

The multivariate prediction model for SEM in 151 patients:

- 2 significant predictors of the medical history for SEM: night pain and Karnofsky score.
- The model used to conduct the multivariate analysis also showed that exacerbation of pain during recumbency was a strong indication against SEM.
- None of the parameters of the neurological examination were predictors for SEM.

Risk Implications.

The number of MRIs excluded and missed cases of SMD:

- At $P < 0.01$, all 80 patients with SMD would be identified, whereas 7 patients would be excluded from MRI.
- With a less strict $P < 9.06$, 75 (94%) of the 80 patients with SMD would be identified among 135 (79%) of 170 patients. This finding means that 35 patients would be excluded from MRI at the expense of 5 patients whose MRIs showed SMD (missed cases).

The number of MRIs excluded and missed cases at several cut off points for SEM:

- At $P < 0.01$, MRI would be excluded in 62 patients at the expense of 1 false-negative case.
- At a lower value of $P < 0.06$, 27 (87%) of the 31 patients with SEM would be identified in 81 patients. At that point, MRI would be excluded in 89 patients; of these, 4 actually had SEM according to MRIs (false-negative results).

General comments

Authors note that the results of a multivariate analysis of risk factors for SMD and SEM derived from the medical history, neurological examination, and plain films. In multivariate analysis, metastatic abnormalities on plain films (32% of our patients) was the main predictor for SMD. Other important predictors were night pain, progressive pain, and Karnofsky score. Advanced age, exacerbation of pain during recumbency, and osteoporotic fracture implied a low risk of SMD.

The main predictors of SEM were night pain and Karnofsky score. Plain films without metastatic abnormalities strongly decreased the risk of SEM. Signs of spinal cord compression had no predictive value for the diagnosis of SEM because spinal cord compression was rare in our patients. Contrary to what we expected, exacerbation of pain during recumbency decreased the risk of SMD.

The results indicated that the discriminating value of medical history, neurological examination, and plain films of the spine was low; MRI would be excluded in too few patients on the basis of the standard neurological checkup. To identify the 80 patients with SMD, only 7 patients would be excluded from MRI. Identification of all the patients with SEM reduces the number of MRIs by only 21 (12%).

Plain films of the whole spine were not useful in identifying SEM and therefore should not be performed. This would potentially represent a substantial overall saving in cost and time. Authors go one to conclude that this study indicated that identification of patients at risk for SEM was not possible with the standard neurological checkup. Therefore, after intake by a neurologist, the next step should be to perform an MRI of the whole spine. Plain films of the spine can be left out.

AM note: while this study did not directly focus on MSCC it did present a condition (SEM) that is strongly related to it.

Metser, Lerman, Blank, Lievshitz, Bokstein & Even-Sapir . Malignant involvement of the spine: assessment by 18F-FDG PET/CT. J Nucl Med 45[2], 279-284. 2004.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: Israel,

Inclusion criteria
patients with malignant involvement of the spinal column:

Exclusion criteria -

Population
number of patients = 51, age range 25 to 83 years, mean age = 62 years.

Interventions
The aim was to assess the added value of CT to PET/CT studies in lesion detection and localisation of vertebral lesions. Special evaluation was described for the detection of SCC on the PET/CT images.

All patients received an IV of 18F-FDG.

CT (head to pelvic floor) was performed first on patients and immediately followed by PET (covering identical transverse field of view).

CT details: scanning was performed first, from the head to the pelvic floor, with 140 kV, 80 mA, a tubero-rotation time of 0.5 s, a pitch of 6, and a 5-mm section thickness, which matched the PET section thickness. Immediately after CT scanning, a PET emission scan was obtained that covered the identical transverse field of view. The acquisition time was 5 min per table position. PET image datasets were reconstructed iteratively using CT data for attenuation correction, and co-registered images were displayed on a workstation (eNTEGRA; ELGEMS).

The PET/CT data were separated into PET and CT image sets. Two specialists, evaluated a blinded and independent interpretation of the CT and PET images.

In a later session the radiologists interpreted the fused PET/CT images. PET/CT image interpretation was considered the gold standard.

Both PET and CT images were assessed using a standardised format, and have been described in detail in the paper.

Outcomes
The sensitivity and specificity of 18F-FDG - PET and CT for differentiation of malignant from benign bone lesions were assessed on both lesion-based and patient-based analyses and compared using the McNemar test. $P < 0.05$ was considered statistically significant.

Follow up -

Results
Overall, 51 patients with 253 lesions were assessed on PET alone, CT alone and fused PET/CT.

Lesion Detection:		
	Sensitivity	Specificity:

PET	96%	56%
CT	68%	56%
	PET identified a significantly greater number of malignant lesions than did CT (209 [96%] lesions, compared with 148 [68%] lesions, respectively [P <0.001, Chi squared = 51.25, 95% CI = 0.354-0.208]).	(P =not significant, Chi squared = 0.05).
Detection of osteoblastic metastases.	Sensitivity	
PET	88%	
CT	19%	
Detection of osteolytic metastases.	Sensitivity	
PET	100%	
CT	59%	
Detection of mixed metastases.	Sensitivity	
PET	100%	
CT	31%	

Patient Based analysis:	Sensitivity	Specificity:
PET	98%	50%
CT	74%	50%
	(P < 0.01, Chi Squared = 7.7, 95% CI= 0.08-0.39)	P = not significant

When interpretations of PET and PET/CT were compared for the presence of spinal metastases on a patient-based analysis, only 1 patient had evidence of a metastasis in the occipital condyle on PET/CT, and that finding was overlooked on the PET-alone Interpretation.

Location of metastases:

Of the 220 lesions that PET detected, 15% were incorrect in determining the level of metastases.

Incorrect localisation of abnormality within the vertebra by PET alone as compared with PET/CT was found for 40 (18%) of all vertebral lesions detected by PET. Most errors on PET (93%) were between posterior portions of the vertebral body and posterior elements.

Soft tissue Abnormalities at the Spinal Region:

79 of the 217 lesions detected in 17 of the 51 patients had either soft-tissue masses in the spinal column or vertebral metastases with an associated soft-tissue abnormality.

Of the 79 lesions, 25 were either :
epidural extension of tumour (n = 7),
neural foramen involvement of tumour (n = 7)
a combination of both (n=11).

Of the 18 epidural lesions:

8 had mild compression,

9 had moderate compression

1 had severe compression of the spinal cord or cauda equina.

Epidural or neural foramen involvement was validated by MRI, contrast-enhanced thin-section full-dose CT, biopsy, or resolution or progression of findings seen on follow-up PET/CT.

General comments

Authors conclude that 18F-FDG PET alone detected approximately 30% more malignant lesions than did CT alone and, overall, almost 20% more extra-vertebral skeletal metastases than did CT alone.

The relatively low specificity of PET and CT in this study was improved when the two were combined. PET/CT improved the specificity of PET interpretation alone by showing degenerative changes on CT in locations corresponding to areas of increased 18F-FDG uptake and by showing that areas of increased uptake suspected of being vertebral were actually physiologic muscular uptake (This was demonstrated by images in the paper rather than by numerical values).

PET/CT was able to correct the localisation of the abnormality from PET alone results, enabling more accurate differentiation between benign and malignant lesions.

The CT in PET/CT enabled detection of pathologic compression fractures in more than 5% of lesions assessed. CT may also aid in determining the presence of spinal cord compression.

Another contribution of CT in PET/CT studies is its ability to detect and localize soft tissue components of tumour involving the vertebral column, specifically epidural space invasion, or neural foramen involvement. The significance of this is the possible association with spinal cord compression or with radiculopathy. In this study, more than 10% of lesions, in one third of the study subjects, PET/CT detected soft-tissue tumor involving the spine.

The limitations of this study are due to the retrospective study design, the heterogeneous patient population, and lack of histologic proof for most lesions.

Andreasson, Petren-Mallmin, Strang, Nilsson, Nyman & Hemmingsson . Diagnostic methods in planning palliation of spinal metastases. Anticancer Res 10[3], 731-733. 1990.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: Sweden,
setting: Secondary care

Inclusion criteria

30 patients with known different primaries and with spinal metastatic disease.

Patients included if conventional radiography or scintigraphy detected spinal mets.

After inclusion all patients then received MRI followed by CT imaging. (within 6 weeks for comparative results)

Exclusion criteria -

Population

number of patients = 30, age range 37 to 80 years, median age = 59 years.

Interventions

MRI
conventional radiography
scintigraphy
computerised CT (Somatom DRH or DR2 - Siemens AG)

Outcomes

pathological lesions:

1. skeletal with suspect metastases
2. other, eg. soft tissue components or lesions with specific information about skeletal lesions such as spinal cord compromise. (results not reported here)

Follow up -

Results

Out of 156 pathological lesions detected, 108 were skeletal, 48 were other lesions (soft tissue components or lesions with specific information about skeletal lesions such as spinal cord compromise.). Where pathological lesions = areas where at least one of the methods indicated a suspect meatstatic process.

With MRI:

For Skeletal mets: 93% of successfully detected,

With scintigraphy:

For skeletal mets: 77% gave correct information. (this was significantly lower than that for MRI (p<0.01))

With conventional radiography:

For skeletal mets: 58% of lesions were detected (this was significantly lower than that for MRI (p<0.0001) and for scinitigraphy (p> 0.01))

Comparisons:

For 30 patients (156 pathological skeletal lesions)

	Imaging Modality:		
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	MRI	Scintigraphy	Conventional Radiography
Sensitivity (as specified in the study)	93% Skeletal 96% Other	77%	58% skeletal 35% other
Specificity	4%	100%	89%

For 28 out 30 patients (120 pathological lesions)

	Imaging Modality:	
	MRI	CT
Sensitivity (as specified in the study)	92%	78%
Specificity (unable to calculate from study)	Reported as high (in study)	Reported as high (in study)

When comparing detection rates of skeletal lesions, Scintigraphy was significantly lower than MRI $p < 0.01$

Conventional radiography was significantly lower than for MRI ($p < 0.0001$) and scintigraphy ($p < 0.01$)

When detecting pathological lesions, MRI was significantly more sensitive than CT ($p < 0.01$)

-

General comments

This study provides some useful comparisons into the differences in detection rates of spinal mets and to some extent spinal cord compression, b/n imaging modalities (MRI, conventional radiography, scintigraphy and computerised CT (Somatom DRH or DR2 - Siemens AG)).

The sample number was small which limits the study.

Authors report that even though scintigraphy has a lower sensitivity than MRI, it can be used prior to palliative radiotherapy for whole skeleton screening but it doesn't provide exact information about pathological lesions.

CT can inform about stability of skeleton, is sensitive in detecting soft tissue components but detection rate for pathological lesions is lower than that of MRI.

MRI provides highest sensitivity compared to other modalities evaluated in this study and gives useful information about soft tissue components. For surgical cases, MRI is most informative.

Colletti, Dang, Deseran, Kerr, Boswell & Ralls . Spinal MR imaging in suspected metastases: Correlation with skeletal scintigraphy. Magn Reson.Imaging 9[3], 349-355. 1991.

Design: Prospective case series evidence level: 3
Country: US

Inclusion criteria

64 patients with spinal lesions (confirmed, by clinical follow-up, radiography, CT or myelography)

Exclusion criteria -

Population –

64 patients with spinal lesions (confirmed, by clinical follow-up, radiography, CT or myelography)

Interventions

Bone scintigraphy and magnetic resonance imaging were prospectively and retrospectively correlated in 64 patients with suspected spinal metastatic disease and possible spinal cord compression

Outcomes detection of spinal metastases.

Follow up -

Results

	Sensitivity from Prospective report	Sensitivity from Retrospective report
MRI	96%	100%
Bone Scintigraphy	77%	88%

General comments

This study confirms that bone scintigraphy is the modality of choice for global evaluation of skeletal metastatic disease. Authors note that patients with suspected spinal metastatic disease based on back pain or SCC will often benefit from spinal MRI. MRI is sensitive in detecting multiple lesions and indicating cord compression.

<p>Venkitaraman R (2007) Detection of occult spinal cord compression with magnetic resonance imaging of the spine. <i>Clinical Oncology</i> article in press.</p>
<p>Design: Retrospective case series, evidence level: 3 Country: UK Setting: Tertiary</p>
<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Metastatic prostate cancer patients who had a MRI of the spine, (requested by clinician - for patients who were thought to be at high risk of developing SCC). • The clinical details of 570 consecutive patients with prostate cancer who had MRI of the spine from January 2001 to May 2005 from the hospital database.
<p>Exclusion criteria The exclusion criteria were FND on clinical examination or any previous SCC.</p>
<p>Population</p> <ul style="list-style-type: none"> • 150 patients were included in the study. • All patients had performance status 0-1. • None of the patients had clinical symptoms of bladder or bowel involvement from metastatic spinal disease.
<p>Interventions This study aimed to determine the role of magnetic resonance imaging of the spine in detecting SCC or occult SCC in patients with metastatic prostate cancer with no functional neurological deficit (FND).</p>
<p>Outcomes MRI of the whole spine was carried out with the aim of detecting SCC by metastatic involvement. MRI findings were classified as: (1) 'Overt SCC', defined as involvement or compression of either the spinal cord or the cauda equine by an epidural or an intramedullary mass lesion, (2) 'Occult SCC', defined as metastatic disease causing impingement, indentation or loss of definition of the thecal sac (3) no SCC</p> <p>For the purpose of statistical analysis, overt and occult SCC were considered together and were termed 'radiological spinal canal compromise' (rSCC). The detection rate of rSCC by MRI of the spine and the clinical factors that could predict for rSCC were analysed.</p>
<p>Follow up</p>
<p>Results 41 (27.33%) were detected to have rSCC. 24 (16%) patients had overt rSCC, 17 (11.3%) patients had occult SCC.</p> <p>The significant clinical determinants of rSCC on univariate analysis were:</p> <ul style="list-style-type: none"> • extensive bone metastasis (P = 0.005) • back pain (P = 0.002), <p>The non-significant factors that did not predict for rSCC were:</p> <ul style="list-style-type: none"> • age (P = 0.97), • time from diagnosis (P = 0.52),

- metastasis at diagnosis (P = 0.535),
- Gleason score (P = 0.34),
- hormone refractory status (P = 0.158),
- time from starting hormonal treatment (P = 0.96) and
- PSA at the time of MRI (P = 0.855)

On multivariate analysis: The significant independent predictors of rSCC were: back pain (P = 0.012; odds ratio (OR) 5.1; 95% CI 1.44-18.25) and extensive bone metastasis (P = 0.047; OR 2.9; 95% CI 1.012-8.35).

General comments

Godersky JC, Smoker WR, Knutzon R (1987) Use of magnetic resonance imaging in the evaluation of metastatic spinal disease. *Neurosurgery* 21, 676-680.

Design: Retrospective case series, evidence level: 3

Country: US

Setting: Secondary Care

Inclusion criteria

patients who had undergone MR examination as part of their evaluation for suspected metastatic spinal disease

Exclusion criteria

Population

58 patients who had undergone MR examination as part of their evaluation for suspected metastatic spinal disease. MR was performed 64 times in 58 patients ranging in age from 5 to 91 years old.

Interventions

This study assessed the efficacy of MR compared with other imaging techniques as a screening examination in the evaluation of patients with suspected spinal cord compression secondary to metastatic disease. The study also identified any additional information that MR may provide.

MRI: Images were obtained on a 0.5-T superconductive scanner (Picker International) using a standard body coil. Surface coils were not used. Both T1 and T2-weighted sagittal MR scans were routinely obtained. Coronal and/or axial scans were additionally obtained in instances in which orthogonal views were required to completely define or exclude an abnormality.

Outcomes

Information recorded during the medical record review included the clinical indication for obtaining the MR scan (asymptomatic, back pain only without neurologic deficit, myelopathy, or radiculopathy).

MRI findings were classified into groups:

1. no metastases
2. Bone mets
3. SAS compression: subarachnoid space compression
4. Cord compression
5. Intramedullary

Follow up

Results

- “Excellent” correlation between the myelographic and MR studies in the 22 patients who underwent both examinations.
- MR examinations were considered diagnostic in 60 of the 64 studies.
- Conventional myelography followed by CT was performed in 22 patients.
- Myelography was considered diagnostic in 16 of 22 examinations (myelography was accurate 89% of the time.)
- When the accuracy of MR is compared with myelography, MR provided the same diagnoses as myelography in 19 of 22 studies.
- In no case did myelography or CT myelography provide more information about a clinically significant epidural lesion than did a technically satisfactory MR examination

Discrepancies:

- 3 of the 4 cases in which MR was considered inaccurate included one false-negative study in which MR failed to demonstrate a small, 3-mm intra-dural drop metastatic lesion identified on myelography and CT myelography;
 - one false-positive study in which MR suggested intradural lesions secondary to “phase-encoding error” but myelography and CT myelography proved normal;
 - one study that was uninterruptible due to motion (in which the degree of subarachnoid space compression could not be determined).
 - One case where an epidural lesion was undetected by MR and myelography but was demonstrated by conventional CT 1 month later.
- MR provided additional information not observed by myelography in 13 of the 22 patients.
 - In 4 patients, MR demonstrated both the upper and lower extent of the lesion where myelography demonstrated only one.
 - In three patients, MR demonstrated para-spinal muscle involvement not observed on myelography.
 - In one of these patients, both MR and myelography demonstrated a normal spinal cord and subarachnoid space but only MR revealed paraspinal tumour that accounted for the patient’s radicular symptoms.
 - MR revealed additional areas of cord compression in two patients.

Overall findings from MRI:

- Out of 64 MRI findings: 27 were Cord compression (42%), 12 (19%) were subarachnoid space compression, 2 (3%) were intramedullary compression. (Other findings included no mets found (11%) and bone mets (25%) found). Therefore, 64% of findings indicated some type of spinal compression.
- When considering the number of patients presenting with back but no neurological symptoms, 23% (5 of 22) of patients with back pain with no neurological abnormality had occult spinal cord compression identified. Out of all 27 patients with myelopathy, 16 had SCC (60%). Out of all 12 patients with radiculopathy; 6 had SCC (50%)

General comments

Fujii, Higashi, Owada, Okuno, Mizuno & Mizuno . Magnetic resonance imaging for the diagnosis of prostate cancer metastatic to bone. Br J Urol 75[1], 54-58. 1995.

Design: Retrospective case series, evidence level: 3

Country: Japan

Inclusion criteria

36 patients with PC (histological proven) had an MRI and BS done 58 times.

Exclusion criteria

Population

36 patients with PC (histological proven) had an MRI and BS done 58 times.

Interventions

MRI

bone scan (BS)

Outcomes

Comparison b/n findings of BS and MRI in the diagnosis of bone metastases and suspected MSCC..

Follow up -

Results

- From the 19 positive bone scans, MRI indicated a negative finding for metastasis in one.
- Of 8 equivocal scans, 2 MR images were interpreted as positive and six as negative.
- Of nine negative BSs, MRI was positive in one. Further MRI demonstrated additional metastatic lesions that were not shown by bone scintigraphy in six patients.
- MRI clearly indicated the areas of spinal cord compression in 5 patients with spinal metastases and associated myelopathy.

General comments

Limitations of this study: results of the BS were done by radiologists who were aware of both MRI and clinical findings.

MRI was able to diagnose metastatic prostate cancer, especially when other radiographic examinations were inconclusive or spinal cord compression is suspected.

Rodichok LD, Harper GR, Ruckdeschel JC, Price A, Roberson G, Barr KD, et al. Early diagnosis of spinal epidural metastases. Am J Med 1981;70:1181–8.

Design: prospective case series, 3

Setting: US

Inclusion criteria

patients with known or suspected cancer who reported back pain, either alone or with symptoms of spinal root or spinal cord injury.

Exclusion criteria

Population

- 87 patients were evaluable for 93 separate episodes.
- Patients were divided into different groups depending on symptoms and initial diagnosis on plain films.
- Patients in one of these groups was suitable for this clinical question:
 - Group IV, back pain, normal neurologic findings, abnormalities on spine film or bone scan
 - Patients reported back pain and had evidence of spinal metastases by roentgenogram or bone scan at a spinal segment appropriate to their symptoms. Myelography was performed on all patients in this group.

Interventions

- Bone scan
- Myelogram

Outcomes

Detection of spinal epidural disease

Follow up

Results

- 25 patients had local back pain without evidence of spinal root or spinal cord injury.
- Neurologic examinations disclosed no abnormalities, but myelography was obtained since plain films of the spine or bone scan showed metastases in the symptomatic area.
- 15 patients (60 %) had myelographic evidence of spinal epidural metastases.
- Myelograms were within normal limits in the other 10 patients, including the 3 patients who were studied on the basis of an abnormality on bone scan alone.

- Over-all, bone scan correctly predicted the presence or absence of epidural metastases in 29 of 46 instances (63%).
- In the 5 instances in which the bone scan showed abnormalities and plain films did not, the findings on myelography were within normal limits.

General comments

Francken AB, Hong AM, Fulham MJ, Millward MJ, McCarthy WH, Thompson JF (2005) Detection of unsuspected spinal cord compression in melanoma patients by 18F-fluorodeoxyglucose-positron emission tomography. European Journal of Surgical Oncology 31, 197-204.

Design: Retrospective case series

Country: Australia

Inclusion criteria

Patients with melanoma who had a PET scan and attended the study site (secondary/tertiary care hospital).

Exclusion criteria

Population

The PET scans were read by 3 investigators, blind to clinical data. They define SCC using the criteria:

- (a) irregular involvement of the bone marrow with markedly increased FDG uptake and a suggestion of posterior extension of disease into the spinal canal or poster laterally,
- (b) circumferential involvement of the bony elements with markedly increased FDG uptake.

Only MR imaging or computed tomography (CT) of the spine were accepted as valid comparative anatomical imaging modalities.

Patients with available comparative imaging were divided into two groups according to their MR imaging/CT result:

- group A: no compression confirmed on anatomical imaging;
- group B: SCC, nerve root compression or cauda equine compression.

Interventions

This study aimed to assess the accuracy of FDG-PET in the detection of SCC.

The PET scans were read by 3 investigators, blind to clinical data. They define SCC using the criteria:

- (a) irregular involvement of the bone marrow with markedly increased FDG uptake and a suggestion of posterior extension of disease into the spinal canal or poster laterally,
- (b) circumferential involvement of the bony elements with markedly increased FDG uptake.

Only MR imaging or computed tomography (CT) of the spine were accepted as valid comparative anatomical imaging modalities.

Outcomes

Information was subsequently collected about the correlative imaging that was performed, the presence of symptoms and signs, the immediate management and the clinical outcomes for each patient.

Symptoms and signs were reviewed only if recorded no more than a week before or after the PET.

Follow up

Follow-up data were collected between 2 and 5 months after the PET or at the last follow-up if the patient died within 2 months of the PET. If no information for that time interval was available, the patient was not included in the analysis of the follow-up results.

Results

From the reports of 1365 PET scans performed, 50 patients were identified with a report indicating risk of SCC. (15 patients were excluded)

- 27 (out of 50) patients were further evaluated by MR imaging
- 8 were further evaluated by CT scanning.
- The median time between the PET and the conventional imaging was 5 days (ranging from 25 days before to 28 days after PET).
- group A: 26 patients did not have confirmation of compression on anatomical imaging (5 had epidural involvement from metastatic melanoma but no compression)
- group B: 9 patients had compression confirmed on anatomical imaging

- Follow-up data were available for 17 patients in group A and for seven patients in group B.

- The median time from PET to the collection of follow-up data was 2.7 months (range 0.5–5.0 months). Within the follow-up time, good functional status was recorded in two patients in group A and three patients in group B.
- Within the follow-up time, 12 patients in group A died and three patients in group B died.
- One of the patients in group A had progressive neurological symptoms, but SCC was not demonstrated on CT of the spine.
- The difference in outcome between group A and group B was not statistically significant.
- 2 of 7 patients in group B evaluated for follow-up developed symptoms of progressive SCC despite treatment.

Overall, 50 patients whose PET study indicated a risk of SCC, 35 were further evaluated with MR imaging or CT. Of these 35 patients nine patients (26%) had compression of the spinal cord or nearby neurological structure confirmed and eight of them received immediate treatment.

General comments

The sensitivity and specificity of FDF-PET is not reported in comparison to MRI or CT.

The study sample is small (<50 patients and was included only because of the limited number of studies investigating FDF PET)

Kosuda S, Kaji T, Yokoyama H, Yokokawa T, Katayama M, Iriye T, Uematsu M, Kusano S (1996) Does bone SPECT actually have lower sensitivity for detecting vertebral metastasis than MRI? Journal of Nuclear Medicine 37, 975-978.

Design: Retrospective case series, evidence level 3

Inclusion criteria

Exclusion criteria -

Population

22 cancer patients who had complained of back pain

Interventions

To compare skeletal scintigrams and MRI studies of the thoracolumbar spine.

Both skeletal scintigraphies, including planar and SPECT imaging, and spinal MRI examinations were performed.

All patients but one underwent skeletal scintigraphies and spinal MRI examinations within 2 wk of each other.

1 patient under went MRI study 2 months after skeletal scintigraphy.

20 patients had MRI studies after bone scans to confirm vertebral metastasis and to examine spinal cord involvement.

Outcomes

The final diagnosis of vertebral or disk lesions was based on the results of all radiological studies, including repeated skeletal scintigraphies, MRI, computed tomographic (CT) scans, plain radiographs and the subsequent clinical course.

Follow up

All patients were followed for at least 18 mo after skeletal scintigraphy and spinal MRI examination. The final diagnosis of vertebral or disk lesions was based on the results of all radiological studies, including repeated skeletal scintigraphies, MRI, computed tomographic (CT) scans, plain radiographs and the subsequent clinical course.

Results

This table shows the comparative sensitivities of the different imaging modalities:

	Planar	Vertebral SPECT	Spinal MRI
Disease detected	70.4%	92%	97.7%

In six of the 20 patients (30%) with vertebral metastases, MRI showed spinal cord and/or dural compression due to a bulging tumor or collapse of the vertebral body.

General comments

Two reviewers independently interpreted each bone planar and vertebral SPECT image. Two other diagnostic radiologists independently reviewed each MR image.

Sarpel S, Sarpel G, Yu E, Hyder S, Kaufman B, Hindo W, Ezdinli E (1987) Early diagnosis of spinal-epidural metastasis by magnetic resonance imaging. Cancer 59, 1112-1116.
Design: Retrospective case series, evidence level 3
Inclusion criteria Not clearly described (patients with cancer)
Exclusion criteria
Population 16 patients with cancer, all patients had recent axial spinal pain and had undergone neurological examination
Interventions MRI, Bone scan, myelograms
Outcomes Detection of spinal mets, compression fractures or SCC
Follow up
Results <ul style="list-style-type: none"> • All 16 patients had MRI positive detection of spinal or spinal-epidural involvement. • 14 patients had multiple areas of vertebral involvement. • 6 patients had evidence of thecal compression, in three of these, myelograms had been interpreted as negative (37.5% detection rate of SCC).
General comments Very small, non-comparative study, Possibly outdated.

Soerdjbalie-Maikoe V, Pelger RC, Nijeholt GA, Arndt JW, Zwinderman AH, Bril H, Papapoulos SE, Hamdy NA (2004) Bone scintigraphy predicts the risk of spinal cord compression in hormone-refractory prostate cancer. European journal of nuclear medicine and molecular imaging. 31, 958-963.

Design: Retrospective case series, evidence level 3

Inclusion criteria

Patients with hormone refractory prostate cancer

Exclusion criteria

Population

84 patients with hormone refractory prostate cancer (rising PSA, appearance or re-appearance of bone mets on bone scintigraphy)

Interventions

The aim of this study was to examine if bone scintigraphy has prognostic value regarding survival without spinal cord compression and overall survival.

All patients underwent bone scintigraphy at the time of diagnosis of hormone refractoriness using 99mTc-labelled methylene diphosphonate.

The prognostic value of scintigraphic parameters for survival and spinal cord compression-free survival was evaluated using the Cox proportional hazards regression model and the value was quantified using relative risk with 95% confidence intervals.

Outcomes

survival and spinal cord compression-free survival

Follow up

Results

- Mean survival after treatment of hormone refractory prostate cancer was 8.6 ±10.6 months
- SCC due to metastatic lesions to the vertebrae developed in 20 of 84 patients (24%) in 3 to 10 months after the bone scint. was performed and after hormone refractoriness established.
- The bone scintigrams (which focussed on the extent of vertebral involvement – partial or total), significantly predicted SCC ($p < 0.0001$).

General comments

Very small, non-comparative study. In order to fully evaluate bone scintigraphy a prospective, comparative study must be conducted.

Venkitaraman, R., Barbachano, Y., Dearnaley, D. P., Parker, C. C., Khoo, V., Huddart, R. A., Eeles, R., Horwich, A. & Sohaib, S. A. (2007) Outcome of early detection and radiotherapy for occult spinal cord compression. *Radiotherapy & Oncology*, 85: 469-472.

Design: Retrospective case series, evidence level 3

Country: UK

Aim: To investigate the outcome of patients with metastatic prostate cancer with clinically occult SCC with MRI and to determine whether early radiotherapy facilitates preservation of neurologic function.

Inclusion criteria

– MRI of the spine of patients with metastatic prostate cancer, where the doctor was concerned that the patient was at high risk of developing SCC.

– 150 consecutive patients included from January 2001 to May 2005.

Exclusion criteria

Patients with functional neurologic deficit on clinical examination or previous SCC.

Population

150 patients (median age 69 years (range 50–88)) with prostate cancer.

From the paper, though not described as such, these patients did not have neurological deficits and it is unclear what exactly triggered the doctor's concerns to have the MRI done (other than advanced disease (75%) and back pain).

Interventions

- Patients with rSCC (Radiologic Spinal Canal Compromise) received radiotherapy (20 Gy in 5 fractions).
- Patients with back pain and no rSCC received palliative radiotherapy, either 20 Gy or 8 Gy (at physician's decision).
- Systemic treatments with hormones, chemotherapy or bisphosphonates administered by the treating doctor, and close follow-up with repeat MRI if SCC was clinically suspected.

• 3 subgroups of patients were identified for the purpose of analysis.

Group A: patients who had rSCC and received radiotherapy

Group B: patients who did not have rSCC but received radiotherapy for back pain

Group C: patients who did not have rSCC or back pain and did not receive radiotherapy.

Outcomes

- Clinical details: RT, neurologic outcome, incidence of repeat episodes of SCC.
- Clinical factors were analysed with respect to overall survival and functional neurologic status at last follow-up.
- Neurologic deficit free interval = the time from the initial MRI scan to the time of development of any neurologic deficit due to involvement of the spinal cord or nerve roots from spinal metastases.
- Overall survival = time from the initial MRI to the time of death (Kaplan–Meier method)

Results

- Median time from diagnosis was 1238 (94–6412) days
- 108 patients had MRI for back pain.
- 41 (27.3%) patients had rSCC and the median follow-up was 301 (range 2–3122) days.

Neurological outcome

Univariate analysis showed the following to be significant predictors of poor neurological

outcome:

- back pain (HR 2.58 (95% CI 1.22–5.46), $p = 0.013$),
- extensive bony disease (HR 2.24 (1.06–4.71), $p = 0.005$)

Multivariate analysis showed back pain to be significant predictors of Neurologic deficit-free interval:

HR 2.62 95% CI 1.21–5.68, $p = 0.015$

Overall survival

- The median overall survival for all patients = 481 days (95% CI 339–634 days).
- Univariate analysis: the predictors of survival were:
back pain (HR 2.22, 95% CI 1.35–3.65, $p = 0.02$)
extensive bony disease (HR 1.92, 95% CI 1.2–3.09), $p = 0.007$
metastasis at diagnosis (HR 1.75, 95% CI 1.15–2.66), $p = 0.009$)
- Again on multivariate analysis, back pain was a significant predictors of survival: HR 2.29, 95% CI 1.34–3.93, $p = 0.003$

Effect of MRI on outcome

- The median neurologic deficit free interval = 804 days for the patients who had rSCC
- The median neurologic deficit free interval = 989 days for those who had no rSCC on MRI.
- rSCC on MRI did not predict for either neurologic deficit (HR 1.74, 95% CI 0.88–3.46, $p = 0.11$) or overall survival (HR 1.49, 95% CI 0.96–2.32, $p = 0.074$).

Influence of radiotherapy

- 39 of 41 patients who had rSCC received radiotherapy. (the remaining 2 patients died and the other was lost to follow-up).
- 50 out of 109 patients who had no rSCC on MRI received radiotherapy to sites of pain in the spine.
- There was no statistical difference in neurologic deficit free interval between patients who had radiotherapy compared to those who did not (HR 1.87, 95% CI 0.93 –3.78, $p = 0.08$),
- There was no statistical difference in overall survival in the two groups (HR 1.13 (0.74 – 1.72); $p = 0.58$).
- There was no difference in outcome at one year in the patients who received radiotherapy (the local control rate at the site of radiotherapy = 88% at 1 year) (the neurologic deficit-free rate at 1 year = 84% in patients who did not receive radiotherapy.)
- 81% of patients who had no rSCC and had no spinal radiotherapy for bone pain remained neurologic deficit-free.
- Comparison of functional neurologic interval between the groups of patients who received the two doses of radiotherapy, either 20 Gy vs 8 Gy, showed no significant difference (median neurologic deficit-free interval 678 days vs 671 days, $p = 0.5$)

Outcome in the patient subgroups

- Analysis of patient subgroups showed:
Group A: patients who had rSCC and received radiotherapy = 39 patients
Group B: patients who did not have rSCC but received radiotherapy for back pain = 50
Group C: patients who did not have rSCC or back pain and did not receive radiotherapy = 59
- The number of patients who developed rSCC or functional neurologic deficit on follow-up was:
12 (30.7%) group A,
16 (32%) group B
11 (18.6%) group C.

- The number of patients who developed rSCC on follow-up MRI at the same site of radiotherapy, compared to that who developed rSCC at a different spinal level:
Group A: 6 (at the same site of radiotherapy) and 4 (those who developed rSCC at a different spinal level) Group B : 4 (at the same site of radiotherapy) and 9 (those who developed rSCC at a different spinal level)
- There was no statistical difference between the three subgroups of patients either in neurologic deficit free interval ($p = 0.13$) or overall survival ($p = 0.33$).
- The author's claim, "patients without pain and impending SCC appear to have a better neurologic outcome the other two groups (HR 0.44 (95% CI 0.19–1.01))"

General comments

- This study demonstrated that back pain and extensive skeletal metastasis were the independent predictors for occult SCC and patients with back pain had worse neurologic outcome and survival, on multivariate analysis.
- The results of this study suggest that MRI surveillance may be important in detecting clinically occult SCC in prostate cancer patients with bone metastases. Preservation of neurologic function may be achieved with prophylactic radiotherapy for patients with pain or radiological SCC (but clinically occult).
- Patients without both pain and impending SCC may do better than the other two groups, but this was not statistically evident in this study.
- Limitations of this study include the retrospective study design, small patient numbers and possible selection bias. In order to demonstrate the statistically significant positive impact of early detection of SCC and impact of early treatment on neurologic function a prospective randomised study with a larger number of patients needs to be conducted.

Health Economic Evaluation

The literature search identified 41 potentially relevant papers. Five of these studies were obtained for appraisal. Three of these studies did not contain an economic evaluation. The remaining two papers both included an economic evaluation but both evaluated the use of MRI scanning to detect cancers in primary care settings, not in people with suspected bone metastases with the aim of preventing MSCC. No de novo modelling was attempted because there was no clinical evidence to suggest that available treatments prevent the development of MSCC. Thus, scanning people with suspected bone metastases using MRI to prevent MSCC can not be considered cost-effective given current clinical evidence.

5.4 Timing of MRI Assessment

Effects of delayed diagnosis and treatment

In patients with MSCC, what effect does delay from presentation to definitive treatment have on clinical outcomes (mobility, urinary continence, lack of pain, survival independent living)?

In patients with MSCC, what effect does performance status at the time of treatment have on clinical outcomes (mobility, urinary continence, lack of pain, survival independent living)?

In patients with a clinical diagnosis of malignant spinal cord compression, how soon should definitive treatment be undertaken to prevent permanent neurological deficit?

Short Summary

Evidence for this question was drawn from several observational studies (Helweg-Larsen *et al.* 1996, Husband *et al.* 1998, Levack *et al.* 2002, Maranzano *et al.* 1995, Mitera *et al.* 2003, Solberg *et al.* 1999, Turner *et al.* 1993). The findings from this evidence consistently reported that early diagnosis and treatment, while functional status is good, leads to better functional outcome and longer survival. Age, primary tumour histology, functional status at treatment and time taken to develop MSCC are predictors of functional outcome.

PICO

Population Group	FACTORS	Outcomes
QUESTION A: Patients with MSCC	The effect of a delay from presentation to definitive treatment (RT, surgery)	<ul style="list-style-type: none"> ▪mobility, ▪urinary continence, ▪lack of pain, ▪survival ▪independent living
QUESTION B: Patients with MSCC	The effect of performance status at the time of treatment	<ul style="list-style-type: none"> ▪mobility, ▪urinary continence, ▪lack of pain, ▪survival ▪independent living ▪Report the effect of delay on treatment choice (Treatment type – i.e. surgery, radiotherapy, chemo, palliative, none)

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

Evidence for this question was drawn from observational studies. The findings from this evidence consistently reported that early diagnosis and treatment, while functional status is good, leads to better functional outcome and longer survival. Age, primary tumour histology, functional status at treatment and time taken to develop MSCC are predictors of functional outcome.

A. The effect of delay from presentation to definitive treatment

A case series report on 86 patients where median time, from the start of symptoms to the first doctor contact was 1 day and to hospital admission and treatment start 6 days, (range 0-158) and 8 days respectively (0-208). Male patients had a median of 1 day to first doctor contact, while female patients had a median of 5 days ($p < 0.05$). Of all patients 80% had a delay of 3 days or more and 55% had a delay of 7 days or more from first symptom to treatment start. (Solberg *et al.* 1999)

There is some evidence from an abstract (which was not published as a full report), that a median time delay of 12 days from symptom onset till RT treatment was experienced by 10 patients, and 64% of this delay resulted from symptom onset to initiation of medical attention. Furthermore, when patients perceived symptoms to be related to their previous cancer, the median time delay was 5.5 days, compared to 17 days when patients related symptoms to other co-morbidities. Deterioration of symptoms was strongly correlated with time delay ($r = 0.87$; $p = 23.92$). (Mitera *et al.* 2003)

Reports on the effect of delay in diagnosis on outcomes

Mobility and Urinary Continence: A cohort study following 209 patients concluded that early diagnosis of MSCC was the most important predictor of outcome, so that patients who had motor function and good bladder function maintained those capacities. Primary tumour histology had significance only when patients were non-ambulatory, paraplegic or had bladder dysfunction. When diagnosis was late, tumours with favourable histology (myeloma, breast and prostate carcinomas) above all responded to RT. Duration of response was influenced by tumour histology. Favourable histology are associated to higher median response. (Maranzano *et al.* 1995)

A prospective observational study of 319 patients concluded that those patients who develop spinal metastases are at risk of irreversible spinal cord damage. Weakness and sensory abnormalities were reported late and identified even later, despite patients reporting pain for a considerable time. Pain was reported by nearly all patients interviewed (94%) and had been present for approximately 3 months (median 90 days). Pain was severe in 84% of cases, with the distribution and characteristics of nerve root pain in 79%. The site of pain did not correspond to the site of compression. At diagnosis most patients were either unable to walk (82%) or only able to walk with help. Where reported, weakness and/or sensory problems had been present for some time before the diagnosis (median 20 and 12 days respectively). Most patients reported early symptoms to the GP and diagnosis was established, following referral and investigation, approximately 2 months later (median 66 days). "Patients with cancer who describe severe back pain or spinal nerve root pain need urgent assessment on the basis of their symptoms, as signs may occur too late." Plain films and bone scans requested for patients in this study predicted accurately the level of compression in only 21% and 19% of cases respectively. The only accurate investigation to establish the presence and site of a compressive lesion is MRI. (Levack *et al.* 2002)

In a preliminary report from a cohort study of 153 patients, early diagnosis, while patients are still ambulatory, is reported as most important prognostic factor. (Helweg-Larsen, 1996).

Lack of pain: no evidence found reporting on this outcome related to delay in diagnosis

Survival: no evidence found on this outcome related to delay in diagnosis

Independent living: no evidence found on this outcome related to delay in diagnosis

Reports on the effect of delay in treatment on outcomes:

A prospective observational study reporting on the outcomes of 37 patients states that prompt treatment, while patients are still ambulant, is effective in maintaining ambulatory

and functional independence and that treatment improves pain in most patients. 81% who were ambulant pre-treatment, remained ambulant after treatment. 16.5% of patients who were non-ambulant regained ambulatory following treatment. Pain improved following treatment in 73% of patients this benefit was seen equally for ambulant and non-ambulant patients. A high level of functional independence was maintained in patients who remained ambulant. The median delay between first assessment and first treatment was 12 hours (range 1-96 hours) (Turner *et al.* 1993)

Reports on the effect of delay in diagnosis and treatment (combined) on outcomes

There is evidence from a prospective observational study of 301 patients that unacceptable delays in diagnosis, investigation and referral occurs in most patients with malignant spinal cord compression and results in preventable loss of function before treatment, which may be irreversible. Improvement in outcome of such patients requires earlier diagnosis and treatment. The median (range) delay from onset of symptoms of SCC to treatment, in a cohort of 310 consecutive patients, was 14 (0-840) days. Of the total delay, 3 (0-300) days by GPs, 4 (0-794) by the District General Hospital and 0 (0-114) days by the Treatment Unit. Initial presentation to the regional cancer centre with symptoms of MSCC led to a significant reduction in delay to treatment and improved functional status at the time of treatment. Deterioration of motor or bladder function ≥ 1 grade occurred at the general practice stage in 28% and 18 % of patients, the general hospital stage in 36% and 29% and the treatment unit stage in 6% and 5% respectively. (Husband *et al* 1998).

The effect of performance status at the time of treatment

Reports on the effect of functional status and histological features (at the time of treatment) on outcomes

Mobility and Urinary Continence: There is good evidence from a cohort study of 153 patients the pre-treatment ambulatory function was reported as the main determinant of post-treatment gait function. The type of primary tumour had a direct influence on the interval between the diagnosis of the primary malignancy and the occurrence of SCC ($p < 0.005$) and on the ambulatory function at the time of diagnosis ($p = 0.016$). There was a clear correlation between the degree of myelographic blockage and gait function ($p = 0.000$) and between the gait function and sensory disturbances ($p = 0.000$). The final gait was dependent on the gait function at the time of diagnosis ($p < 0.0005$). (Helweg-Larsen *et al.* 2000)

In a case series report of 86 patients, 32% of patients did not respond to therapy, 43% of patients had a minor response or stabilisation (grade 1), 17% had a moderate to pronounced improvement on motor function (grade 2) and 9% gained full recovery (grade 3). While there was no measurable improvement in paraplegic patients, 36% of severe paraparesis and 19% of mild to moderate paraparesis patients improved. A significantly larger part of ambulant patients (35%) achieved treatment response 2 or 3, compared to 22% of non-ambulant patients. Among patients achieving full restoration of motor function 72% were ambulant and 28% were non-ambulant at the time of treatment. After treatment 43% of patients were ambulant. Gait function was regained in 33% of previously non-ambulant patients and lost in 25% of previously ambulant patients. (Solberg *et al.* 1999)

Another retrospective observational study of 70 patients reports that radio-therapeutic success ceiling of 80% may be reached for Findlay grade I patients with MSCC, for which early diagnosis is of utmost importance. A powerful predictor of response to RT was the patient's neurological status (Findlay grade) at the time of diagnosis: 66% of previously ambulatory patients remained so, whereas 30% of non-ambulatory patients and only 16% of paraplegic patients regained the ability to walk. Another important predictor response was primary tumour histology, with the most favourable response to RT being observed in lympho-proliferative diseases and in breast cancer, but with some response to radiosensitive malignancies as well. (Leviiov *et al.* 1993)

In a prospective observational study of 59 patients with extradural spinal cord compression the pre-treatment motor function was found to be a significant factor in determining functional prognosis. There is a significant correlation between the degree of spinal cord block and motor function at presentation. Patients with abnormal sphincter function had a higher frequency of almost complete block than patients with normal sphincter function. (Kim *et al.* 1990)

An observational study of 209 patients established the median survival time as 6 months, with a 28% probability of survival for 1 year. Survival time was longer for patients who were able to walk at the time of treatment, those with favourable histologies and females. There was a correlation between patient survival and duration of response, systemic relapse of disease being generally the cause of death. (Maranzano *et al.* 1995).

There is some evidence from a report on the outcomes of 775 patients that pre-treatment functional status independently predicted for post-treatment motor, sensory and autonomic function and time to functional recovery on multivariate analyses. Multivariate analysis revealed that increased survival was predicted by better motor function before treatment, younger age, longer intervals from cancer diagnosis to MSCC

and tumour primary sites of breast, prostate and myeloma. Median survival was 4.1 months. (Loblaw *et al.* 2003)

A large cohort study reporting on the comparison of five RT schedules reported similarities in functional outcome, irrespective of RT schedule; on multivariate analysis, age, performance status, primary tumour, involved vertebrae, interval from cancer diagnosis to MSCC, pre-treatment ambulatory status and time to developing motor deficits were significantly associated with functional outcome, whereas RT schedule was not. The three more protracted schedules resulted in in-field recurrences. Motor function improved in 26% (1 x 8 Gy), 28% (5 x 4 Gy), 27% (10 x 3 Gy), 31% (15 x 2.5 Gy) and 28 % (20 x 2 Gy); post-treatment ambulatory rates were 69 %, 68%, 63%, 66% and 74% respectively ($p=0.578$). (Rades, Stalpers *et al.* 2005)

Survival correlated positively to preserved gait function at admission, to treatment response grade and to the employment of combined surgical laminectomy and radiotherapy. In a case series report of 86 patients, the pre-treatment grade of paresis, preservation of gait function and primary tumour histology were strong predictors for treatment response. Primary tumour histology was an important predictor, as breast cancer and prostate cancer had a 3 to 6 fold longer survival compared to lung cancer patients. (Solberg *et al.* 1999)

Survival time after diagnosis depended directly on the ambulatory function at the time of treatment ($p=0.018$) and on the ambulatory function after treatment. (Helweg-Larsen *et al.* 2000).

This is confirmed by a retrospective observational study in which in all 131 patients median survival was 5 months. Survival rates were 76% after 3 months, 65% after 4 months, 50% after 5 months, and 40% after 6 months. (Rades *et al.* 2001)

Further evidence from retrospective case series reported that survival correlated positively to preserved gait function at admission and to treatment response grade. Median overall survival from treatment start was 4.1 months (range 0.03-101) and only 13% and 7 % are alive after 2 and 5 years respectively. While all patients with paresis grade 3 are dead within 1 year from treatment start 7% and 10% of grade 2 and 1 paresis patients are alive at 5 years. Survival correlated to classified motor function response to treatment, ($p<0.0001$). There were significant post-treatment survival differences with regard to primary malignancies: breast cancer and prostatic cancer patients constituted 71% of patients surviving 12 months, as only one of the lung cancer patients survived more than 5 months. Whether patients were ambulant or not at admission did not have any significant impact on post-treatment survival. On the other hand, patients that were ambulant at the time of treatment had significantly longer survival than the non-ambulant ones 7.7 vs. 2.0 months ($p< 0.0001$). At one year after treatment 42% of ambulant patients and 12% of non-ambulant patients were alive. (Solberg *et al.* 1999)

A retrospective review of 166 cases reports that survival was significantly better from those presenting with good functional status. Performance and neurological status have prognostic significance. A comparison of performance status before and after treatment reveals no significant change. In only 16%, there was an improvement, 59% of patients having no change and 25% having a worse performance status after treatment. Similarly, there was no change in neurological status with 20% of patients showing an improvement, 55% having no change and 25% having a worse neurological status following treatment. The median survival of all patients from the date of confirmation of SCC was 82 days (range 1-1349 days) (Cowap *et al.* 2000).

For patients with spinal metastases and cord compression, the factors found to affect survival include preoperative neurological status, anatomic site of primary carcinoma, and number of vertebral bodies involved. Patients with vertebral column disease and two or more of the poor prognostic indicators have a short life expectancy and therefore, radical surgery is not recommended because the benefits may not be substantial. The overall median survival was 10 months. Patients preoperatively ambulatory survived statistically significantly longer than non ambulatory patients or those with sphincter incontinence ($p=3.469 \times 10^{-6}$). Patients with renal cell carcinoma survived the longest, followed by those with breast, prostate, lung and colon cancer. Patients with breast cancer survived statistically longer than those with lung cancer ($p=0.039$). Patients with one vertebral body involved survived statistically significantly longer than patients with multiple vertebral level involvement ($p=0.027$). Extent of disease, age, and tumour location did not significantly influence survival. In patients with vertebral column disease, the presence of two or more poor prognostic indicators (leg strength 0/503/5, lung or colon cancer, multiple vertebral body involvement), had a compounding adverse effect on survival. (Sioutos *et al.* 1995)

In a retrospective observational study of 355 breast cancer patients with diagnosed MSCC, survival was reported as negatively affected by the presence of visceral metastases ($p<0.001$), deterioration of motor function after RT ($p<0.001$) reduced performance status ($p<0.001$) and the rapid development of motor deficits ($p= 0.044$). (Rades *et al.* 2006)

Lack of pain: Pain relief correlated to treatment response grade. Of all patients 74% reported pain at admittance. Treatment effect: 82% experienced significant pain reduction while 18% did not. Pain relief was obtained in all patients with full motor function recovery (grade 3) and in 92%, 88% and 58% of patients with response grade 2 1 and 0 respectively. 50% of lung cancer patients reported pain relief, while this was significantly more frequent in breast and prostate cancer patients, 100% and 95% respectively. Following treatment, 90% of patients ages above 60 years reported pain relief compared to 69% under 60 years ($p<0.04$). (Solberg *et a.* 1999)

Independent living: no study reported on independent living as outcome related to initial functional status

Reports on the effect of length of time from primary tumour diagnosis to developing MSCC

Mobility: Data from a further retrospective observational study confirms that a slower development of motor deficits before RT predicts a better functional outcome. In patients with rapid deterioration before RT motor dysfunction might be explained by generally irreversible spinal cord infarction. Rates of ambulatory patients before RT were comparable in groups of patients. Two weeks after RT 83% of the patients in the group which had taken >14 days to develop motor deficit before RT were ambulatory, compared to only 24% of patients in the group which has taken 1-7 days to develop motor deficit before RT. This was also observed 3 months after RT. Besides type of primary tumour and pre-treatment ambulatory status, the time of developing motor deficit before RT is considered a relevant prognostic factor in MSCC (Rades *et al.* 2001)

This is confirming partial reports from a previous prospective observational study demonstrating that a slower development of motor deficits before RT predicts a better post-treatment functional outcome. In patients with rapid deterioration of motor function within 48 hours before treatment prognosis was extraordinarily poor. Directly after RT 93% of patients of the group developing motor deficits >14 days showed improvement of motor function, in comparison to 10% of the group developing motor deficits in 1-14 days ($p<0.001$). Deterioration rates were 0% (>14 days) and 45% (1-14 days). In patients with rapid deterioration of motor function <48 hours before RT, prognosis was

poor (improvement 0%, no change 43%, deterioration 57%). Results were comparable 6, 12 and 24 weeks after RT. (Rades, et al., 2000). The final report on 98 patients reinforced the preliminary report: in the group that took >14 days to develop motor deficits, improvement occurred significantly ($p<0.001$) more often than in the other subgroups (8-14 days and 1-7 days), 86% versus 29% and 10%, and the post-treatment ambulatory rate was significantly higher (86% vs. 55% and 35%, $p=0.026$). multivariate analysis revealed the time to development of motor deficits before RT to be the strongest prognostic factor. (Rades *et al.* 2002)

The same seems to be applicable to treatment with RT of MSCC associated with prostate cancer. A retrospective observational study of 281 prostate cancer patients points out that functional outcome after RT was significantly influenced by the time taken to develop motor deficits before RT (more than 14 days better than 8-14 days and 1-7 days $p<0.001$) and number of involved vertebrae (1-2 better than 3 or more, $p=0.013$), but not by the radiation schedule ($p=0.859$). Local control was significantly better after application of long course RT. Overall response to RT was 86% (33% improvement of motor function, 53% no further progression). Of the non-ambulatory patients 33% regained the ability to walk. The 2 year local control of MSCC was 84% depending on the radiation schedule (better after long course RT, $p=0.001$). (Rades, Stalpers *et al.* 2006)

In a retrospective observational study of 355 breast cancer patients with diagnosed MSCC functional outcomes after RT for MSCC in breast cancer patients are associated with slower development of motor deficits ($p<0.001$) and being ambulatory before RT ($p<0.001$). The overall recurrence rate of MSCC was greater if other bone metastases were present and if short course RT was used. (Rades *et al.* 2006)

Survival: Evidence from a cohort study of 153 patients suggested that survival time after diagnosis depended directly on the time from primary tumour diagnosis until spinal cord compression ($p=0.002$). (Helweg-Larsen *et al.* 2000).

A prospective case series study reported that a long interval between primary tumour diagnosis and primary surgery for MSCC was associated with a better survival rate. Pathologic fractures, visceral and brain metastases are negative prognostic variables for 1 year survival. Solitary metastases, breast and kidney cancer and myeloma were positive predictive variables. (Bauer *et al.* 1995).

Reports on effect of functional status, histological features (at the time of treatment) and treatment choice (surgery, RT, combination of both) on functional outcomes

The effectiveness of RT plus steroids was apparent. When diagnosis was late tumours with favourable histology (myeloma, breast and prostate carcinomas) above all responded to RT. Duration of response was influenced by tumour histology. Favourable histology are associated to higher median response. (Maranzano *et al.* 1995)

There is further evidence from a retrospective observational study of 75 patients in which two radiation schedules (30 Gy /10 fractions and 37.5 Gy /15 fractions) were compared for post-treatment functional outcome and ambulatory status that no significant difference existed between the two radiation schedules (30 Gy /10 fractions and 37.5 Gy /15 fractions) for post-treatment ambulatory status (p values: 0.450-0.888) nor for functional outcome (p values: 0.940-0.999). According to the multivariate analysis the strongest predictors for the functional outcome were the time of developing motor deficits before RT ($p<0.001$) and the pre-treatment ambulatory status ($p<0.001$) followed by the type of primary tumour ($p=0.058$). (Rades & Karstens, 2002)

A large cohort study reporting on the comparison of five RT schedules (1 x 8 Gy), (5 x 4 Gy), (10 x 3 Gy), (15 x 2.5 Gy) and (20 x 2 Gy) reported similarities in functional outcome, irrespective of RT schedule; on multivariate analysis, age, performance status, primary tumour, involved vertebrae, interval from cancer diagnosis to MSCC, pre-treatment ambulatory status and time to developing motor deficits were significantly associated with functional outcome, whereas RT schedule was not. The three more protracted schedules resulted in in-field recurrences. (Rades, Stalpers *et al* 2005)

In a prospective observational study of 59 patients with extradural spinal cord compression there was no significant difference reported in outcome between dose schedule (3,000 cGY x 10 fractions and 3,000 cGY x 9 fractions with higher initial dose fractionation 400 cGY for the first 3 doses). Degree of spinal cord block and radio-sensitivity of tumour were not significant independent factors. (Kim *et al.* 1990)

In a preliminary report from a cohort study of 153 patients early diagnosis, prognosis for recovery of ambulatory function is reported as good, if supplementary systemic therapy is employed. In total 21/74 of non-ambulatory patients regained motor function after therapy. 10/57 patients regained urinary function. Radicular pain is reported to have disappeared after therapy in 95/116 patients. (Helweg-Larsen, 1996).

A retrospective observational study of 81 patients shows that despite initial delays in referral and even if the patient is incontinent and immobile, emergency surgical spinal decompression leads to better outcome. A greater proportion of patients which have undergone emergency surgery rather than electively (within 24 hours) showed functional improvement (61.5% versus 25%). Overall, 70% of patients were mobile post-operatively. Patients who underwent laminectomy had a good functional outcome (functional improvement, or preservation of mobility and continence), compared to patients in the laminectomy and fusion and in anterior corpectomy and fusion group. (Harris *et al.* 1996)

A retrospective observational study of 107 patients reported that surgery in vertebral metastasis without neural deficit results in substantial functional improvement but does not increase the survival rate. Mean survival varies, according to primary neoplasm. (Chataigner *et al.* 2000)

There is fairly good evidence from a retrospective review of 398 cases that patients treated by decompressive laminectomy followed by RT had a better response than patients treated with surgery or RT alone, but when the patient's pre-treatment motor function was taken into account no significant difference was observed. Of the patients who were ambulatory before the treatment 79% remained ambulatory, whereas only 18% of the non-ambulatory patients regained walking ability. (Bach, 1990)

There is some evidence from a retrospective case series comparing RT with surgery and a combination of both, stated that, of the treatments given, a combination of surgery followed by RT was associated with the greatest functional improvement ($p=0.001$). The coexistence of 'liver failure' was the only patient-related factor identified which was associated with outcome ($p=0.041$). Complete resolution of individual pre-treatment symptoms that were measured 1 month after treatment occurred as follows: pain (30/88), sensory disturbance (12/61), weakness (8/17), bladder dysfunction (10/42), and bowel dysfunction (10/36). Complete resolution of motor deficit occurred in 7/82 and sensory deficit in 9/73. The ability to walk was regained in 19/51 previously non-ambulatory patients, and bladder function improved sufficiently to remove an indwelling catheter in 9/32 previously catheterised patients. As judged by functional improvement scores, 67 patients improved, 15 patients remained stable and 12 patients deteriorated. (Milross *et al.* 1997).

This is confirmed by a later study in which survival correlated positively to the employment of combined surgical laminectomy and radiotherapy. A retrospective case series reported that survival after surgery correlated positively to treatment response grade and to the employment of combined surgical laminectomy and radiotherapy. Primary tumour histology was an important predictor, as breast cancer and prostate cancer had a 3 to 6 fold longer survival compared to lung cancer patients. Survival correlated to classified motor function response to treatment. ($p < 0.0001$). Whether patients were ambulant or not at admission did not have any significant impact on post-treatment survival. On the other hand, patients that were ambulant at the time of treatment had significantly longer survival than the non-ambulant ones. (Solberg *et al.* 1999)

An earlier observational study reports no differences in outcome between those treated by combined surgery with RT and those treated with RT alone, but states that patients with radiosensitive tumours and those ambulatory at the onset of treatment benefited most, regardless of treatment method. 75% of living patients who improved from treatment remained ambulatory at 6 months, and approximately 50% of living patients were ambulatory at 1 year. (Gilbert *et al.* 1978)

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Summary of Evidence Tables

Table 1: Paraparetic patients

Reference:	Population Group Paraparesis (walking or not)	Patient Characteristics Tumour type -Cord or cauda	Time from diagnosis to treatment (days or hours)	Outcomes: Number that remained ambulant	Change in Functional status
Levirov, M., et al., 1993	70 patients Ambulant (n=24); Paraparetic/Non-ambulant (n=27)	Breast; Prostate; Lung; Lymphoma; Unknown (not broken down by ambulatory status) MSCC or cauda (numbers not reported separately)	Not reported	From Ambulant Group: Remained ambulant (n=16, 66%); From Paraparetic Group: Became ambulant (n=8, 30%)	Not reported
Bach, F., et al., 1990	398 patients Paraparetic (n=165)	Breast; Prostate; Lung; Kidney; (not broken down by ambulatory status) - cord only	Mean duration from first symptom to diagnosis: 58 days (average 30 days, range 0-420 days) Mean duration from first visit to doctor and diagnosis of SCC: 23 days (average 4 days, range 0-360 days)	No deficit (n=5); Mild deficit (n=30); Remained paraparetic (n=98); Became paraplegic (n=32)	Not reported as a functional status
Gilbert, R.W., Kim, J-H., Posner, J.B., 1978	235 patients Paraparetic (n=116, 49%)	Breast; Prostate; Lung; Kidney; Lymphoma / myeloma; melanoma; GI; others (not broken	Not reported	Became ambulant (n=52, 45%)	Duration of improvement: 75% of living patients who improved from treatment remained ambulatory at 6

		down by ambulatory status) - cord only			months; 50% at one year
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Reference:	Population Group Paraparesis (walking or not)	Patient Characteristics Tumour type -Cord or cauda	Time from diagnosis to treatment (days or hours)	Outcomes: Number that remained ambulant	Change in Functional status
Solberg, A. Bremnes, R.M., 1999	86 patients Mild/moderate motor function deficit (n=29); Severe motor function deficit (n=46)	Breast; Prostate; Lung; Kidney (breakdown of numbers not reported) - cord only	Median duration from first symptom to first doctor contact: 4 day (range 0-30) Median duration to hospital admission and treatment start: 6 days (range 0-158) 8 days (range 0-208)	From Mild/moderate Group: No deficit (n=5); Mild/moderate deficit (n=17); Severe deficit (n=3); Paraplegic (n=2) From Severe Group: No deficit (n=2); Mild/moderate deficit (n=14); Severe deficit (n=24); Paraplegic (n=5)	A significantly larger part of ambulant patients (35%) achieved treatment response 2 or 3, compared to 22% of non-ambulant patients; 82% experienced significant pain reduction; pain relief was obtained in all patients with full motor function recovery

Table 2: Paraplegic patients

Reference	Population Group – Paraplegic	Patient Characteristics – Tumour type -Cord or cauda	Time from diagnosis to treatment (days or hours)	Outcomes: Number that regained ambulence	Change in Functional status
Helweg-Larsen, S., 1996	153 patients Total Paralysis (n=43)	Breast (n=6); Prostate (n=17); Lung (n=14); Others (n=6)	Not reported	n=9	
Maranzano, E., Latini, P.,	209 patients Paraplegic (n=18,	Breast; Prostate; Myeloma (not broken	Not reported	n=2, 11%	Not reported

1995	9%)	down by ambulatory status)			
Levirov, M., et al., 1993	70 patients Complete paraplegia (n=19, 27%)	Breast; Prostate; Lung; Lymphoma; Unknown (not broken down by ambulatory status) MSCC or cauda (numbers not reported separately)	Not reported	Became ambulant (n=3, 16%)	Not reported
Reference	Population Group – Paraplegic	Patient Characteristics – Tumour type -Cord or cauda	Time from diagnosis to treatment (days or hours)	Outcomes: Number that regained ambulence	Change in Functional status
Bach, F., et al., 1990	398 patients Paraplegic (n=49)	Breast; Prostate; Lung; Kidney; (not broken down by ambulatory status) - cord or cauda (numbers not reported separately)	Mean duration from first symptom to diagnosis: 58 days (average 30, range 0-420) Mean duration from first visit to doctor and diagnosis of SCC: 23 days (average 4, range 0-360)	No deficit (n=0); Mild deficit (n=3); Became paraplegic (n=15); Remained paraplegic (n=31)	Not reported as a functional status
Gilbert, R.W., Kim, J-H., Posner, J.B., 1978	235 patients Paraplegic (n=39, 17%)	Breast; Prostate; Lung; Kidney; Lymphoma / myeloma; melanoma; GI; others (not broken down by ambulatory status) - cord only	Not reported	Became ambulant (n=2, 22%)	Duration of improvement: 75% of living patients who improved from treatment remained ambulatory at 6 months; 50% at one year
Solberg, A.	86 patients	Breast; Prostate; Lung;	Median duration	No deficit (n=0);	Not reported

Bremnes, R.M., 1999	Paraplegic (n=11)	Kidney (breakdown of numbers not reported)	from first symptom to first doctor contact: 4 day (range 0-30) Median duration to hospital admission and treatment start: 6 days (range 0-158) 8 days (range 0-208)	Mild/moderate deficit (n=0); Severe deficit (n=0); Paraplegic (n=10) No patient regained the ability to walk	
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Note: not all studies included in the review did report on the status of patients grouped into paraparesis or paralysis clusters, but rather on ambulant or non-ambulant. It cannot be implied that all non-ambulant patient would form the paralysis group - some of them might have been only paraparetic. Also, some of the patients reported ambulant might have had a mild paraparesis, especially those reported with assisted gait. Therefore, only those studies that reported specifically population grouped as 'paraparesis' and/or 'paralysis' have been included in the table above. Table 3 below, summarises the studies reporting on patients grouped as ambulant or non-ambulant or various degrees of functional impairment.

Table 3: Patients not defined by paraparetic/paraplegic

Reference	Population Group – Not defined by paraparesis/paraplegia category	Patient Characteristics – Tumour type -Cord or cauda	Time from diagnosis to treatment (days or hours)	Outcomes: Number that remained ambulant	Change in Functional status
Rades, D., Stalpers, J.A., et al., 2005	1,304 patients Ambulatory (n=825); Non-ambulatory (n=479)	Primary tumour type not reported; Tumour status: Favourable (n=142); Intermediate (n=861); Unfavourable (n=301) - cord only	Days: 1-7 days (n=336); 8-14 days (n=360); >14 days (n=608)	From Ambulatory Group: Improvement of Motor Function (n=224, 27%) No Change in Motor Function (n=492, 60%) From Non-ambulatory Group:	From Ambulatory Group: Deterioration of Motor Function (n=109, 13%) From Non-ambulatory Group: No Change in Motor Function (n=247, 51%)

Reference	Population Group – Not defined by paraparesis/paraplegia category	Patient Characteristics – Tumour type -Cord or cauda	Time from diagnosis to treatment (days or hours)	Outcomes: Number that remained ambulant	Change in Functional status
				Improvement of Motor Function (n=133, 28%)	Deterioration of Motor Function (n=99, 21%)
Helweg-Larsen, S., 1996	153 patients Unaided gait (n=60); Walk with assistance (n=19); No gait function (n=31);	Breast (n=56); Prostate (n=43); Lung (n=27); Others (n=27) (breakdown includes 43 total paralysis patients, reported in table 2) - cord only	Not reported	Not reported	21/74 of non-ambulatory patients regained motor function; 10/57 recovered from bladder dysfunction; 95/116 reported no radicular pain.
Maranzano, E., Latini, P., 1995	209 patients Walking (n=73, 35%); Walking with aid (n=36, 17%); Non-walking (n=82, 39%)	Breast; Prostate; Myeloma (Not broken down by ambulatory status) - cord only	Not reported	73/73 (100%) 34/36 (94%) 49/82 (60%)	76% achieved full recovery or preservation of motor function and 44% with bladder dysfunction improved. At 3 months: 146/209 walking; 118/209 reported no pain; 145/209 reported no bladder dysfunction
Reference	Population Group – Not defined by paraparesis/paraplegia category	Patient Characteristics – Tumour type -Cord or cauda	Time from diagnosis to treatment (days or hours)	Outcomes: Number that remained ambulant	Change in Functional status
Turner, S., et al., 1993	37 patients Ambulant (n=16, 46%); Non-ambulant (n=20, 54%)	Primary tumour not reported - cord only	Median delay between first assessment and first treatment was 12 hours (range 1-96 hours).	From Ambulatory Group: Remained ambulant (13/16, 81%); Became non-ambulant (3/16, 19%)	Functional independence maintained in patients who remained ambulant. Pain improved in 22/30 (73%);

Reference	Population Group – Not defined by paraparesis/paraplegia category	Patient Characteristics – Tumour type -Cord or cauda	Time from diagnosis to treatment (days or hours)	Outcomes: Number that remained ambulant	Change in Functional status
				From Non-ambulatory Group: Became ambulant (2/16, 12.5%); Remained non-ambulant (14/16, 87.5%)	
Chataigner, H., Onimus, M., 2000	107 patients Karnofsky Index: 80% or more (n=38); 50-70% (n=53); 40% or less (n=16) Tokuhashi Score: 9 or more (n=63); 5 or less (n=7)	Breast (n=30); Digestive tract (n=6); Lung (n=37); Kidney (n=8); Prostate (n=2); Others (n=17); Unknown (n=9) (primary tumour not reported as a variable linked to the functional index) - cord only	Not reported	Not reported	Mean Survival (months): Karnofsky Index: 80% or more (11.8); 50-70% (7.3); 40% or less (4.4) Tokuhashi Score: 9 or more (8); Between 5 and 9 (9.5); 5 or less (2)
Cowap, J., Hardy, J.R., A'Hern, R., 2000	166 patients Fully ambulatory (n=56, 34%); Moderate functional impairment (n=48, 29%);	Primary tumour not reported - cord only	Not reported	Improvement (16%); No change (59%); Worse performance (25%)	Neurological status: Improved (20%); No change (55%); Worse (25)
Harris, J. K., et al., 1996	81 patients Mobile (n=19);	Primary tumour not reported - cord or cauda (numbers not reported)	Not reported	Improved (n=39); Unchanged (n=37); Deteriorated (n=4)	Good outcome (n=54); Poor outcome (n=22); Other outcome (n=4)

Reference	Population Group – Not defined by paraparesis/paraplegia category	Patient Characteristics – Tumour type -Cord or cauda	Time from diagnosis to treatment (days or hours)	Outcomes: Number that remained ambulant	Change in Functional status
Reference	Population Group – Not defined by paraparesis/paraplegia category	Patient Characteristics – Tumour type -Cord or cauda	Time from diagnosis to treatment (days or hours)	Outcomes: Number that remained ambulant	Change in Functional status
Rades, D., Stalpers, J. A, et al, 2006	281 patients Ambulant (n=161); Non-ambulant (n=120)	Primary tumour not reported - cord only	Days to developing motor deficit: 1-7 (n=71); 8-14 (n=89); >14 (n=121)	From Ambulatory Group: Improved (n=51, 32%); Changed (n=94, 58%); Deteriorated (n=16, 10%) From Non-ambulatory Group: Improved (n=41, 34%); Changed (n=56, 47%); Deteriorated (n=23, 19%)	The 2-year local control was 84% depending on the radiation schedule.
Rades, D., Veninga, T., et al., 2006	355 patients Ambulant (n=258); Non-ambulant (n=77)	Primary tumour not reported - cord only	Days to developing motor deficit: 1-7 (n=57); 8-14 (n=90); >14 (n=188)	From Ambulatory Group: Improved (n=84, 33%); Changed (n=150, 58%); Deteriorated (n=24, 9%) From Non-ambulatory Group: Improved (n=21, 27%); Changed (n=42, 55%); Deteriorated (n=14, 8%)	Survival negatively effected by the presence of visceral metastases, deterioration of motor function, reduced performance status and rapid development of motor deficits.
Milross, C. G., et al., 1997	94 patients Motor deficit (n=82); Non-ambulant (n=51)	Prostate (n=32); Breast (n=11); Lung (n=10); Lymph Node	Not reported	Complete resolution of motor deficit: Motor deficit group	Functional Improvement Score: Improved (n=67);

Reference	Population Group – Not defined by paraparesis/paraplegia category	Patient Characteristics – Tumour type -Cord or cauda	Time from diagnosis to treatment (days or hours)	Outcomes: Number that remained ambulant	Change in Functional status
		(n=8); Bone Marrow (n=6); Kidney (n=5); Bone & Connective Tissue (n=4); Head and Neck (n=2) Others (n=5); Unknown (n=11) (primary tumour not reported as a variable linked to the functional index) - cord only		(7/82); Non-ambulant group (19/51) No change: Motor deficit group (n=75); Non-ambulant group (n=37)	Remained stable (n=15); Deteriorated (n=12) Bladder function improved (9/32)

Evidence Tables
Cohort Studies

Study Identification: Rades, D., Stalpers, Veninga, Schulte, Hoskin, P., Obralic., Bajrovic, A., Rudat, V., Schwartz, R., Hulsof, M.C., Poortmans, P., Schild, S.E., Evaluation of Five Radiation Schedules and Prognostic Factors for Metastatic Spinal Cord Compression, Journal of Clinical Oncology (2005) 23: 3366-75
Design: Cohort Study, Evidence Level 3
Country: International
Setting: Hospital
Inclusion criteria: motor dysfunction at the lower extremities, no previous surgery or RT of the spinal region concerned, no concurrent chemotherapy and survival at least one month after RT to allow for evaluation of motor function.
Exclusion criteria: patients with a history of brain tumour, brain metastases or other major neurological diseases which may result in motor dysfunction.
Population: 1,304 patients
Intervention: comparison of five radiation schedules and prognostic factors
Outcomes: functional outcome, survival, response to treatment
Follow-up: at least 6 months or until death
Results: the five RT schedules were similar in functional outcome. The three more protracted schedules resulted in in-field recurrences. Motor function improved in 26% (1 x 8 Gy), 28% (5 x 4 Gy), 27% (10 x 3 Gy), 31% (15 x 2.5 Gy) and 28 % (20 x 2 Gy); post-treatment ambulatory rates were 69 %, 68%, 63%, 66% and 74% respectively (p=0.578). On multivariate analysis, age, performance status, primary tumour, involved vertebrae, interval from cancer diagnosis to MSCC, pre-treatment ambulatory status and time to developing motor deficits were significantly associated with functional outcome, whereas RT schedule was not.

Study Identification: Helweg-Larsen, S., Clinical Outcome in Metastatic Spinal Cord Compression: A Prospective Study of 153 patients, Acta Neurol. Scand., (1996) 94: 269-275
Design: Cohort Study, Evidence Level 2
Country: Denmark
Setting: Hospital
Inclusion criteria: patients with known malignant solid tumour and diagnosis of MSCC
Exclusion criteria: not reported
Population: 153 patients , characteristics described in [Helweg-Larsen, et al., 2000]
Intervention: analysis of prognosis factors
Outcomes: ambulatory function; bladder function; radicular pain
Follow-up: median 2.6 months (range 0-41); generally until death of patient
Results: Early diagnosis, while patients are still ambulatory is most important but prognosis for recovery of ambulatory function is good if supplementary systemic therapy is employed. In total 21/74 of non-ambulatory patients regained motor function after therapy. 10/57 patients recovered from bladder dysfunction. Radicular pain is reported to have disappeared after therapy in 95/116 patients.
General comments: -

Study Identification: Helweg-Larsen, S., Sorensen, P.S., Kreiner, S., Prognostic Factors In Metastatic Spinal Cord Compression: A Prospective Study Using Multivariate Analysis Of Variables Influencing Survival And Gait Function In 153 Patients, Int. J. Oncology Biol. Phys, (2000) 46:1163-1169
Design: Cohort Study, Evidence Level 2
Country: Denmark
Setting: Hospital
Inclusion criteria: patients with known malignant solid tumour and diagnosis of MSCC
Exclusion criteria: not reported
Population: 153 patients
Intervention: analysis of prognosis factors
Outcomes: ambulatory function; survival
Follow-up: at least one year or until death of patient
Results: The pre-treatment ambulatory function is the main determinant of post-treatment gait function. Survival time is rather short, especially in non-ambulatory patients. The type of primary tumour had a direct influence on the interval between the diagnosis of the primary malignancy and the occurrence of SCC ($p < 0.005$) and on the ambulatory function at the time of diagnosis ($p = 0.016$). There was a clear correlation between the degree of myelographic blockage and gait function ($p = 0.000$) and between the gait function and sensory disturbances ($p = 0.000$). The final gait was dependent on the gait function at the time of diagnosis ($p < 0.0005$). Survival time after diagnosis depended directly on the time from primary tumour diagnosis until spinal cord compression ($p = 0.002$), on the ambulatory function at the time of diagnosis ($p = 0.018$) and on the ambulatory function after treatment.
General comments: -

Prospective Observational Studies

Study Identification: Bauer, H.C.F., Wedin, R.; Survival after surgery for spinal cord and extremity metastases, Acta. Orthop. Scand. (1995) 66: 143-146
Design: Prospective Observational Study, Evidence Level 3
Country: Sweden
Setting: Hospital
Inclusion criteria: consecutive prospective series of cancer patients with extremity and spinal cord metastases
Exclusion criteria: not reported
Population: 241 patients (158 with extremities metastasis and 88 patients with spinal cord metastases)
Intervention: assessment of survival
Outcomes: survival, correlation between interval to diagnosis and treatment and survival rate
Follow-up: 4, respectively 8 years
Results: A long interval between diagnosis and primary surgery was associated with a better survival rate in MSCC patients. Pathologic fractures, visceral and brain metastases are negative prognostic variables for 1 year survival. Solitary metastases, breast and kidney cancer and myeloma were reported as positive predictive variables.
General comments: -

Study Identification: Husband, D J., Malignant Spinal Cord Compression: Prospective Study of Delays in Referral and Treatment, BMJ, (1998) 317:18-21
Design: Prospective Observational Study, Evidence Level 3
Country: UK
Setting: Hospital
Inclusion criteria: consecutive patients referred to regional cancer centre for treatment of a first episode of malignant spinal cord compression (MSCC)
Exclusion criteria: patients with insufficient details of referral and presentation.
Population: 301 consecutive patients:
Intervention: examine delay in presentation, diagnosis and treatment of MSCC and define the effect of this delay in motor and bladder function at the time of treatment.
Outcomes: interval from onset of symptoms to presentation and treatment, delay at each stage of referral, and functional deterioration.
Follow-up: n/a; duration 3 years.
Results: Unacceptable delays in diagnosis, investigation and referral occurs in most patients with malignant spinal cord compression and results in preventable loss of function before treatment. Improvement in outcome of such patients requires earlier diagnosis and treatment. The median (range) delay from onset of symptoms of SCC to treatment, in a cohort of 310 consecutive patients, was 14 (0-840) days. Of the total delay, 3 (0-300) days by GPs, 4 (0-794) by the district general hospital and 0 (0-114) days by the treatment unit. Initial presentation to the regional cancer centre with symptoms of MSCC led to a significant reduction in delay to treatment and improved functional status at the time of treatment. Deterioration of motor or bladder function ≥ 1 grade occurred at the general practice stage in 28% (57) and 18 % (36) of patients, the general hospital stage in 36% (83) and 29% (66) and the treatment unit stage in 6% (19) and 5% (15) respectively.
General comments: -

Study Identification: Kim, R.Y., Spencer, S.A., Meredith, R.F, Weppelmann, B., Lee, J.Y., Smith, J.W., Salter, M.M., Extradural Spinal Cord Compression: prognosis - prospective study, Radiology (1990) 176: 279-282
Design: Prospective Observational Study, Evidence Level 3
Country: USA
Setting: Hospital
Inclusion criteria: patients with thoracic, lumbo-sacral or cervical ESCC, treated with RT, receiving dexamethasone.
Exclusion criteria: death during treatment
Population: 59 patients, median age 63.5 years, range (18-87); male: 43; female: 22; most common primary tumour: lung (27%) followed by prostate (19%), unknown primary tumour (12%), breast cancer (10%), kidney (8%); non-ambulatory (78%);
Intervention: analysis of prognostic significance of pre-treatment motor function, degree of spinal cord block, radiosensitivity of tumour and radiation dose schedule
Outcomes: motor function
Follow-up: duration: 18 months
Results: Pre-treatment motor function was found to be significant factor in determining functional prognosis. There is a significant correlation between the degree of spinal cord block and motor function at presentation. Patients with abnormal sphincter function had a higher frequency of almost complete block than patients with normal sphincter function. There was no significant difference in outcome between dose schedule (3,000 cGy x 10 fractions and 3,000 cGy x 9 fractions with higher initial dose fractionation 400 cGy for the first 3 doses). Degree of spinal cord block and radiosensitivity of tumour were not significant independent factors.
General comments: -

Study Identification: Levack, P., Graham, J., Collie, D., Grant, R., Kidd, J., Kunkler, i., Gibson, A., Hurman, D., McMillan, N., Rampling, R., Slider, L., Statham, P., Summers, D., The Scottish Cord Compression Study Group, Don't wait for a sensory Level- Listen to the symptoms: a prospective audit of the delays in diagnosis of malignant cord compression, <i>Clinical Oncology</i> (2002) 14: 472-480
Design: Prospective Observational Study, Evidence Level 3
Country: UK
Setting: Hospital
Inclusion criteria: consecutive patients with definitive diagnosis (by MRI) of MSCC or cauda equina compression
Exclusion criteria: patients with suspected MSCC but not referred to MRI
Population: 319 consecutive patients: (203 male, 116 female) median age 65 (89% > 50 years at diagnosis) primary tumours: 21% lung, 20.5% prostate, 17.5%breast, 10% GI tract, 10% haematological, 7% unidentified sites of compression: thoracic (over 2/3), with 35% upper thoracic (T1-T6), 32% lower (T7-T12), lumbar 21%, cervical 7%, sacral 4%. Two or more concurrent compressive levels identified in 17% of patients. cord compression as the first presentation of malignancy: 77% were diagnosed with cancer
Intervention: reporting details concerning symptom (especially pain) preceding the development of MSCC
Outcomes: delays between reporting and confirmed diagnosis of MSCC
Follow-up: n/a; duration 14 months.
Results: Patients who develop spinal metastases are at risk of irreversible spinal cord damage. Weakness and sensory abnormalities were reported late and identified even later, despite patients reporting pain for a considerable time. Patients with cancer who describe severe back pain or spinal nerve root pain need urgent assessment on the basis of their symptoms, as signs may occur too late. Plain films and bone scans requested for patients in this study predicted accurately the level of compression in only 21% and 19% of cases respectively. The only accurate investigation to establish the presence and site of a compressive lesion is MRI. At diagnosis most patients were either unable to walk (82%) or only able to walk with help. Pain was reported by nearly all patients interviewed (94%) and had been present for approximately 3 months (median 90 days). It was severe in 84% of cases, with the distribution and characteristics of nerve root pain in 79%. The site of pain did not correspond to the site of compression. Where reported, weakness and/or sensory problems had been present for some time before the diagnosis (median 20 and 12 days respectively). Most patients reported early symptoms to the GP and diagnosis was established, following referral and investigation, approximately 2 months later (median 66 days).
General comments: -

Study Identification: Maranzano, E., Latini, P., Effectiveness of Radiation Therapy without surgery in metastatic spinal cord compression: final trial results from a prospective trial, Int. J. Radiation Oncology, (1995), 32:959-967
Design: Prospective Observational Study, Evidence Level 3
Country: Italy
Setting: Hospital
Inclusion criteria: patients with MSCC treated with RT plus steroids or surgery for selected cases.
Exclusion criteria: early death, RT without steroids.
Population: 209 consecutive patients; median age 62 ; 110 female, 99 male;
Intervention: assessing effectiveness of RT in MSCC
Outcomes: back pain, motor and bladder function
Follow-up: median 49 months (range 13-88)
Results: Early diagnosis of MSCC was the most important predictor of outcome, so that patients who had a motor function and good bladder function maintained those capacities. Primary tumour histology had significance only when patients were non-ambulatory, paraplegic or had bladder dysfunction. The effectiveness of RT plus steroids was apparent. When diagnosis was late tumours with favourable histology (myeloma, breast and prostate carcinomas) above all responded to RT. Duration of response was influenced by tumour histology. Favourable histology are associated to higher median response. Median survival time was 6 months with a 28% probability of survival for 1 year. Survival time was longer for patients who were able to walk at the time of treatment, those with favourable histologies and females. There was a correlation between patient survival and duration of response, systemic release of disease being generally the cause of death. Back pain total response was 82%. About 76% of patients achieved full recovery or preservation of motor function and 44% with sphincter dysfunction improved.
General comments: -

Study Identification: Rades, D., Blach, M., Bremer, M., Wildfang, I., Karstens, J., Heidenreich, F., Prognostic Significance Of The Time Of Developing Motor Deficits Before Radiation Therapy In Metastatic Spinal Cord Compression: One-Year Results Of A Prospective Trial, Int. J. Radiation Oncology Biol. Phys. (2000) 48: 1403-1408
Design: Prospective Observational Study, Evidence Level 3
Country: Germany
Setting: Hospital
Inclusion criteria: patients with motor deficits due to MSCC to thoracic or lumbar spine, no previous surgical or RT treatment to the region concerned, treatment with dexamethasone before and during RT; diagnostic of MSCC confirmed by CT scan or MRI
Exclusion criteria: not reported other than not fulfilling the inclusion criteria
Population: 57 patients, median age 63 years (range 23-87)
Intervention: prospective investigation of prognostic value of developing motor deficits before RT for post-treatment functional outcome
Outcomes: functional outcome
Follow-up: 1 year
Results: A slower development of motor deficits before RT predicts a better post-treatment functional outcome. In patients with rapid deterioration of motor function within 48 hours before treatment prognosis was extraordinarily poor. Directly after RT 26/28 (93%) patients of the group developing motor deficits >14 days showed improvement of motor function, in comparison to 3/29 (10%) of the group developing motor deficits in 1-14 days (p< 0.001). Deterioration rates were 0% (>14 days) and 45% (1-14 days). In patients with rapid deterioration of motor function <48 hours before RT, prognosis was poor (improvement 0%, no change 43%, deterioration 57%). Results were comparable 6, 12 and 24 weeks after RT.
General comments: -

Study Identification: Rades, D., Heidenreich, F., Karstens, J., Final Results Of A Prospective Study Of The Prognostic Value Of The Time To Develop Motor Deficits Before Irradiation In Metastatic Spinal Cord Compression, Int. J. Radiation Oncology Biol. Phys. (2002) 53: 975-979
Design: Prospective Observational Study, Evidence Level 3
Country: Germany
Setting: Hospital
Inclusion criteria: patients with motor deficits due to MSCC to thoracic or lumbar spine, no previous surgical or RT treatment to the region concerned, treatment with dexamethasone before and during RT; diagnostic of MSCC confirmed by CT scan or MRI
Exclusion criteria: not reported other than not fulfilling the inclusion criteria
Population: 98 patients
Intervention: prospective investigation of prognostic value of developing motor deficits before RT for post-treatment functional outcome.
Outcomes: functional outcome
Follow-up: duration 2 year; follow-up 24 weeks
Results: A slower development of motor deficits before RT predicts a significantly better functional outcome. In the group that took >14 days to develop motor deficits, improvement occurred significantly ($p<0.001$) more often than in the other subgroups (8-14 days and 1-7 days), 86% versus 29% and 10%, and the post-treatment ambulatory rate was significantly higher (86% vs. 55% and 35%, $p=0.026$. multivariate analysis revealed the time to development of motor deficits before RT to be the strongest prognostic factor.
General comments: -

Study Identification: Turner, S., Marosszky, B., Timms, I., Boyages, J. Malignant spinal cord compression: a prospective evaluation. Int. J Radiation Oncol Biol Phys (1993). 26:141-6
Design: Prospective Observational Study, Evidence Level 3
Country: Australia
Setting: Hospital
Inclusion criteria: Patients with MSCC treated with palliative RT, surgery followed by RT or surgery alone
Exclusion criteria: not reported
Population: 37 patients, median age and range not reported, male/female ratio not reported; Non-ambulant 20 (54%), Ambulant 16 (46%)
Intervention: Assessing the influence of treatment on ambulancy, pain control and functional outcome
Outcomes: Motor function; Urinary function; Pain control
Follow-up: Median 2 months (range 2 days to 16 months)
Results: Prompt treatment while patients are still ambulant, is effective in maintaining ambulancy and functional independence and that treatment improves pain in most patients. 13/16 patients (81%) who were ambulant pre-treatment, remained ambulant after treatment. 2/16 patients (16.5%) who were non-ambulant regained ambulancy following treatment. Pain improved following treatment in 22/30 patients (73%) this benefit was seen equally for ambulant and non-ambulant patients. A high level of functional independence was maintained in patients who remained ambulant. The median delay between first assessment and first treatment was 12 hours (range 1-96 hours).
General comments: Very poor reporting, this study is not reliable evidence

Retrospective Observational Studies

Study Identification: Chataigner, H., Onimus, M., Surgery in spinal metastasis without spinal cord compression: indications and strategy related to the risk of recurrence. Eur. Spine J (2000) 9: 523-527
Design: Retrospective Observational Study, Evidence Level 3
Country: France
Setting: Hospital
Inclusion criteria: patients presenting with vertebral metastasis without neural deficit
Exclusion criteria: not reported
Population: 107 patients, mean age 58 years (range 29-87 years)
Intervention: assessment of prognostic factors and treatment strategies
Outcomes: functional motor status; survival recurrence
Follow-up: 8 months or until death
Results: Surgery in vertebral metastasis without neural deficit results in substantial functional improvement but does not increase the survival rate. Mean survival varies, according to primary neoplasm.
General comments: -

Study Identification: Cowap, J., Hardy, J.R., A'Hern, R., Outcome of Malignant Spinal Cord Compression at a Cancer Centre: Implications for Palliative Care Services, Journal of Pain and Symptom Management, (2000) 19:257-263
Design: Retrospective Observational Study, Evidence Level 3
Country: UK
Setting: Hospital
Inclusion criteria: malignant spinal cord compression proven by MRI, treated with RT
Exclusion criteria: not reported
Population: 166 patients; median age 60 years (range 13-88); 83 males, 83 females; the most common malignancies were breast, lung, prostate and myeloma.
Intervention: assessing functional outcome and its relevance to planning future care needs.
Outcomes: performance (PS), neurological status (NS)
Follow-up: 6 months
Results: Survival was significantly better from those presenting with good functional status. PS and NS have prognostic significance. A comparison of performance status before and after treatment reveals no significant change. In only 16%, there was an improvement, 59% of patients having no change and 25% having a worse performance status after treatment. Similarly, there was no change in neurological status with 20% of patients showing an improvement, 55% having no change and 25% having a worse neurological status following treatment. The median survival of all patients from the date of confirmation of SCC was 82 days (range 1-1349 days).
General comments: -

Study Identification: Harris, J.K., Sutcliffe, J.C., Robinson, N.E., The Role Of Emergency Surgery In Malignant Spinal Extradural Compression: Assessment Of Functional Outcome, British Journal of Neurosurgery (1996) 10:27-33
Design: Retrospective Observational Study, Evidence Level 3
Country: UK
Setting: Hospital
Inclusion criteria: patients with spinal cord or cauda equina compression secondary to extradural metastases , requiring surgery
Exclusion criteria: cases with vertebral collapse secondary to metastases, but with no extradural tumour
Population: 81 patients; 49 male, 32 female; median age 65, mean 60.0, range 15-86; 3 patients with two separate episodes at different sites; location: cervical spine 3 (3.6%), thoracic 64 (76.2), thoraco-lumbar 6 (7.1%), lumbar 9 (10.7%), sacral 2 (2.4%); 19 patients were mobile pre-operatively, 43 patients were continent
Intervention: assessment of functional outcomes
Outcomes: functional outcome: mobility and bladder function
Follow-up: 3 months
Results: Despite initial delays in referral and even if the patient is incontinent and immobile, emergency spinal decompression leads to better outcome. A greater proportion of patients which have undergone emergency surgery rather than electively (within 24 hours) showed functional improvement (61.5% versus 25%). Overall, 70% of patients were mobile post-operatively.
General comments: -

Study Identification: Leviiov, M., Dale, J., Stein, M., Ben-Shahar, M., Ben-Arush, M., Milstein, D., Goldsher, D., Kuten, A., The Management of Metastatic Spinal Cord Compression: a Radiotherapeutic Success Ceiling, Int. J. Radiation Biol. Phys. (1993) 27:231-234
Design: Retrospective Observational Study, Evidence Level 3
Country: Israel
Setting: Hospital
Inclusion criteria: patients with MSCC or cauda equine who received RT, with or without surgery
Exclusion criteria: not reported other than not fulfilling inclusion criteria
Population: 70 patients, age range 3.5 months- 85 years
Intervention: assessment of the effectiveness of the management of MSCC or cauda equine
Outcomes: functional motor status
Follow-up: 4 years or until death
Results: Radiotherapeutic success ceiling of 80% may be reached for Findlay grade I patients with MSCC, for which early diagnosis is of utmost importance. A powerful predictor of response to RT was the patient's neurological status (Findlay grade) at the time of diagnosis: 66% of previously ambulatory patients remained so, whereas 30% of non-ambulatory patients and only 16% of paraplegic patients regained the ability to walk. Another important predictor response was primary tumour histology, with the most favourable response to RT being observed in lymphoproliferative diseases and in breast cancer, but with some response to radiosensitive malignancies as well.
General comments: -

Study Identification: Rades, D., Heidenreich, f., Bremer, M., Karstens, J.H., Time of Developing Motor Deficits before radiotherapy as a New and Relevant Prognostic Factor in Metastatic Cord Compression: Final Results of a Retrospective Analysis, European Neurology, (2001) 45:266-269
Design: Retrospective Observational Study, Evidence Level 3
Country: Germany
Setting: Hospital
Inclusion criteria: patients with motor deficit of lower extremities, no previous surgery or RT of the spine, dexamethasone treatment during RT, sufficient data concerning motor deficits, effect of RT and follow-up. Diagnosis confirmed by MRI or CT
Exclusion criteria: cancer related death, insufficient data.
Population: 131 patients, median age 65 (range 28-83);
Intervention: determine the prognostic value of the time to develop motor deficit before RT
Outcomes: time to developing motor deficit
Follow-up: median
Results: In all 131 patients median survival was 5 months. Survival rates were 76% after 3 months, 65% after 4 months, 50% after 5 months, and 40% after 6 months. A slower development of motor deficits before RT predicts a better functional outcome. In patients with rapid deterioration before RT motor dysfunction might be explained by generally irreversible spinal cord infarction. Rates of ambulatory patients before RT were comparable in groups of patients. Two weeks after RT 83% of the patients in the group which had taken >14 days to develop motor deficit before RT were ambulatory, compared to only 24% of patients in the group which has taken 1-7 days to develop motor deficit before RT. This was also observed 3 months after RT. Besides type of primary tumour and pre-treatment ambulatory status, the time of developing motor deficit before RT is considered a relevant prognostic factor in MSCC.
General comments: -

Study Identification: Rades, D., Karstens, J., A Comparison Of Two Different Radiation Schedules For Metastatic Spinal Cord Compression Considering A New Prognostic Factor, <i>Strahlentherapie und Onkologie</i> (2002) 10: 556-561
Design: Retrospective Observational Study, Evidence Level 3
Country: Germany
Setting: Hospital
Inclusion criteria: patients with motor deficits due to MSCC to thoracic or lumbar spine, no previous surgical or RT treatment to the region concerned, treatment with dexamethasone before and during RT; diagnostic of MSCC confirmed by CT scan or MRI
Exclusion criteria: not reported other than not fulfilling the inclusion criteria
Population: 153 patients
Intervention: two radiation schedules (30 Gy /10 fractions and 37.5 Gy /15 fractions) compared for post-treatment functional outcome and ambulatory status
Outcomes: functional outcome and ambulatory status
Follow-up: duration 5 years; follow-up 12 months
Results: No significant difference was observed between the two radiation schedules (30 Gy /10 fractions and 37.5 Gy /15 fractions) for post-treatment ambulatory status (p values: 0.450-0.888) and for functional outcome (p values: 0.940-0.999). According to the multivariate analysis the strongest predictors for the functional outcome were the time of developing motor deficits before RT (p<0.001) and the pre-treatment ambulatory status (p< 0.001) followed by the type of primary tumour (p=0.058).
General comments: -

Study Identification: Rades, D., Stalpers, J. A, Veninga, T., Rudat, V., Schulte, R. Evaluation Of Functional Outcome And Local Control After Radiotherapy For Metastatic Cord Compression In Patients With Prostate Cancer, The Journal of Urology (2006) 175: 552-556
Design: Retrospective Observational Study, Evidence Level 3
Country: International
Setting: Hospital
Inclusion criteria: patients with prostate cancer, confirmed MSCC by CT scan or MRI, motor deficits to lower extremities, no previous surgery or RT of the spinal region concerned, dexamethasone treatment during RT
Exclusion criteria: not reported
Population: 281 patients; 147 (52%) aged \leq 70 years, 134 (48%) aged $>$ 70 years
Intervention: evaluation of prognostic factors.
Outcomes: functional outcome, local control
Follow-up: 11 years
Results: Functional outcome after RT was significantly influenced by the time taken to develop motor deficits before RT (more than 14 days better than 8-14 days and 1-7 days $p < 0.001$) and number of involved vertebrae (1-2 better than 3 or more, $p = 0.013$), but not by the radiation schedule ($p = 0.859$). Local control was significantly better after application of long course RT. Overall response to RT was 86% (33% improvement of motor function, 53% no further progression). Of the non-ambulatory patients 88% regained the ability to walk. The 2 year local control of MSCC was 84% depending on the radiation schedule (better after long course RT, $p = 0.001$)
General comments: -

Study Identification: Rades, D., Veninga, T., Stalpers, L.J.A., Schulte, R., Hoskin, P., Poortmans, P., Schild, S.E., Rudat, V., Prognostic Factors Predicting Functional Outcomes, Recurrence-Free Survival And Overall Survival After Radiotherapy For Metastatic Spinal Cord Compression In Breast Cancer Patients, Int. J. Radiation Oncology Biol. Phys. (2006) 64: 182-188
Design: Retrospective Observational Study, Evidence Level 3
Country: International
Setting: Hospital
Inclusion criteria: breast cancer patients irradiated for MSCC, with motor deficit of the lower extremities, due to MSCC of the thoracic or lumbar spine, had not undergone previous surgery or RT to the involved sites
Exclusion criteria: not reported other than not fulfilling the inclusion criteria
Population: 355 patients
Intervention: identifying significant prognostic factors after RT for MSCC
Outcomes: functional outcomes, recurrence-free survival and overall survival
Follow-up: 11 years
Results: Functional outcomes after RT for MSCC in breast cancer patients are associated with slower development of motor deficits ($p < 0.001$) and being ambulatory before RT ($p < 0.001$). The overall recurrence rate of MSCC was greater if other bone metastases were present and if short course RT was used. Survival was negatively affected by the presence of visceral metastases ($p < 0.001$), deterioration of motor function after RT ($p < 0.001$) reduced performance status ($p < 0.001$) and the rapid development of motor deficits ($p = 0.044$)
General comments: -

Study Identification: Sioutos, P.J., Arbit, E., Meshulam, C.F., Galicich, J. H. Spinal Meatastases from Solid Tumours: analysis of factors affecting survival, Cancer, (1995), 76:1453-1459
Design: Retrospective Observational Study, Evidence Level 3
Country: USA
Setting: Hospital
Inclusion criteria: patients with thoracic spine metastases and cord compression; surgical decompression of the spinal cord and RT
Exclusion criteria: not reported
Population: 109 patients; median 59 years, mean 58.7 years (range 31-80); Male 61 / Female 48
Intervention: analysis of factors affecting survival
Outcomes: survival
Follow-up: 5 months
Results: For patients with spinal metastases and cord compression, the factors found to affect survival include preoperative neurological status, anatomic site of primary carcinoma, and number of vertebral bodies involved. Patients with vertebral column disease and two or more of the poor prognostic indicators have a short life expectancy and therefore, radical surgery is not recommended because the benefits may not be substantial. The overall median survival was 10 months. Patients preoperatively ambulatory survived statistically significantly longer than non-ambulatory patients or those with sphincter incontinence ($p = 3.469 \times 10^{-6}$). Patients with renal cell carcinoma survived the longest, followed by those with breast, prostate, lung and colon cancer. Patients with breast cancer survived statistically longer than those with lung cancer ($p = 0.039$). Patients with one vertebral body involved survived statistically significantly longer than patients with multiple vertebral level involvement ($p = 0.027$). Extent of disease, age, and tumour location did not significantly influence survival. In patients with vertebral column disease, the presence of two or more poor prognostic indicators (leg strength 0/503/5, lung or colon cancer, multiple vertebral body involvement), had a compounding adverse effect on survival.

Retrospective Case Series

Study Identification: Bach, F., Larsen, B.H., Rohde, K., Borgesen, S.E., Gjerris, F., Boge-Rasmussen, T., Agerlin, N., Rasmusson, B., Stjernholm, P., Sorensen, P.S, Metastatic Cord Compression: Occurrence, Symptoms, Clinical Presentation and Prognosis in 398 Patients with Spinal Cord Compression, Acta Neurochirurgica, (1990) 107:37-43
Design: Retrospective Case Series, Evidence Level 3
Country: Denmark
Setting: Hospital
Inclusion criteria: all records of patients with spinal cord or cauda equina compression secondary to cancer, in eastern Denmark from 1979 to 1985.
Exclusion criteria: none reported
Population: 398 cases; average age 63 years (range 14-84); 260 Male / 138 Female
Intervention: assessment of occurrence, symptoms, clinical presentation and prognosis
Outcomes: functional outcome (motor deficit, bladder dysfunction)
Follow-up: n/a
Results: Patients treated by decompressive laminectomy followed by RT had a better response than patients treated with surgery or RT alone, but when the patient's pre-treatment motor function was taken into account no significant difference was observed. Of the patients who were ambulatory before the treatment 79% remained ambulatory, whereas only 18% of the non-ambulatory patients regained walking ability. Several patients had symptoms long before the SCC was diagnosed. The mean duration from the first symptom until the diagnosis was established was 58 days (average 30 days, rang 0-420 days). No significant difference between primary malignancy was demonstrated, although lung cancers seem to progress more rapidly (65% within the first seven days). In 259 patients the time interval between the first visit to a doctor with symptoms indicating incipient SCC, and the diagnosis of SCC, called "doctor's delay" had a mean value of 23 days (average 4 days, range 0-360 days).
General comments: -

Study Identification: Gilbert, R.W., Kim, J-H., Posner, J.B., Epidural Spinal Cord Compression from Metastatic Tumour: Diagnosis and Treatment, Ann Neurol (1978) 3:40-51
Design: Retrospective Case Series, Evidence Level 3
Country: USA
Setting: Hospital
Inclusion criteria: patients with spinal cord compression by metastatic extradural tumours, treated with RT alone or surgical decompression followed by RT.
Exclusion criteria: not reported
Population: 130 in the new series; gender: 80 male and 50 female; average age: 58 (range 4-85); compared to 105 in an old series, characteristics not reported ; site of epidural tumour: cervical 20 (15%), thoracic 89 (68%), lumbar or sacral in 21 (116%); primary tumours: breast 48, lung 30, prostate 21, kidney 17, lymphoma/myeloma 35, melanoma 8, GI 9 and others 31 - treatment in both series: surgical decompression followed by RT 65, RT without surgery: 170; ambulatory status: ambulatory: 80 (34%), paraparetic 116 (49%) and paraplegic 39 (17%)
Intervention: compare effectiveness of treatment
Outcomes: ambulatory status
Follow-up: 1 year
Results: There were no differences in outcome between those treated by combined surgery with RT and those treated with RT alone. Patients with radiosensitive tumours and those ambulatory at the onset of treatment benefited most, regardless of treatment method. 75% of living patients who improved form treatment remained ambulatory at 6 months , and approx 50% of living patients were ambulatory at 1 year.
General comments: -

Study Identification: Milross, C. G., Davies, M. A., Fisher, R., Mameghan, J., & Memeghan, H. The efficacy of treatment for malignant epidural spinal cord compression. <i>Australasian Radiology</i> (1997), 41: 137-142.
Design: Retrospective Case Series, Evidence Level 3
Country: Australia
Setting: Hospital
Inclusion criteria: patients diagnosed with malignant ESCC treated by RT, laminectomy, or combination
Exclusion criteria: second episode of ESCC
Population: 94 patients; median age 65 years (range 18 to 80 years)
Intervention: assessing efficacy of treatment
Outcomes: functional improvement score (FIS) (pain, weakness, non-ambulation, urinary dysfunction)
Follow-up: 1 month
Results: Of the treatments given, a combination of surgery followed by RT was associated with the greatest functional improvement ($p=0.001$). The coexistence of 'liver failure' was the only patient-related factor identified which was associated with outcome ($p=0.041$). Complete resolution of individual pre-treatment symptoms that were measured 1 month after treatment occurred as follows: pain (30/88), sensory disturbance (12/61), weakness (8/17), bladder dysfunction (10/42), and bowel dysfunction (10/36). Complete resolution of motor deficit occurred in 7/82 and sensory deficit in 9/73. The ability to walk was regained in 19/51 previously non-ambulatory patients, and bladder function improved sufficiently to remove an indwelling catheter in 9/32 previously catheterised patients. As judged by FIS, 67 patients improved, 15 patients remained stable and 12 patients deteriorated.
General comments: -

Study Identification: Solberg, A. Bremnes, R.M., Metastatic Spinal Cord Compression: Diagnostic Delay, Treatment and Outcome, Anticancer Research, (1999) 19: 6777-684

Design: Retrospective Case Series, Evidence Level 3

Country: Norway

Setting: Hospital

Inclusion criteria: unselected series of cases with SCC due to malignant disease

Exclusion criteria: - not reported

Population: 86 patients, median age 65 years, preponderantly male (73%); primary malignancies: 66% prostate, lung, breast, kidney; grade prior to treatment: I - 34%, II - 53%, III - 13%; intervention: surgical laminectomy with postoperative radiotherapy- 33%, radiotherapy only - 67 %

Intervention: estimate diagnostic delay, treatment, outcome and prognostic factors in patients with MSCC

Outcomes: diagnostic delay, treatment delay, predictors of survival and treatment response, functional status at treatment start.

Follow-up: median 39 months

Results: Prolonged survival in a minority of patients signified the importance of optimal treatment. Median time from the start of symptoms to the first doctor contact was 1 day (range 0-30) and to hospital admission and treatment start, 6 days (range 0-158) and 8 days respectively (0-208).

The pre-treatment grade of paresis, preservation of gait function and primary tumour histology were strong predictors for treatment response. Primary tumour histology was an important predictor, as breast cancer and prostate cancer had a 3 to 6 fold longer survival compared to lung cancer patients.

Pain relief correlated to treatment response grade.

Median survival from start of treatment 4.1 months - survival correlated positively to preserved gait function at admission, to treatment response grade and to the employment of combined surgical laminectomy and radiotherapy

RESULT

Delay: Male patients had a median of 1 day to first doctor contact, while female patients had a median of 5 days ($p < 0.05$). Of all patients 80% had a delay of 3 days or more and 55% had a delay of 7 days or more from first symptom to treatment start.

Response: 26 patients (32%) did not respond to therapy, 35 (43%) patients had a minor response or stabilisation (grade 1), 14 (17%) had a moderate to pronounced improvement on motor function (grade 2) and 7 (9%) gained full recovery (grade 3). While there was no measurable improvement in paraplegic patients, 36% of severe paraparesis and 19% of mild to moderate paraparesis patients improved.

A significantly larger part of ambulant patients (35%) achieved treatment response 2 or 3, compared to 22% of non-ambulant patients. Among patients achieving full restoration of motor function 72% were ambulant and 28 % were non- ambulant at the time of treatment. After treatment 43% of patients were ambulant. Gait function was regained in 33% of previously non-ambulant patients and lost in 25% of previously ambulant patients.

Motor function before and after treatment

Pain: of all patients 74% reported pain at admittance. Treatment effect: 82% experienced significant pain reduction while 18% did not. Pain relief was obtained in all patients with full motor function recovery (grade 3) and in 92%, 88% and 58% of patients with response grade 2 1 and 0 respectively. Of lung cancer patients 50% reported pain relief, while this was significantly more frequent in breast and prostatic carcinoma patients, 100% and 95% respectively. Following treatment, 90% of patients ages above 60 years reported pain relief compared to 69% under 60 years ($p < 0.04$).

Survival: median overall survival from treatment start was 4.1 months (range 0.03-101) and only 13% and 7% are alive after 2 and 5 years respectively. While all patients with paresis grade 3 are dead within 1 year from treatment start 7% and 10% of grade 2 and 1 paresis patients are alive at 5 years. Survival correlated to classified motor function response to treatment ($p < 0.0001$). There were significant post-treatment survival differences with regard to primary malignancies: breast cancer and prostatic cancer patients constituted 71% of patients surviving 12 months, as only one of the lung cancer patients survived more than 5 months. Whether patients were ambulant or not at admission did not have any significant impact on post-treatment survival. On the other hand, patients that were ambulant at the time of treatment had significantly longer survival than the non-ambulant ones 7.7 vs. 2.0 months ($p < 0.0001$). At one year after treatment 42% of ambulant patients and 12% of non-ambulant patients were alive.

Study Identification: Loblaw, D.A., Smith, K., Lockwood, G., Laperriere, N., The Princess Margaret Hospital experience of malignant spinal cord compression. In: Program/Proceedings of the 39 th Annual Meeting of the American Society of Clinical Oncology: May 31-June 3 (2003): Abstract 477.
Design: Abstract, Evidence Level 4
Country: Canada
Setting: Hospital
Inclusion criteria: Patients with MSCC
Exclusion criteria: not reported
Population: 775 patients; mean age 61 years; Male 54% Female 46%; multiple episodes (up to 5) in 15% of patients; time between primary tumour diagnosis and the first MSCC episode – median time 1.4 years
Intervention: analyse functional outcome and predictors thereof
Outcomes: motor function; survival
Follow-up: not reported
Results: Pre-treatment functional status independently predicted for post-treatment motor, sensory and autonomic function and time to functional recovery on multivariate analyses. Median survival was 4.1 months. Multivariate analysis revealed that increased survival was predicted by better motor function before treatment, younger age, longer intervals from cancer diagnosis to MSCC and tumour primary sites of breast, prostate and myeloma.
General comments: -

Study Identification: Mitera, G., Loblaw, A., Delays from symptom onset to treatment in malignant spinal cord compression: quantification and effect on pre-treatment neurological status. Radiother. Oncol (2003) 69: Abstract 141
Design: Abstract, Evidence Level 4
Country: Canada
Setting: Hospital
Inclusion criteria: patients with MSCC
Exclusion criteria: not reported
Population: 10 patients
Intervention: assessing impact of delay (from symptom onset to treatment) on pre-treatment neurological status
Outcomes: pre-treatment neurological status
Follow-up: not reported
Results: A median time delay of 12 days from symptom onset till RT treatment was experienced and 64% of this delay resulted from symptom onset to initiation of medical attention. Furthermore, when patients perceived symptoms to be related to their previous cancer, the median time delay was 5.5 days, compared to 17 days when patients related symptoms to other co-morbidities. Deterioration of symptoms was strongly correlated with time delay ($r = 0.87$; $p = 23.92$).
General comments: -

5.5 An Economic Evaluation of Extending MRI Scanning Hours at a District General Hospital for People With Suspected Metastatic Spinal Cord Compression

Introduction

People with metastatic spinal cord compression (MSCC) and early signs of neuralgia are at high risk of developing irreversible spinal cord damage and paralysis if not diagnosed and treated urgently. Indeed, there is evidence to suggest that better patient outcomes (survival and quality of life) are achieved when the time between the early signs and symptoms of MSCC and appropriate treatment is minimised [1-4].

There are a number of reasons why appropriate diagnosis and treatment might be delayed. These include a failure by health care professionals to refer potential MSCC patients for appropriate specialist diagnosis and a lack of awareness by patients in terms of identifying the early signs and symptoms of the condition. However, another is that NHS diagnostic facilities at District General Hospitals (DGHs) are often only open during 'standard working hours'. Thus, patients with suspected MSCC referred outside of these times, have to wait until at least the next morning to undergo the appropriate diagnostic test, usually a MRI, or are referred to tertiary treatment centres. While MRI clinic opening hours at DGHs could be extended, it is not clear whether it's cost-effective to do so in the context of identifying people with MSCC.

Aim

The aim of this study is to assess the cost-effectiveness of expanding the opening hours of existing NHS MRI scanning services at DGHs to identify people with suspected MSCC.

Method

Existing Economic Evidence

A systematic review of the literature did not identify any existing economic evaluations on this topic. Thus *de novo* modelling was undertaken using results from the systematic review of the clinical literature and a number of other supplementary non-systematic literature searches.

The economic evaluation was performed using a decision tree approach. Decision trees consist of relevant events (given the subject matter for the model), probabilities of these events occurring, and the costs and health consequences of each of these events. It is a basic but frequently used form of decision modelling and was chosen because the time frame over which salient events can happen is relatively short and they do not frequently recur. Thus more complex forms of modelling such as Markov models were not considered to be necessary.

The evaluation was performed from a NHS and Personal Social Services cost perspective and health outcomes were expressed in terms of Quality-Adjusted Life-Years (QALYs); both approaches are recommended in NICEs Clinical Guidelines Manual. QALYs are calculated by adjusting evidence on patient survival by evidence on health-related quality-of-life. The index used to represent health-related quality-of-life is known as a 'utility'. A utility value of 1 is taken to be equivalent to perfect health whereas a value of 0 is equivalent to death. Remaining health states have values somewhere between these levels, although values below 0 for particularly poor health states are plausible.

Future costs and benefits were not discounted because in all but a small number of scenarios, these events occurred within a year of initial diagnosis and treatment.

The Decision Problem

An economic evaluation is essentially a comparison of the cost and benefits of two or more courses of action. In this instance, the courses of action are 'MRI during standard working hours (SWH)' compared with 'extended opening hours (EOH)'. However, as both SWH and EOH are continuous / variable concepts rather than absolutes (meaning that many different combinations of SWH and EOH are possible), and after consultation with various members of the GDG, only five strategies have been formally evaluated (**Error! Reference source not found.**). It should also be noted that the model relates specifically to patients arriving at DGHs, as the GDG have already made the recommendation that 24/7 MRI scanning should be made available at tertiary / specialist units.

People with suspected MSCC can present with a number of different signs and symptoms ranging from non-specific back pain to established paraplegia. However, for the purposes of this modelling exercise the patient group has been restricted to people with 'early onset paralysis' on the assumption (as discussed with the Guideline Chair) that people who are still mobile can feasibly 'wait' for a MRI without adversely affecting the outcome of treatment (if required) and people who have been paralysed for longer periods of time are less likely require 'urgent' diagnosis and treatment. Thus the only patients considered in the model are those considered to require an 'urgent' MRI.

Table 1: Scenario descriptions for the base case analysis

Scenario	Description
1a	SWH defined as 9am to 5pm Monday to Friday only. In this scenario it is assumed that all DGH clinic slots are full, and that any person who requires an urgent MRI for suspected MSCC who arrives at the clinic Sunday to Thursday, is therefore required to wait until the next morning to have a MRI at the DGH. People arriving Friday or Saturday are required to wait until the following Monday for a MRI.
1b	All patients arriving at a DGH with suspected MSCC require immediate transfer to a tertiary treatment centre under the assumption that all the DGH MRI slots for that day are full. On arrival at the tertiary centre patients receive an immediate MRI and treatment if necessary.
2a	SWH again defined as 9am to 5pm Monday to Friday but with the added option that if a person urgently requires a MRI for suspected MSCC <i>during these opening hours</i> , they are immediately added to the clinic list and receive a MRI that day. The 'expense' of this approach is that the remaining patients on the waiting list for that day are required to wait an extra two hours, meaning that overtime is paid for the MRI-related staff. No MRI facilities are available outside of these times during the week or at the weekend.
2b	The same as 2a) except patients who require a MRI outside of these opening hours are immediately transferred to a tertiary treatment centre for scanning and treatment if required.
3	MRI clinics are assumed to extend their weekday opening hours to 8am to 8pm Monday to Friday and to be open at the weekend 9am to 3pm Saturday and Sunday. Patients requiring a MRI during these times are assumed to receive a scan the same day. People arriving outside of these hours are required to wait until the next morning for a MRI. As weekend cover is included in this scenario, it is implied that no 'urgent' patients are required to wait longer than 24 hours for a MRI.

(Note that although only these five scenarios have been evaluated, the model is sufficiently flexible to consider most other plausible options).

The 'exclusivity' assumption

An important issue when assessing the cost-effectiveness of extending MRI opening hours for people with suspected MSCC is that MRI facilities are (routinely) used for a

number of other patient groups eg. spinal trauma and transient ischaemic attack. This means that extending MRI opening hours benefits more than just MSCC patients and that the costs of this potential extension are therefore not solely attributable to this patient group. Two approaches to accommodating this cost issue were possible: attribute *all* of the additional costs to patients with suspected MSCC and conduct appropriate sensitivity analysis or, attribute *an appropriate proportion* of the extra costs to patients with suspected MSCC and conduct appropriate sensitivity analysis. The problem with the second approach is that it is not clear that it would be cost-effective to extend opening hours for these unknown patient groups, which is implicit in this approach. Moreover, the proportion of patients with suspected MSCC who receive a MRI is likely to be negligible given all demands for MRIs. Thus, the additional costs of extending hours for patients with suspected MSCC would be negligible, and in all likelihood it would be cost-effective option in all scenarios. For these reasons, it has been assumed that all the costs and benefits of extending opening hours are 'exclusive' to patients with MSCC.

Time horizon

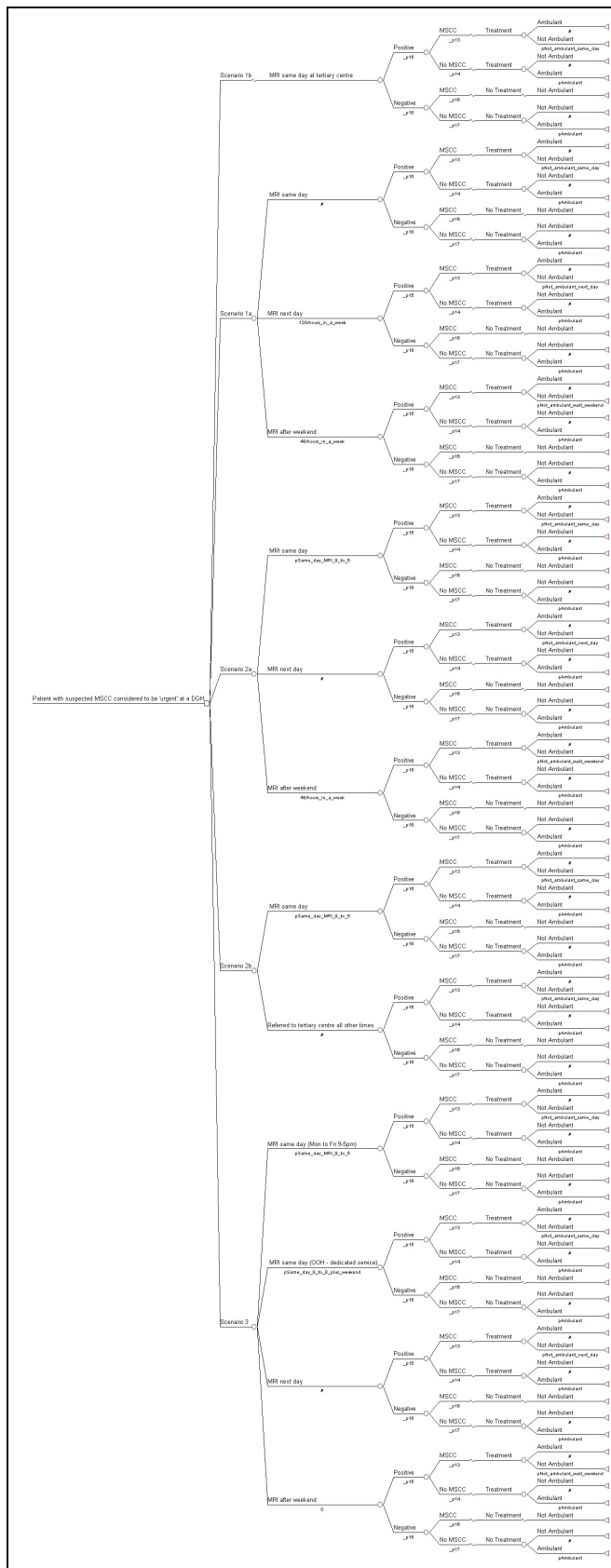
The model considers a range of possible events over an 'average' week for an 'average' DGH, in terms of estimating the costs and benefits of providing EOH services compared with SWH. However, the actual time horizon for the analysis is the time from referral for a MRI to the death of the patient from metastatic disease, which was approximately one year in most scenarios for ambulant patients. Thus the model estimates the expected costs and benefits of diagnosis and treatment for patients referred over an average week until death.

That activity within a DGH over a week period has been chosen is important in terms of explaining the models construction but has no significance in terms of the actual model results. For example, if a period of two- or four-weeks had instead been chosen, *all* the costs and benefits of diagnosis and treatment would be multiplied by two and four respectively, making no difference to the overall incremental cost-effectiveness ratio (ICER).

The Model Structure

The model structure is shown in Figure 1. Broadly speaking it is the same for all three scenarios, but the probabilities associated with the events differ as a result of different MRI opening hours. People who arrive at the clinic with suspected MSCC requiring an urgent MRI either receive a scan that day, the next day or on the following Monday if they are required to wait over the weekend. Patients who are required to wait until the next day for a MRI are assumed to have poorer health outcomes compared with people who receive an immediate MRI. Moreover, people who are required to wait for a MRI until after the weekend are assumed to experience poorer health outcomes compared with people who had to wait until the next day. Thus, the benefit of longer and more frequent opening hours is faster access to diagnosis / treatment with subsequently improved health outcomes. Once a MRI has been undertaken, patients with correctly diagnosed MSCC are assumed to undergo appropriate decompression treatment with an associated probability of being ambulant / not ambulant post this treatment.

Figure 1: Outline of model decision tree



Four possible MRI scan results were assumed to be possible:

True Positives (people who tested positive who had MSCC)

People who are true positives were assumed to undergo emergency spinal cord decompression with a subsequent chance of being ambulant or non-ambulant post surgery.

False Positives (people who tested positive who did not have MSCC)

All false positive patients were assumed to incur the cost of spinal cord decompression but were not assumed to actually undergo it, 50% were assumed to return to an ambulant health state until death.

True Negatives (people who tested negative who did not have MSCC)

All true negative patients did not undergo decompression treatment and 50% were assumed to return to an ambulant health state until death.

False Negatives (people who tested negative but did have MSCC)

All false negative patients were assumed not to undergo decompression (despite needing it) and to become non-ambulant until death.

Event Probabilities

The probability of a person with suspected MSCC requiring an urgent MRI during SWH was calculated to be 27% in the base case analysis, on the basis that patients uniformly¹ arrive at clinics and that there are 168 hours (7 x 24 hours) in a week and therefore a 27% (45/168) chance of arriving at a clinic during SWH. For scenario 3), the equivalent probability was calculated to be 43% (72/168) given that the clinic is open 72 hours per week (note that a 0% probability is equivalent to a clinic being permanently closed whereas 100% is equivalent to it being open 24 hours 7 days a week).

The probability of testing true / false / negative / positive is a function of three factors: the sensitivity of the test (here MRI), its specificity and the prevalence (also known as a 'prior' or 'pre-test probability') of the condition (here MSCC) in people attending the clinic. More formally, the likelihood of each of these test results can be calculated using the following formula[5]:

$$P(H|E) = ((PE|H) * P(H)) / P(E)$$

Where H is the hypothesis being tested (that is, whether or not a person has MSCC), E is the test result (positive or negative) and P(H) is the 'prior' associated with the condition (or the proportion of people attending a clinic with early paralysis that is directly attributable to the presence of MSCC).

Evidence suggests that both the sensitivity and specificity of MRI in detecting MSCC are extremely high; therefore both values were set to 0.99 in the baseline analysis. However, there is little evidence on which to estimate the proportion of people with early paralysis specifically associated with MSCC in people attending UK clinics. The most appropriate study was considered to be by Lu *et al.*[6] in 2005. The study was undertaken between 1998 and 1999 in two US teaching hospitals and consisted of patients attending clinics with suspected MSCC, a previous diagnosis of cancer, confirmation from the treating physician that the aim of the MRI was to rule out the possibility of metastatic epidural cancer and no prior diagnosis of metastatic epidural cancer. Clinical records for a total of 136 cases were reviewed, with MRI revealing that 37% of patients had thecal sac compression. This value was used in the baseline analysis to estimate the prior, however it was increased to 81% in the sensitivity analysis as the study showed that this value could be achieved if the patient group was restricted to including only people with at least 3 predictive factors (either an abnormal

¹ This uniformity assumption means that patients are equally likely to arrive at a clinic on any day at any time throughout the given week.

neurological examination, stage IV cancer at initial diagnosis, known vertebral metastases and middle / upper back pain).

The probabilities associated with post-treatment outcomes were taken from randomised and non-randomised sources; the RCT by Patchell *et al.*[7] did not provide sufficient information to be used as the sole source of information. The RCT only included non-ambulant patients if they had been paraplegic for less than 48 hours. Of the non-ambulant patients in the surgery plus radiotherapy treatment arm, 62.5% were ambulant post-treatment (n= 10/16). This percentage was used in the model to estimate the probability of being ambulant post surgery for patients who were diagnosed with MSCC and treated immediately (that is, those with early onset paraplegia, see Table 2). The non-randomised study by Bach *et al.*[4] was used to estimate the probability of being ambulant post treatment for people with more established paralysis as it contained the largest number of patients. Its results showed that only 6% of people with paraplegia were ambulant post-surgery, although it should be noted that this study was performed in 1990 and few details are provided as to the duration of pre-treatment paraplegia. All patients required to wait longer than 24 hours for a MRI were assumed to be paraplegic post treatment.

Table 2: Base case input variables by health state for patients with MSCC

Health State Pre Treatment	Health State Post Treatment		Source
	Ambulant	Not Ambulant	
Immediate MRI and treatment if needed (percentage)	62.5%	37.5%	Assumption based on Patchell et al.[7]
Wait <24 hours for MRI and treatment if needed (percentage)	6%	94%	Assumption based on Bach et al.[4]
Wait > 24 hours for MRI (percentage)	0%	100%	Complete assumption
Time to paraplegia after being ambulant post treatment (years)	0.61	-	Patchell et al.[7]
Survival – ambulant patients (years)	0.96	-	Thomas et al. [8]
Survival – paraplegic patients (years)	-	0.24	Maranzano et al.[9]
Utilities	0.7	0.4	Assumption based on Falicov et al.
Costs – mean home care post treatment (per diem)	£12.65	£192.80	Calculated as part of Section 6.8
Costs – mean rehabilitation cost (one-off cost)	£844		Calculated as part of Section 6.8

While the aim of decompression surgery is to prevent paraplegia, the results from the Patchell *et al.*[7] RCT showed that of the 60% of people who were paraplegic pre treatment, the average post-treatment time to paraplegia was approximately 0.61 years. Thus in the baseline analysis it was assumed that people for whom treatment was successful remained ambulant for 0.61 years, after which time they became paraplegic until death (Table 2). However, this value was altered in the sensitivity analysis to allow for the assumption that successful treatment was permanent.

Post-treatment patient survival for ambulant patients was assumed to be 0.96 years on the basis of the Patchell *et al.* RCT [7] for people who underwent decompression surgery and radiotherapy. However, two limitations with this data should be noted.

First, this value includes an unspecified proportion of patients who were paraplegic post-treatment, although it is likely to be small. Second, older, but recently published UK data, suggest that this median time was nearer to 6 months (Conway *et al.*[3]). A corresponding survival time for people who were paraplegic post surgery was not available from the RCT [7], but was estimated to be 0.24 years based on an adjusted analysis of the results reported in the uncontrolled study by Maranzano *et al.*[9] While other studies were available with which to estimate this parameter, the reported mean / median survival times were broadly similar. The analysis does not formally consider patient outcome by underlying histology. However, post-treatment survival times can be varied in the sensitivity analysis, which is entirely equivalent.

Utility Values

A number of studies have reported utility values that have relevance to this analysis. However, they all have significant limitations in terms of their direct use for this modelling exercise. For example, the results do not relate specifically to ambulant / non-ambulant health states, which are the outcomes used in this model. Moreover, the study by Hollingworth *et al.*[10] is based on the Quality of Well Being Scale, which is not a utility-based instrument.

In order to be consistent with Section 6.8, utility values of 0.7 and 0.4 were chosen as representing the health states 'ambulant' and 'not ambulant' respectively in the base case analysis. Briefly, Falicov *et al.*[11] reported these values in people with MSCC, but they were reported as bi-modal values, rather than scores that related specifically to the two health states. Thus they represent poor quality evidence.

Costs

Decompression Treatment

The hospital cost of 'major surgery' was calculated to be £13,410 per procedure in Section 6.8. An additional average rehabilitation cost of £844 per patient was also calculated for patients who were ambulant post-surgery. The cost of 'major surgery' was chosen to represent the cost of decompression treatment from amongst the various options costed in Section 6.8, as it encompasses a number of different types of surgery. However, it should be noted that as the sensitivity / specificity of the MRI test are high and all patients in the model bar a small minority receive treatment, the precise value of the treatment cost has negligible effect on the results. That is, the cost of decompression treatment has virtually no influence on the cost-effectiveness of expanding MRI opening hours². All decompression treatment was assumed to be undertaken at tertiary treatment centres. Thus an additional cost was incurred of transferring patients (if they received their MRI at a DGH, see later in the methods section).

Health state specific costs (ambulant / non-ambulant)

The analysis from Section 6.8 also suggests that the average post-treatment home care costs associated with being 'ambulant and 'non-ambulant' are £12.65 and £192.80 per diem respectively. A full description of how these values were calculated is provided in appendices in the Full MSCC Guideline. However, broadly speaking they include the costs of community nursing and caring from social services.

The costs of expanding MRI opening hours

Estimating the additional costs of expanding MRI opening hours is complex not least because 1) there is no (published) information on the topic and 2) because it depends on the configuration of existing services, which varies across existing scanning units.

² The exception to this, which is not included in this model, would be if MRI was sufficiently delayed to completely remove any clinical rationale for intervention.

Therefore, the following steps were followed and assumptions made with the aim of estimating the additional cost of a MRI:

- The cost of each MRI during SWH was assumed to be £244 on the basis of national NHS unit cost information. The cost of a MRI at tertiary treatment centres was also assumed to be £244 per scan.
- Two MRI costs were applied in scenario 2a. Patients requiring a scan that had to wait until at least the next day for a scan were again assumed to cost £244 per scan. However, those who arrived during SWH (Monday to Friday 9am to 5pm) who were slotted into the day's list were assumed to cost: the standard cost of a MRI plus 2 hours radiographer overtime with an additional 20% overtime allowance (£42), and a quarter programmed activity per consultant radiologist (£57). Thus the cost of a MRI in scenario during SWH for scenario 2) was (£244 + £42 + £57) = £343 per scan.
- Similarly for scenario 3, two different MRI tariffs were assumed to apply, depending on the time the MRI was undertaken. As per scenario 1) patients requiring a MRI between Monday to Friday 9am to 5pm, and patients who were required to wait until the next day for a scan, were assumed to cost £244 per scan. However, people requiring a scan during the extended opening hours (ie. between 8-9am Mondays to Fridays, 5-8pm Mondays to Fridays and between 9am-3pm Saturdays and Sundays) were assumed to cost £3,878 *per scan*³. Based on the following assumptions:

- a. It was estimated (assumed) that moving from scenario 1) to 3) would require 2 extra fulltime radiographers, each costing £33500 per annum, or £644 per week. This is equivalent to an extra 32-hours per week of clinic opening time.
- b. Each MRI during these extended hours is also assumed to require an additional quarter programmed activity per consultant radiologist (£57).
- c. Audit data from James Paget University Hospital showed that 19⁴ people with suspected MSCC required a MRI over a 10-week period, equivalent to 1.9 scans a week.
- d. If it is assumed that there are 168 hours in a week, and patients uniformly require MRIs, then 19% (32 hours / 168 hours) of 1.9 patients will attend during the extended daily working hours, equivalent to 0.36 patients per week.
- e. Thus the *cost per scan during the extended opening hours* is equal to $[(£644*2) / 0.36] + £244 + £57 = £3,878$. Note that this is calculated on the basis that all costs of extending the opening hours are attributable to diagnosing suspected MSCC patients, as described earlier in the methods section under the 'exclusivity assumption'.

Tertiary treatment centre costs

The costs of emergency transfers to tertiary treatment centres were assumed to be £247 per transfer, on the basis of HRG PSTEU – Paramedic emergency transfers in an urban setting. The call out costs for a radiographer was assumed to be £42 per scan as per scenario 2a. The additional costs of calling out a neuroradiologist were not included as they were already assumed to be on call.

Results and sensitivity analysis

Results are presented as expected costs, QALYs and ICERs for each treatment strategy. An ICER is defined as the difference in health benefits between the strategies

³ Attributing the additional costs only to the periods of additional / extended hours, rather than averaging across all opening hours, is consistent with the marginal cost principle and thus is correct.

⁴ Note that 19 patients is a maximum number of patients, as data for 7 of the patients had yet to be fully analysed.

divided by the difference in the clinical benefits. This is the traditional method of presenting the results of economic evaluations.

A number of sensitivity analyses (where input variables are changed, the model re-run and a revised ICER calculated) were undertaken to highlight the variables that were the most important in terms of determining the cost-effectiveness of treatment.

Results

Results from the baseline analysis are shown in Table 3. The results show that the marginal benefits of moving across the strategies are relatively modest, but that the ratio of marginal benefits to costs of moving to scenario 2a from scenario 1a, and to 2b from 2a, are beneath NICE's considered willingness to pay for an extra QALY range of £20,000-£30,000 per QALY level. The base case results also show that scenarios 1b and 3 are 'dominated' by other scenarios meaning that in the baseline analyses, they cannot be considered to be cost-effective options.

Table 3: Base case results

Scenario	Expected Costs	Expected QALYs	ICER*
1a	£18,431	0.26	-
2a	£18,591	0.28	£7,726
2b	£19,256	0.35	£9,785
1b	£19,310	0.35	Dominated**
3	£19,383	0.30	Dominated**

*Exact results may vary due to rounding expected costs and QALYs

**'Dominated' in this instance means that other scenarios are associated with more or the same number of QALYs but at less cost

The results from the sensitivity analyses are shown in Tables 4-10. Although they show that the expected costs and QALYs, and to a lesser extent the associated ICERs, are relatively labile, the ordering of the scenarios is relatively constant and consistent with the base case results. That is, scenario 2b appears to be the most cost-effective option in most of the analyses. Indeed, 2b remains the most cost-effective option (at a £30,000 per additional QALY threshold) even if the prior / prevalence of MSCC in suspected patients is as low as 6%. Moreover, in most of the results, scenarios 1b and 3 are shown not to be cost-effective. Changing the utility associated with the health state not-ambulant from 0.4 to 0.1 had negligible affect on the base case ICER. The same is true for the survival time associated with this health state. This is because patients in all scenarios who enter the health state not-ambulant, only remain in it for relatively short periods of time. Indeed, both variables only become a significant predictor of the cost-effectiveness ratio if it was firstly assumed that patients ambulant post surgery remained so until death.

Table 4: Sensitivity analysis – halving the costs of a MRI scan (£1,939 instead of £3,878) for scenario 3

Scenario	Expected Costs	Expected QALYs	ICER	ICER*
1a	£18,431	0.26	-	-
2a	£18,591	0.28	£7,726	£7,726
3	£19,044	0.30	£23,607	ED
2b	£19,256	0.35	£4,444	£9,785
1b	£19,310	0.35	Dominated	Dominated

*A second set of ICERs are calculated in this scenario because at least one of the scenarios is 'extendedly dominated' (ED) by a blend of other scenarios. In this example, scenario 3 is extendedly dominated by a blend of scenarios 2a and 2b. ED means that a preferable ratio of benefits to costs can be achieved by 'skipping over' an existing option.

Table 5: Sensitivity analysis – doubling the costs of radiographer over time (£82 instead of £42) for scenario 2a and 2b

Scenario	Expected Costs	Expected QALYs	ICER
1a	£18,431	0.26	-
2a	£18,601	0.28	£8,200
2b	£19,306	0.35	£10,241
3	£19,351	0.30	Dominated
1b	£19,383	0.35	Dominated

Table 6: Sensitivity analysis – halving the prior prevalence of MSCC in patients attending a DGH (0.185 instead of 0.37)

Scenario	Expected Costs	Expected QALYs	ICER
1a	£14,616	0.30	-
2a	£14,708	0.31	£8,856
2b	£15,155	0.35	£12,974
1b	£15,200	0.35	Dominated
3	£15,437	0.32	Dominated

Table 7: Sensitivity analysis – increasing the utility of being ambulant post treatment (0.8 instead of 0.7)

Scenario	Expected Costs	Expected QALYs	ICER
1a	£18,431	0.29	-
2a	£18,591	0.31	£6,670
2b	£19,256	0.39	£8,562
1b	£19,310	0.39	Dominated
3	£19,383	0.33	Dominated

Table 8: Sensitivity analysis – increasing the probability of not being ambulant post treatment if treated immediately (50% instead of 37.5%)

Scenario	Expected Costs	Expected QALYs	ICER
1a	£18,431	0.26	-
2a	£18,560	0.27	£8,047
2b	£19,138	0.33	£10,467
1b	£19,183	0.33	Dominated
3	£19,329	0.29	Dominated

Table 9: Sensitivity analysis – doubling the time to paraplegia following successful treatment (1.22 years instead of 0.61 years)

Scenario	Expected Costs	Expected QALYs	ICER	ICER
1a	£19,347	0.40	-	-
2a	£19,643	0.44	£7,161	£7,161
3	£20,562	0.48	£23,934	ED
2b	£20,771	0.58	£2,107	£8,191
1b	£20,817	0.58	Dominated	Dominated

Table 10: Sensitivity analysis – assuming that patients post who are ambulant post treatment remain so (ie. they can not ‘relapse’ to paraplegia)

Scenario	Expected	Expected	ICER
----------	----------	----------	------

	Costs	QALYs	
2b	£16,039	0.42	-
1b	£16,084	0.42	Dominated
2a	£17,841	0.33	Dominated
3	£17,943	0.35	Dominated
1a	£18,425	0.29	Dominated

Discussion

The aim of this analysis was to assess the cost-effectiveness of extending / altering MRI scanning hours for people with suspected MSCC who arrive at DGHs. The results from the analysis suggests that there could be economic merit in scanning suspected patients sooner rather than later if the resources required to do this are only employed when required (ie. paying over time to staff), rather than being permanently on station. Moreover, that this option should be explored prior to transferring patients to tertiary centres for diagnosis and treatment, but in its absence, transferring patients is the next economically viable option. The analysis also showed that in virtually no circumstance was extending MRI scanning hours purely for the benefit of suspected MSCC patients cost-effective. This is perhaps an artefact of the assumptions used to cost this service, but reflects the fact that MSCC is a relatively rare condition meaning that the additional costs incurred opening for longer hours is shared by a relatively small number of patients.

Having said this, the results from the sensitivity analysis show that the cost-effectiveness ratios are dependent on a number of assumptions and variables for which the evidence is relatively poor. For example, the model is underpinned by the notion that faster access to diagnosis and treatment ultimately leads to improved health outcomes. While there is reasonable clinical evidence to show that better health outcomes are achieved if patients are ambulant rather than immobile prior to decompression treatment, there is almost no evidence that has specifically quantified the impact of faster access to diagnosis and treatment. Thus, these results must be treated with a certain degree of caution.

One of the particular difficulties of undertaking this analysis was estimating the costs of extending scanning hours - the results from the sensitivity analysis clearly show that cost-effectiveness of scenario 3 is highly dependent on this variable. This is because there is no (published) information on MRI cost functions (that is, the relationship between inputs and outputs) and the additional costs are clearly dependent on existing service configurations. Thus one units extended hours might already represent another unit's standard working hours and even defining what is meant by extended hours is in itself problematic. It should be noted therefore, that the additional costs of extending standard working hours have been based exclusively on expert opinion rather than on data per se and the analysis has been restricted to the consideration of five scenarios, which were discussed with relevant GDG members. A more robust analysis of the costs and effects of extending MRI opening hours could benefit from a specially commissioned primary analysis of MRI cost data.

As described in the methods section, the assumption was made that all of the additional costs of extending scanning hours (for scenario 3) were attributable to patients with suspected MSCC. While in the context of performing an analysis for a MSCC specific clinical guideline, this approach was considered to be the most appropriate approach⁵, it is clearly unrealistic as the costs are likely to be shared across the many patient groups who utilise the service. While it is not precisely clear which other patient groups are likely to be involved, it is likely that suspected MSCC patients will be a small minority.

⁵ Because the guideline can only include recommendations with respect to MSCC patients and consideration of other patients would require recommendations for these additional patient groups to be made
Metastatic Spinal Cord Compression: evidence review

Thus, while the base case analysis suggests that dedicated extended opening scanning hours for suspected MSCC patients is probably not cost-effective, this does not mean to say that patients with suspected MSCC should not be scanned urgently if extended opening hours *are already* in place as the additional costs of doing so are likely to be much smaller than estimated in this analysis.

The analysis includes the costs of staffing the MRI clinic, the MRI scan itself, the costs of undertaking any subsequent treatment and the costs associated with the resulting health states (that's, whether a person is ambulant or not ambulant post treatment). However, it does not include the potential costs of calling in surgical staff out of hours as it is understood that in most tertiary centres they are already on call, thus the expense has already been incurred. Similarly the inpatient costs of having to wait until the next day or until after the weekend have not been included in the analysis. However, including them would only increase the cost-effectiveness of some of the scenarios, including 2b. Thus while it is feasible that the ordering (in terms of cost-effectiveness) may alter, scenario 2b will remain the option of choice.

A number of other assumptions that are implicit in the analysis require highlighting. The analyses involving scenario 2a assume that people with suspected MSCC are slotted onto the day's scanning list whenever feasible. Moreover, that this is achieved at the expense of delaying scanning for other non-MSCC patients *at no health consequence to them*. Whether this is an accurate assumption or not clearly depends on the type of patient(s) who are required to wait. But as the incremental health benefits associated with scenario 2a are relatively small (0.02 QALYs), any dis-benefit experienced by other patients as a consequence of having to wait longer for a scan could easily cause the this over-time scenario to become a non-cost-effective option. Similarly, it has been assumed that patients transferred to tertiary centres do not experience any dis-utility associated with travelling, and that travelling does not affect treatment outcome.

In summary, the results from this model and base case analysis suggest that scanning patients with suspected MSCC outside of standard working hours is cost-effective in some circumstances. However, it should be noted that the clinical evidence on which the cost-effectiveness estimates have been based is poor.

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Chapter 6 – Treatment Selection and Strategies

6.2 Treatments primarily for pain or the prevention of collapse/cord compression

What is the effectiveness of Bisphosphonates at treating spinal pain and/or preventing spinal collapse and/or spinal cord compression?

Bisphosphonates

Short summary

Bisphosphonates have been evaluated in several meta-analyses including patients with different cancer types. (Imrie *et al.* 2005; Saad *et al.* 2004; Tripathy *et al.* 2004; Warr *et al.* 2004; Weinfurt *et al.* 2004; Weinfurt *et al.* 2005; Wong and Wiffen 2002; Yuen *et al.* 2006). Consistently this evidence demonstrates that pain is altered or reduced with bisphosphonates (for breast cancer and multiple myeloma). A meta-analysis by Yuen *et al.* (2006) showed a trend favouring bisphosphonates over placebo for the relief of pain from bone metastases in men with prostate cancer, although this was not statistically significant. There was no significant difference between the analgesic consumption of bisphosphonate and placebo groups.

Bisphosphonates have also been reported to manage skeletal complications in patients with metastatic cancer, although some inconsistencies do exist. There is evidence that skeletal related events (SRE) are reduced in patients with multiple myeloma and breast cancer (Imrie *et al.* 2005; Tripathy *et al.* 2004; Warr *et al.* 2004). For prostate cancer the meta-analysis by Yuen *et al.* (2006) showed a modest reduction in skeletal events with bisphosphonate treatment (using trial authors' definitions of skeletal events). The estimated rates for skeletal events were 37.8% and 43.0% for the bisphosphonate and placebo groups respectively: an absolute risk difference of 5.2%. There was inconsistent evidence about the effect of bisphosphonates on the rate of pathological fractures. The rates of spinal cord compression, bone surgery and bone radiotherapy did not differ significantly between bisphosphonate and placebo groups. There were no significant group differences in overall survival or in quality of life. From an included study (Saad *et al.* 2002) in this review and from a follow-up publication (Saad *et al.* 2004), 4mg zoledronic acid was reported to be statistically more effective than placebo with respect to reducing SREs (with SCC a component of the SRE definition). Interestingly, the 8/4mg arm of this study did not show a significant difference for SREs (Saad *et al.* 2002). In Saad *et al.* (2002), SCC occurred less frequently in patients who received either dose of zoledronic acid than in those who received placebo. Yuen *et al.* (2006) conducted statistical analysis on these figures and showed that it was not statically significantly different.

From an RCT that compared zoledronic acid (4 or 8 mg) with a placebo in patients with lung cancer and other solid tumours (Rosen *et al.* 2003) there was no statistically significant difference in SREs (which excluded hypercalcaemia of malignancy - HCM), between 4 mg zoledronic acid versus placebo. However, there was a statistically significant difference between 8/4 mg zoledronic acid versus placebo. In the analysis of all skeletal events (including HCM), 4 mg ZA significantly reduced the proportion of patients with an event as compared with the placebo group. There was minimal difference in the proportion of patients experiencing SCC in any treatment group (4 or 8/4 mg ZA or placebo) – no statistical analysis provided. A multiple event analysis showed a significant 27% risk reduction for multiple skeletal events, in favour of 4 mg zoledronic acid, among patients in both the NSCLC (non small cell lung cancer) and other solid tumour group, versus the placebo group. From an extended treatment time of this RCT (Rosen *et al.* 2004), fewer (though not statistically analysed) patients treated with zoledronic acid developed at least 1 SRE at 21 months compared with patients

treated with placebo. There was a statistically significant difference for those treated at the 8/4-mg dose, compared to those treated with placebo. Again as in Rosen *et al* (2003), there was minimal difference in the proportion of patients experiencing SCC in any treatment group (4 or 8/4 mg zoledronic acid or placebo) – no statistical analysis provided. A 31% reduction in the risk of developing an SRE (including HCM) for a patient treated with 4 mg of zoledronic acid compared with placebo.

Overall, the most common adverse effects reported in this extensive body of evidence are nausea, vomiting, anaemia, bone pain and renal toxicity.

Cross reference to CG58 Prostate cancer: NICE guidance (see Chapter 7 – Bone Targeted Therapies).

<http://www.nice.org.uk/guidance/index.jsp?action=download&o=39626>

PICO

Population	Intervention	Comparison	Outcomes
Patients with known vertebral metastases (inc both asymptomatic & symptomatic)	Bisphosphonates: <ul style="list-style-type: none">• Clodronate treatment• Zoledronate• Pamidronate• Alendronate• Risedronate• Etidronate• Tiludronate	<ul style="list-style-type: none">• Placebo• Same bisphosphonate• Other bisphosphonate treatment (eg. Zoledronate, active control)• No treatment	<ul style="list-style-type: none">• Improvement in pain• Prevention of vertebral collapse• Prevention of spinal cord compression

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

There is a considerable body of evidence included for this question. It included meta-analyses and systematic review that have included several studies and 3 major cancer types. These studies included in the reviews have a varied study populations (patients with and without vertebral metastases) in general these populations are described as patients with bony metastases.

There is high level evidence that pain is altered/reduced with bisphosphonates (for all cancer types)

There is high level evidence that skeletal related events (SREs) are reduced in multiple myeloma and breast cancer patients, however, not all the patients included in the trials (in the large reviews) had vertebral metastases, at best nearly all patients had bone metastases.

For prostate cancer patients there is a no significant difference favouring bisphosphonates for preventing SREs ($p=0.05$). From the results of the review, only 2 papers reported spinal outcomes (Vertebral fractures or MSCC).

Bisphosphonates for the relief of pain secondary to bone metastases

From all the studies reported here, pain reduction was associated with the use of bisphosphonates. To some extent, a lack of standardisation in pain measurement hindered conclusions across studies. Results from the included studies are presented below.

A Cochrane Review by Yuen *et al.* (2006) reported in a meta analysis of included studies that pain can be effectively managed using bisphosphonates. This meta-analysis included 4 studies (3 evaluated clodronate and 1 etidronate) suggested a trend favouring bisphosphonates over placebo in terms pain relief (overall OR = 1.54, CI=0.97-2.44, $p=0.07$, intention to treat analysis). A sensitivity analysis (for evaluable patients) showed statistical significance that favoured bisphosphonates treatment for pain relief (OR=1.64, CI=1.02-2.61, $p=0.04$). The rates for pain response were 27.9% and 21.1% for the treatment group and the control group respectively, with an absolute risk difference of 6.8%.

Another Cochrane review by Wong *et al.* (2006) determined the effectiveness of bisphosphonates for the relief of pain from bone metastases. Data were reported for different time points: five studies reported at four weeks, one study at eight weeks, and five studies at twelve weeks. (bisphosphonates evaluated included; clodronate, pamidronate, etidronate and diphosphonate):

- At week 4: OR =2.21 (95% CI 1.19-4.12), NNT (number needed to treat) 11 (95% CI 6-36) *That is, you would need to treat 11 patients with a bisphosphonate to bring pain relief in 4 weeks to 1 additional patient.*
- At week 8: only one study provided these data so pooling for this time point was not meaningful
- At week 12: OR =2.49 (95% CI 1.38-4.48), NNT 7 (95% CI 5-12)
- Both week 4 and week 12 results showed a significant benefit for patients receiving bisphosphonates. Given the limited number of studies in which data were available, the results for 'best pain response within 12 weeks' were synthesized as follows: OR 2.37 (95% CI 1.61-3.5) , NNT 6 (95% CI 5-11) in favour of the treatment group. (This approach was adopted retrospectively, after the data extraction process revealed the limited data available).

A systematic review which was also drawn from the Cancer Care Ontario guideline program on the same topic (Imrie *et al.*2005), investigated the role of bisphosphonates in the management of skeletal complications in patients with multiple myeloma. While it cannot be confirmed that the patient group were all metastatic stages of the disease, or that all patients had vertebral disease, useful conclusions from this work can still be drawn. The Cancer Care Ontario guideline has been appraised using the AGREE instrument (2003) – the work was judged to be of high quality.

Evidence identified that use of a bisphosphonate (etidronate, clodronate, pamidronate, or ibandronate) was associated with a reduction in pain, but the authors commented that there was less confidence in this conclusion because data had been reported in an inconsistent manner across studies. The OR for the occurrence of pain in bisphosphonates compared to control = 0.59, (95%CI 0.46 to 0.76), p value= 0.00005, indicating that an occurrence in pain is reduced by bisphosphonates and a NNT of 11 (95% CI, 7 to 28) is required in order to avoid pain in one patient.

An RCT by Tripathy *et al* (2004) randomised patients to receive oral ibandronate at one of two different doses (20mg or 50mg daily) or placebo reported no statistically significant difference between ibandronate and placebo with respect to bone pain scores.

An RCT by Saad *et al.*(2004) reported periodic measures of Bone Pain Intensity scores (at 3-month intervals) and demonstrated a statistically significant and durable palliation of bone pain for patients treated with zoledronic acid compared with a placebo group. The BPI score point difference of 0.47 was reported.

The guideline by Warr *et al.*(2002) was produced by Cancer Care Ontario and has been appraised using the AGREE instrument – the work was judged to be of high quality. The original 2002 document included analysis of a Cochrane systematic review (Pavakis *et al.* 2005), 28 RCTs and two other evidence-based guidelines (ASCO and SIGN). The 2004 update added further data from meetings and papers that were incomplete at the time of the first publication. Studies included any bisphosphonate (clodronate, pamidronate, ibandronate or zoledronate) compared with another bisphosphonate, with placebo or no treatment; different routes of administration or different dosages. The findings were that oral clodronate and i.v. pamidronate significantly reduced the incidence of SREs and bone pain. Direct comparisons found that 4mg zoledronate was equivalent to 90mg i.v. pamidronate given every 3-4 weeks. Overall, the conclusions were that bisphosphonates did not improve overall survival but reduced the incidence of SREs and pain.

Bisphosphonates and Skeletal Related Events

The Cochrane Review (which evaluated oral clodronate or pamidronate disodium or zoledronic acid) (Yuen *et al.*2006) described the rates for skeletal events were 37.8%

and 43.0% for the treatment group and the control group respectively, with an absolute risk difference of 5.2%. From the same Cochrane Review, results for patients having MSCC indicated no significant difference between bisphosphonates (pamidronate iv infusion and 4mg or 8/4mg ZA) and control (placebo). Overall OR=0.82, 95%CI=0.44-1.55, p=0.54.

A multiple event analysis conducted as part of one RCT (Saad *et al.*2004) reported that 4mg Zoledronic acid reduced the risk of skeletal complications by 36% at 24 months when compared to placebo.

The systematic review and meta-analyses by Imrie *et al.*(2005) concluded that there was evidence to support using a bisphosphonate to reduce vertebral fractures. The OR for the occurrence of vertebral fractures in bisphosphonates group compared to control = 0.59, (95%CI 0.45 to 0.78), p value= 0.0001, indicating that an occurrence in vertebral fractures is reduced by bisphosphonates. The meta-analysis results translate to a NNT of 10 (95% CI, 7 to 20) in order to avoid one patient with a vertebral body fracture. This outcome was the closest related to the outcomes listed in the PICO table which essentially provides a fairly inaccurate surrogate measure.

The Tripathy *et al* (2004) RCT reported the relative risk of having a SRE (which includes vertebral or non-vertebral fractures, bone RT or bone surgery) was significantly lower in the ibandronate arms of this RCT compared with placebo (RR = 0.61).

Bisphosphonates and Adverse Effects

In the Yuen *et al.*(2006) review a significant increase in nausea was observed in patients who received bisphosphonates compared to placebo. No increase in other adverse events was observed.

Renal toxicity: Treatments evaluated were pamidronate iv infusion and 4mg or 8/4mg ZA (zoledronic acid) and iv/oral clodronate. No renal failure due to iv/oral clodronate was reported. Rates of urinary symptoms were reported, 2% for the oral clodronate gp and 6% for the placebo gp. Deteriorated renal function was reported in 15.2%, 20.7% and 11.5% of patients for ZA 4mg gp, ZA 8/4mg gp, and placebo gp respectively. Kaplan-Meier estimates of time to first renal function deterioration was not significant for either 4mg or 8/4mg when compared to placebo gp. Patients treated with 8mg ZA had a higher incidence of elevated serum creatinine levels than did patients treated with 4mg ZA. Trial protocol was amended and patients were then only given 4mg = 8/4mg ZA. No change from mean baseline serum creatinine for both pamidronate gp and placebo gp was reported.

Vomiting was an adverse effect reported in the Wong *et al.*(2006) review, the Odds ratio: 1.11 (95% CI 0.79-1.58).

A broad heading of gastrointestinal symptoms was reported in Imrie *et al.*(2005) review, the result indicated an OR 1.28 (0.95 to 1.74), p=0.11. No significant difference between the groups.

In Tripathy *et al.*(2004) approximately 10% of ibandronate treated patients experienced upper GI tract problems and 6 patients (1 placebo) withdrew because of oesophagitis or dyspepsia. Renal effects were not significantly different between groups and 1 patient (group B) withdrew because of azotemia.

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Evidence Tables

Systematic Reviews

Yuen KK, Shelley M, Sze WM, Wilt T, Mason MD. Bisphosphonates for advanced prostate cancer. *Cochrane Database of Systematic Reviews* 2006, Issue 4. Art. No.: CD006250. DOI:10.1002/14651858.CD006250

Design

Cochrane Systematic Review
Grade 1++

Inclusion criteria Eligible participants include those with confirmed bone metastases from prostate cancer. All participants in the eligible studies were included. There was no restriction on age, performance status, life expectancy or previous treatment of the participants. Studies including non-metastatic prostate cancer or other primary site(s) of cancer were excluded. Animal studies were excluded.

Exclusion criteria -

Population

Twenty-three studies were identified as potential trials for inclusion in this review. Thirteen studies were excluded from the analysis. These included eight uncontrolled studies, two non-randomized studies and three studies evaluating histomorphometric or biochemical outcomes. The details were described in the 'characteristics of excluded studies' section. A total of 1663 patients from ten trials were included.

Interventions

The studies must include a bisphosphonate as one of the studied interventions. Any type of bisphosphonate was considered eligible. However, radioactive bisphosphonates were excluded. There was no restriction on the dose, route or duration of bisphosphonate treatment.

The control arm could be placebo, no bisphosphonate treatment (open control) or another bisphosphonate treatment (active control). Studies with an active control could compare different types of bisphosphonates, or different doses, different durations or different routes of administration of the same bisphosphonate. Comparisons involving active control were analysed separately.

Concurrent or sequential use of other types of treatment, such as hormones, chemotherapy or radiotherapy were allowed, provided that all arms in the study used the same protocol.

Outcomes

control of pain (pain response, change in pain, use of analgesia)
skeletal events
adverse effects
patient survival
disease progression
PSA response
radiological response
quality of life
performance status

Results

PAIN RESPONSE

The rates for pain response were 27.9% and 21.1% for the treatment group and the control group respectively, with an absolute risk difference of 6.8%.
4 studies reported a pain response (3 evaluated clodronate and 1 etidronate) were included in a meta-analysis. One study that reported pain response was not included in this analysis due to missing data, however it showed that there was no statistically significant difference b/n active (different doses and duration of oral clodronate) and control (placebo) groups.

Meta-analysis suggested a non significant outcome of bisphosphonates over placebo in terms pain relief (overall OR = 1.54, CI=0.97-2.44, p=0.07, intention to treat analysis). A sensitivity analysis (for evaluable patients) showed statistical significance that favoured bisphosphonates treatment for pain relief (OR=1.64, CI=1.02-2.61, p=0.04).

MEAN PAIN CHANGE

Mean Pain change was reported by 4 studies but pooling results was not possible. Individual study results for mean pain change were not provided.

PROPORTION OF PATIENTS WITH REDUCED ANALGESIC CONSUMPTION

4 studies (3 evaluated clodronate and 1 etidronate) reported a proportion of patients with reduced analgesic consumption (and were included in a meta-analysis). One study that reported a proportion of patients with reduced analgesic consumption and was not included in this analysis due to missing data, however it showed that there was no statistically significant difference b/n active (different doses and duration of oral clodronate) and control (placebo) groups.

Meta-analysis showed no difference b/n bisphosphonates and placebo in terms of reducing analgesic consumption (OR=1.27, 95% CI=0.82-1.98, p=0.28).

MEAN DIFFERENCE IN ANALGESIC CONSUMPTION

Pooling results was shown not to provide meaningful conclusions. One study reported a statistically significant decrease in analgesic consumption after the administration of clodronate and another reported a non statistical significant difference b/n treatment and control groups in analgesic consumption.

SKELETAL EVENTS

(Hypercalcemia, pathological fractures, requiring RT for bone pain or to treat or prevent fractures or MSCC, surgery to bone or symptomatic and asymptomatic bone progression)

Meta-analysis was conducted using data from 1332 patients.

Results for any skeletal events:

The rates for skeletal events were 37.8% and 43.0% for the treatment group and the control group respectively, with an absolute risk difference of 5.2%.

Overall OR=0.79, CI=0.62-1.00, p=0.05. No significant difference favouring bisphosphonates. Sensitivity analysis with evaluable patients indicated the same result and statistical pooling data was valid. Sensitivity analysis comparing different doses of Zoledronic Acid-ZA (4mg or 8 followed by 4mg (8/4mg)) showed a statistical significant reduction in skeletal events for patients given 4mg ZA and no difference for patients given 8mg followed by 4mg ZA.

When active arms of the study that compared different doses of Zoledronic Acid-ZA (4mg or 8 followed by 4mg (8/4mg)) were analysed separately the meta-analysis indicated a statistically significant difference, however, when the active arms were combined in a meta-analysis, the difference was not observed.

Results for pathological fractures

(statistical pooling data not valid - no appropriate conclusions could be made from results)

Results for patients having vertebral fractures

(statistical pooling data not valid - no appropriate conclusions could be made from results)

Results for patients having non-vertebral fractures

Overall OR=0.74, 95%CI=0.49-1.12, p=0.15, indicating no significant difference b/n bisphosphonates (pamidronate iv infusion and 4mg or 8/4mg ZA) and control (placebo).

Results for patients having MSCC

Overall OR=0.82, 95%CI=0.44-1.55, p=0.54, indicating no significant difference b/n bisphosphonates (pamidronate iv infusion and 4mg or 8/4mg ZA) and control (placebo).

Results for patients receiving RT to bone

OR=0.83, 95%CI=0.62-1.11, p=0.21, indicating no significant difference b/n bisphosphonates (pamidronate iv infusion and 4mg or 8/4mg ZA or clodronate till disease progression) and control (placebo).

Results for patients receiving surgery to bone: OR=0.80, 95%CI=0.38-1.70, p=0.57, indicating no significant difference b/n bisphosphonates (pamidronate iv infusion and 4mg or 8/4mg ZA) and control (placebo).

QUALITY OF LIFE

2 studies reported QoL outcomes. Results not pooled.

Study 1.

Pain score recorded using Present Pain Intensity and QoL used Prostate Cancer Specific Quality of Life Instrument (PROSQOLI). No statistical significant difference b/n clodronate and placebo gp in terms of QoL response. No significant difference in the median changes from baseline in the PROSQOLI scores in 8 out of 9 domains. The pain domain had a significant difference (p=0.022) in favour of the clodronate gp.

Study 2.

QoL parameters included pain score (Brief Pain Inventory), analgesic scores, ECOG performance status and 2 QoL questionnaires (Functional Assessment of Cancer Therapy General and EURO Quality of life EQ-5D). No statistical difference among 3 study groups wrt the scores from the QoL questionnaires was found. This study evaluated Zoledronic acid.

PATIENT SURVIVAL

4 studies reported patient death and were included in a meta-analysis. This analysis showed no statistical significant difference b/n the bisphosphonate group and control group. The overall OR=0.82, 95%CI 0.61-1.11, p=0.21.

1 study was not included in the meta-analysis, reported median time of survival of 464 days for placebo compared to 546 days for 4mg ZA, p=0.091 versus placebo, and 407 days 8/4mg ZA, p=0.386.

Bone and non-bone disease progression was evaluated by 2 studies which were included in a meta-analysis. No statistical significant difference b/n bisphosphonate group and control group was shown, overall OR=0.76, 95%CI 0.53-1.8, p=0.12.

ADVERSE EVENTS

8 studies reported adverse events, the most common included nausea, vomiting, anaemia, bone pain and renal toxicity.

For Nausea: Treatments evaluated were pamidronate iv infusion and 4mg or 8/4mg ZA.

Overall OR = 1.35, 95%CI 1.02-1.77, p=0.03 indicating that a statically significant result of more patients in the bisphosphonate gp experienced nausea than the control gp. Proportions having nausea:39.2% (treatment gp) and 29.7% (control gp), absolute risk difference = 9.5%.

For vomiting: Treatments evaluated were pamidronate iv infusion and 4mg or 8/4mg ZA.

Overall OR = 1.22, 95% CI 0.89 - 1.69, p=0.22. No significant difference b/n bisphosphonate gp and control gp. Proportion of patients having vomiting were 22.8% (treatment gp) and 18.3%

(control gp), absolute risk difference = 4.5%

For anaemia: Treatments evaluated were pamidronate iv infusion and 4mg or 8/4mg ZA and iv clodronate. Overall OR = 1.04, 95%CI 0.76-1.41, p=0.83. No significant difference b/n bisphosphonate gp and control gp. Proportion of patients having anaemia were 20.2% (treatment gp) and 19.8% (control gp), absolute risk difference = 0.4%.

For bone pain: Treatments evaluated were pamidronate iv infusion and 4mg or 8/4mg ZA. Overall OR = 0.93, 95% CI 0.72-1.21, p=0.58. No statistically significant difference b/n bisphosphonate gp and control gp. Proportion of patients having bone pain 51.5% (treatment gp) and 50%(control gp), absolute risk difference =1.5%

For renal toxicity: Treatments evaluated were pamidronate iv infusion and 4mg or 8/4mg ZA and iv/oral clodronate.

No renal failure due to iv/oral clodronate was reported. Rates of urinary symptoms were reported, 2% for the oral clodronate gp and 6% for the placebo gp. Deteriorated renal function was reported in 15.2%, 20.7% and 11.5% of patients for ZA 4mg gp, ZA 8/4mg gp, and placebo gp respectively. Kaplan-Meier estimates of time to first renal function deterioration was not stat significant for either 4mg or 8/4mg when compared to placebo gp. Patients treated with 8mg ZA had a higher incidence of elevated serum creatinine levels than did patients treated with 4mg ZA. Trial protocol was amended and patients were then only given 4mg = 8/4mg ZA. No change from mean baseline serum creatinine for both pamidronate gp and placebo gp was reported.

COMPARISONS B/N DIFFERENT ROUTES OF ADMINISTRATION, DOSES AND TYPES OF BIPHOSPHONATES

Intramuscular VS oral clodronate: a significant fall in analgesic consumption was reported but not pain measured by visual analogue scale.

ZA, 4mg VS 8mg (initially 8mg then reduced to 4mg - 8/4mg) VS placebo: At 15 months stat. significant change in mean pain score in favour of 8/4mg over placebo (p=0.026). No significant difference in analgesic scores. No direct comparison b/n ZA 4mg VS 8/4mg wrt pain and analgesic scores.

Studies included in this review:

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Ernst DS, Tannock IF, Winkler EW, Venner PM, Reyno L, Moore MJ, Chik, Ding K, Elliot C, Parulekar W. Randomized, double-blind, controlled trial of mitoxantrone/prednisone and clodronate versus mitoxantrone/prednisone and placebo in patients with hormone-refractory prostate cancer and pain. *Journal of Clinical Oncology* 2003; 21 (Sept 1 (17)):3335-3342.

Kylmala T, Tammela T, Risteli L, Risteli J, Taube T, Elomma I. Evaluation of the effect of oral

clodronate on skeletal metastases with type I collagen metabolites. A controlled trial of the Finnish Prostate Cancer Group. *European Journal of Cancer* 1993;29A(6):821–825.

Kylmala T, Taube T, Tammela TL. Concomitant i.v. and oral clodronate in the relief of bone pain: A double-blind placebo-controlled study in patients with metastatic prostate cancer. *British Journal of Cancer* 1997;76:939–942.

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Wong R, Wiffen PJ.

Bisphosphonates for the relief of pain secondary to bone metastases.

Cochrane Database of Systematic Reviews 2002, Issue 2.

Art. No.: CD002068. DOI: 10.1002/14651858.CD002068

Design

Cochrane Systematic Review

Grade 1++

Inclusion criteria

Exclusion criteria

Population

Cancer patients (including breast, prostate, multiple myeloma) requiring palliation for pain from bone metastasis.

Interventions

Biphosphonates

Comparator: Placebo/ control

Outcomes

- Pain relief at week 4
- Pain relief at 12 weeks
- Best pain relief within 12 weeks
- Mean pain score
- Proportion of patients with reduction of analgesics at week 4.
- Proportion of patients with reduction of analgesics at week 12.
- Mean analgesic consumption
- Adverse Drug Reactions: vomiting
- Discontinuation of therapy due to adverse effects
- Quality of life

Follow up

Results

Outcomes	Effect Size	Comments
Pain relief at week 4	5 studies: Odds ratio: 2.21 (95% CI 1.19-4.12) NNT (number needed to treat) 11 (95% CI 6-36). That is, need to treat 11 patients with a bisphosphonate to bring pain relief in 4 weeks to 1 additional patient. 4 studies: reported on the lack of difference between the pain response for treatment and control groups although a specific time period was not specified.	The response pattern at less than 4 weeks could not be assessed due to lack of data. No clinical or statistical heterogeneity was observed across the outcomes of interest permitting pooling of the data to provide summary statistics.
Pain relief at 12 weeks	5 studies: Odds ratio: 2.49 (95% CI 1.38-4.48) NNT 7 (95% CI 5-12), 4 studies: reported on the lack of difference between the pain response	

	for treatment and control groups although a specific time period was not specified.	
Best pain relief within 12 weeks	Odds ratio: 2.37 (95% CI 1.61-3.5) NNT 6 (95% CI 5-11) in favour of the treatment group, 4 studies: reported on the lack of difference between the pain response for treatment and control groups although a specific time period was not specified.	This approach was adopted retrospectively, after the data extraction process revealed the limited data available.
Mean pain score	There was a general trend showing the mean pain score was lower for the treatment arm, the magnitude of difference between the treatment and control arms ranged from -0.53 to 2.1 at week 4 and -0.37 to 1 at week 12.	Standardisation of the different pain scores was not attempted and the standard deviations of the studies were not provided.
Proportion of patients with reduction of analgesics at week 4.	Odds ratio in favour of the treatment group: 2.81 (95% CI:1.24-6.38)	Data was reported at different time frames for studies reporting results.
Proportion of patients with reduction of analgesics at week 12.	Odds ratio in favour of the treatment group: 2.37 (95% CI: 1.1-5.12)	
Mean analgesic consumption	3 studies reported a lack of difference in analgesic consumption and 3 studies reported that the patients on the treatment arm required less analgesia than those on the control arm.	There was insufficient information to allow a quantitative synthesis.
Adverse Drug Reactions: vomiting	Odds ratio: 1.11 (95% CI 0.79-1.58)	
Discontinuation of therapy due to adverse effects	Odds ratio: 8.53 (95% CI 1.25-58) NNH (number needed to harm) 16 (95% CI 12-27), that is, for every 16 patients who receive a bisphosphonate, an additional person will be harmed.	
Quality of life	Small but non-significant improvement in quality of life compared with baseline in the pamidronate arm at four weeks, quality of life worsened in the placebo arm.	Other studies reported QoL data outside the time frame of interest.

Included studies in Wong Review:

Arıcan A, İcli F, Akbulut H, et al. The effect of two different doses of oral clodronate on pain in

patients with bone metastases. *Medical Oncology* 1999;16(3):204–10.

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Cascinu S, Graziano F, Alessandrini P, Ligi M, Del Ferro E, et al. Different doses of pamidronate in patients with painful osteolytic bone metastases. *Support Care Cancer* 1998;6:139–43.

Coleman RE, Houston S, Purohit OP, Rubens RD, Kandra A, Ford J. A randomised phase II study of oral pamidronate for the treatment of bone metastases from breast cancer. *European Journal of Cancer* 1998;34(6):820–4.

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Daragon A, Humez C, Michot C, et al. Treatment of multiple myeloma with etidronate: results of a multicentre double-blind study. Groupe d'Etudes et de Recherches sur le Myelome (GERM). *European Journal of Medicine* 1993;2:449–52.

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Ernst DS, MacDonald RN, Paterson AH, Jensen J, Brasher P, Bruera E. A double-blind, crossover trial of intravenous clodronate in metastatic bone pain. *Journal of Pain and Symptom Management* 1992;7(1):4–11.

Ernst DS, Brasher P, Hagen N, Paterson AH, MacDonald RN, Bruera E. A randomized, controlled trial of intravenous clodronate in patients with metastatic bone disease and pain. *Journal of Pain and Symptom Management* 1997;13(6):319–26.

Glover D, Lipton A, Keller A, et al. Intravenous pamidronate disodium treatment of bone metastases in patients with breast cancer. A dose-seeking study. *Cancer* 1994;74(11):2949–55.

Heim M, Clemens MR, Queisser W, Pechersorfer M, Boewer Ch, et al. Prospective randomized trial of dichloromethylene bisphosphonate (clodronate) in patients with multiple myeloma requiring treatment. A multicenter study. *Onkologie*. *Onkologie* 1995;18:439–48.

Hortobagyi GN, Theriault RL, Porter L, et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. *Protocol 19 Aredia*

Breast Cancer Study Group. *New England Journal of Medicine* 1996;335(24):1785–91.

Hultborn R, Gundersen S, Ryden S, et al. Efficacy of pamidronate in breast cancer with bone metastases: a randomized double-blind placebo controlled multicenter study. *Acta Oncol* 1996;35(Suppl 5): 73–4.

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Lahtinen R, Laakso M, Palva I, Virkkunen P, Elomaa I. Randomised, placebo-controlled multicentre trial of clodronate in multiple myeloma. Finnish Leukaemia Group. *Lancet* 1992;340:1049– 52.

Martoni A, Guaraldi M, Camera P, Biagi R, Marri S, Beghe F, Pannuti F. Controlled clinical study on the use of dichloromethylene diphosphonate in patients with breast carcinomametastasizing to the skeleton. *Oncology* 1991;48:97–101.

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O'Rourke N, McCloskey E, Houghton F, Huss H, Kanis JA. Double-blind, placebo-controlled, dose-response trial of oral clodronate in patients with bone metastases. *Journal of Clinical Oncology* 1995;13 (4):929–34.

Piga A, Bracci R, Ferretti B, et al. A double blind randomized study of oral clodronate in the treatment of bone metastases from tumours poorly responsive to chemotherapy. *J Exp Clin Cancer Res* 1998;17 (2):213–7.

Robertson AG, Reed NS, Ralston SH. Effect of oral clodronate on metastatic bone pain: a double-blind, placebo-controlled study. *Journal of Clinical Oncology* 1995;13(9):2427–30.
Siris E, Hymann G, Canfield R. Effects of dichloromethylene diphosphonate in women with breast carcinoma metastatic to the skeleton. *American Journal of Medicine* 1983;74:401–6.

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vanHolten-Verzantvoort AT, Kroon HM, Bijvoet OL, et al. Palliative pamidronate treatment in patients with bone metastases from breast cancer. *Journal of Clinical Oncology* 1993;11(3):491–8.

Vinholes JJ, Purohit OP, Abbey ME, Eastell R, Coleman RE. Relationships between biochemical and symptomatic response in a double-blind randomised trial of pamidronate for metastatic bone disease. *Annals of Oncology* 1997;8(12):1243–50.

Imrie, K., Stevens, A., Makarski, J., Esmail, R., Meharchand, J., & Meyer, R. M. (referred to as the Hematology Disease Site Group HDSG) 2005, "Role of bisphosphonates in the management of skeletal complications in patients with multiple myeloma", *Current Oncology*, vol. 12, no. 1, pp. 3-17.

Also :

A Cancer Care Ontario evidence based guideline: The Role of Bisphosphonates in the Management of Skeletal Complications for Patients with Multiple Myeloma. Practice Guideline Report #6-4.

K. Imrie, A. Stevens, J. Makarski, R. Esmail, J. Meharchand, R. Meyer, and the members of the Hematology Disease Site Group 2004.

<http://www.cancercare.on.ca/pdf/pebc6-4f.pdf>

Design

Systematic Review : 1++

Evidence based guideline – appraised using the AGREE tool and found to be of high quality.

Inclusion criteria

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of any one of the following:

1. Systematic reviews or practice guidelines evaluating bisphosphonate use in patients with multiple myeloma.
2. Randomized controlled trials (RCTs) or meta-analyses of RCTs comparing one bisphosphonate agent with another bisphosphonate, or comparing a bisphosphonate with placebo or no treatment in patients with multiple myeloma.

The trials were required to report on at least one of the following outcomes: overall survival, skeletal-related survival, quality of life, bone pain, pathological fractures (non-vertebral 2 or vertebral), progression of bone disease (osteolytic lesions), or hypercalcemia. Treatment-related toxicity was also an outcome of interest. Many trials have evaluated endpoints assessing metabolic parameters of bone disease; while these outcomes may provide useful information establishing a “proof-of principle” for using bisphosphonates in patients with myeloma, these outcomes were not considered to be sufficient to determine recommendations for treatment.

Exclusion criteria

1. RCTs that included patients with various types of malignancies in which the results for patients with myeloma were not reported separately.
2. Phase I and II studies.
3. Letter and editorials.
4. Reports published in a language other than English.

Population

Adult patients with active plasma cell myeloma (symptomatic stage 1 or greater).

Interventions

To investigate the effectiveness of bisphosphonates in preventing bone resorption and the delay or prevention of progressive bone disease in patients with myeloma.

Bisphosphonates include:

Etidronate

Clodronate

Pamidronate

Ibandronate
Zoledronate

Outcomes

- Improvement in survival
- Improvement in quality of life
- Reduction in bone pain
- Reduction or delay in the development of skeletal complications (pathological fractures: total and vertebral, spinal cord compression, progression of bone disease)
- Incidence of hypercalcemia

Results

The Haematology Disease Site Group (HDSG) developed the guideline and conducted a systematic search of the literature. The evidence included in this review included a Cochrane systematic review by Djulbegovic et al. 2002 and an evidence based guideline from ASCO 2002.

The HDSG then went on to make their own recommendations from this evidence. All evidence has been described (in general terms) below.

Systematic review:

When conducting the search for literature for this review, the HDSG identified a Cochrane Systematic Review by Djulbegovic et al. 2002. The HDSG identified 12 RCTs, 11 of these trials were included in the Djulbegovic et al. systematic review. A trial reported by Rosen 2001 comparing zoledronate with pamidronate was not included in the systematic review, (possibly because the trial compared bisphosphonate agents rather than a bisphosphonate with placebo or no treatment)

Bisphosphonates evaluated :

Etidronate (10 mg/kg/d for 4 mo)/ Oral (Daragon 1993)

Etidronate (5 mg/kg/d)/ Oral (Belch 1991)

Clodronate (1600 mg/d) / Oral (McCloskey 2001)

Clodronate (1600 mg/d for 1 y)/ oral (Heim 1995)

Clodronate (2.4 g/d for 24 mo)/ Oral (Lahtinen 1992)

Clodronate (1600 mg/d planned for 2y)/ oral (Delmas 1982)

Pamidronate (60 mg monthly)/ intravenous (Kraj 2000)

Pamidronate (90 mg, monthly)/ intravenous (Terpos 2000)

Pamidronate (90 mg every 4 wk for 21 mo)/ intravenous (Berenson 1998)

Pamidronate (300 mg/d)/ oral (Brincker 1998)

Ibandronate (2 mg/mo for 12 to 24 mo)/ intravenous (Menssen 2002)

Results of the Djulbegovic et al. 2002 meta-analysis (for evaluable patients):

Mortality: OR = 0.99 (0.88 to 1.12), p=0.9

Vertebral fractures: OR = 0.59 (0.45 to 0.78), p = 0.0001

Pain (reporting of pain was not uniform across trials; the number of patients who reported pain was pooled):

OR = 0.59 (0.46 to 0.76), p= 0.00005

Gastrointestinal symptoms ((grade III/IV) were the most commonly reported adverse events in all trials; however, because the manner by which specific symptoms were reported varied among trials, all gastrointestinal symptoms were pooled): OR = 1.28 (0.95 to 1.74), p = 0.11

Djulbegovic (2002) concluded that there was evidence to support using a bisphosphonate to reduce vertebral fractures. Additional evidence identified that use of a bisphosphonate was associated with a reduction in pain, but inconsistent reporting across studies limited the conclusions. Djulbegovic (2002) translated the results to a NNT of 10 (95% CI, 7 to 20) to avoid one patient with a vertebral body fracture and a NNT of 11 (95% CI, 7 to 28) in order to avoid pain in one patient. The authors recommended that clodronate and pamidronate might be the

preferred agents among the bisphosphonates reviewed.

Other Guidelines:

When conducting the search for literature for this review, the HDSG also identified a practice guideline developed by ASCO 2002 evaluating the role of bisphosphonates in patients with myeloma with specific attention to the role of these agents in preventing and treating bone disease.

This guideline addressed several components of bisphosphonate use and reached the following conclusions (with the evidence level included) – cited from the HDSG report:

- i)** use of a bisphosphonate is recommended for patients with myeloma who have lytic bone disease (data from RCTs and a meta-analysis);
- ii)** patients with myeloma treated with a bisphosphonate should have an evaluation of 24-hour urine protein excretion and serum creatinine every three to six months. The drug should be discontinued if albuminuria of more than 500 mg per 24 hours or an increase in the serum creatinine of more than 1.4 mg/dL (123 µmol/litre) is observed. The drug may be re-instituted if the renal problems resolve; a longer infusion time should then be considered (data from case series);
- iii)** a bisphosphonate should be continued until there is a general decline in the patient's performance status necessitating an assessment of the balance between the benefits and the inconvenience of continued therapy (panel consensus);
- iv)** myeloma patients with osteopenia as the sole marker of bone disease should be treated with a bisphosphonate (panel consensus);
- v)** patients with a solitary plasmacytoma, smoldering myeloma, or a monoclonal gammopathy of undetermined significance as their sole indication for therapy should not be treated with a bisphosphonate (panel consensus);
- vi)** monitoring of biochemical markers of bone disease is not required for patients being treated with a bisphosphonate (panel consensus); and,
- vii)** myeloma patients experiencing bone pain should receive a bisphosphonate (data from randomized trials).

The ASCO guideline panel recommended that when a bisphosphonate is used, IV pamidronate or zoledronate are the drugs of choice. The panel concluded that data supporting the use of oral clodronate was limited because clodronate had not yet been approved for use in the United States (US), there were methodological issues in the studies evaluating clodronate that might result in an over-estimation of benefits (due to use of events per year rather than a time-to-event analysis), there was incomplete follow-up in one of the studies evaluating clodronate, and the studies did not combine multiple outcome measures into an aggregate endpoint. The publication states that the panel did not reach unanimous consensus on the interpretation of the clodronate data obtained from the published meta-analysis.

The recommendations from the HDSG – cited from the report:

- It is recommended that all patients with myeloma who have lytic bone lesions, osteopenia, or osteoporosis receive a bisphosphonate.
- For patients with myeloma who do not have lytic bone lesions, osteopenia, or osteoporosis, health care providers should inform patients of the potential benefits and risks of therapy and offer treatment with a bisphosphonate to these patients.
- Evidence exists to support the use of clodronate (800 mg orally twice daily), pamidronate (90 mg intravenously every four weeks), or zoledronate (4 mg intravenously every four weeks). Patient preference, tolerance, and convenience will influence the choice of agent. Patients who are unable to tolerate the initial agent should be offered an alternative agent.

Qualifying Statements

- Twenty-four hour urinary protein levels and serum creatinine values should be monitored in patients with myeloma who are receiving a bisphosphonate. Patients with new unexplained albuminuria or an increasing serum creatinine should have the bisphosphonate withheld

pending additional evaluation. Reintroduction of bisphosphonate therapy at a slower infusion rate (for intravenous formulations) can be considered for patients demonstrating resolution of the progressive albuminuria or increasing serum creatinine.

- Clodronate is contraindicated in patients with a serum creatinine value greater than 440 µmol/L. Limited experience exists with pamidronate and zoledronate in patients with severe renal impairment; these agents may be used with careful monitoring of renal function.
- No dose modification of pamidronate or zoledronate is required for patients with renal dysfunction.

Comments

The review of the evidence did not specify in detail results about preventing SCC, although an outcome in at least 2 individual studies, it was not reported as an individual result. The closest result to SCC was the occurrence of vertebral mets.

Included references for Imrie review:

Daragon A, Humez C, Michot C, Le Loet X, Grosbois B, Pouyol F, et al. for the Groupe d'Etudes et de Recherches sur le Myélome (GERM). Treatment of multiple myeloma with etidronate: results of a multicentre double-blind study. *Eur J Med* 1993;2:449-52.

Belch AR, Bergsagel DE, Wilson K, O'Reilly S, Wilson J, Sutton D, et al. Effect of daily etidronate on the osteolysis of multiple myeloma. *J Clin Oncol* 1991;9:1397-402.

McCloskey EV, Dunn JA, Kanis JA, MacLennan ICM, Drayson MT for the Medical Research Council Working Party on Leukaemia in Adults. Long-term follow-up of a prospective, double-blind, placebo-controlled randomized trial of clodronate in multiple myeloma. *Brit J Haem* 2001;113:1035-43.

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controlled trial. *Brit J Haem* 1998;101:280-6.

Menssen HD, Sakalová A, Fontana A, Herrmann Z, Boewer C, Facon T, et al. Effects of long-term intravenous ibandronate therapy on skeletal-related events, survival, and bone resorption markers in patients with advanced multiple myeloma. *J Clin Oncol* 2002;20:2353-9.

Tripathy, Lichinitzer, Lazarev, MacLachlan, Apffelstaedt, Budde, Bergstrom & Study Group. Oral ibandronate for the treatment of metastatic bone disease in breast cancer: efficacy and safety results from a randomized, double-blind, placebo-controlled trial.(see comment). Annals of Oncology 15(5). 2004.

Design: Randomized controlled trial (therapy),
Grade: 1+
Country: United States

Inclusion criteria

Women with histologically confirmed BC with radiologically confirmed bone metastases
WHO performance status = 0-2
Minimum age = 18 years
Written informed consent

I assume these patients did have vertebral mets b/c scans were taken and it was an included outcome.

Exclusion criteria

Bisphosphonates or gallium nitrate within 6 months
Life expectancy < 60 weeks
Hyper- or hypo-calcaemia
Serum creatinine > 3 mg per dl
Paget's disease of bone
Primary hyperparathyroidism
Known liver or brain metastases
Treatment with aminoglycoside antibiotics within past 4 weeks

Population

number of patients = 435, age range 29 to 92 years, median age = 57 years.

Interventions

Patients were randomised to receive either:
group A: oral ibandronate 20mg daily (n =144)
group B: oral ibandronate 50mg daily (n =148) or
placebo (n =143) for up to 96 weeks, with instructions on self administration. Drug use was monitored by return of packaging

Outcomes

Primary outcome: Skeletal morbidity (SMPR) broadly defined as the number of 12-week periods with new SREs (vertebral or non-vertebral fractures, bone RT or bone surgery) divided by the number of periods on the study.

Bone pain. Bone pain was rated on a self assessment scale from 0 (none) - 4 (intolerable). Analgesia use was also scaled from 0 (none) - 6 (opiates \geq 100mg morphine or equivalent daily).

Time to first new bone event
Relative risk (RR) of experiencing a SRE
Adverse events

Follow up

Baseline and X-rays were repeated at 4-weekly intervals together with assessment for fractures, bone pain and analgesia consumption.

Adverse events were recorded throughout the study.

Follow-up included collecting post-withdrawal data regarding safety and efficacy up to the point

of death or last scheduled visit for those patients who left the trial early.

In the placebo group, a total of 89 patients left the trial, also 89 in group A and 85 in group B. The most common reasons for withdrawal from the study in all groups were cancer progression, death or personal reasons. None were related to the oral administration e.g. difficulty in taking the tablets.

A total of 18 patients were lost to follow-up: 4 in group A, 8 in group B and 6 in the placebo group

Results

Efficacy:

Patients with active treatment had a significant improvement in mean SMPR compared with patients on placebo. This was mainly due to the significant reduction in patients requiring RT ($P = 0.004$) whilst receiving ibandronate. Other components of SMPR were not significantly different between groups.

The RR of having SREs was significantly lower with both group A (RR = 0.62, $P = 0.009$) and group B (RR = 0.61, $P = 0.005$) compared with placebo.

Time to the 1st new bone event after randomisation was 48 weeks for the placebo group which, whilst shorter, was not significantly different from either group A (76 weeks) or group B (54 weeks).

From baseline to study end point, bone pain scores increased in the placebo group (+0.21) and group B (+0.03) but decreased for group A (-0.06) - these differences were not statistically significant.

From baseline to study endpoint, the mean analgesia score was higher in the placebo group (0.96) compared with group A (0.43, $P=0.006$) or group B (0.73, not significantly different).

Adverse events:

Treatment related events (nausea, hypocalcaemia and abdominal pain) were more common in group A (26.4%) and group B (27.9%) compared with placebo (21.7%). Approximately 10% of ibandronate treated patients experienced upper GI tract problems and 6 patients (1 placebo) withdrew because of oesophagitis or dyspepsia. Renal effects were not significantly different between groups and 1 patient (group B) withdrew because of azotemia.

General comments

This paper presents data from a large (68) multi-centre (6 countries) randomised, double blind, placebo controlled trial of two doses of ibandronate versus placebo.

The authors stated 'randomisation was according to a pre-determined randomisation list based on block randomisation'. This is appropriate to the smaller trial and ensures an equal number of participants in each group.

Authors identified differences in baseline characteristics between study groups including WHO status and time since diagnosis.

An appropriate regression analysis was performed to determine the risk of developing a SRE during the study period whilst adjusting for baseline differences in the three study groups.

Efficacy data were analysed on an intention to treat principle whilst safety included all randomised patients who had received at least one treatment and at least one follow-up assessment.

This is a good quality study which reports the effectiveness of self administered, oral

ibandronate at reducing pain and the incidence of SREs, mainly through a reduction in the need for RT. The only feasible source of distortion was the high drop-out rate (~60%).

The outcome of MSCC was not measured directly and some extrapolation from the SREs results is required.

Saad et al. 2004 JNCI 96:11, 879-882 Long term Efficacy of Zoledronic Acid for the Prevention of Skeletal Complications in Patients with Metastatic Hormone Refractory Prostate Cancer.

Design RCT

(This trial is an extension of a trial included in the Cochrane Review with 24 month follow-up compared to 15 month follow up)

Inclusion criteria

Men with hormone refractory PC and a history of bone metastasis.

Exclusion criteria

Population number of patients entered trial = 186, number of patients who completed trial = 122.

Interventions

Active arm 1: zoledronic acid (ZA) 4mg, 214 patients

Active arm 2: zoledronic acid 8mg, 221 patients

Control arm: placebo q3w x 20 cycles (15 months), 208 patients. Ca supplement and vit D.

Outcomes

primary endpoints of trial were the proportion of participants having at least one SRE which was prospectively defined as a pathological fracture, SCC, RT or surgery to bone or change in the antineoplastic therapy to treat bone pain. Secondary endpoints time to first SRE, annual incidence of SREs, multiple event analysis using Anderson-Gill model and mean change from baseline brief pain inventory score (BPI)

Follow up

24 months

Results

SREs:

Zoledronic acid (4 mg via a 15-minute infusion every 3 weeks for 15 months) reduced the incidence of skeletal-related events (SREs) in men with hormone-refractory metastatic prostate cancer. Among 122 patients who completed a total of 24 months on study, fewer patients in the 4-mg zoledronic acid group than in the placebo group had at least one SRE (38% versus 49%, difference -11.0%, 95% confidence interval (CI) -20.2% to -1.3%; P = 0.028), and the annual incidence of SREs was 0.77 for the 4-mg zoledronic acid group versus 1.47 for the placebo group (P = 0.005). The median time to the first SRE was 488 days for the 4-mg zoledronic acid group versus 321 days for the placebo group (P= .009). Compared with placebo, 4 mg of zoledronic acid reduced the ongoing risk of SREs by 36% (risk ratio 0.64, 95% CI 0.485 to 0.845; P= 0.002). Patients in the 4-mg zoledronic acid group had a lower incidence of SREs than did patients in the placebo group, regardless of whether they had an SRE prior to entry in the study.

Extended follow up results demonstrated continued benefit among patients who remained in the trial (an extra 9 months of follow up). During the extended trial follow up time (15 to 24 month period) fewer patients in the 4mg ZA gp than in placebo gp had at least one SRE (19% VS 38%, difference of -19%, 95%CI -34.3 to -3.7%, p=.017).

Bone Pain:

Periodic measures of BPI scores (at 3-month intervals) demonstrated statistically significant and durable palliation of bone pain for patients treated with zoledronic acid (both 4 and 8/4-mg groups) compared with results of the placebo group. Changes from baseline pain scores showed a dose response. BPI score of 0.58 (4mg ZA) compared to BPI score of 1.05 (placebo gp), 95% CI -0.88 to -0.06, p=0.024. A BPI score point difference of 0.47.

Adverse Events:

The incidence of events (e.g., mild-to-moderate fatigue, myalgia, and fever) occurred more

frequently in patients treated with zoledronic acid than with placebo during the initial trial (included in the Cochrane Review); the incidence of these adverse events was similar between the zoledronic acid and placebo groups during the extension phase (data not shown). Moreover, the rate of study discontinuation due to adverse events did not differ substantially among the three treatment groups.

General comments

Author's comment: Long-term treatment with 4 mg of zoledronic acid is safe and provides sustained clinical benefits for men with metastatic hormone-refractory prostate cancer.

Reviewer's comment: Although the statistics appear effective with respect to ZA to reducing skeletal events and pain scores, the clinical relevance remains unclear.

Secondary Analysis of the previous RCT

Weinfurt, K.P et al. 2005 Annals of Oncology 16: 579-584 The significance of skeletal-related events for the health-related quality of life of patients with metastatic prostate cancer.

Design

Secondary Analysis of the Saad et al RCT 04 (see above)

Inclusion criteria

Exclusion criteria -

Population

Data were from a clinical trial of zoledronic acid versus placebo in the treatment of SREs associated with advanced prostate cancer metastatic to bone (see Saad 2002/2004 trial). Patients (n=248) were included if they experienced an SRE during the study.

Interventions

Active arm 1: zoledronic acid 4mg, 214 patients

Active arm 2: zoledronic acid 8mg, 221 patients

Control arm: placebo q3w x 20 cycles (15 months), 208 patients. Ca supplement and vit D.

Outcomes

Outcome measures were assessed at fixed intervals. We used mixed-effects models to estimate changes in outcomes after each patient's first SRE.

Follow up -

Results

The relationship b/n SREs and patient reported outcomes was assessed. There were clinically meaningful and statistically significant declines in physical well-being after: radiation and pathologic fractures; functional well-being after radiation; and emotional well-being after radiation and pathologic fractures. There were meaningful and significant declines in preference and utility scores after radiation and fracture. Pain intensity declined after radiation, but not after other SREs; no other pain measure changed substantively.

There were declines in physical well being after 3 categories of SREs (radiation to the bone, pathological fractures and other SREs- SCC, surgery to bone or change in antineoplastic therapy to treat bone pain) as well as significant declines in function ability after radiation to the bone and other SREs. These changes were not attributable to disease progression.

There were differences to which aspect of a patient's experience were affected:

Radiation to the bone affected 4 out 5 FACT-G scores. (reflecting the side effects if RT)

Pathological fractures were associated with changes to 2 out of 5 FACT-G scores and the 2 measures of the EURQoL score.

For other SREs no significant scores were reported, however numbers were very small and some deficits were seen across multiple domains of FACT-G.

BPI reported small changes in scores. This may have been due to the SRE definition and trial protocol not collecting SRE events more frequently. That is, outcome assessments were conducted every 90 days. If an event occurred early in this period by the time of the next assessment, the intensity of pain was possibly diminished also the assessment instrument (FACT-G) only records for the last 7 days.

General comments –

Author's CONCLUSIONS:

SREs have important and significant effects on measures of health-related quality of life in men with prostate cancer. Treatments that prevent SREs may not demonstrate corresponding effects on outcomes if the effects of SREs occur between scheduled outcome assessments.

Implications for trial design are discussed.

Reviewers comments: This study presented a complex analysis of quality of life outcomes based on existing trial results. Interpretation of the outcomes is complicated and requires careful consideration.

Observational Studies

Weinfurt, Castel, Li, Timbie, Glendenning & Schulman . Health-related quality of life among patients with breast cancer receiving zoledronic acid or pamidronate disodium for metastatic bone lesions. Medical care. 42(2). 2004.

Design: Prospective cohort study (prognosis),
Grade : 2-
Country: United States

Inclusion criteria:

Histologically confirmed BC
At least 1 bone metastasis confirmed by radiography
Ambulatory
Over 18 years
ECOG status 0-3
In receipt of anti-neoplastic therapy
Good clinical condition
Not more than 2nd line endocrine therapy unless combined with chemotherapy

Exclusion criteria:

Pregnancy
Treatment with bisphosphonates <12 months before 1st visit
Lymphangitic lung metastases
Symptomatic brain metastases
History of treatment non-compliance or unreliable behaviour
Grade III or IV heart disease

Population:

number of patients = 1124, mean age = 58 years.

Interventions:

Zoledronate at 4mg (n = 377) or 8mg (n = 360) as a 5 min iv infusion or pamidronate at 90mg (n = 387) by 90 min iv infusion every 3-4 weeks for 12 months in addition to current anti-cancer treatment.

At some unspecified point, patients were removed from the 8mg zoledronate dose and were put on 4mg as a 15 min iv infusion (8/4mg).

Outcomes:

Health related quality of life.

Follow up:

Baseline data collected included age, education, employment status, geographic region, current therapy, treatment group, previous SRE, days from initial cancer diagnosis to randomisation and days from first bone metastasis to randomisation.

Quality of life (QOL) was assessed by analysis of FATG questionnaires completed by patients at baseline and after 12, 24, 36 and 51 weeks on arrival at the clinic and before seeing the physician or receiving medication. Data were analysed on the intention to treat principle.

The percentage of patients completing the full course of treatment was 63% in the 4mg zoledronate arms and 60% in each of the other two arms. 30% of the drop-outs were due to adverse events and 26% to death.

Results:

The Authors concluded that over a 1 year period, the average patient on these treatments experienced a gradual improvement in overall, physical, functional and emotional wellbeing.

The results were illustrated by non-linear, 2nd or 3rd degree polynomial growth curves for

FATG data: emotional and functional well-being - the lack of linearity was due to an initial increase followed by a plateau effect. These models did not fit data for the social/family well-being which was therefore un-interpretable.

There were significant variations among women in their experiences over time some of which were explained by differences in baseline status due to factors discussed above.

Women who had previously experienced a SRE before starting treatment began the study with significantly worse physical and functional well being. Authors conclude by saying that the positive mean change in health related QOL observed for patients treated with either regime was consistent with the notion that prevention of SREs could lead to a better QOL.

General comments:

This paper details a double blind, randomised controlled trial of two doses of zoledronate against pamidronate in patients with either multiple myeloma or stage IV breast cancer. The results for quality of life are reported here for only the latter group.

The trial was conducted at 207 centres in Canada, the USA, South America, Europe, Australia, New Zealand, Scandinavia and South Africa.

Health related QOL scores were analysed by conditional and unconditional models that took into account covariates that might explain variations between patients. These models appear to be complex but are thoroughly described. The covariates are as described by demographic data collected from each patient at baseline e.g. age, education etc. ECOG status was dichotomised and incorporated into the model.

This paper was predominantly based on testing the models to predict outcomes and contains little useful information on the treatment per se.

Evidence Based Clinical Guidelines

Warr, Johnston & Breast Cancer Disease Site Group . Use of bisphosphonates in women with breast cancer: practice guideline report #1-11 (Version 2.2002). 2004. Cancer Care Ontario Program. Program in Evidence-based Care (A Cancer Care Ontario Program).

Design: Guideline (prognosis),
Grade :1++
Country: Canada (federal state, Commonwealth Realm)

Inclusion criteria:

Included studies:
Women with bone metastases due to breast cancer (it was not apparent whether or not patients may have had other metastatic disease or if any had solitary bone metastasis).

Exclusion criteria:

None stated

Population:

Women with bone metastases due to breast cancer

Interventions:

Any bisphosphonate compared with other bisphosphonate, placebo or no treatment. Different doses or routes of administration of any bisphosphonate.

Clodronate (iv or oral), pamidronate (iv or oral), ibandronate (iv or oral) and iv zoledronate were used in the included studies.

Outcomes:

Included studies reported on at least one of the following:
survival, quality of life, adverse events, bone pain (measured by pain scales and/or analgesia use) and skeletal related events (excluding hypercalcaemia).

Results:

See Use of Bisphosphonates in Women with Breast Cancer. Practice Guideline Report #1-11 (Version 2.2002)

D Warr, M Johnston, and members of the Breast Cancer Disease Site Group:
<http://www.cancercare.on.ca/pdf/pebc1-11f.pdf>

General comments:

This guideline was originally written in 1998 and was updated in 2002 and 2004. Three patient groups were reviewed of which only the evidence for women with MBC and bone metastases is included here.

The 2002 literature search found the following relevant articles and abstracts, which are summarized in the practice-guideline report: 2 evidence-based practice guidelines from other guideline-development groups (ASCO and SIGN), 1 Cochrane systematic review with meta-analysis, published in 2002 (Pavlakis *et al.* 2002) and 28 RCTs, only 9 of which were not included in the Cochrane review.

The 2004 search found 1 update to the ASCO guideline, 1 RCT updating an abstract included in the Cochrane review, 1 RCT updating an abstract in the original guideline and the results from a study, presented in two abstracts at the 2003 San Antonio Breast Cancer Symposium, which pooled data from three RCTs to compare IV and oral ibandronate with placebo.

Evidence summary:

Oral clodronate and intravenous (iv) pamidronate significantly reduced skeletal events and pain in women with breast cancer metastatic to bone. The review of the evidence did not specify in detail results about preventing MSCC, although an outcome in at least 2 individual studies, it was not reported as an individual result. The closest result was the rate of SREs.

Direct comparisons found 4mg zoledronate equivalent to 90mg pamidronate given iv every 3 to 4 weeks.

Bisphosphonates did not improve survival but did reduce skeletal events and pain in women with breast cancer metastatic to bone. There was no significant difference in adverse effects between those receiving bisphosphonates and controls.

This guideline was appraised using the AGREE tool and found to be of high standard.

UPDATE NOTE

In 2005 the Cochrane Review (Pavlakakis 2002) was updated; additional studies to both this Warr 2004 Review and Pavlakakis 2002 are: Body et al 2004 and Kohno 2005.

Findings from Body 2004:

When 50mg oral ibandronate was compared to placebo in women with advanced breast cancer the mean bone-pain scores at study endpoint showed a significant reduction in favour of 50 mg oral ibandronate.

A significant improvement in global quality of life was reported in patients 50 mg oral ibandronate (P = 0.032).

The incidence of renal adverse events was low and comparable between treatment and placebo arms. The proportion of patients reporting an adverse event was generally low (and included dyspepsia, nausea, oesophagitis and hypocalcaemia)

Findings from Kohno 2005:

This study evaluated zoledronate versus placebo in Japanese women with stage IV breast cancer.

This study provides the only available data on the effect of stage IV disease zoledronate on incidence of skeletal events compared with placebo. Results showed that zoledronate statistically reduces the risk of a skeletal event compared to placebo (RR = 0.59, 95% CI 0.42 to 0.82). The study also showed that the median time to first skeletal event was not reached in the zoledronate arm, versus 364 days in the placebo arm; p = 0.007.

From a Brief Pain Inventory, there was a statistically significant reduction with zoledronate.

There was a higher incidence of grade I hypocalcaemia with zoledronate. There was no evidence of decreased renal function in the zoledronate treated patients.

References included in this Guideline:

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Saad F, Gleason DM, Murray R. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. Journal of the National Cancer Institute 94: 1458- 68 2002;94(No 19):1458–1468.

This paper was included in the Yuen et al Cochrane Review and the summary of findings have been lifted from this review and copied below:

AIM: To evaluate the effectiveness and safety of zoledronic acid (ZA) in terms of reducing skeletal-related events associated with metastatic bone disease men with hormone-refractory prostate cancer.

METHODS:

- Randomized double blind placebo-controlled study.
- 3 arm study: 2 active arms, 1 placebo arm.
- Quality score (2/2/1) – means high methodological quality: randomisation; blinding and attrition rate. Allocation concealment was not used
- Primary outcome: skeletal-related event (pathologic fracture, spinal cord compression, change in anti-neoplastic therapy for bone pain, bone surgery or radiotherapy).
- Secondary outcomes: time to first skeletal-related event, skeletal morbidity rate, proportion of patients with skeletal-related events, time to disease progression, bone lesion response, bone biochemical markers, quality of life parameters.
- Pain assessment: Brief Pain Inventory pain score
- Analgesic assessment: analgesic score 0-4
- Pain assessment schedule: 3,6,9,12,15 months

PARTICIPANTS:

- Prostate cancer (hormone refractory). Bone metastases required. Pain not required.
- ECOG performance status of 0,1,2.
- Co-intervention: Antineoplastic therapy allowed.
- Exclusion: bone pain requiring strong narcotic therapy, chemotherapy (except estramustine), RT within 3 months, previous bisphosphonate treatment, severe heart disease or hypertension, a serum creatinine of more than 3mg/dL or calcium less than 8mg/dL or greater than 11.6mg/dL.
- Randomized 643 patients: active arm-1 214, active arm-2 221, control 208
- Baseline pain, Mean BPI, active1 = 2 +/- 2, active2 = 2.5 +/- 2.1, control 2.1 +/- 2.0

INTERVENTIONS:

Active arm 1: zoledronic acid 4mg, 214 patients
Active arm 2: zoledronic acid 8mg, 221 patients
Control arm: placebo q3w x 20 cycles (15 months), 208 patients..
Ca supplement and vit D.

OUTCOMES:

- Pain score, mean change (95% control 0.42 (0.22)
 - Analgesic score: No statistically significant difference (scores not included).
 - Patients having skeletal-related events: active1 71/214, active2 85/221, control 92/208, pathologic fractures 28/214 33/221 46/208, vertebral fractures 8/214, 8/221, 17/208, non-vertebral fractures 22/214, 22/221, 33/208, bone radiotherapy 49/214 53/221 61/208, bone surgery 5/214 6/221 7/208, spinal cord compression 9/214, 11/221, 14/208.
- Saad 2002 definition of “skeletal related events” and this included pathologic fracture, spinal cord compression, surgery to bone, radiation therapy to bone or a change of antineoplastic*

therapy to treat bone pain.

- Time to first skeletal-related event: active1 but not active2 is significantly longer than control.
- Patients with radiological bone response: active1 56/214 (CR0,PR9,SD47), active2 52/221 (CR0,PR6,SD46), control 43/208 (CR0,PR8,SD35)
- Patients with adverse events: bone pain (active1 108/214, active2 133/218, placebo 127/208), nausea (active1 77/214, active2 115/218, placebo 77/208), constipation, fatigue, anaemia (active1 57/214, active2 60/218, placebo 37/208), myalgia, vomiting (active1 46/214, active2 115/218 placebo 43/208), weakness, anorexia, fever, lower limb oedema, dizziness, diarrhoea, weight increase.
- ECOG performance scores, FACT-G QoL and EURO-QOL scores: No statistically significant difference.
- Median time to cancer progression = 84 days in all treatment groups.
- PSA, percent change from baseline, no statistically significant difference.
- Median survival (days) (active1, active2, placebo): 546, 407, 464 p = 0.091 (active1 vs placebo), p = 0.386 (active2 vs placebo).

RESULTS: see Yuen review plus below

Skeletal-Related Events

- At least one skeletal-related event occurred in: 92 (44.2%) patients who received placebo and 71 (33.2%) patients who received zoledronic acid at 4 mg (difference= -11.0%, 95% CI - 20.3% to -1.8%; P=0.021)
- At least one skeletal-related event occurred in: 85 (38.5%) patients who received zoledronic acid at 8/4 mg (difference= -5.8%, 95% CI - 15.1% to 3.6%, P=0.222 versus placebo).
- Compared with patients who received the placebo, fewer patients who received zoledronic acid at 8/4 mg (22.1% versus 14.9%, P=0.054 – not significant) and statistically significantly fewer patients who received zoledronic acid at 4 mg experienced a fracture (22.1% versus 13.1%, P=0.015).
- Compared with patients who received the placebo, fewer patients who received Zoledronic acid at 8/4 mg (29.9% versus 34.6%, P=0.300 – not significant) and statistically significantly fewer patients who received 4 mg ZA (25.7%, P=0.048 versus placebo) experienced any skeletal-related event other than fracture.
- Individual non-fracture skeletal-related events (radiation therapy to bone, surgery to bone, and spinal cord compression) occurred less frequently in patients who received either dose of zoledronic acid than in those who received placebo. This was not the case for changes in antineoplastic treatment
- Two additional efficacy variables associated with skeletal related events were assessed: The difference in the time to the first occurrence of any skeletal-related event between patients who received zoledronic acid at 4 mg and those who received placebo was statistically significant (P = 0.011).

Kaplan–Meier estimates of event rates for time to the first on-study skeletal-related event for all intent-to-treat patients with metastatic prostate cancer randomly assigned to receive zoledronic acid at 4 mg, zoledronic acid at 8/4 mg, or placebo.

Percentage of patients (95% confidence interval [CI]) without a skeletal-related event:

At 90 days: zoledronic acid at 4 mg, 90.9% (95% CI 86.8% to 94.9%); zoledronic acid at 8/4 mg, 83.3% (95% CI 78.2% to 88.4%); placebo, 83.5% (95% CI 78.4% to 88.7%);
at 270 days: Zoledronic acid at 4 mg, 70.0% (95% CI 63.0% to 76.9%); zoledronic acid at 8/4 mg, 58.0% (95% CI 50.5% to 65.6%); placebo, 57.3% (95% CI 49.7% to 64.8%);
at 450 days: zoledronic acid at 4 mg, 55.1% (95% CI 46.9% to 63.4%); zoledronic acid at 8/4 mg, 46.8% (95% CI 38.2% to 55.4%); placebo, 42.8% (95% CI 34.4% to 51.2%).
At the last study evaluation (450 days), P=0.011 for ZA at 4 mg versus placebo (indicating a significant finding) and P=0.491 (not significant) for zoledronic acid at 8/4 mg versus placebo.

- The time to the first skeletal-related event was not reached for patients who received 4 mg ZA and therefore, considered as at least 420 days (based on the fact that the estimated event rate was <50% at day 420, the end of treatment), whereas the median time to the first skeletal-related event was 321 days for patients who received placebo.
- The median time to the first skeletal-related event for patients who received 8mg ZA = 363 days, not statistically significantly different from that of patients who received placebo (P = 0.491).
- The mean skeletal morbidity rates for all skeletal-related events combined and for each individual type of skeletal-related event were lower for patients who received 4 mg ZA or at 8/4 mg than for those who received the placebo, with the exception of changes in antineoplastic therapy, which occurred more frequently for those who received 8/4 mg ZA at than for those in the other groups. (no significant difference observed)

Pain:

- Mean pain scores (range 0–10) increased from baseline in all three groups at every 3-month interval, with one exception at 3 months where the ZA groups had a slight decrease from baseline.

The mean increase from baseline in pain score at 15 months was:

0.88 (95% CI .61 to 1.15) for patients who received the placebo compared with 0.58 (95% CI 0.29 to 0.87) for patients who received zoledronic acid at 4 mg (P=0.134 versus placebo) and 0.43 (95% CI 0.16 to 0.70) for patients who received zoledronic acid at 8/4 mg (P=0.026 versus placebo).

- Analgesic scores (range 0–4) were also increased slightly more from baseline at every time point for patients who received the placebo than for patients who received either dose of ZA.

The differences in analgesic scores were not statistically significant.

QoL: The mean ECOG performance scores increased from baseline to the last measurement, with no statistically significant difference among the three groups.

The total FACT-G quality-of-life and the EURO-QOL scores decreased from baseline to the last measurement, with no statistically significant differences among the three groups.

Adverse events: The most common adverse events that occurred during the trial were Fatigue, anemia, myalgia, fever, and lower-limb edema which occurred in at least 5% more patients in both of the ZA groups than in the placebo group.

Rosen et al. (2003) Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumours. JCO; 21 No 16 p.3150-3157.

Design: RCT, Evidence level 1+

Country: International

Aim: To investigate the effectiveness of zoledronic acid (ZA) in the treatment of patients with bone metastases secondary to solid tumors other than breast or prostate cancer.

Inclusion criteria

- Adult patients (≥18 years of age) with bone metastases secondary to lung cancer and other solid tumors not including breast or prostate cancer were included.
- All patients had to have at least one site of bone metastasis and an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.

Exclusion criteria

- Patients who had liver metastases with total bilirubin level higher than 2.5 mg/dL at screening, serum creatinine level higher than 3.0 mg/dL, or symptomatic brain metastases.
- Patients who had more than a single exposure to a bisphosphonate within 30 days, a diagnosis of severe cardiovascular disease, hypertension refractory to treatment, symptomatic coronary artery disease, or pregnancy within 6 months of randomisation.

Population

773 patients with osteolytic, osteoblastic, or mixed bone metastases from solid tumors other than breast or prostate cancer were enrolled in the study.

257 patients received 4 mg zoledronic acid – 68 patients completed study

266 patients to received 8/4 mg zoledronic acid – 65 patients completed study

250 patients to received placebo – 63 patients completed study

The main reason for discontinuation was death followed by adverse event and patient withdrawing consent. Discontinuation rates were similar between the treatment groups

Interventions

Patients were randomly assigned in a double-blind method to receive: zoledronic acid (4 or 8 mg) or placebo every 3 weeks for 9 months.

- Initially, patients received zoledronic acid via 5-minute infusion in 50 mL of infusate; however, due to concerns over renal safety, a protocol amendment changed the infusion time to 15 minutes and increased the volume of the infusion to 100 mL (195 patients were accrued before this amendment).
- A subsequent amendment to the protocol was implemented because of concerns over decreased renal tolerability at the higher dose level, required patients originally randomly assigned to receive 8 mg zoledronic acid to instead receive 4 mg zoledronic acid; this arm is referred to as the 8/4-mg arm.
- All patients were accrued before this amendment, and 198 patients (75%) in the 8/4-mg group had completed or discontinued study treatment and received only the 8-mg dose; however, 67 patients (25%) were still receiving treatment and were switched to the lower dose.

Outcomes

For all efficacy variables analyzed, comparisons of 4 mg zoledronic acid versus placebo were used to assess the effectiveness of zoledronic acid.

The proportion of patients with at least one SRE during the 9 months on study.

(Skeletal-related events included pathologic fracture, spinal cord compression, radiation therapy to bone, or surgery to bone.)

Secondary efficacy analyses of SREs included time to first SRE, the skeletal morbidity rate (defined as the number of SREs per year), and a multiple event analysis.

Other secondary outcomes included:
change from baseline in BPI composite pain score,
analgesic use,
ECOG performance status,
best bone lesion response,
time to progression of bone lesions,
changes from baseline in biochemical markers of bone resorption,
time to progression of overall disease,
survival.

Quality of life (using the Function Assessment of Cancer Therapy – General (FACT-G) instrument

Note on reported results:

- Andersen-Gill multiple event analysis accounts for all complications and for the timing of complications to provide a sensitive and comprehensive assessment of cumulative skeletal morbidity.
- The hazard ratio represents the risk of experiencing a skeletal complication relative to a comparator or placebo; a hazard ratio < 1 indicates decreased risk.

Results

SREs

- There was no statistically significant difference in SREs (which excluded hypercalcemia of malignancy - HCM), between 4 mg zoledronic acid versus placebo (38% v 44%; P =0.127)
 - There was statistically significant for the comparison of 8/4 mg zoledronic acid versus placebo (35% v 44%; P=0 .023).
 - In the analysis of all skeletal events (including HCM), 4 mg ZA significantly reduced the proportion of patients with an event as compared with the placebo group (38% v 47%; P=0.039).
 - 35% of patients treated with 8/4 mg ZA had an event (P=0.006 compared with the placebo group).
 - The most common SREs were radiation to bone and pathologic fracture.
 - A treatment benefit was observed across all event types; in particular, no patients treated with 4 mg ZA developed HCM compared with 8 patients (3%) in the placebo group (P=0.004).
 - Compared with the placebo group, patients in the 8/4-mg group experienced significant decreases in HCM (P=0.044), pathologic fracture (P=0.003), and vertebral fracture (P=0.004).
 - WRT spinal cord compression event: 3% in 4 mg ZA; 3% in 8/4 mg ZA; 4% in the placebo group. (No stats provided –see table 3 from paper)
-
- ZA significantly extended the median time to first SRE by more than 2 months compared with placebo
 - Median time to first SRE (excluding HCM) was statistically significant different: 230 days for 4 mg zoledronic acid versus 163 days for placebo (P =0.023);
 - Median time to first SRE (including HCM) was calculated but I have not reported it here as HCM was thought not to be relevant to MSCC.

- A multivariate analysis adjusting for previous SRE experience showed that this comparison remained statistically significant ($P=0.028$).
- The median time to first event was not reached for individual SREs. However, the time to first pathologic fracture was significantly longer in patients treated with 4 mg zoledronic acid compared with the placebo group (first quartile, 238 v 161 days; $P=0.031$).
- The time to first vertebral fracture and the time to first radiation therapy were significantly longer ($P=0.05$) in the 4-mg group.
- Patient survival in this study was short (approximately 6 months), time to first SRE was also reported including death as an event. Results were similar as reported earlier: for patients treated with 4 mg zoledronic acid, the median time to first event (excluding HCM, including death) was 136 days versus 93 days for the placebo group ($P=0.039$).
- For each analysis, event rates were similar in the 4-mg and 8/4-mg groups.
- The skeletal morbidity rate for all events (SREs excluding HCM) was lower among patients treated with either 4 mg zoledronic acid (mean \pm SD, 2.24 ± 9.12 ; $P=0.069$) or 8/4 mg zoledronic acid (mean \pm SD, 1.55 ± 3.8 ; $P=0.005$) compared with the placebo group (mean SD, 2.52 ± 5.11).
- The skeletal morbidity rate (the number of events per year; including HCM) was significantly lower among patients treated with either 4 mg zoledronic acid (mean \pm SD, 2.24 ± 9.12 ; $P=0.017$) or 8/4 mg zoledronic acid (mean \pm SD, 1.59 ± 3.8 ; $P=0.001$) compared with the placebo group (mean \pm SD, 2.73 ± 5.29).
- The skeletal morbidity rate for each type of SRE was lower in the Zoledronic acid treatment groups compared with the placebo group except for surgery to bone and spinal cord compression.
- A multiple event analysis (using the Andersen-Gill approach) showed a significant 27% risk reduction for multiple skeletal events, in favour of 4 mg zoledronic acid (hazard ratio =0.732; $P=0.017$), among patients in both the NSCLC cancer and other solid tumour group, versus the placebo group
- The results were similar when HCM was included in the analysis.

Sub-group analysis:

NOTE: This trial was powered for the primary end point, and so subset analyses were not expected to detect statistically significant differences. The authors however did go onto conduct subgroup analyses for the NSCLC and other solid tumour patient groups.

- The proportion of patients with an SRE was not significantly different for patients in the NSCLC group treated with 4 mg zoledronic acid versus placebo (42% v 45%; $P=0.557$);
- There was no significance for time to first event (median 171 v 151 days; $P=0.188$) for patients treated with 4 mg zoledronic acid.
- In the other solid tumour group: 4 mg zoledronic acid reduced the proportion of patients with an SRE (33% v 43%; $P=0.110$, not significantly different) and extended the time to first event (median, 314 v 168 days; $P=0.051$, not significant) compared with placebo.

Bone Lesion Response and Time to Progression of Bone Lesions

- Analysis of best radiographic bone lesion response at month 9 showed a partial response in 8% of patients treated with 4 mg ZA versus 4% of placebo-treated patients.
- Bone lesions progressed in 33% with 4 mg ZA and 36% of patients treated with placebo.
- The time to progression of bone lesions was longer in patients treated with 4 mg ZA (median, 145 days; $P=0.340$) and in patients treated with 8/4 mg zoledronic acid (median, 238 days; $P=0.009$) compared with the placebo group (median, 109 days).

Other Outcomes:

Pain:

- The mean BPI composite pain score increased slightly from baseline to month 9 for all three treatment groups,
- indicating increases in pain.
- The mean composite pain score decreased among patients in the 4-mg zoledronic acid group who had pain at baseline.

Analgesic use: ECOG performance status:

- Mean analgesic score and ECOG performance status increased from baseline to month 9 for all three treatment groups, indicating increases in analgesic use and decreases in functional capacity due to progressive disease.

QoL:

- There were no statistically significant differences between zoledronic acid and placebo with respect to any of these global quality-of-life outcomes.
- Changes in FACT-G scores were also comparable between treatment groups.

Time to Disease Progression and Overall Survival:

- The median time to overall disease progression was 89 days in patients treated with 4 mg zoledronic acid, compared with 84 days in patients treated with placebo (P=0.117, no significant difference).
- The median time to death was the same in both treatment groups: median of 203 days for ZA treated patients, compared with 183 days for the placebo group (P=0.623).

Safety:

- The most commonly reported adverse events (all grades) in all treatment groups were bone pain, nausea, anemia, vomiting, constipation, dyspnea, and fatigue
- The proportion of patients having nausea (46%), vomiting (36%), and dyspnea (33%) was higher in the 4-mg zoledronic acid treatment group compared with the placebo group (34%, 29% and 26% respectively).
- The proportion of patients experiencing bone pain, was higher in the placebo group (59%) compared with either ZA treatment group (51% 4 mg ZA and 49% 8mg ZA group).
- Serious adverse events affected similar proportions of patients in all treatment groups.
- The most frequently reported serious adverse events, regardless of drug group, were anemia, dehydration, aggravated malignant neoplasm, and dyspnea, and these were similar across the treatment groups.
- Before the implementation of the 15-minute infusion amendment, the proportion of patients with decreased renal function was substantially higher in the zoledronic acid treatment groups compared with the placebo group (hazard ratio = 3.8). After the implementation of the 15-minute infusion-time amendment, the proportion of patients with decreased renal function was no significant difference between the 4-mg zoledronic acid and placebo groups (10.9% v 6.7%).

General comments

- Randomisation, blinding and power calculations were conducted which reduced the level of bias that could influence the result.
- Intention to treat analysis is mentioned
- No Follow up reported.
- QUESTION: Is HCM relevant to MSCC?



Rosen et al. (2004) Long-term efficacy and safety of zoledronic acid for the treatment of skeletal metastases in patients with Non small cell Lung carcinoma and other solid tumours. *Cancer*; p.2613-2621.

Design: RCT, Evidence level 1+

Aim: To report the long-term efficacy and safety results of the above trial (Rosen et al 2003) trial after 21 months of continued therapy in patients with advanced carcinoma of the lung and other solid tumors.

Inclusion criteria

See above

Exclusion criteria

See above

Population

- Of the 773 patients enrolled, 196 patients completed the 9-month core phase (see Rosen 2003 above) and 101 patients elected to continue in the extension phase of treatment.
- Approximately 25% of these patients in the extension phase (n=26) completed 21 months of treatment
- Discontinuation rates were similar between the treatment groups; death and adverse events were the most commonly reported reasons for discontinuation of therapy.

Interventions

See above

Outcomes

• The primary efficacy analysis was the percentage of patients with ≥ 1 SRE at 21 months. [SREs included pathologic fracture, spinal cord compression, radiation therapy to bone, or surgery to bone.]

• Secondary outcomes:

Time to first SRE, the annual incidence of SREs (also known as the skeletal morbidity rate), and multiple-event analysis.

[The multiple event analysis is a comprehensive analysis that considers not only the number of events but also the time it takes to develop the first and subsequent events, thereby providing an overall estimate of the clinical impact of the skeletal complications.]

Time to first SRE, time to progression of bone metastases, time to overall disease progression, and overall survival were compared between treatment groups using the Kaplan-Meier method and the logrank test.

- QoL
- Safety

Results

SREs:

Efficacy analyses are based on a comparison of a dose of 4 mg of zoledronic acid versus placebo.

- No statistical significant difference between 4 mg of ZA versus placebo when HCM (hypercalcemia of malignancy) was excluded (39% vs. 46%; $P=0.127$) in terms of the proportion of patients with an SRE at 21 months (as reported, after 9 months of treatment, Rosen 2003)

- 4% of patients in the placebo group developed HCM, compared with no patients in the 4-mg zoledronic acid group. Consequently, when HCM was counted as an SRE, the 4-mg zoledronic acid dose was found to significantly reduce the proportion of patients with an SRE compared with placebo (39% vs.48%; P=0.039).
- Treatment with ZA consistently reduced all types of skeletal complications.
- Radiation to bone was the most common type of SRE in all treatment groups, followed by pathologic fractures
- Spinal cord compression was reported: 3% of patients given 4 mg ZA; 3% in 8/4 mg ZA and 4% in placebo group (see table 2 from paper)
- Treatment with 4 mg of zoledronic acid delayed the onset of skeletal complications, significantly extending the median time to first SRE (including HCM) by >2 months (median, 236 days for 4 mg of zoledronic acid vs. 155 days for placebo; P=0.009).
- ZA (4 mg) significantly extended the time to first pathologic fracture compared with placebo (25% quartile =294 days for the 4-mg zoledronic acid dose vs. 161 days for placebo; P=0.020)
- The annual incidence of skeletal complications is expressed as the number of SREs divided by time on study. Patients in 4 mg ZA group were reported to have a 36% lower annual incidence of SREs (including HCM) compared with patients treated with placebo (mean of 1.74 SREs per year for the 4-mg ZA dose vs. mean of 2.71 SREs per year for placebo; P=0.012).
- Patients treated with the 8/4-mg ZA dose had a mean of 1.56 SREs per year (P=0.001 vs. placebo).

NOTE:

Multiple-event analysis accounts both for the absolute number of SREs and for the timing between them to provide a more sensitive assessment of the risk of skeletal complications between the two treatment groups.

- The hazard ratio for the 4-mg ZA dose versus placebo = 0.693 (95% CI, 0.542–0.886; P=0.003), indicating a 31% reduction in the risk of developing an SRE (including HCM) for a patient treated with 4 mg of ZA compared with placebo. (These results were consistent with Rosen 2003).

Other outcomes:

QoL:

- Mean ECOG scores increased from baseline in all treatment groups (in which an increased ECOG score indicates worsening performance status); however a “trend” toward a smaller increase in ECOG scores at the end of the study for the 4-mg dose of ZA versus placebo was reported by authors.
- At 21 months, the mean increase in the ECOG performance status was 0.99 ± 1.20 for the 4-mg ZA dose and 1.20 ± 1.22 for placebo (P= 0.080 not significantly different).

Safety:

ZA at dose of 4 mg was found to be safe and well tolerated with long-term administration. The most commonly reported adverse events in all treatment groups were bone pain, nausea, anaemia, emesis, constipation, and dyspnoea.

General comments

Radiotherapy

What is the effectiveness of RT at treating spinal pain and/or preventing spinal collapse and/or spinal cord compression?

Short Summary

From high quality studies (RCTs and systematic reviews) there was consistent findings that single and multifraction radiotherapy were equally effective for pain palliation (Falkmer *et al.* 2003; Hartsell *et al.* 2005; Katagiri *et al.* 1998 ; Kida *et al.* 2000 ; Kraiwattanapong *et al.* 2004; Tombolini *et al.*1994; van der Linden *et al.* 2004, 2006; Roos *et al.* 2003, 2005; Sze *et al.* 2006; Wu *et al* 2004; Zaidat *et al.* 2002). There was also no apparent dose response relationship from one meta-analysis (Wu *et al* 2003).

PICO

Population Group	Intervention	Comparison	Outcomes
Patients with known vertebral metastases (asymptomatic & symptomatic)	RT	<ul style="list-style-type: none">• No therapy• Surgery• Chemotherapy• Bisphosphonates• vertebroplasty	<ul style="list-style-type: none">• Prevention of spinal collapse• Prevention of spinal cord compression• Improvement in pain• Quality of life or performance status• Survival

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

Pain relief

Pain relief was assessed mainly as Overall Pain Response (OPR) and Complete Pain Response (CR). In the high quality systematic review (Sze *et al.* 2006) single fraction radiotherapy was as effective as multifraction radiotherapy.

- Overall pain response 60% for single fraction arm vs 59% in multifraction arm ($p=0.7$). OR 1.03 [95%CI 0.89, 1.19] $p=0.7$
- Complete pain response 34% for single fraction arm vs 32% in multifraction arm ($p=0.2$). OR 1.11 [95% CI 0.94, 1.30] $p=0.2$

This was consistent with the finding from the later RCT by Roos *et al.* (2005) (not included in the review) :

- Overall response rate (ITT): no statistically significant difference between arms (53% sf vs 61% mf) RR 57% (95%CI 51,63) $p=0.18$
- Complete response rate (ITT): no statistically significant difference between arms [26% sf (95%CI 18,34)vs 27% mf (95%CI 19,35), $p=.89$]

In the single fraction comparisons by Wu *et al.* (2003), Overall Pain Response rates were significantly lower with 4Gy fractions (statistical significance not reported). However complete pain response rates were not significantly different between doses (statistical significance not reported).

The Roos *et al.* (2003) study also reported no differences in pain response by treatment sites:

No difference by treatment site (spine vs non-spine): 57% single fractionation (sf) vs 58% multifractionation (mf). Complete response (ITT) 26% sf vs 26% mf. Overall (ITT) RR by primary site were breast 70%, prostate 58%, lung 58%, other 52%, these differences were not statistically significant (P=0.50).

Pathological fracture

The strongest SR by Sze *et al.* (2006) reported that pathological fracture rates were higher in patients with single fraction radiotherapy (3% vs 1.6%, p=0.03). In the review by Wu *et al.* (2003) pathological fracture rates were reported in the text as not showing any difference in rates by treatment assignment for multifraction regimes, an exception was the solitary metastasis group of the Tong study (1982) for multifraction comparisons. Pathological fracture rates were higher in the high dose arm. Falkmer also reported this finding with a two to three times higher incidence of pathological fracture associated with single fraction compared with multifraction schedules (2 RCTs).

Roos *et al.* (2003) found 11 new or progressive pathological fractures reported at the index sites (8/1:20/5 =6:5). This represents 4% of randomised patients.

Prevention of spinal cord compression

Sze *et al.* (2006) reported that MSCC rates were similar in patients with single or multifraction radiotherapy. Re-analysis of data from a subgroup of patients with spinal metastases from these studies found that MSCC rates were similar in patients with single or multifraction radiotherapy. Wu *et al.* (2003) also reported this finding.

Falkmer *et al.* (2003) reported the occurrence of MSCC in 4/13 studies, (50 patients / 1456 participants; 3.4%) but it was not clearly stated whether this occurred at the index field. Two single fraction vs multifraction RCTs reported low incidence rates of 1-2% with no differences between arms. One smaller single fraction RCT reported MSCC incidences of between 3.6%-4.6% with no differences between arms. The other study was a prospective nonrandomised design of moderate quality.

The RCT by Roos *et al.* (2003) found 17 cord/cauda compressions developed at the index site (8/1:20/5 =9:8). This represents 6% of 272 randomized patients and 7% of 241 with spinal index sites. Two of the cord compressions developed whilst the protocol was awaited (one in each arm). There were no statistically significant differences in serious complication rates between the 2 arms for MSCC or pathological fracture either separately or combined.

Re-treatment

Sze *et al.* (2006) reported that re-treatment rates are higher in patients with single fraction radiotherapy.

Wu *et al.* (2003) reported re-irradiation rates were higher in the low dose arm of 1 study (Tong *et al.* 1982) and the same in a smaller study (Niewald *et al.* 1996), however, re-irradiation rates were consistently higher in lower dose arms in the remaining 7 trials reported in the paper.

Van der Linden *et al.* reported time to re-treatment:

- Overall, mean time to re-treatment was 13 weeks in SF vs. 21 weeks in MF patients.
- Mean pain score in the week before re-treatment was 6.8 in SF vs. 7.5 in MF patients.

Side effects

Sze *et al.* (2006) reported that ten of the studies reported side effects of the treatment. The most common were nausea and vomiting, and severity was similar for both treatment arms. One study reported more transient increases in pain after single dose treatment, but quantitative data were not available. Wu (2003) also reported acute

toxicity (9 studies) as measured by nausea and vomiting was not significantly different between fractionation schedules.

Survival

In the RCT by Roos *et al.* (2003) median overall survival for all 272 patients was 4.8 months (95%CI 4.2, 5.7) with 27% (95%CI 22, 32) surviving 1 year. There were no statistically significant differences in survival between treatment arms (P=0.66) or index site (spine vs non-spine, P=0.89).

Van der Linden (2006) found that from randomization patients with breast cancer had the best median overall survival > prostate ca> other cancers. Lung cancer patient's had the lowest.

Multivariate analysis of prognostic factors stratified by primary tumour type (n=1157) were a good Karnofsky Performance Score (KPS), no visceral metastases, and non-opiate analgesics intake (all factors, P<0.001).

Functional and neurological outcomes were assessed by lower quality studies

Ambulation

Zaidat *et al.* (2002), in a study of patients with spinal metastases, found statistically significant differences for:

Likelihood of walking after therapy was different for patients who could walk before treatment of their spinal epidural metastases compared with non ambulatory patients ($p < 0.001$, RR 2.09 (95%CI 1.58, 2.77))

Likelihood of walking after treatment was different for patients with more than one spinal epidural metastasis compared with patients with one spinal epidural metastasis ($p < 0.001$, RR 3.13 (95%CI 1.53, 6.41))

Starting treatment <12hours after loss of walking ability increased the likelihood of regaining ambulation, in comparison to starting treatment >12 hours after onset: (P<0.00,1RR 6.86 (95%CI 1.81, 26.0)

Recovery from bowel and bladder dysfunction (BBD) and loss of sacral sensation was more likely in ambulatory patients (P=0.006)

These findings were reported for a population of elderly males, and may not be transferable to other populations.

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Wu, J. S., Wong, R. K., Lloyd, N. S., Johnston, M., Bezjak, A., Whelan, T., & Supportive Care Guidelines Group of Cancer Care Ontario. (2004), Radiotherapy fractionation for the palliation of uncomplicated painful bone metastases - an evidence-based practice guideline *BMC Cancer*, vol. 4, p. 71.

Zaidat, O. O. & Ruff, R. L. (2002), Treatment of spinal epidural metastasis improves patient survival and functional state. *Neurology*, vol. 58, no. 9, pp. 1360-1366.

Evidence table

Systematic review of RCTs

Sze WM, Shelley M, Held I, Mason M. Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy. Cochrane Database of Systematic Reviews 2002, Issue 1. Art. No.: CD004721. DOI: 10.1002/14651858.CD004721.

Design: Cochrane systematic review

Rating 1++

Country:

setting:

Inclusion criteria

Randomized controlled trials of published studies in any language, comparing single fraction external radiotherapy versus multifraction external radiotherapy in patients with painful bone metastases from any primary tumour.

Exclusion criteria

Studies of pain relief comparing radioisotopes or drugs.

Population

Eleven trials involving 3435 patients and 3487 painful bone sites. Commonest primaries were prostate, breast and lung cancer. Most frequent treatment sites were spine (34%) and pelvis (32%).

Interventions

Radiation dose of single fraction arms ranged from 8-10 Gy. Schedules of multifraction arms ranged from 3 fractions of 5 Gy (5 Gy x 3) to 10 fractions of 3 Gy (3Gy x 10). The most common schedules were 4 Gy x 5 and 3 Gy x 10.

Outcomes

All types of pain outcome assessment; re-treatment rates; frequency of pathological fracture and spinal cord compression.

Follow up

Significant numbers of patients failed to complete the course with dropout rates of between 0% and 69%. This did not change the direction of the review findings.

Results

Treatment of pain

Single fraction radiotherapy is as effective as multifraction radiotherapy.

Overall pain response 60% for single fraction arm vs 59% in multifraction arm (p=0.7).

Complete pain response 34% for single fraction arm vs 32% in multifraction arm (p=0.2).

Pathological fracture

Pathological fracture rates were higher in patients with single fraction radiotherapy (3% vs 1.6%, p=0.03).

Prevention of spinal cord compression

SCC rates were similar in patients with single or multifraction radiotherapy.

Reanalysis of data from a subgroup of patients with spinal metastases from these studies found that SCC rates were similar in patients with single or multifraction radiotherapy.

Re-treatment

Re-treatment rates are higher in patients with single fraction radiotherapy.

Heterogeneity (clinical) not statistically significant across all comparisons.

Side effects

Ten of the studies reported side effects of the treatment. The commonest were nausea and vomiting, and severity was similar for both treatment arms. One study reported more transient increases in pain after single dose treatment, but quantitative data were not available.

OUTCOME OF INTEREST	INTERVENTION	COMPARISON	OVERALL RESULT
Overall pain response 11 studies	Single fraction 1779 painful sites 1059/1779 (60%) Evaluable patients reanalysis: 1059/1519 (70%)	Multifraction 1769 painful sites 1038/1769 (59%) Evaluable patients reanalysis: 1038/1447(71.7%)	OR 1.03 [95%CI 0.89, 1.19] p=0.7 Heterogeneity NS Evaluable patients: OR 0.90 [95%CI 0.76, 1.06] p=0.19
Complete pain response, 7 studies 2876 patients	497/1441 (34%) Evaluable patients reanalysis: 497/1246 (40%)	463/1435 (32%) Evaluable patients reanalysis: 463/1186 (39%)	OR 1.11 [95% CI 0.94, 1.30] p=0.2 Heterogeneity NS Evaluable patients: OR 1.03 [95%CI 0.87, 1.22] p=0.7
Pathological fracture 5 studies 2478 patients	37/1240 (3%)	20/1236 (1.6%)	OR 1.82 [95%CI 1.06, 3.11] p=0.03 Heterogeneity NS NNT 77 patients
Prevention of MSCC 3 studies 2206 patients	21/1102 (1.9%)	15/1104 (1.4%)	OR 1.41 [95%CI 0.72, 2.75] p=0.3 Heterogeneity NS
Prevention of MSCC in patients with spinal metastases 739 patients	21/371 (5.6%)	15/368 (4.0%)	OR 1.43 [95%CI 0.72, 2.83] p=0.3 Heterogeneity NS
Re-treatment rates 5 studies 2476 patients	267/1240 (21.5%)	91/1236 (7.4%)	OR 3.44 [95%CI 2.07, 4.43] p=0.00001 Heterogeneity NS

General comments –

Refer to a critical appraisal of published review conducted the Centre for Reviews & Dissemination:

Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy. A systematic review of randomised trials. [Abstract Number:12003002011] Database of Abstracts of Reviews of Effects, available

<http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?View=Full&ID=12003002011>
[31 May 2005] Abstract of: Palliation of metastatic bone pain: single fraction versus

multifraction radiotherapy. A systematic review of randomised trials. Sze W M, Shelley M D, Held I, Wilt T J, Mason M D (2003) *Clinical Oncology* 15 (6) 345-352
CRD Summary: "This review found single fraction radiotherapy to have similar efficacy to multifraction radiotherapy in relieving metastatic bone pain. However, the rates of re-treatment, and possibly pathological fracture, were higher after single fraction radiotherapy. The interpretation of the findings was limited by the lack of detail on the primary studies."

Studies included in the review

Bone Pain Trial Working Party. 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up. Bone Pain Trial Working Party. *Radiotherapy Oncology* 1999;52(2):111-21.

Cole DJ. A randomized trial of a single treatment versus conventional fractionation in the palliative radiotherapy of painful bone metastases. *Clinical Oncology* 1989;1(2):59-62.

Foro P, Algara M, Reig A, Lacruz M, Valls A. Randomized prospective trial comparing three schedules of palliative radiotherapy. Preliminary results. [Spanish]. *Oncologia* 1998;21(11):55-60.

Gaze MN, Kelly CG, Kerr GR, Cull A, Cowie VJ, Gregor A, Howard GC, Rodger A. Pain relief and quality of life following radiotherapy for bone metastases: a randomised trial of two fractionation schedules. *Radiotherapy Oncology* 1997;45(2):109-16.

Kagei K, Suzuki K, Shirato H, Nambu T, Yoshikawa H, Irie G. [A randomized trial of single and multifraction radiation therapy for bone metastasis: a preliminary report]. *Gan No Rinsho* 1990;36(15):2553-8.

Koswig, S, Budach V. Recalcification and pain relief following radiotherapy for bone metastases. A randomized trial of 2 different fractionation schedules (10 x 3 Gy vs 1 x 8 Gy). [German]. *Strahlentherapie und Onkologie* 1999;175(10):500-508.

Nielsen OS, Bentzen SM, Sandberg E, Gadeberg CC, Timothy AR. Randomized trial of single dose versus fractionated palliative radiotherapy of bone metastases. *Radiotherapy Oncology* 1998;47(3):233-40.

Ozsaran Z, Yalman D, Anacak Y, Esassolak M, Haydaroglu A. Palliative radiotherapy in bone metastases: Results of a randomized trial comparing three fractionation schedules. *Journal BUON* 2001;6:43-48.

Price P, Hoskin PJ, Easton D, Austin D, Palmer SG, Yarnold JR. Prospective randomised trial of single and multifraction radiotherapy schedules in the treatment of painful bony metastases. *Radiotherapy Oncology* 1986;6(4):247-55.

Steenland E, Leer JW, van Houwelingen H, Post WJ, van den Hout WB, Kievit J, de Haes H, Martijn H, Oei B, Vonk E, van der Steen-Banasik E, Wiggeraad RG, Hoogenhout J, Warlam-Rodenhuis C, van Tienhoven G, Wanders R, Pomp J, van Reijn M, van Mierlo I, Rutten E, Leer J, van Mierlo T. The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. *Radiotherapy Oncology* 1999;52(2):101-9.

Warde PR, Kirkbride P, Panzarella T. Single fraction vs fractionated radiation therapy in the palliation of skeletal metastases - a randomised phase III trial." *International Journal of Radiation Oncology, Biology, Physics* 48(3 Suppl. Proceedings of the American

Abbreviations

ITT = Intention to treat analysis (by the groups randomized)

NS = not statistically significant

OR = Odds ratio

RT = Radiotherapy

SCC = Spinal Cord Compression

Wu, J. S., Wong, R., Johnston, M., Bezjak, A., Whelan, T., (& Cancer Care Ontario Practice Guidelines Initiative Supportive Care Group). (2003) "Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases.", *International Journal of Radiation Oncology, Biology, Physics*, vol. 55, no. 3, pp. 594-605.

Associated publications:

Wu, J. S., Wong, R. K., Lloyd, N. S., Johnston, M., Bezjak, A., Whelan, T., & Supportive Care Guidelines Group of Cancer Care Ontario. 2004, "Radiotherapy fractionation for the palliation of uncomplicated painful bone metastases - an evidence-based practice guideline", *BMC Cancer*, vol. 4, p. 71. <http://www.biomedcentral.com/1471-2407/4/71>

AND Practice Guideline Report #13.2. 2003, Wu, J. S., Wong, R. K., Johnston, M., Bezjak, A., Whelan, T., Laetsch, N. <http://www.cancercare.on.ca/>

Design: Systematic review

Rating 1+

Country:

setting:

Inclusion criteria

RCTs comparing 2 or more dose fractionation schedules for treatment of painful bone metastases with localized RT.

Exclusion criteria

Studies using hemi-body RT or radio nucleotides.

Population

Heterogeneous population of patients with a range of tumour types and performance status scores. Spinal cord compression and pathologic fractures were exclusion criteria in all studies except the study by Tong (RTOG 1982) which included pathologic fractures regardless of surgical fixation (multifraction comparisons). Some studies restricted the prescription of dose to a depth approximating the depth of the spine.

16 studies included.

Interventions

Three categories of intervention:

Comparisons of different doses of single fraction RT (2 studies with doses median 8Gy, range 8-10Gy);

Comparisons of different doses of multifraction RT (6 studies with doses median 20Gy in 5 fractions, range 20Gy in 5 fractions to 30Gy in 10 fractions) – number of fractions ranged from 2 to 15, total doses ranged from 15-40 Gy, schedules ranged from 2x10Gy to 15x2Gy.

Four studies compared 2 fractionation schedules and two studies compared more than 2 fractionation schedules.

Comparisons of single-fraction vs multifraction RT (these 8 studies were included in the Sze Cochrane SR discussed in the previous section).

Outcomes

Pain relief response data.

Re-treatment rates.

Follow up –

Drop outs ranged from 0% to 63% across all studies. Reasons included death before RT or first follow-up, or progressive illness preventing follow-up.

Results

Only results from single fraction comparisons and multifraction comparisons are reported here.

Single vs multifraction findings are reported in the more up to date Sze SR.

ITT analyses used.

Single fraction vs single fraction regimes

2 studies compared single doses of 4Gy with 8Gy (Jeremic *et al.* 1998, Hoskin *et al.* 1992)

Outcomes:

Overall pain response rates were significantly lower with 4Gy fractions (statistical significance not reported).

Complete pain response rates were not significantly different between doses (statistical significance not reported).

Re-irradiation rates were higher in lower dose arms (statistical significance not reported).

Multifraction vs multifraction regimes

6 studies included. One study was a four arm comparison of 15Gy vs 20Gy vs 25Gy vs 30 Gy for multiple metastases and a two arm comparison of 20Gy/5 vs 40Gy/15 for solitary metastases (Tong 1982). The low column in the table refers to the 15Gy/5 fractions and the high column to the 30Gy/10 fractions for multiple metastases.

Outcomes:

- No apparent differences in overall pain response rates were found between multifraction regimes, however statistical tests were not reported.
- Complete pain response rates were similar between arms in 2 small studies (Niewald *et al.* – (1996) 100 patients, Okawa *et al.* (1988) - 80 patients). The larger study by Tong *et al.* (1982) reported lower complete pain responses with low dose rates for the solitary (266 patients) and multiple metastases (750 patients).
- Re-irradiation rates were higher in the low dose arm of 1 study (Tong *et al.* 1982) and the same in a smaller study (Niewald *et al.* 1996), however, re-irradiation rates were consistently higher in lower dose arms in the remaining 7 trials reported in the paper.
- Pathological fracture rates were reported in the text as not showing any difference in rates by treatment assignment, an exception was the solitary metastasis group of the Tong study for multifraction comparisons. Pathological fracture rates were higher in the high dose arm.
- No significant difference was observed between regimens for spinal cord compression rates in any of the trials.
- Biologically equivalent dose (BED) meta analysis included single fraction RT vs multifraction and multifraction vs multifraction studies with cut-offs of 30Gy and 35Gy. No statistically significant differences in complete pain response were found between high and low dose schedules for either cut-off. This indicates that a dose response relationship for complete pain response was not evident in these trials. (Single vs single dose fraction studies were excluded from this meta-analysis). Another report (Ben-Josef *et al.* 1999) which pooled data from 4 RCTs (1982-1992) demonstrated that there was no dose response relationship between RT dose and early (4 weeks) complete pain relief. However, for late complete pain relief a relationship between response rates and BED was found, with a higher number of patients with late complete pain relief at high dose rates (in Falkmer 2003).

- Trials reporting analgesic consumption before and after RT found a reduction in the amount consumed after RT. No trials detected a difference in the pattern of analgesic reduction between fractionation schedules.
- Acute toxicity (9 studies) as measured by nausea and vomiting was not significantly different between fractionation schedules.
- Three studies performed functional quality of life assessments. There was no difference between treatment arms.
- Author comments on all studies in paper: The median duration of pain relief reported by 7 studies in the paper (including single vs multifraction studies) ranged between 11 and 24 weeks, with no significant difference in the duration of pain relief between the treatment arms.
- Re-irradiation rates were consistently and significantly higher for patients in the lower dose arms in the 7 studies reporting this outcome.

OUTCOME OF INTEREST	INTERVENTION Single fraction 4Gy	COMPARISON Single fraction 8Gy	OVERALL RESULT
Overall pain response 2 studies	Jeremic 59% Hoskin 44%	78% 69%	Overall pain response rates lower with 4Gy
Complete pain response, 2 studies	Jeremic 21% Hoskin 36%	32% 39%	Complete response rates similar
Re-irradiation rates 2 studies	Jeremic 42% Hoskin 20%	38% 9%	Re-irradiation rates higher in lower dose arms
	Multifraction Low dose	Multifraction High dose	
Overall pain response 6 studies	Niewald 77% Rasmusson 69% Hirokawa 75% Okawa 78% Madsen 48% Tong (solitary met) 82% (multiple mets) 85%	86% 66% 75% 76% 47% 85% 87%	No apparent differences in overall pain response rates between multifraction regimes.
Complete pain response, 3 studies	Niewald 33% Okawa 37% Tong (solitary met) 53% (multiple mets) 49%	31% 41% Tong 61% 57%	Variable responses, no statistical tests reported. Tong had the most patients in the trial.
Re-irradiation rates 2 studies	Niewald 2% Tong	2% 11%	Variable responses, however Niewald

	(solitary met) 24%	(multiple mets) 23%	12%				is a smaller study than Tong.
Pathological fracture	Tong solitary met group (from associated study)		20Gy x 5	4%	40Gy x 15	18%	P=0.02 in evaluable patients
	All dose				fractionation		Result
Biologically equivalent dose (BED)	Lower				Higher		
Complete pain response for trials of less than (lower) and greater than (higher) a BED of 30 Gy (ITT)	500/1496		508/1541				OR 1.01 [0.91,1.11] P=0.8
Complete pain response for trials of less than (lower) and greater than (higher) a BED of 35 Gy (ITT)	266/813		271/788				OR 0.93 [0.82,1.07] P=0.3

General comments –

Author comments for all studies in paper: No strong difference could be found in the meta-analysis of single fraction vs multifraction treatments (agrees with Sze but fewer studies). Furthermore, no apparent dose-response relationship was detected when data from all trials were analyzed.

A review of median duration of response did not show significant differences between dose fractionation schedules. Treatment toxicities were comparable.

When achieving pain relief is the main goal of palliation then single fractionation is appropriate. When other treatment objectives are important then the available evidence from these studies is not sufficient to select an optimal choice of dose fractionation. More evidence is needed on the role of re-irradiation on bone mets and other palliative endpoints.

At the time of writing (2003) three ongoing RCTs were listed that may provide additional evidence:

- RTOG 9714 (single vs multifractions) Hartsell *et al* 2005
- TROG 96.05 (single vs multifractions) Roos *et al* 2006
- NCIC CTG SC.20 (single vs multifractions)

Authors conclusions: A meta-analysis of RCTs found no difference in complete and overall pain relief between single- and multiple-fraction RT for bone metastases. No dose-response relationship could be detected by including data from the multi-fraction

versus multi-fraction trials. Additional trials are needed to evaluate the role of re-irradiation and the impact of RT on other treatment end points such as quality of life.

Refer to a critical appraisal of this review conducted the Centre for Reviews & Dissemination:

Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases [Abstract Number: 12003000564] Database of Abstracts of Reviews of Effects, available <http://www.crd.york.ac.uk/crdweb/> [31 July 2004] Abstract of: Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. Wu J S, Wong R, Johnston M, Bezjak A, Whelan T. Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. *International Journal of Radiation Oncology, Biology, Physics*, vol. 55, no. 3, pp. 594-605.

CRD Summary statement: "This meta-analysis compared pain relief achieved with various dose-fractionation schedules of localised radiotherapy in patients treated for painful bone metastases of cancer. The authors found no difference between single- and multiple-fraction radiotherapy. The evidence presented supports the authors' conclusions but some of the review methods were not reported so it is difficult to evaluate the reliability of the conclusions"

References included

Single fraction RT comparisons

P.J. Hoskin, P. Price, D. Easton *et al.*, A prospective randomised trial of 4 Gy or 8 Gy single doses in the treatment of metastatic bone pain. *Radiother Oncol* **23** (1992), pp. 74–78

B. Jeremic, Y. Shibamoto, L. Acimovic *et al.*, A randomized trial of three single-dose radiation therapy regimens in the treatment of metastatic bone pain. *Int J Radiat Oncol Biol Phys* **42** (1998), pp. 161–167.

Multifraction RT comparisons

Hirokawa, K. Wadasaki, K. Kashiwado *et al.*, A multi-institutional prospective randomized study of radiation therapy of bone metastases [Japanese] . *Nippon Igaku Hoshasen Gakkai Zasshi* **48** (1988), pp. 1425–1431.

E.L. Madsen , Painful bone metastasis: Efficacy of radiotherapy assessed by the patients—A randomized trial comparing 4 Gy × 6 versus 10 Gy × 2. *Int J Radiat Oncol Biol Phys* **9** (1983), pp. 1775–1779.

M. Niewald, H.J. Tkocz, U. Abel *et al.*, Rapid course radiation therapy vs. more standard treatment: A randomized trial for bone metastases. *Int J Radiat Oncol Biol Phys* **36** (1996), pp. 1085–1089.

T. Okawa, M. Kita, M. Goto *et al.*, Randomized prospective clinical study of small, large and twice-a-day fraction radiotherapy for painful bone metastases. *Radiother Oncol* **13** (1988), pp. 99–104.

B. Rasmusson, I. Vejborg, A.B. Jensen *et al.*, Irradiation of bone metastases in breast cancer patients: A randomized study with 1 year follow-up. *Radiother Oncol* **34** (1995), pp. 179–184.

D. Tong, L. Gillick and F.R. Hendrickson , The palliation of symptomatic osseous metastases: Final results of the Study by the Radiation Therapy Oncology Group. *Cancer* **50** (1982), pp. 893–899.

Systematic review of RCTs and prospective nonrandomised studies

Falkmer, U., Jarhult, J., Wersall, P., & Cavallin-Stahl, E. 2003, "A systematic overview of radiation therapy effects in skeletal metastases. [Review] [65 refs]", *Acta Oncologica*, vol. 42, no. 5-6, pp. 620-633

Design: Systematic review

Rating 1+

Country:

setting: Update of a previous Swedish Council of Technology Assessment in Health Care (SBU) SR

Inclusion criteria

Meta analyses, RCTs, prospective and retrospective nonrandomised controlled studies (1994-2001) for radiation therapy

Exclusion criteria

Not stated

Population

Reports from 65 studies were included on RT effects in skeletal metastases.

Interventions

External beam radiation with local and half body fields; systemic radiotherapy with radionuclides; treatment with bisphosphonates.

Outcomes

Bone pain, palliation, fracture prevention and treatment, SCC treatment

Follow up –

Length of follow-up only reported for one study in the review.

Results

All the RCTs identified were also used in the Sze or Wu reviews.

Additional analyses included Half Body Irradiation (HBI) and systemic radionuclide therapy.

Conclusions from RT therapy studies (RCTs (8) and prospective (5) studies):

- Overall pain relief (OPR): frequency varied between 59% and 90%
- Pain relief achieved with a single 4Gy fraction was significantly lower than that of other fraction schedules
- The mean rate of OPR was 84% when the 4Gy single treatment was excluded
- The lowest pain relieving single fraction was 6Gy
- OPR did not depend on the fractionation schedule (as shown by Sze *et al.* (2002)).
- The large RCTs reported a median time to progression of 5 and 6 months after RT, and first increase in pain score in 40% of patients after one year. Time to pain progression did not depend on fractionation schedule.
- Re-treatment frequency reported in 7/13 studies and ranged from 2% to 44%. Two single fraction vs multifraction RCTs found higher re-treatment rates in the single fraction arms of 25% vs 10% and 23% vs 10% (see also meta analysis by Sze).
- The occurrence of SCC was reported in 4/13 studies, (50 patients / 1456 participants; 3.4%) and not clearly stated whether this occurred at the index field. Two single fraction vs multifraction RCTs reported low incidence rates of 1-2% with no differences between arms. One smaller single fraction RCT reported SCC incidences of between 3.6%-4.6% with no differences between arms. The other study was a prospective nonrandomised design of moderate quality.
- Two to three times higher incidence of pathological fracture was associated with single fraction compared with multifraction schedules (2 RCTs).

Half body irradiation

One RCT (Salazar *et al.* 2001, quality score C1)) and one retrospective study (Chua *et al.* 1994, quality score R3).

RCT (Salazar *et al.* 2001):

Pain relief occurred in 3 to 9 days, no difference between the 3 arms.

Complete pain relief (CPR) significantly lower in group B than A or C.

No difference in quality of life (QoL) between groups (RTOG grading).

Toxicity grade 3-4 in 18 patients, no difference between groups.

Radionuclide therapy

Three RCTs, 10 prospective and 1 retrospective study were identified. Five of the prospective studies had less than 50 patients. The RCTs had between 114 and 305 patients.

Overall conclusions

- Irradiation of skeletal metastases is palliative treatment.
- There is strong evidence that RT of skeletal metastases gives an overall (complete and partial) pain relief in more than 80% of patients.
- There is strong evidence that pain relief in terms of degree and duration, does not depend on fractionation schedules applied.
- Irrespective of the fractionation schedule used at irradiation, the number of later complications, such as SCC or pathological fractures, at the index field is low.

OUTCOME OF INTEREST	INTERVENTION HBI	COMPARISON	OVERALL RESULT	
Overall Pain Relief 156 patients (A 51 pt)	A: 3 Gy/5fr, 15Gy/week		%OPR 91	Duration 155days
B 56 pts	B: 4 Gy/1fr, 2fr/d (8Gy/d)		89	101
C 49 pts	C: 3Gy/fr, 1fr/d (6Gy/2d)		94 NS	112 p<0.034

General comments –

Author conclusions:

- Irradiation of skeletal metastases is, with few exceptions, a palliative treatment.
- There is strong evidence that radiotherapy of skeletal metastases gives an overall (complete and partial pain relief) in more than 80% of patients.
- There is strong evidence that the duration of pain relief in at least 50% of patients lasts for \geq 6 months.
- There is convincing evidence that pain relief, in terms of degree and duration, does not depend on the fractionation schedules applied.
- Irrespective of the fractionation schedule used at irradiation, the number of later complications, such as spinal cord compression or pathological fractures, at the index fields are low.
- There are some data showing that the difference in cost between single and multifraction treatment is small. However, these data do not permit any firm conclusions to be drawn.
- Several reports indicate that early diagnosis and early therapy of spinal cord compression are the two most important predictors of a favourable clinical outcome

after radiotherapy. However, no controlled studies have been undertaken.

- When the diagnosis of spinal cord compression is late, a favourable outcome might depend on the radio-responsiveness of the tumour.

The documentation is weak and no conclusions can be drawn:

- There is some evidence that a small proportion of totally paralytic patients can regain walking function after radiotherapy.
- There is strong evidence that the radionucleotides ⁸⁹Sr and ¹⁵³Sm are efficient when they are used as a systemic treatment of generalized bone pain due to metastasis from carcinomas of the prostate and breast. Overall bone pain relief occurs in about 60 to 80% of patients with a median response duration of 2 to 4 months.
- There is strong evidence that intravenous treatment with bisphosphonates in patients with myeloma and osteolytic bone metastasis due to carcinoma of the breast significantly decreases the number of skeleton-related events and bone pain.

Other comments:

This qualitative assessment, also includes lower quality studies. Single fraction, multifraction, and single vs multifraction studies were assessed together, no separate analysis of single and multifraction studies was performed.

References

Prospective studies

Arcangeli G, Giovinazzo G, Saracino B, et al. Radiation therapy in the management of symptomatic bone metastases: the effect of total dose and histology on pain relief and response duration. *Int J Radiat Oncol Biol Phys* 1998; 42: 1119-26

Bremer M, Rades D, Blach M, et al. Effectiveness of hypofractionated radiotherapy in painful bone metastases. Two prospective studies with 1- 4 Gy and 4-4 Gy. *Strahlenther Onkol* 1999; 175: 382- 6.

Huguenin PU, Kieser S, Glanzmann C, et al. Radiotherapy for metastatic carcinomas of the kidney or melanomas: an analysis using palliative end points. *Int J Radiat Oncol Biol Phys* 1998; 41: 401-5.

Tombolini V, Zurlo A, Montagna A, et al. Radiation therapy of spinal metastases: results with different fractionations. *Tumori* 1994; 80: 353-6

Uppelschoten JM, Wanders SL, de Jong JM. Single-dose radiotherapy (6 Gy): palliation in painful bone metastases. *Radiother Oncol* 1995; 36: 198- 202

Hemi body irradiation

Salazar OR, Sandhu T, Motta NW, et al. Fractionated half body irradiation (HBI) for the rapid palliation of widespread, symptomatic, metastatic bone disease: a randomized phase III trial of the international atomic energy agency (IAEA). *Int J Radiat Oncol Biol Phys* 2001; 50: 765-75.

Randomized controlled trials

Roos, D. E., Turner, S. L., O'Brien, P. C., Smith, J. G., Spry, N. A., Burmeister, B. H., Hoskin, P. J., Ball, D. L., & Trans-Tasman Radiation Oncology Group 2005, "Randomized trial of 8 Gy in 1 versus 20 Gy in 5 fractions of radiotherapy for neuropathic pain due to bone metastases (Trans-Tasman Radiation Oncology Group, TROG 96.05)", *Radiotherapy & Oncology*, vol. 75, no. 1, pp. 54-63.

Design: RCT, multicentre, 2 arm Phase III

Rating 1+

Country: Australia, NZ, UK, setting: Cancer centres

Aim To compare the efficacy of a single 8Gy fraction with 20Gy in 5 fractions for neuropathic pain due to bone metastases.

Inclusion criteria

Confirmed **malignancy to bone with neuropathic pain**, life expectancy at least 6 weeks, able to complete pain assessments.

Exclusion criteria

Metastasis within distribution of neuropathic pain, prior RT to index site, MSCC, pathological fracture of long bone at index site, change in systemic therapy within 6 weeks before or 4 weeks after RT, neuropathic pain due to extra-skeletal tumour.

Population number of patients = 272 randomized, 252 eligible

Index sites were spine (89%), rib (9%), other (2%); 72% male patients; Median age 67 years (range 29-89); Commonest primary cancers were lung (31%), prostate (29%), breast (8%).

Interventions

Single 8Gy fraction (8/1) vs 20Gy in 5 fractions to the spine over 1 week (20/5), stratified by treatment centre, 1:1 randomization

Outcomes

Pain assessment by patients at pre-treatment, 2 and 4 weeks after start of RT, 2 months, 3 months, then 3 mthly until treatment failure or death, assessed as *overall response, complete response, time to treatment failure, duration of complete response*. Other outcomes: toxicity; re-treatment; complications; survival.

Definition of complete response was no pain and no analgesia for the index site.

Follow up

2 and 4 weeks after RT, 2 and 3 months, then until treatment failure or death.

ITT n=272; 252/272 eligible patients were assessed (93%); 245/272 per protocol (90%).

Results

Treatment Response

Overall response rate (ITT): no statistically significant difference between arms (53% sf vs 61% mf)

Complete response rate (ITT): no statistically significant difference between arms (26% sf vs 27% mf)

No difference by treatment site (spine vs non-spine):

Overall ITT RR 57%sf vs 58%mf

Complete response ITT 26% sf vs 26% mf

Overall ITT RR by primary site were breast 70%, prostate 58%, lung 58%, other 52%, these differences not statistically significant (P=0.50).

Time to treatment failure (TTF)

At close of the trial 9 patients remained alive, one was lost to follow-up without failure.

160 had treatment failure and 102 died without failure.

Multifactor analyses were adjusted for treatment site and primary cancer (however data were reported for unadjusted rates which were higher than adjusted rates):

TTF (ITT) 82 failures in 8/1 fraction and 78 failures in 20/5 fraction arm
Hazard Ratio (HR) 1.35 (95%CI 0.99, 1.85); (90%CI 1.04, 1.76) ; Log rank P=0.056 NS unadjusted rates. (Criterion for significant difference P<0.047) unadjusted.
Criterion for non-inferiority of 8/1 arm: upper limit of 90%CI for HR is less than 1.55.

Adjusted rates were 1.26-1.31 across the populations analyzed (ITT, eligible and per protocol)

From this analysis the authors suggest that the 8/1 fraction was not as effective as the 20/5 fraction, however the difference between treatment arms was shown not to be statistically significant.

Statistically significant differences reported in TTF by index site and primary cancer:

Spine vs non spine index sites

ITT analysis 3.5 months(95%CI 2.8, 4.6) vs 2.2 months (95%CI 1.4, 3.0) (MA comment CI overlap therefore not statistically different at 95% level)

Estimated % without failure at 1 year was 23% (95%CI 16, 32) vs 0% (P=0.006)

Median TTF (months) for breast, prostate, lung, other cancers were: 9.1, 3.5, 3.0, 2.5 respectively (P=0.003 from TTF curves)

Duration of complete response (failures/complete responders) ITT analysis

17/35 in 8/1 arm

19/36 in 20/5 arm

Hazard Ratio (HR) 0.99 (95%CI 0.51, 0.91); (90%CI 0.57, 1.72) ; Log rank P=0.97 NS unadjusted rates.

Re-treatment

160 patients with treatment failure, 73 irradiated. The difference between arms was not significant. (8/1 vs 20/5 40/137 (29%) vs 33/135 (24%) P=0.41

Survival

Median overall survival for all 272 patients was 4.8 months (95%CI 4.2, 5.7) with 27% (95%CI 22, 32) surviving 1 year. There were no statistically significant differences in survival between treatment arms (P=0.66) or index site (spine vs non spine, P=0.89).

Survival differences were by primary site (P<0.0001)

Median survival times at 1 year for breast, prostate, lung, other cancers were:

	23.5	10.8	3.0	3.9	months
% surviving	65	45	7	19	

Prevention of SCC

17 cord/cauda compressions developed at the index site (8/1:20/5 =9:8).

This represents 6% of 272 randomized patients and 7% of 241 with spinal index sites. Two of the cord compressions developed whilst the protocol was awaited (one in each arm).

Pathological fractures

- Eleven new or progressive pathological fractures were reported at the index sites (8/1:20/5 =6:5). This represents 4% of randomized patients.
- There were no statistically significant differences in serious complication rates between the 2 arms for SCC or pathological fracture either separately or combined.

OUTCOME OF INTEREST	INTERVENTION Single fr 8/1 n=137	COMPARISON Multifraction 20/5 n=135	RESULT
Overall Pain response I=ITT (N=272) E=eligible (N=252) P=per protocol (N=245)	I 53% (95%CI 45,62) E 53% P 53%	61% (95%CI 53,70) 62% 64%	ITT (n=272) RR 57% (95%CI 51,63) p=0.18 Eligible p=0.13 Per protocol p=0.092
Complete pain response (CR)	I 26% (95%CI 18,34) E 24% P 24%	27% (95%CI 19,35) 28% 29%	ITT p=0.89 Eligible p=0.57 Per protocol p=0.47
Time to Treatment Failure (TTF) all randomised (months)	Median time (ITT) 2.4 (95%CI 2.0, 3.3)	3.7 (95%CI 3.1, 5.9)	NS
% patients without failure at 1 year	15 (95%CI 7.0,28.0)	24 (95%CI 16, 36)	NS
TTF for responders (n=156) (months)	Median time from randomization 3.5 (95%CI 2.8, 7.7)	5.5 (95%CI 3.6, 9.1)	NS
% responders without failure at 1 year	15 (95%CI 6, 34)	25 (95%CI 14, 41)	NS
Duration CR for complete responders (n=71) (months)	Median time from complete response 2.6 (95%CI 1.7, 10.5)	4.7 (95%CI 1.2, 14.1)	NS

General comments –

Author conclusions:

8/1 regimen was not shown to be as effective as 20/5 regimen, nor was it statistically significantly worse. Outcomes were generally poorer for 8/1, although the quantitative differences were relatively small.

Methodology

Sample size of 272 was sufficient to ensure a power of 80% to achieve a 2 sided 90% CI for the difference in RR within $\pm 15\%$.

Blinding to treatment schedule was not possible. Blinding of outcome assessors was not

reported. Patients were questioned for pain responses.

Forty one (15%) of patients were given new systemic therapy after randomization. Since the best response to RT was based on assessments up to 2 months after commencing RT this was not considered to affect the results. Systemic therapy may have postponed treatment failure at some index sites.

Hartsell, W. F., Scott, C. B., Bruner, D. W., Scarantino, C. W., Ivker, R. A., Roach, M., III, Suh, J. H., Demas, W. F., Movsas, B., Petersen, I. A., Konski, A. A., Cleeland, C. S., Janjan, N. A., & DeSilvio, M. 2005, "Randomized trial of short-versus long-course radiotherapy for palliation of painful bone metastases.[see comment]", *Journal of the National Cancer Institute*, vol. 97, no. 11, pp. 798-804.

Design: RCT (RTOG trial 9714)

Rating 1+

Country: USA

setting: Cancer Centres

Aim: To investigate whether 8 Gy delivered in a single treatment fraction provides pain and narcotic relief that is equivalent to that of the standard treatment course of 30 Gy delivered in 10 treatment fractions over 2 weeks.

Inclusion criteria

Patients with breast or prostate cancer with **1-3 sites of painful bone metastases**, and moderate to severe pain, Karnofsky performance status of at least 40, estimated life expectancy of at least 3 months. Patients receiving other co-interventions (bisphosphonates, hormone therapy, chemotherapy, immunotherapy, radioisotopes) were eligible if no systemic therapy given within 30 days before entry to the study.

Exclusion criteria

Patients with previous RT or palliative surgery, pathological fracture, impending fracture of treatment site, or planned surgical fixation of bone., spinal cord or cauda equina compression or effacement.

Population number of patients= 898 (455 in single fraction SF; and 443 in multifraction MF)

Mean age 65 years (range 31-92)

51% of patients had spinal metastases.

Interventions

Objective was to determine whether 8Gy in a single fraction provides pain and narcotic relief equivalent to 30Gy in 10 fractions over 2 weeks.

8Gy x1 fraction vs 30Gy x 10 fractions.

Study designed to show equivalence if at least 36% of patients in the 8Gy arm achieved complete pain and narcotic relief.

Outcomes

After initial response to treatment at 3 months.

Pain relief at 3 months with Brief Pain Inventory (BPI) (mild pain 1-4; moderate pain 5-6; severe pain 7-10).

Functional Assessment of Cancer Therapy instrument for quality of life (FACT).

Health Utilities Index III

Pain and narcotic scores

Survival

Follow up –

Follow-up questionnaires and telephone interviews with poor-compliance patients at 2 and 4 weeks, then 2, 3, 6, 9, 12, 18, 24, 30, 36, 48 and 60 months.

63.8% (573/898) patients analyzed.

BPI completed by 67.8% (573/845) at 3 months, or by 83.6% (573/685) of those alive and able to complete the form.

Results

Definitions:

Time to maximum pain relief defined as time from the first day of RT until the lowest pain score for worst pain after RT.

Treatment response= worst pain score.

Complete response = no pain at 3 mths after RT

Partial response = a pain score at least 2 points lower than the initial response

Stable response= a 1 point change of score in either direction

Progressive response= a pain score at least 2 points higher than the initial score

Brief Pain Inventory at 3 months:

573/845 patients (68%) No difference between scores for SF vs MF, P=0.85

Overall pain response:

See Table 3

375/573 patients (66%)

No statistically significant differences between arms for complete, partial, stable and progressive pain responses. P=0.6

Treatment of solitary painful sites

	8Gy N=165	30Gy N=156
Complete response	29 (18%)	32 (21%)
Partial response	85 (52%)	79 (51%)

P=0.17

Analgesic and narcotic use at 3 months:

628 patients, no difference between arms (P=0.48)

33% of patients no longer required narcotics.

Of these 12% were using non-narcotic analgesics.

Toxicity:

See table for acute toxicity

Late toxicity (after 90 days) in both arms 4% (28/696 patients)

Incidence of pathologic fractures

Within treatment field (or within plus adjacent to treatment field):

	8Gy 5%	30Gy 4%
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An additional 3-4% of patients had fractures adjacent to the treatment site.

Re-treatment

(At discretion of treating physician)

3 year re-treatment rates:

	8Gy 18% (76/449)	30Gy 9% (33/432)	P<0.001
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Difference in rates apparent by 3 months after initial treatment.
 Most re-treatment given in first 9 months.
 Re-treatment rarely given after 1 year.

OUTCOME OF INTEREST	INTERVENTION SF	COMPARISON MF	OVERALL RESULT
Median survival (months)	9.1	9.5	P=0.82
Overall survival	44% at 1 year 22% at 2 years	42% at 1 year 22% at 2 years	
Acute toxicity within 90 days (grades 2-4)	42 events 10%	70 events 17%	Difference (95%CI 3, 12) P=0.002

**Observational studies:
Prospective Cohort**

van der Linden, Y. M., Steenland, E., van Houwelingen, H. C., Post, W. J., Oei, B., Marijnen, C. A., Leer, J. W., & The Dutch Bone Metastasis Study Group. 2006, "Patients with a favourable prognosis are equally palliated with single and multiple fraction radiotherapy: results on survival in the Dutch Bone Metastasis Study", *Radiotherapy & Oncology*, vol. 78, no. 3, pp. 245-253.

Design: Prospective cohort: analysis of survivors from RCT (1996-1998). Rating 2++

Country:Holland, setting: Community

Aim: Palliative effects of single and multifraction RT in the DBMS patients with an observed favourable prognosis, and prognostic factors for survival in the DBMS.

Inclusion criteria:

Metastases from solid tumours, Pain score min of 2 (11 pt scale 0=no pain, 10 worst pain), Metastases treatable in 1 RT target volume, no previous RT to same metastases.

Exclusion criteria

Pathological fracture or impending fracture, SCC, metastases of renal ca or melanoma, metastases in cervical spine, patients with expected favourable prognosis.

Population number of patients = 320 survivors after 1 year from the DBMS.

26% SF had spinal metastases, 31% MF had spinal metastases.

Interventions Single fraction (SF) 8Gy vs Six fractions (MF) 4Gy

Outcomes

Complete response, duration of response, progressive pain.

Survival analyses of patients by type of primary tumour. Overall survival from randomization and diagnosis. Prognostic factors for survival were age, gender, KPS, primary tumour, treatment site, presence of other bone or visceral metastases, analgesics intake, concomitant systemic treatment, pain score at randomization, treatment schedule.

Follow up

Questionnaires were mailed to patients weekly for 13 weeks, then monthly for 2 years or until death.

Analysis of response to initial treatment in 97% of 320 patients with survival > 52 weeks.

Results

Definitions:

Response was defined as (a) a decrease in initial pain score by at least 2 points without analgesic increase, or (b) a change in analgesics from phase 3 or 4 to a lower phase without an increase in pain.

Complete response was defined as a decrease in the pain score to zero on the pain scale without analgesic increase.

Progression after response was defined as (a) an increase in pain with return to the initial pain score or higher, without analgesic increase, or (b) an increase in analgesics from a lower phase to phase 3 or 4 irrespective of the pain score.

Net Pain Relief (NPR) defined as duration of pain relief related to overall survival.

Characteristics of long term survivors:

Primary tumours: 63% breast, 24% prostate, 8% lung, 5% other. No major differences between SF and MF survivors. 51% from SF group, 49% from MF group. No major differences in age, gender, KPS, primary tumour, treatment site, presence of other bone or visceral metastases, analgesics intake, concomitant systemic treatment, pain score at randomization. Only treatment site differed between the 2 regimens (P=0.04), but the clinical implications were considered minor. More than 60% of survivors had more than 1 bone metastasis.

Response to treatment:

Hazard Ratios for response and complete response shown in table.

Mean time to response was 4 weeks in both treatment groups.

Mean duration of response was 29 weeks (median 35 weeks) after SF

Mean duration of response was 30 weeks (median 42 weeks) after MF

Progressive pain in 55% SF and 53% MF.

Mean time to progression of pain after response was 17 weeks for SF and 18 weeks for MF.

Net pain relief was 56% for SF and 58% for MF responders.

There were no statistically significant differences observed for response to treatment between SF and MF across the primary tumour groups.

Pain scores overlapped consistently over the year for SF and MF groups.

Re-treatment:

Overall 24% (76/320) received a second RT course, 61 in first year and 15 the following year.

36% (58 patients) in SF group vs 11% (18 patients) in the MF group were retreated.

Mean time to re-treatment was 25 weeks in (range 2-78 weeks) SF vs 39 weeks (range 5-83 weeks) in MF patients.

Survival

From randomization patients with breast cancer had the best median overall survival > prostate cancer> other cancers. Lung cancer patient's had the lowest.

Multivariate analysis of prognostic factors stratified by primary tumour type (n=1157) were a good Karnofsky Performance Score (KPS), no visceral metastases, and non-opiate analgesics intake (all factors, P<0.001).

OUTCOME OF INTEREST	INTERVENTION SF	COMPARISON MF	RESULT
Response to treatment	87%	85%	HR 0.9 (95%CI 0.7, 1.2) P=0.54
Complete response	62%	48%	HR 0.8 (95%CI 0.6, 1.0) P=0.07
Response to initial treatment (excluding effect of re-treatment)	80%	85%	HR 1.0 (95%CI 0.8, 1.3) P=0.95
Direct effect of re-treatment (change in pain score compared to week before re-treatment)	84%	64%	HR 1.3 (95%CI 0.7, 2.7) P=0.44
Median overall survival			Breast ca 16.4 mths (95% CI 14.2, 18.5)

(months)
(n=1157)

Prostate ca 9.5 mths
(95% CI 7.8, 11.1)
Other ca 3.9 mths
(95% CI 3.4, 4.4)
Lung ca 3.2 mths
(95% CI 2.8, 3.5)

General comments –

Authors conclusions:

Single fraction RT should be the standard dose schedule for all patients with painful bone metastases, including those with an expected favourable survival. General prognostic indicators are useful in predicting survival.

Comments:

Analysis of factors on the subgroup of survivors from this trial.

van der Linden, Y. M., Lok, J. J., Steenland, E., Martijn, H., van, H. H., Marijnen, C. A., Leer, J. W., & Dutch Bone Metastasis Study Group. 2004, "Single fraction radiotherapy is efficacious: a further analysis of the Dutch Bone Metastasis Study controlling for the influence of re-treatment", *International Journal of Radiation Oncology, Biology, Physics*, vol. 59, no. 2, pp. 528-537.

Design: Prospective cohort: analysis of survivors from RCT (1996-1998). Rating 2++

Country:Holland, setting: Community

Aim: The purpose of the present study was to evaluate factors influencing re-treatment and its effect on response from the Dutch Bone Metastasis Study.

Inclusion criteria:

Metastases from solid tumours, Pain score min of 2 (11 pt scale 0=no pain, 10 worst pain), Metastases treatable in 1 RT target volume, no previous RT to same metastases.

Exclusion criteria

Pathological fracture or impending fracture, SCC, metastases of renal ca or melanoma, metastases in cervical spine, patients with expected favourable prognosis.

Population number of patients = 1157 from Dutch RCT

26% SF had spinal metastases, 31% MF had spinal metastases.

Non-responders = 310; responders = 789; Progression = 387

Interventions Single fraction (SF) 8Gy vs Six fractions (MF) 4Gy

Outcomes

Complete response, duration of response, progressive pain.

Patients reported the maximum pain experienced at the treatment site during the preceding week on the 11 point scale.

Concomitant use of drugs was noted.

Rotterdam Symptom checklist was adapted to measure acute treatment side effects (4 point scale from 1 (none) to 4 (very much).

All patients were re-evaluated for their response to initial treatment with a focus on the 173 patients re-treated within the first year after randomization. Patients were clustered by primary tumour type.

Follow up

Questionnaires were mailed to patients weekly for 13 weeks, then monthly for 2 years or until death.

58 patients did not return enough questionnaires, analysis of response to initial treatment was possible in 1099 patients (95%)

Of 145/173 (84%) first year retreated patients were included.

Results

Definitions:

Response was calculated taking into account changes in opioid use.

(a) a change in analgesics from phase 1 or 2 to phase 3 or 4 was noted as an analgesic increase

(b) If the patient stopped using phase 3 or 4 analgesics this was noted as an analgesic decrease.

Partial response was defined as (1) a decrease in the initial pain score by at least 2 points on the 11 point scale without analgesic increase, or (2) analgesic decrease without an increase in pain.

Complete response was defined as a decrease in the initial pain score to zero on the pain scale without concomitant analgesic increase.

When pain scores remained unchanged or increased, the patient was considered to be

a non-responder.

Progression after response was defined as (a) an increase in pain with return to the initial pain score or higher, without analgesic increase, or (b) an increase in analgesics irrespective of the pain score.

Response calculations

Patients not retreated during the first year of follow-up (n=984), the timescale started at randomization and ended at the end of follow-up.

Patients retreated during the first year of follow-up (n=173), times were split into the period before and the period after re-treatment.

The response to treatment was calculated if at least 2 successive follow-up pain scores were available.

Response to initial treatment:

71% of 556 SF and 73% of 543 MF patients responded (p=0.84, HR 1.0 [95%CI 0.9, 1.1])

There were differences in response rates by primary tumour type, with breast and prostate cancers providing the highest response rates (77%-80%), followed by other primary tumours (63% SF and 60% MF), then lung ca (58% SF and 62% MF).

Re-treatment increased response to 75% for SF, whilst MF was unchanged (P=0.54)

The response status after initial treatment did not predict occurrence of re-treatment: 35% SF vs. 8% MF non-responders and 22% SF vs. 10% MF patients with progressive pain were retreated.

Logistic regression analyses showed the randomization arm and the pain score before re-treatment to significantly predict re-treatment (P < 0.001).

Re-treatment for non-responders was successful in 66% SF vs. 33% MF patients (P = 0.13).

Re-treatment for progression was successful in 70% SF vs. 57% MF patients (P= 0.24).

Time to re-treatment:

Overall, mean time to re-treatment was 13 weeks in SF vs. 21 weeks in MF patients.

Mean pain score in the week before re-treatment was 6.8 in SF vs. 7.5 in MF patients.

Studies about treatment of spinal metastases

Observational Studies (eg. Prospective Cohort or Retrospective Cohort or Case Series)

Katagiri, H., Takahashi, M., Inagaki, J., Kobayashi, H., Sugiura, H., Yamamura, S., & Iwata, H. 1998, "Clinical results of nonsurgical treatment for spinal metastases", *International Journal of Radiation Oncology, Biology, Physics*, vol. 42, no. 5, pp. 1127-1132.

Design: Prospective cohort

Rating 2-

Country: Japan (1990-1995), setting: Hospital

Aim: to determine the extent of success attainable with currently available multimodal non-surgical treatment in patients with spinal metastases.

Inclusion criteria

Spinal metastases

Exclusion criteria

Decompression surgery preceding non-surgical treatment; patients who underwent surgery at other hospitals

Population number of patients = 101 patients; 59 men, 42 women

Mean age 61 years (range 14 to 81 years). Primary tumours: NSC lung 17%, breast 15%, prostate 11%, multiple myeloma 10%, other cancers 47%.

20% cervical spine, thoracic spine 58%, lumbar spine 60%.

Solitary lesions in 28%, multiple lesions in 72%.

Metastases detected by bone scans and radiographs, and where possible MRI and/or CT

Interventions

RT and/or chemotherapy (including anti-cancer hormone therapy) without surgical intervention.

20% patients received RT; 19% received chemotherapy; 62% received combined RT and chemotherapy. Of patients receiving RT, 93% were given a dose of 40Gy in 20 fractions over 4 weeks. All patients with neurological deficits were given corticosteroids during the first 7 days of RT.

Outcomes

Frankel classification of neurological function, pain relief, survival.

Follow up

Minimum of 24 months or until death. Mean 11 months (2 weeks to 70 months) for those who were dying; mean 53 months (24 to 81 months) for survivors.

Results

Definitions:

Frankel classification: A to E (A = complete motor and sensory loss, E normal motor and sensory function)

Patients regaining a D or E functional status considered to be good responders; those who were non-ambulatory after treatment considered to be non-responders.

Pain relief: improvement defined as disappearance or marked reduction of pain accompanied by decreases in narcotic and non-narcotic analgesic intake.

Functional status I to IV (I able to walk outdoors to IV bedridden)

Patients scoring as a good responder on all 3 scales were defined as having been treated successfully.

Response assessed within 1 month after completion of RT or 1-2 months after start of chemotherapy.

Successful treatment expressed as survival.

Endpoints defined as the time when neurological status or functional ability deteriorated, or pain recurred from any cause.

Results

For data analysis patients were divided into 2 groups according to primary tumour responsiveness to RT and/or chemotherapy.

Responsiveness group composed of 46 patients (lymphoma, breast, prostate, ovarian and small cell lung carcinomas, multiple myeloma)

Less responsiveness group composed of 55 patients (colon, hepatocellular and non-small cell lung carcinomas)

Frankel classification:

67/101 (66%) maintained or regained Frankel type D or E status and considered good responders.

Responsiveness vs less response

40/46 (87%) vs 27/55 (49%) were considered good responders P<0.001 (Chi sq)

See table

Of 54 patients with Frankel type E classification, 46 (85%) were considered good responders.

Only 21/47 (45%) of patients with neurological deficits were good responders. P<0.001

Vertebral collapse

One (1%) patient experienced vertebral collapse caused by radiation related osteonecrosis.

OUTCOME OF INTEREST	Responsiveness N=46	Less responsiveness N=55	Overall response N=101	RESULT Response v less response
Neurological deficits	15 (33%)	32 (58%)		
Frankel type D or E	40 (87%)	27 (49%)	67 (66%)	Favours responsiveness P<0.001
Pain relief	38 (83%)	30 (55%)	68 (67%)	Favours responsiveness P=0.0027
Functional status	39 (85%)	26 (47%)	65 (64%)	Favours responsiveness P<0.001
Time	6 months	12 months	24 months	
Cumulative survival rate	0.63	0.45	0.3	

(CSR)(overall)				
CSR		0.87	0.76	Resp v less
Responsiveness				resp
group				P<0.001
CSR	Less	0.42	0.16	
response				

General comments –

This study did not analyze the effects of the interventions, RT and/or chemotherapy regimes. They have split the participants into 2 groups- responders and those with less response and compared the outcomes between groups. The question is why? There was possibly no difference in response between different interventions because the intervention groups may not have been large enough (20% RT, 19% CT, 62% combined).

The study is also confounded by conducting the analysis by tumour responsiveness to RT, the findings only confirm what is probably already known, but provides a quantitative assessment of response by primary tumour type.

Zaidat, O. O. & Ruff, R. L. 2002, "Treatment of spinal epidural metastasis improves patient survival and functional state", *Neurology*, vol. 58, no. 9, pp. 1360-1366.

Design: Prospective cohort (1991-1996)

Rating 2+

Country: USA, setting: Veterans Medical Centre and community

Aim: The effects of treatment of spinal epidural metastases on ambulation, pain control, recurrence and survival.

Inclusion criteria

Back pain and history of cancer caused by spinal epidural metastases, and diagnosed by imaging of entire spine.

Exclusion criteria

Bone fragments in spinal canal requiring surgical decompression, metastatic epidural compression of cauda equine.

Population number of patients = 139 male veterans, consecutive sample

Prostate ca 55%, lung ca 37%

Ambulatory at start 60%

Solitary metastasis 81%

Mean age 68 ±3 years

Interventions

RT covering 2 vertebral bodies beyond the upper and lower borders of spinal epidural metastases. 36Gy delivered, exceptions were patients with more than one spinal epidural metastasis who received 25Gy to each site.

Co-interventions of 100mg dexamethasone IV four times daily for 2 days, then 24mg four times daily for 2 days, then decreasing doses four times daily for 2 days of 12mg, 8mg, 4mg, 2mg, 1mg, finally 1mg twice daily for 2 days.

Paracetamol offered to patients with pain scores of 4 or less. Those with intense pain offered narcotics.

Outcomes

Highest pain level experienced by patients during the prior 24 hours was recorded. Pain was assessed before treatment commenced and at end of treatment.

Ambulation.

Survival

Recurrence

Complications

Follow up

Patients followed until death. After treatment patients followed up by monthly telephone contact, and 3 monthly outpatient visits.

Results

Definitions:

Pain levels scored 0 to 10 (0 no pain, 10 unbearable pain)

Ambulatory defined as being able to walk 15 m without human assistance or stopping.

Results:

Table 2. Response of patients to treatment of spinal epidural metastases (ambulation):

* Likelihood of walking after therapy was different for patients who could walk before treatment of their spinal epidural metastases compared with non ambulatory patients ($p < 0.001$):

RR 2.09 (95%CI 1.58, 2.77)

† Likelihood of walking after treatment was different for patients with more than one spinal epidural metastasis compared with patients with one spinal epidural metastasis ($p < 0.001$):

RR 3.13 (95%CI 1.53, 6.41)

Likelihood of not walking after RT for the initially non ambulatory patients compared with the initially ambulatory patients:

RR 44.3 (95%CI 6.21, 316)

Starting treatment <12hours after loss of walking ability increased the likelihood of regaining ambulation, in comparison to starting treatment >12 hours after onset: ($P < 0.001$)

RR 6.86 (95%CI 1.81, 26.0)

Likelihood of not walking after treatment for patients with more than one spinal epidural metastasis, compared to patients with a solitary spinal epidural metastasis:

RR 3.40 (95%CI 1.36, 8.49)

Patients were more likely to be ambulatory after completion of treatment of the initial spinal epidural metastasis compared with that of the recurrent spinal epidural metastases.

RR 4.31 (95%CI 1.23, 15.2).

See Table 3 for results of Pain response

All patients reported a decrease in pain after treatment with lower pain levels in ambulatory than non ambulatory patients.

28/29 nonambulatory patients before or after treatment had reductions in pain levels of ≥ 1 on the pain scale.

Patients with spinal epidural metastases who were able to walk at completion of treatment of SEM had less pain than patients who were not able to walk after treatment

† Probabilities listed at the end of a row compare pain values before and after treatment. The probability listed beneath a column compares pain values for ambulatory and non ambulatory patients. Probabilities were determined with analysis of variance.

Recurrent spinal epidural metastases

12/139 (8.6%) of patients developed recurrent spinal epidural metastases at 65.4 ± 12.8 weeks (range 25 to 112) after completion of the initial course of RT.

Patients were less likely to be ambulatory before ($p = 0.00146$) and after ($p = 1.57 \times 10^{-6}$) treatment for recurrent spinal epidural metastases compared with the initial spinal epidural metastasis.

Bowel and bladder dysfunction

Recovery from BBD and loss of sacral sensation was more likely in ambulatory patients (see table).

Survival

Median survival was 104 weeks for patients who could walk after RT compared with 6 weeks for non-ambulatory patients ($p < 0.001$).

The median survival for ambulatory patients varied according to the type of cancer that

patients had. Patients with prostate cancer had the longest survival times with a median of 121 weeks, and patients with lung cancer had shorter survival times with a median of 80.7 weeks.

The mean interval between loss of ambulation and death was 4.0 ± 0.5 weeks. Eighty-four of 109 patients (77.1%) who were ambulatory after treatment of their spinal epidural metastases could walk within 5 weeks of death.

OUTCOME OF INTEREST	OF	INTERVENTION		RESULT
		Before	After	
Bowel and bladder dysfunction (BBD)	and	11/55 (20%) non-ambulatory	0/11 recovered	
		44/55 (80%) ambulatory	29/44 (59.1%) recovered	
			(p=0.006)	

General comments –

Author conclusions:

Patients who walked after treatment lived longer, were ambulatory for most of their remaining life, had less pain, and a lower incidence of depression.

Comments:

Population restricted to elderly males only which may limit the generalisability of the study. Time points for pain response were not clear. There may be some confounding in pain response because of the analgesics administered, especially to non-ambulatory patients.

Tombolini, V., Zurlo, A., Montagna, A., Notarianni, E., Osti, M. F., Enrici, R. M., & Pirolli, C. 1994, "Radiation therapy of spinal metastases: results with different fractionations", *Tumori*, vol. 80, no. 5, pp. 353-356.

Design: Prospective cohort

Rating 2+

Country: Italy, setting: Institute of Radiology (1991-1993)

Aim: To report the results of radiation therapy of spinal metastases using different fractionation schedules.

Inclusion criteria

Radiologically detectable spinal metastases

Exclusion criteria

Patients treated with analgesic RT for vertebral collapse. Presence of bone involvement for contiguity, evidence of pathological fracture or vertebral collapse.

Population number of patients = 95 patients, 103 spinal metastases.

54 female (57%) 41 male (43%)

Median age 51 years (range 28-82)

Primary tumours: 34 breast, 25 lung, 9 prostate, 10 kidney, 25 other ca

Interventions

Single fractions of 800cGy (n=48)

500cGy over 4 consecutive days, total dose 20Gy (n=7)

400cGy over 5 consecutive days, total dose 20Gy (n=15)

10 fractions of 300cGy for 5 days/week, total dose 30Gy (n=20)

20 fractions of 300cGy for 5 days/week, total dose 40Gy (n=13)

5 patients received multiple RT treatments

A mean depth of 7.8cm (range 6-9cm)

Outcomes Pain scale of 5 grades (no pain to intolerable)

Follow up Patients followed with a clinical examination at 1 month after RT and successively with intervals of 2-3 months. Av follow up 9 months (median 8 mths, range 4-22 mths)

Results

Since this study was included in the SR by Falkmer for evaluation of fractionation schedules, only the findings of other relevant outcomes are included here.

Vertebral collapse after RT was not observed.

General comments –

Author conclusion:

Hypofractionated and single fraction treatments showed equal efficacy compared to more prolonged therapy.

Other comments:

Patients were selected for fractionation scheduled by radiotherapist and influenced by a range of factors including metastatic site, performance status, risk of vertebral collapse and home residence.

Kida, A., Taniguchi, S., Fukuda, H., & Sakai, K. 2000, "Radiation therapy for metastatic spinal tumors", *Radiation Medicine*, vol. 18, no. 1, pp. 15-20.

Design: Retrospective case series (1986-1995)

Rating 3

Country: Japan, setting: Hospital

Aim: Evaluation of the efficacy of RT for pain relief and improvement of neurological impairment

Inclusion criteria

Symptomatic patients with spinal metastases

Exclusion criteria

Not reported

Population number of patients = 52 patients (52 lesions)

31 male (60%) 21 female (40%)

Median age 62.5 years (16-87)

Primary tumours: lung cancer 14 (27%), hepatocellular ca 8 (15%), breast cancer 5 (10%), malignant lymphoma 5 (10%), gastrointestinal ca 7 (13%), unknown origin 6 (11%)

47/52 (90%) had pain.

The 5 patients without pain had neurological impairment.

At the start of treatment 28/52 (54%) had neurological impairment.

34/52 (65%) patients had other metastatic lesions.

Interventions

Daily RT fractions were between 1.8 to 5 Gy.

Fraction size was 1.8Gy to 2.0Gy in 10 patients without neurological impairment and severe pain, and 3Gy in 28 patients with neurological impairment and 14 patients with no neurological impairment.

Total doses ranged from 20 to 51Gy, median 39Gy.

The 28 patients with neurological impairment received 45Gy (10 patients), 39Gy (16 patients), less than 39Gy (2 patients).

Median duration of treatment was 19 days.

Outcomes

Pain relief using Okawa classification (0 = no pain to 4= unendurable pain requiring narcotics). Improvement of more than 1 point considered effective. (pain relief only evaluated in irradiated painful metastases).

Neurological improvement by Frankel's classification grades A (complete paraplegia) to E (recovery). Response assessed within one month of completion of RT.

Cumulative survival.

Follow up

Pain and neurological response within one month of RT completion.

Results

Pain relief

In patients with painful metastases: 29/47 (62%)

Patients with neurological impairment 12/23 (52%)

Patients without neurological impairment 17/24 (71%)

Of 47 patients with pain:

14/29 (48%) irradiated with TDF<80 obtained relief

15/18 (83%) irradiated with TDF≥80 obtained relief

Difference was statistically significant (values not reported).

Improvement of neurological impairment

Patients with neurological impairment 7/28 (25%) improved.

Of these 7 patients, two were Frankel grade A and five were grade C before treatment.

Cumulative dose

There were no significant differences between neurological improvement and the dose delivered.

Survival rates

Overall at 6 months (18/52) 34.5%; 25.3% were neurological impairment grades A-D, 44.4% grade E

Overall at 12 months (10/52) 19.9%; 15.2% were neurological impairment grades A-D, 24.7% grade E

General comments

Author conclusions

RT was effective treatment for pain relief in patients with metastatic spinal tumours. In patients with neurological impairment less pain relief was observed than in those without neurological impairments. Improvement of neurological impairment was restricted, but radiation therapy was thought to be effective in some cases in the early stage of neurological deterioration.

RT for metastatic spinal tumours contraindicated for surgery was considered effective for improvement of patients' activities of daily living.

Comments

Although this study demonstrated that RT was effective in reducing pain and improving neurological functioning, the study was small and a range of doses were delivered. It was not reported whether any patients were using analgesics for pain relief as a co-intervention. Smaller doses were applied to patients without neurological impairments. Larger doses appeared to be more effective in providing pain relief, however this was not one of the objectives of the study, and no other data were provided about this finding.

Kraiwattanapong, C., Buranapanitkit, B., & Kiriratnikom, T. 2004, "Results of radiotherapy in non round cell spinal metastasis", *Journal of the Medical Association of Thailand*, vol. 87, no. 3, pp. 239-245.

Design: Retrospective case series (1997-2001)
Country: Thailand, setting: Hospital

Rating 3

Inclusion criteria

Tissue diagnosis of a malignant tumour not of round cell or central nervous system origin

Exclusion criteria

Insufficient follow-up of clinical data (9 patients), surgical treatment (5 patients)

Population number of patients = 31

Age 38-87 years, mean 57.2 years

Primary tumours: lung, prostate, breast, unknown

20 patients or 65% had neurological deficit at first examination, duration 40-60 days (mean 27 days)

16 patients or (52%) had multiple metastases, 15 patients had single site metastases

17 cases classified as tumoural compression, 17 cases structural compression

10 patients (32%) had concomitant bone metastases.

Interventions

Total of 30Gy in 10 doses

Dexamethasone (4mg) given every 6 hours until RT completed.

Outcomes

Neurological status (Frankel classification A-E)

Follow up

Neurological deficits evaluated at first visit (4 weeks after RT)

Results

Neurological recovery

Neurological recovery in 7 patients (23%)

2 cases recovered from Frankel C to E

2 cases recovered from Frankel D to E

2 cases recovered from Frankel C to D

1 case recovered from Frankel B to E

6/7 (86%) of these patients had tumour compression.

Pain relief

Pain improved in 24/31 (77%)

16 from the tumour group

Pain worsened in 2/17 (12%) cases from the structural group

There were no major complications from RT.

Complications included urinary tract infections in 5 cases (16%)

Multivariate analysis

The only factor associated with both neurological and pain improvement was the cause of compression.

Neurological improvement OR 0.04 (95%CI 0.00,0.58) P=0.02

Pain improvement OR 0.06 (95%CI 0.00,0.89) P=0.04

General comments*Author conclusions*

Radiotherapy remains a good treatment for patients with non round cell spinal metastases. Cause of spinal cord compression is the only factor predicting the result of treatment.

Other comments

This is a very small retrospective study. The method of assessment of pain relief was not stated. Although the title implies treatment of spinal metastases, 32% of patients had other bone metastases.

Vertebroplasty and Kyphoplasty

What is the effectiveness of Vertebroplasty/ Kyphoplasty at treating spinal pain and/or preventing spinal collapse and/or spinal cord compression?

Short Summary

Systematic reviews (Hulme *et al.* 2006 and Taylor *et al.* 2006 and 2007) and international evidence-based guidelines (Blue Cross Blue Shield Association 2005, Adelaide-Health-Technology-Assessment-on-behalf-of-MSAC 2005) provide evidence and commentary about the effectiveness and safety of both vertebroplasty and kyphoplasty for both osteoporotic and neoplastic vertebral collapse. The literature includes no controlled-comparative studies and comprises lower quality evidence from non-randomised comparative studies and several case series studies. This is the best available evidence and provides important insight into the effectiveness and safety of these procedures. The evidence suggests that vertebroplasty is an effective therapy in the management of patients with symptomatic osteoporotic vertebral compression fractures and neoplastic disease. Balloon kyphoplasty is a reasonable alternative to vertebroplasty, although this conclusion is based on evidence from biased study designs. In general, this low level evidence suggests that vertebroplasty and kyphoplasty provides pain relief, and improvement in ambulation. Adverse effects included cement leakage and was more commonly reported for vertebroplasty than for balloon kyphoplasty.

PICO

Population Group	Intervention	comparison	Outcomes
Patients with known vertebral metastases (both asymptomatic & symptomatic)	Vertebroplasty/ Kyphoplasty	<ul style="list-style-type: none">• No therapy• Radiotherapy• Chemotherapy• Bisphosphonates• DXT	<ul style="list-style-type: none">• Prevention of spinal collapse• Prevention of spinal cord compression• Improvement in pain• Quality of life or performance status• Survival

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

A number of reviews and international evidence based guidelines provided evidence about the effectiveness and safety of both vertebroplasty and kyphoplasty for both osteoporotic and neoplastic aetiologies. The literature body lacks definitive evidence of effectiveness of each of these interventions from randomised, controlled trials. There is however, considerable numbers of lower grade evidence (some non randomised comparative studies and a plethora of case series studies). This is the best available evidence and provides some insight into the effectiveness and safety of these procedures. Of this evidence body 3 systematic reviews (Hulme 2006 and Taylor 2006, 2007) of effectiveness and safety concluded “that there is level 3 evidence to support vertebroplasty as effective therapy in the management of patients with symptomatic osteoporotic vertebral compression fractures refractory to conventional medical therapy. Furthermore, the use of kyphoplasty in patients with symptomatic vertebral compression fractures from osteoporotic or neoplastic etiology was also promoted”

Guidance from other NICE publications:

NICE have Interventional Procedure guidance

Guidance exists for both Vertebroplasty and Balloon Kyphoplasty:

The guidance from these documents has been reproduced in this document. It is important to understand that evidence for Interventional Procedures is selected to provide information about safety and efficacy. The procedures were not exclusively focussed on cancer patients and included patients with osteoporosis.

GUIDANCE FOR Balloon kyphoplasty (IPG020), November 2003

Current evidence on the safety and efficacy of balloon kyphoplasty for vertebral compression fractures does not appear adequate to support the use of this procedure without special arrangements for consent and for audit or research. Although the benefits and risks of this procedure appear similar to those for percutaneous vertebroplasty in the first few months after the procedure is carried out (see IPG012), there is insufficient long-term evidence to substantiate this at present.

Clinicians wishing to undertake balloon kyphoplasty for vertebral compression fractures should inform the clinical governance leads in their Trusts. They should ensure that patients offered it understand the uncertainty about the procedure's safety and efficacy and should provide them with clear written information. Use of the Institute's Information for the Public is recommended. Clinicians should ensure that appropriate arrangements are in place for audit or research. Publication of safety and efficacy outcomes will be useful in reducing the current uncertainty. NICE is not undertaking further investigation at present.

The following are recommended:

This procedure should only be undertaken when there are arrangements for good access to a spinal surgery service, and with prior discussion between a specialist multidisciplinary team that includes a radiologist and a spinal surgeon.

Clinicians should receive training to reach an appropriate level of expertise before carrying out this procedure. In particular, they must follow the manufacturer's instructions for making the cement, to reduce the risk of embolisation.

The procedure should be limited to patients whose pain is refractory to more conservative treatment.

GUIDANCE FOR Vertebroplasty (IPG0012), September 2003

Current evidence on the safety and efficacy of percutaneous vertebroplasty appears adequate to support the use of the procedure, provided that normal arrangements are in place for consent, audit and clinical governance.

The following are recommended.

This procedure should only be undertaken when there are arrangements for good access to a spinal surgery service, and with prior discussion between a specialist multidisciplinary team that includes a radiologist and a spinal surgeon.

Clinicians should receive training to reach an appropriate level of expertise before carrying out this procedure. In particular, they must follow the manufacturer's instructions for making the cement, to reduce the risk of embolisation.

The procedure should be limited to patients whose pain is refractory to more conservative treatment.

Evidence from included studies by outcome:

Vertebroplasty

Pain:

The change in pain scores was consistent across the 3 studies included in the Blue Cross and Blue Shield Association Report, showing that mean VAS pain scores went

from 7 to 10 at baseline to 0 to 3 after the procedure; all changes from baseline were statistically significant across all studies. (The 3 studies : Alvarez *et al.* 2003, Fourney *et al.* 2003 and Chow *et al.* 2004)

In a prospective study (Shimony *et al.* 2004) 82% patients reported an improvement in pain.

From the review by Hulme *et al.* (2006); Some pain relief independent of the type of procedure was reported for 87% of patients (n = 1552, 95% CI 78% to 95%); Visual analog pain scores (VAS) (normalised to 10-point scale) were reduced: Vertebroplasty: 8.2 (n = 666, 95% CI 7.8–8.6) to 3.0 (95% CI 2.4 –3.6)

Ambulation:

Alvarez *et al.* (2003) showed that the proportion of fully ambulatory patients improved from 38% to 76%, but the study by Fourney *et al.* (2003) showed no statistically significant improvement in ambulatory status.

From the review by Hulme *et al.* (2006);

- A 16% to 47% full-scale improvement in physical function was reported (7 studies using different variants of a 5-point mobility scale)
- Between 49% and 90% of patients reported ambulation improvements in 4 studies (assessed by qualitative patient response.)
- There were 3 studies that showed improvements in physical function using a validated health-related outcome instrument: Nottingham Health Profile and Oswestry Disability Index (ODI) (preoperative 61%, postoperative 46%, n = 23 patients).

Other outcomes:

The study by Chow *et al.* (2004) reported that changes in analgesic usage were not statistically significant, and changes in nausea and depression in the Edmonton Symptom Assessment Scale were statistically significant, but specific quantitative results are not reported.

From the review by Hulme *et al.* (2006); Neurologic complications occurred in 0.6% for vertebroplasty. New vertebral fractures that occurred using vertebroplasty, 60% were adjacent to the augmented vertebra.

Adverse effects:

The adverse effects reported in these studies revealed a rate of leakage of cement ranging from 9% to 'most', with a small proportion of the patients with cement leakage having symptoms due to the leak.

From the review by Hulme *et al.* (2006); Cement leakage: 41% (n = 2283 vertebrae, 27 studies, 95% CI 32% to 50%) of vertebrae. Pulmonary emboli occurred in 0.6% of augmented vertebrae.

Kyphoplasty

Pain:

Three studies were identified (Dudeney *et al.* 2002, Lane *et al.* 2004 and Fourney *et al.* 2003) for inclusion in the Blue Cross and Blue Shield Association Report (2005).

- Dudeney 02 reports improvements in several SF-36 subscales, including physical function, pain, vitality, and
- social function.
- Fourney 03 reported improvements in pain score from a mean of 8 preoperatively to 2 postoperatively.
- Lane 04 reported improvement in the Oswestry Disability Index score from 48.94 to 32.6 at 3 months.

Review authors (Blue Cross Review 2005) note that these improvements appear to be similar to the degree of pain relief that occurs in patients with osteoporotic vertebral fractures who undergo kyphoplasty.

From the review by Hulme *et al.* (2006); Some pain relief independent of the type of procedure was present in 92% of the patients (n= 447, 95% CI 86% to 98%). Visual analog pain scores (VAS) (normalised to 10-point scale) were reduced from 7.15 (n = 183, 95% CI 6.6 –7.7) to 3.4 (95% CI 2.7– 4.1). Body pain scores increased between 22.4 and 47.1 points, while the physical function scores decreased between 17.2 and 29.3 points.

Physical Function:

- From the review by Hulme *et al.* (2006); Two studies showed improvements in disability.
- Functional status was reported to be improved in Khanna *et al* (2006).

Adverse effects:

Results from the Blue Cross and Blue Shield Association Report (2005).

- Leakage of cement occurred in 11%, 0%, and 26% in the 3 studies. None of the leaks caused symptoms.
- Fourney *et al.* 2003 reported that, over time, 14% of patients had recurrent fractures at other sites. However the absence of a control group, makes it difficult to attribute these fractures to the kyphoplasty procedure.
- Review authors (Blue Cross Review 2005) note that this is similar to the situation for kyphoplasty performed for osteoporotic fractures, the major limitation of this body of evidence is that there is no control group; thus placebo effects and natural history may account for some or all of the apparent benefits of treatment.

From the review by Hulme *et al.* (2006);cement leakage was reported in 9% of patients (n = 1486 vertebrae, 18 studies, 95% CI 2.6% to 15.8%) of vertebrae. Pulmonary emboli occurred in 0.01% of augmented vertebrae for kyphoplasty. Neurologic complications occurred in 0.03% of vertebrae for kyphoplasty.

Other Outcomes:

From the review by Hulme *et al.* (2006); 66% of new vertebral fractures that occurred were adjacent to the augmented vertebra.

Comparison of results from the 2 reviews by Taylor *et al.* (2006) and Taylor *et al.* (2007)

<p><u>Results from the review by Taylor <i>et al</i> (2006):</u> This systematic review compared vertebroplasty with balloon kyphoplasty using an indirect comparison approach.</p>	<p><u>Results from the review by Taylor <i>et al</i> (2007)</u> This systematic review updates the evidence reviewed in the previously published review (Taylor <i>et al.</i>2006) about balloon kyphoplasty (BKP) in the management of vertebral compression fractures. Prognostic factors for pain relief and cement leakage were examined using meta-regression. This updated review included more prospective comparative studies than the earlier review (Taylor <i>et al.</i>2006).</p>
<p>Population Patients:</p>	<p>Population Patients:</p>

<ul style="list-style-type: none"> • Patients with VCFs of osteoporotic or neoplastic (i.e., myeloma, metastasis, or osteolysis) aetiology. • 87% of patients in included studies had osteoporotic disease • 18% of patients in included studies had neoplastic (i.e., myeloma, metastasis, or osteolysis) <p>Studies:</p> <ul style="list-style-type: none"> • In total, 524 papers were identified; final inclusion included: For balloon kyphoplasty: 4 non randomised comparative studies, 13 case series studies For vertebroplasty: 2 non-randomised comparative studies, 57 case series studies. 	<ul style="list-style-type: none"> • Populations across the included studies were mixed populations in terms of disease type and varied across studies. • The majority of the studies included patients with osteoporosis 58%, 30% studies included mixed populations of patients with osteoporosis or neoplastic disease and 9% included only patients with neoplastic disease, one study (2%) did not report the patient indication. • The majority of studies were undertaken in older women with osteoporotic vertebral compression fractures with long-term pain that was refractory to medical treatment <p>Studies:</p> <ul style="list-style-type: none"> • 8 studies were comparative (5: BKP with vertebroplasty and 3: with conventional medical care), n= 313 patients • 35 were case series studies, n= 2047 patients • Studies were from the US or Europe. • Reporting in the included studies hindered assessment of methodological quality <p>The majority of studies used validated outcome measures the case series studies were prospective and used consecutive sampling therefore limiting the level of bias</p>
<p>Intervention: Balloon kyphoplasty or vertebroplasty used as a single therapy, or in combination with other therapies. Comparator: Any surgical or medical therapy.</p>	<p>Intervention: balloon kyphoplasty Comparator: any invasive, semi-invasive or medical treatment</p>
<p>Outcomes: Pain:</p> <ul style="list-style-type: none"> • When balloon kyphoplasty was compared with vertebroplasty, both procedures appeared to provide a similar level of pain relief after surgery (P = 0.68), although there was insufficient patients with follow up in order to comment on 1-year outcome • When the mean of pain scores were pooled from case series studies, there was a statistically significant reduction (P < 0.0001) in the pooled level of pain following both balloon kyphoplasty and vertebroplasty. <p>Functional capacity: When considering all study designs included, there was a statically significant improvement in functionality.</p>	<p>Outcomes: Pain:</p> <ul style="list-style-type: none"> • When balloon kyphoplasty was compared with medial care (3 studies): VAS pain was stat. sig. reduced with BKP, p<0.001, at 3, 6, 12 and 36 month follow up. The reductions were greater (p<0.0001) than those for the same time points with medical care alone. • For case series studies; 14 studies reported a reduction in pain after BKP (mean reduction = 5.4mmm, 95%CI 6.3—4.4mm, p<0.0001, random effects) <p>Functional Capacity: In general when considering all study designs included, there was a statically significant improvement in functionality.</p>

Quality of Life

From case series studies, a statically significant improvement in quality of life was reported.

Vertebral height

Across the 3 before and after studies, there was evidence of a significant increase in vertebral height ($P < 0.0001$) and reduction in kyphotic angle ($P < 0.0001$) following balloon kyphoplasty.

Adverse effects:

- The rates of adverse events (pulmonary embolism, neurologic complications, and perioperative mortality) were low for both procedures although poorly reported across studies.
- A significantly higher rate ($P < 0.0001$) of cement leakages was reported for vertebroplasty than balloon kyphoplasty.
- No leaks were reported to be symptomatic with balloon kyphoplasty, while some 3% of leaks with vertebroplasty were reported to be symptomatic.
- Across all studies, the pooled reported incidence of new vertebral fractures, both total and adjacent, was higher for balloon kyphoplasty than vertebroplasty, although their 95% confidence intervals overlapped.

Predictive factors

- In the multivariate analysis, no factors were found to be statistically significant predictive of the level of pain relief.
- For the outcome of the risk of cement leakage, the choice of procedure was found to be a highly significant predictor of cement leakage ($P \leq 0.0001$), the level of cement leakage being higher for vertebroplasty than balloon kyphoplasty.

- From 2 Comparative studies improvement at 6 and 12 months following BKP was reported ($p < 0.0001$). This improvement exceeded standard care at 6 months in both studies ($p < 0.001$) but was not significant at 12 months.
- After pooling different functional capacity outcomes from 4 case series studies: an improvement was observed following BKP by an average of 1.1 SD units, 95%CI 0.6-1.5, $p < 0.0001$, random effects)

BKP with Vertebroplasty:

- 3 studies reported that both BKP and Vertebroplasty reduced VAS pain and improved disability scores (Oswestry index score) up to 24 months post-procedure, however there was no sig. difference b/n the interventions.

QoL

From 5 Case series studies; (measured using the SF-36): reported significant improvements in 6 of the 8 items of the SF-36.

Safety:

Outcomes from all the studies that collected this data a total of 9% cement leakages occurred from 2239 vertebra that underwent BKP, i.e. 81 cement leakages in 1000 fractures.

Survival:

The overall mortality rate = 3.2% (author suggest that this is due to the age of the patients and cancer related disease)
From this review, authors calculated that for every 1000 patients treated with BKP;
1.7 patients may experience a PE
1.6 patients will experience SCC
1.7 patients may experience a radiculopathy
1.3 patients may die within the perioperative period (30 days)

Extra notes:

A considerable level of heterogeneity was observed when the results for pain relief and cement leakage were calculated. In order to explain this, several sub-group analyses were conducted.

Predictive factors

	<p>From a univariate analysis: When the duration of pain or fracture age were combined a significant association with BKP pain relief was observed, $p=0.047$. The longer the duration of pain or the older the fracture, the smaller the magnitude of pain relief following BKP</p> <p>From a multivariate analysis: Osteoporotic vertebral compression fractures indicated an association with a higher rate of cement leakage with BKP compared to neoplastic vertebral compression fractures (univariate: $p<0.0001$ and multivariate: $p<0.013$)</p>
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From the Taylor *et al.* (2007) review a table of current and ongoing RCTs was included and will have an important impact to this body of evidence about the effectiveness of balloon kyphoplasty. Some of the details are provided in the table below, adapted from Table 9 in Taylor *et al.* (2007):

Trial Name/ Registration (setting)	'FREE' NCT00211211 (Europe)	'CAFÉ' NCT00211237 (US/Europe)	'CEEP' NCT00279877 (US)	KAVIAR NCT00323609 (worldwide)
Intervention/ Comparator	Balloon kyphoplasty/medi cal therapy	Balloon kyphoplasty/medi cal therapy	Balloon kyphoplasty/ Vertebroplasty	Balloon kyphoplasty/ Vertebroplasty
Population	Vertebral body compression fractures (VCF) from primary or secondary osteoporosis, multiple myeloma or osteolytic metastatic tumours.	Painful VCFs in cancer patients.	Painful osteoporotic compression fractures	Painful osteoporotic compression fractures
Outcomes	QoL, pain, functional ability, vertebral height, spinal deformity, health care resources, safety, cost effectiveness	QoL, pain, ambulatory status, vertebral height, disability, safety,	QoL, pain, functional ability, health care resources, safety, cost effectiveness	Proportion with subsequent fracture, change in back pain, QoL, rate of serious adverse events, change in vertebral height, and spinal deformity. Health care resources with respect to VCFs.
Expected end date	December 2005	Not known	31 May 2007	August 2011

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EVIDENCE TABLES

Systematic Reviews Of Mixed Study Designs

Taylor, Taylor & Fritzell . Balloon kyphoplasty and vertebroplasty for vertebral compression fractures - A comparative systematic review of efficacy and safety. Spine 31[23]. 2006.

Design: systematic review (combined study designs included)

Evidence Level: ranges from 2- to 3

For **balloon kyphoplasty**: four nonrandomised comparative studies and 13 case series

For **vertebroplasty**: two nonrandomised comparative studies and 57 cases series

Aims:

1. To systematically review the efficacy and safety of balloon kyphoplasty in VCF patients;
2. To update the previous systematic review of the efficacy and safety of vertebroplasty in VCF patients;
3. To examine the prognostic factors predicting outcome after the two procedures.

Inclusion criteria

Searches were conducted from 1983 onwards until first March 2004.

Study Design. Experimental studies (i.e., randomized and nonrandomized trials), observational studies (i.e., cohort studies, case-control studies, or cross sectional studies), and uncontrolled studies (i.e., case series).

Exclusion criteria

- Studies including patients undergoing repeat interventions (balloon kyphoplasty or vertebroplasty) were excluded.
- Case reports were excluded, as were case series published only as abstracts.

Population

- Patients with VCFs of osteoporotic or neoplastic (i.e., myeloma, metastasis, or osteolysis) aetiology.
- In total, 524 papers were identified; final inclusion included:
For balloon kyphoplasty: 4 non randomised comparative studies, 13 case series studies
For vertebroplasty: 2 non-randomised comparative studies, 57 case series studies.

Interventions

Intervention: Balloon kyphoplasty or vertebroplasty used as a single therapy, or in combination with other therapies.

Comparator: Any surgical or medical therapy.

Outcomes

efficacy, pain relief, functional capacity, and health-related quality of life; safety, cement leakage, incident (adjacent and nonadjacent) fractures, complications.

Analysis:

- Where possible, the results of individual studies were combined.
- Not all studies reported on all outcomes of interest.
- Separate meta-analyses were undertaken for each procedure and outcome
- All based on random effects meta-analysis.
- Meta-regression was used to examine the influence of a number of factors on both the level of pain relief and cement leakage outcomes reported across studies. The factors were defined *a priori*.
- Heterogeneity between studies was explored by way of univariate and multivariate analysis.

Follow up

Depended on individual studies and is reported in results section.

Results**Comparative studies** (*The quality of these studies was variable*)**Pain**

- Compared with medical therapy alone, balloon kyphoplasty significantly improved patients' level of pain
 - Pre to post VAS pain (0-10mm) was reduced by 3.6mm [-3.6 (-7.0 to -0.3); P=0.03]
- In the one vertebroplasty study no difference in pain relief compared with medical therapy (P = 0.97) was reported.
- In the one study that compared balloon kyphoplasty and vertebroplasty, both procedures appeared to provide a similar level of pain relief after surgery (P = 0.68), although there was insufficient patients with follow up in order to comment on 1-year outcome.

Functionality

- Compared with medical therapy alone, balloon kyphoplasty significantly improved patients' functionality (P = 0.006)
 - Pre to post functional capacity (SD units) improved by 4.7 SD units [(8.0 to 1.4); P=0.006]
- In the one vertebroplasty study an improvement in functional capacity was observed (P=0.03).

Vertebral height

- Vertebral height (P= 0.0001) and kyphotic angle (P = 0.001) significantly improved following balloon kyphoplasty.
- The study of Kasperk *et al* reported statistically significant improvements in both vertebral height and kyphotic angle following balloon kyphoplasty (both P = 0.0001).

Quality of Life

QoL was not reported in the included comparative studies

Case series studies (*The quality of the case series studies was generally poor*)**Pain**

There was a statically significant reduction (P < 0.0001) in the pooled level of pain following both balloon kyphoplasty and vertebroplasty.

Functionality

- Following balloon kyphoplasty, statistically significant (P= 0.02) improvements in functional capacity (Oswestry Disability Score, Index of Back Function and physical activity levels) were reported.
- Only one vertebroplasty study reported to use a validated outcome tool (Oswestry Disability Index) and failed to report numerical outcomes

Quality of Life

- Of the 6 balloon kyphoplasty studies that assessed health-related quality of life, 4 used the Short-Form 36 (SF-36), with substantial (P < 0.0001) overall improvements in 6 of the 8 SF-36 domains.

- Five vertebroplasty studies reported quality of life, four using a variety of validated health-related quality of life measures, (Nottingham Health Profile; SF-36; and Tokuhashi Score).
- 3 out of the 5 reported significant ($P \leq 0.05$) improvement in quality of life following vertebroplasty while one study reported no change. Given the differences in outcomes, pooling was not possible.

Vertebral height

- Across the 3 before and after studies, there was evidence of a significant increase in vertebral height ($P < 0.0001$) and reduction in kyphotic angle ($P < 0.0001$) following balloon kyphoplasty.
- Four vertebroplasty studies reported a significant increase in vertebral height ($P < 0.0001$)
- 3 out of these 4 studies reported on a reduction in kyphotic angle.
- 3 of these 4 studies analysed the subset of fractures with “vacuums” or “clefts” resulting from bony necrosis due to pseudarthrosis or a vascular necrosis of the vertebral body. There were minimal changes in vertebral body height in vertebral bodies without clefts.

Safety Outcomes

- Safety outcomes were pooled across both comparative studies and case series.
- The rates of adverse events (pulmonary embolism, neurologic complications, and perioperative mortality) were low for both procedures although poorly reported across studies.
- A significantly higher rate ($P < 0.0001$) of cement leakages was reported for vertebroplasty (overall pooled mean = 0.46, 95% CI = 0.31 to 0.61 ($P < 0.0001$)) than balloon kyphoplasty (overall pooled mean = 0.08, 95% CI = 0.05 to 0.11 ($P < 0.0001$))
- No leaks were reported to be symptomatic with balloon kyphoplasty, while some 3% of leaks with vertebroplasty were reported to be symptomatic (0.04, 95% CI = 0 to 0.08 ($p = 0.045$))
- Across all studies, the pooled reported incidence of new vertebral fractures, both total and adjacent, was higher for balloon kyphoplasty than vertebroplasty, although their 95% confidence intervals overlapped.

Predictive factors

- In the multivariate analysis, no factors were found to be statistically significant predictive of the level of pain relief.
- For the outcome of the risk of cement leakage, the choice of procedure was found to be a highly significant predictor of cement leakage ($P \leq 0.0001$), the level of cement leakage being higher for vertebroplasty than balloon kyphoplasty.

General comments

About interventions examined:

Although not consistently reported across all studies, the majority of vertebral compression fractures would have been refractory to conventional medical treatment (mean duration of pain or mean fracture age across studies, 4–7 months).

Review Limitations:

The following points highlight the areas in which this review is flawed

Quality of studies:

The absence of RCTs in the evidence body limits what the review can report. The inclusion of case series studies provides evidence that is prone to selection bias, confounding and for retrospective studies; evidence is influenced by outcomes.

Selection bias is associated with the way the intervention or control groups were assembled.

Indirect Comparisons:

- Only one study directly compared vertebroplasty with balloon kyphoplasty, this study was of poor quality and contained considerable bias.
- The review compared outcomes from individual case series studies of vertebroplasty with outcomes from individual case series studies of balloon kyphoplasty, this is an indirect comparison.
- Authors point out “Indirect comparisons require careful interpretation as outcome differences reported between balloon kyphoplasty and vertebroplasty case series may simply reflect systematic differences between the two groups of studies such as a difference in the case-mix of patients undergoing the two procedures.”
- However, little difference in the patient case-mix between the balloon kyphoplasty and vertebroplasty case series was observed, which supports an indirect comparison of these interventions (to some extent).

Publication Bias

- Publication bias refers to the publication of only positive results and the limited publication of adverse events and negative results. This review attempted to address publication bias by sourcing and retrieving studies from a variety of sources (which may include a variety of results).
- Of note, is the observation that a higher proportion of balloon kyphoplasty case series studies (85%) reported cement leakage outcomes, than were reported by vertebroplasty cases studies (69%). Given the lack of high level evidence to compare the interventions it is unclear whether this is a true difference.

Heterogeneity

- Statistical heterogeneity describes the differences in outcomes between studies that is beyond chance.
- There was evidence of significant statistical heterogeneity across a number of outcomes.
- Potential explanations for such heterogeneity include differences between studies in: their methodological quality; the characteristics of included patients; the nature of the intervention; and the method of outcome assessment.
- Using meta-regression methods, heterogeneity was investigated further in the level of pain relief and cement leakage rate.

Authors Conclusions

There is Level III evidence to support balloon kyphoplasty and vertebroplasty as effective therapies in the management of patients with symptomatic osteoporotic vertebral compression fractures refractory to conventional medical therapy. Although there was a good ratio of benefit to harm for both procedures, balloon kyphoplasty appears to have a better short-term adverse event profile. These conclusions require confirmation by randomised controlled trials.

Other factors:

- No data about the prevention of spinal cord compression or spinal collapse was evaluated or reported in these studies.
- This review is systematic in its approach: clearly stated question, systematic and diverse literature search, clearly stated inclusion and exclusion criteria, study quality assessment, clearly defined statistical analysis. This method is high quality, however, due to the level of evidence included the grade allocated is low (evidence level 2- to 3).

- Applicability: Over 80% of patients were women of 60 years or over with osteoporotic vertebral compression fractures (VCFs). This indicates the level of evidence relevant or including MSCC patients.

Research Recommendations from authors:

Future research should address patients in whom this procedure will be most effective and addressing parameters such as time from fracture, multiple versus single fractures, and degree of kyphotic angle, and also provide data on cost-effectiveness.

Taylor, R. S., Fritzell, P. & Taylor, R. J. (2007) Balloon kyphoplasty in the management of vertebral compression fractures: an updated systematic review and meta-analysis. *European Spine Journal*, 16: 1085-1100.

Design: systematic review (Comparative studies and case series studies included)
Evidence Level: ranges from 2- to 3

Aim: This systematic review updates the evidence reviewed in the previously published review (Taylor et al 2006) about balloon kyphoplasty (BKP) in the management of vertebral compression fractures. Prognostic factors for pain relief and cement leakage were examined using meta-regression.

Inclusion criteria

Studies: Comparative studies (Randomised and non randomised trials) and observational studies (eg. case series studies)

Patients: Patients with vertebral compression fractures from osteoporotic and neoplastic disease.

Exclusion criteria

Patients with burst fractures and fractures from trauma (including balloon kyphoplasty combined with other invasive or semi-invasive interventions)

Population

Patients:

- Populations across the included studies were mixed populations in terms of disease type and varied across studies. The majority of the studies included patients with osteoporosis 58%, 30% studies included mixed populations of patients with osteoporosis or neoplastic disease and 9% included only patients with neoplastic disease, one study (2%) did not report the patient indication.
- The majority of studies were undertaken in older women with osteoporotic vertebral compression fractures with long-term pain that was refractory to medical treatment

Studies:

- 8 studies were comparative (5: BKP with vertebroplasty and 3: with conventional medical care), n= 313 patients
- 35 were case series studies, n= 2047 patients
- Studies were from the US or Europe.
- Reporting in the included studies hindered assessment of methodological quality
- The majority of studies used validated outcome measures the case series studies were prospective and used consecutive sampling therefore limiting the level of bias

Interventions

balloon kyphoplasty compared to any invasive, semi-invasive or medical treatment

Outcomes

Efficacy, pain relief, functional capacity, QoL (health related), deformity correction, safety, adverse events/complications

Mean differences were calculated for outcomes reported across different studies.

Results

Comparative Studies:

Pain:

- BKP compared to medical care (3 studies)
- VAS pain was stat. sig. reduced with BKP, $p < 0.001$, at 3, 6, 12 and 36 month follow up.
- The reductions were greater ($p < 0.0001$) than those for the same time points with medical care alone.

Functional Capacity (2 studies)

Improvement at 6 and 12 months following BKP was reported ($p < 0.0001$).

This improvement exceeded standard care at 6 months in both studies ($p < 0.001$) but was not significant at 12 months.

BKP with Vertebroplasty:

- 3 studies reported that both BKP and Vertebroplasty reduced VAS pain and improved disability scores (Oswestry index score) up to 24 months post-procedure, however there was no sig. difference b/n the interventions.

Case Series Studies:**Pain:**

14 studies reported a reduction in pain after BKP (mean reduction = 5.4mm 95% CI 6.3—4.4mm, $p < 0.0001$, random effects)

Functional capacity:

After pooling different functional capacity outcomes from 4 studies: an improvement was observed following BKP by an average of 1.1 SD units, 95%CI 0.6-1.5, $p < 0.0001$, random effects)

QoL (measured using the SF-36):

5 studies reported significant improvements in 6 of the 8 items of the SF-36.

Safety:

Outcomes from all the studies that collected this data were combined

A total of 9% cement leakages occurred from 2239 vertebra that underwent BKP, i.e. 81 cement leakages in 1000 fractures.

The overall mortality rate = 3.2% (author suggest that this is due to the age of the patients and cancer related disease)

From this review, authors calculated that for every 1000 patients treated with BKP;

1.7 patients may experience a PE

1.6 patients will experience SCC

1.7 patients may experience a radiculopathy

1.3 patients may die within the perioperative period (30 days)

A considerable level of heterogeneity was observed when the results for pain relief and cement leakage were calculated. In order to explain this, several sub-group analyses were conducted.

From a univariate analysis: When the duration of pain or fracture age were combined a significant association with BKP pain relief was observed, $p = 0.047$. The longer the duration of pain or the older the fracture, the smaller the magnitude of pain relief following BKP

From a multivariate analysis: Osteoporotic vertebral compression fractures indicated an association with a higher rate of cement leakage with BKP compared to neoplastic vertebral compression fractures (univariate: $p < 0.0001$ and multivariate: $p < 0.013$)

General comments

Overall, the main limitation with this body of evidence is the lack of unbiased studies, that is, randomised controlled studies. The RCT study design is the most appropriate way in which to evaluate an intervention. Taylor et al. 2007, do however, reported some important findings from prospective studies and case series studies that add to their earlier review. This review also described current and ongoing RCTs which will have important impact to this body of evidence of effectiveness of balloon

kyphoplasty.

References of Included Studies:

The list of included studies was provided but not reproduced in this table.

Hulme, Krebs, Ferguson & Berlemann . Vertebroplasty and kyphoplasty: a systematic review of 69 clinical studies. Spine 31[17]. 2006.

Design: systematic review (combined study designs included)

Evidence Level: ranges from 2- to 3

Aims: This review addressed the following questions:

1. Does vertebroplasty/kyphoplasty reduce patient pain? How does this compare to conservative treatment? Is pain reduction durable over the long term?
2. Does vertebroplasty/kyphoplasty restore patient function?
3. Does vertebroplasty/kyphoplasty restore the normal spinal alignment?
4. What are the complications associated with the procedures?
5. Does the incidence of augmented or adjacent vertebral fracture increase after vertebroplasty/kyphoplasty?
6. Does kyphoplasty offer a significant improvement in terms of restoration of spinal alignment, pain management, and reduction in cement leakage over traditional vertebroplasty?

Inclusion criteria (Study Design)

- Due to the lack of RCT evidence, non randomised clinical trials were included.
- No restrictions were placed on the age or gender of the patients, or the duration, localization, and type of symptoms experienced.

Included studies:

- 37 retrospective, 25 prospective, and 7 study design not reported
- Mean quality score was 17.6 ± 3.7 standard deviation (SD) (range 9–23.5) of a maximum of 29.

Exclusion criteria

Articles were excluded from further analysis for reporting no clinical outcomes (i.e. article was a review, editorial, technical, or animal study), involving techniques other than vertebroplasty/kyphoplasty, or if the study was published in a language other than English, German, French, or Spanish.

Population

Patients with primary or secondary osteoporotic vertebral compression fractures.

Interventions

Vertebroplasty

Kyphoplasty

- procedures that used polymethyl methacrylate cement.

Outcomes

Pain (VAS scores)

Physical Function

Kyphosis/Vertebral Height Correction

Complications

New Fracture rate after intervention

Follow up

Depended on individual studies. The review authors comment that follow-up data was poorly investigated and reported across the studies.

Results

Vertebroplasty studies

12 prospective, 29 retrospective, and 6 unreported

Results of 2958 patients (n = 47 studies), who underwent 4456 procedures.

Kyphoplasty studies

13 prospective, 8 retrospective, and 1 unreported

Results of 1288 patients (n= 22 studies), who underwent 1624 procedures.

Of vertebroplasty and kyphoplasty procedures, 50% and 60%, respectively, were performed within the thoracolumbar region of the spine (T11–L2 inclusive).

Pain:

- Some pain relief independent of the type of procedure:

Vertebroplasty: 87% (n = 1552, 95% CI 78% to 95%);

Kyphoplasty: 92% (n= 447, 95% CI 86% to 98%).

- Visual analog pain scores (VAS) (normalised to 10-point scale) were reduced:

Vertebroplasty: 8.2 (n = 666, 95% CI 7.8–8.6) to 3.0 (95% CI 2.4 –3.6)

Kyphoplasty: 7.15 (n = 183, 95% CI 6.6 –7.7) to 3.4 (95% CI 2.7– 4.1)

- There were 2 studies that showed SF-36 scores for kyphoplasty.

Body pain scores increased between 22.4 and 47.1 points, while the physical function scores decreased between 17.2 and 29.3 points.

The only items that did not have any statistically significant improvement were general health, role emotional, and mental health.

Physical Function:

Vertebroplasty:

- A 16% to 47% full-scale improvement in physical function was reported (7 studies using different variants of a 5-point mobility scale)
- Between 49% and 90% of patients reported ambulation improvements in 4 studies (assessed by qualitative patient response.)
- There were 3 studies that showed improvements in physical function using a validated health-related outcome instrument: Nottingham Health Profile and Oswestry Disability Index (ODI) (preoperative 61%, postoperative 46%, n = 23 patients).

Kyphoplasty

- Two kyphoplasty studies showed improvements in disability (mean ODI preoperative 60%, postoperative 32%, n = 77 patients).
- Reporting improvements in physical function was inconsistent, thus scores were not pooled.

Complications:

- Immediate complications associated with vertebroplasty and kyphoplasty were separated into 2 categories: procedural and cement leakage (ratio 5:14 kyphoplasty, 25:49 vertebroplasty).

Procedural complications: include infection, fractures of the transverse process, pedicle, sternum and ribs, and respiratory distress caused by the anesthetic.

Cement leakage:

- Vertebroplasty: 41% (n = 2283 vertebrae, 27 studies, 95% CI 32% to 50%) of vertebrae
- Kyphoplasty: 9% (n = 1486 vertebrae, 18 studies, 95% CI 2.6% to 15.8%) of vertebrae
- Most leaks were clinically asymptomatic.

Serious adverse effects:

- Pulmonary emboli occurred in 0.6% of augmented vertebrae for vertebroplasty and 0.01% of augmented vertebrae for kyphoplasty.
- Neurologic complications occurred in 0.6% for vertebroplasty and 0.03% of vertebrae for kyphoplasty.

New Fracture Rate After Vertebroplasty or Kyphoplasty

- 17 vertebroplasty (n = 933 subjects) clinical trials that reported new fractures.
- Of new vertebral fractures using vertebroplasty (n = 120 fractures, 12 studies) 60% were adjacent to the augmented vertebra.
- 12 kyphoplasty (n = 766 subjects) clinical trials that reported new fractures
- Of new vertebral fractures using kyphoplasty (n = 115 fracture, 9 studies), 66% were adjacent to the augmented vertebra.

General comments

Bias involved with case series studies:

To reduce potential confounding factors, included studies were limited to subject populations that had more than 80% primary or secondary osteoporotic vertebral compression fractures and procedures that used polymethyl methacrylate cement.

The most prominent limitation of this review is the inclusion of case series studies and lack of randomised, controlled studies. A flaw of the evidence body rather than the review itself.

Case series studies will always provide low grade evidence for an effectiveness of treatment clinical question. They do not use a control group to make direct comparisons from, the patient inclusion criteria is inconsistent and lacking and fracture definition used deficient and prevents definitive conclusions to be made.

Applicability:

Approximately 50% of the studies definitively evaluated Vertebroplasty and Kyphoplasty in osteoporotic patients. It is assumed that the other proportion of studies included a case mix of neoplastic and osteoporotic patients. No study reported the outcomes of only neoplastic patients.

Limitation associated with the review.

Publication bias may be present with the searches of the evidence limited to 3 databases.

Pooling of means of case series studies is problematic as the inclusion criteria of patients into studies will vary (that is, studies may have different primary tumours or more severe disease status).

Percutaneous Kyphoplasty for Vertebral Fractures Caused by Osteoporosis or Malignancy.

Assessment Program Volume 20, No. 7 August 2005

Blue Cross and Blue Shield Association.

Design: Prospective case series, evidence level: 3

Developed in the US

Inclusion criteria

Patients who have painful vertebral fractures associated with osteolytic destruction from malignant disease (e.g., bone metastasis).

The review methodology (inclusion criteria for studies) :

- Full-length article published in the English language
- Population consists of patients with vertebral fractures due to osteoporosis or malignancy
- Patient population is a consecutive series of patients, or near-consecutive series ($\geq 90\%$)
- Treatment uses kyphoplasty
- Reports on relevant clinical outcomes of pain, functional status, or quality of life
- Pre- and post-procedure values for outcomes are reported, as quantitative or categorical measures
- Sample size of ≥ 10 for malignancy

Abstracts were not systematically included in the study selection process, and results of case series reported in abstract form only are not included in the Assessment.

Status updates and abstract reports for comparative clinical trials were sought and summarised in this Assessment.

Search terms were described in detail, the only limit was that only Medline was searched, other databases were not included.

Exclusion criteria

This procedure does not include patients with evidence of spinal cord compression or compromise.

Population

Patients who have painful vertebral fractures associated with osteolytic destruction from malignant disease (e.g., bone metastasis).

Interventions

1. What are the effects of kyphoplasty (KP) on health outcomes for patients who have painful vertebral fractures associated with osteolytic destruction from malignant disease?

2. How do the outcomes of kyphoplasty compare with outcomes of alternative treatments?

Kyphoplasty is a recent variation of percutaneous vertebroplasty PV. This procedure uses a specialised bone tamp with an inflatable balloon to expand a collapsed vertebral body as close as possible to its natural height. The vertebral body then undergoes mechanical fixation by injecting Polymethyl methacrylate (PMMA) into the expanded cavity. The expansion of a cavity by the balloon tamp permits infusion of PMMA into the cavity under lower pressure than PMMA injection during PV.

Outcomes

The primary health outcomes of interest include pain and ability to function (particularly with regard to activities of daily living)

Beneficial effects of treatment would include reduction in pain and increased ability to function, which is primarily achieved through decreased pain and increased mobility.

Although kyphosis is improved among some patients undergoing KP, this is an intermediate outcome unless actual health outcomes result from this improvement.

Follow up

3 to 7.4 months

Results

Three studies were identified and met the inclusion criteria reporting a outcomes for 52 patients with osteolytic destruction from malignant disease, Dudeney *et al.* 2002, Lane *et al.* 2004 and Fourney *et al.* 2003.

Summary of results:

Two of the studies (Dudeney *et al.* 2002 and Lane *et al.* 2004) included only patients with multiple myeloma. Each of the studies reports a different set of outcomes.

Pain:

Dudeney *et al.* 2002 reports improvements in several SF-36 subscales, including physical function, pain, vitality, and social function.

Fourney *et al.* 2003 reported improvements in pain score from a mean of 8 preoperatively to 2 postoperatively.

Lane *et al.* 2004 reported improvement in the Oswestry Disability Index score from 48.94 to 32.6 at 3 months.

Review authors note that these improvements appear to be similar to the degree of pain relief that occurs in patients with osteoporotic vertebral fractures who undergo kyphoplasty.

NOTE: In the study by Fourney *et al.* 2003 the patient populations were substantially different, patients with more severe fractures receiving balloon kyphoplasty. This means that considerable bias particularly in terms of confounding and selection bias was present, given the non-identical ways in which patients were allocated to procedure or control.

Adverse effects:

Leakage of cement occurred in 11%, 0%, and 26% in the 3 studies. None of the leaks caused symptoms.

Fourney *et al.* 2003 reported that, over time, 14% of patients had recurrent fractures at other sites. However the absence of a control group, makes it difficult to attribute these fractures to the kyphoplasty procedure.

Review authors note “this is similar to the situation for kyphoplasty performed for osteoporotic fractures, the major limitation of this body of evidence is that there is no control group; thus placebo effects and natural history may account for some or all of the apparent benefits of treatment.”

Included studies in this review:

Dudeney S, Lieberman IH, Reinhardt M-K, et al. (2002). Kyphoplasty in the treatment

of osteolytic vertebral compression fractures as a result of multiple myeloma. J Clin Oncol, 20:2382-7.

Fourney DR, Schomer DF, Nader R et al. (2003). Percutaneous vertebroplasty and kyphoplasty for painful vertebral body fractures in cancer patients. J Neurosurg Spine, 98:21-30.

Lane JM, Hong R, Koob J et al. (2004). Kyphoplasty enhances function and structural alignment in multiple myeloma. Clin Orthop, (426):49-53.

General comments

This report by the Blue Cross Blue Shield Association of America was the most up to date and relevant document found about kyphoplasty.

The methods were systematic and clearly described. It provides a thorough evaluation of the effectiveness of vertebroplasty in patients with cancer, for pain management, improvement in QoL, ambulation. Survival was not evaluated but deaths reported. Adverse effects were also reported.

No data about the prevention of spinal cord compression or spinal collapse was evaluated or reported in these studies.

Percutaneous Vertebroplasty for Vertebral Fractures Caused by Osteoporosis or Malignancy.

Assessment Program Volume 20, No. 6 August 2005

Blue Cross and Blue Shield Association.

Design: Prospective case series (therapy), evidence level: 3

Country: United States

Inclusion criteria

Patients who have painful vertebral fractures associated with osteolytic destruction from malignant disease (e.g., bone metastasis).

The review methodology (inclusion criteria for studies):

- Full-length article published in the English language
- Population consists of patients with vertebral fractures due to osteoporosis or malignancy
- Patient population is a consecutive series of patients, or near-consecutive series (.90%)
- Treatment uses percutaneous vertebroplasty with PMMA
- Reports on relevant clinical outcomes of pain, functional status, or quality of life
- Pre- and post-procedure values for outcomes are reported, as quantitative or categorical measures
- Sample size is ≥ 10 for malignancy

Search terms were described in detail, the only limit was that only Medline was searched, other databases were not included.

Exclusion criteria

This procedure does not include patients with evidence of spinal cord compression or compromise.

Population

Patients who have painful vertebral fractures associated with osteolytic destruction from malignant disease (e.g., bone metastasis).

Interventions

This Assessment evaluates the available evidence to determine whether percutaneous vertebroplasty (PVP) is demonstrated to be an effective treatment for vertebral fractures caused by osteoporosis or malignancy. This table reports outcomes for patients with a malignancy.

Percutaneous vertebroplasty is a minimally invasive treatment involving percutaneous needle injection of bone cement into a diseased vertebral body. The cement is polymethyl methacrylate (PMMA).

Outcomes

The primary health outcomes of interest include pain and ability to function (primarily achieved through decreased pain and increased mobility)

Follow up

Ranged from 3 months to 4.5 months.

Results

Three studies evaluating a total of 70 patients were included in the review. (Alvarez *et al* 2003, Fourney *et al.*2003 and Chow *et al* 2004)

Summary of results:

All patients had severe pain unresponsive to conservative management. All studies evaluated pain relief using VAS both before and after the procedure. However,

evaluating the duration of benefit in these patients is problematic because of their very short remaining life span and due to other treatments being performed such as radiation that may alleviate pain.

In all of the studies, there were substantial losses to follow-up due to death as early as 1 month after the procedure.

Pain:

The change in pain scores was consistent across the 3 studies, showing that mean VAS pain scores went from 7 to 10 at baseline to 0 to 3 after the procedure; all changes from baseline were statistically significant across all studies.

Ambulation:

Alvarez *et al.* (2003) showed that the proportion of fully ambulatory patients improved from 38% to 76%, but the study by Fourney *et al.* (2003) showed no statistically significant improvement in ambulatory status.

Other outcomes:

The study by Chow *et al.* (2004) reported that changes in analgesic usage were not statistically significant, and changes in nausea and depression in the Edmonton Symptom Assessment Scale were statistically significant, but specific quantitative results are not reported.

Adverse effects:

The adverse effects reported in these studies revealed a rate of leakage of cement ranging from 9% to 'most', with a small proportion of the patients with cement leakage having symptoms due to the leak.

Included studies references:

Alvarez L, Perez-Higueras A, Quinones D *et al.* (2003). *Vertebroplasty in the treatment of vertebral tumors: postprocedural outcome and quality of life. Eur Spine J*, 12:356-60.

Chow E, Holden L, Danjoux C *et al.* (2004). *Successful salvage using percutaneous vertebroplasty in cancer patients with painful spinal metastases or osteoporotic compression fractures. Radiother Oncol*, 70:265-7.

Fourney DR, Schomer DF, Nader R *et al.* (2003). *Percutaneous vertebroplasty and kyphoplasty for painful vertebral body fractures in cancer patients. J Neurosurg Spine*, 98:21-30.

General comments

This report by the Blue Cross Blue Shield Association of America was the most up to date and relevant document found about vertebroplasty.

The methods were systematic and clearly described. It provides a thorough evaluation of the effectiveness of vertebroplasty in patients with cancer, for pain management, improvement in QoL, ambulation. Survival was not evaluated but deaths reported. Adverse effects were also reported.

No data about the prevention of spinal cord compression or spinal collapse was evaluated or reported in these studies.

Vertebroplasty and kyphoplasty for the treatment of vertebral compression fracture 2005.

Adelaide Health Technology Assessment (on behalf of The Medical Service Advisory Committee (of Australia))

Summary Statement:

- The review by MSAC included a mixed patient group (people with osteoporosis or vertebral malignancies).
- All results were combined for each outcome making it difficult to separate results only about people with vertebral malignancies. Therefore individual studies that included the patient group of interest are presented below.
- The studies included in this MSAC review also appeared in the Blue Cross reviews and they are presented again.

For vertebroplasty:

- Studies with a patient group (with metastatic neoplastic vertebral disease) $n \geq 30$ are presented (therefore the number of studies = 5)
- Outcomes for studies with $n \geq 30$:
 - Adverse effects only
 - Pain reduction was reported by studies that included a patient group $n \leq 10$ and are therefore not presented in this table. In general terms, from the evidence these studies ($n = 3$) reported a statically significantly pain improvement.
 - Functional Status was reported by one study that included a patient group ≤ 10 and are therefore not presented in this table. Briefly, at 6 weeks post – op, a stat significant improved change in functional status was reported.

For Kyphoplasty:

Studies included in the MSAC review including patient groups with metastatic neoplastic vertebral disease = 8. The sample number of these studies ranged from 4 to 80. Only 1 study (Khanna *et al* 2004) included a patient group = 80, the rest were ≤ 19 .

The Khanna *et al* 2004 study included in the MSAC review was only an abstract and since the review it has been updated and reported in full. This update is Khanna 2006 and is reported separately.

From the studies that had a sample number of ≤ 19 , an overview of outcomes reported include:

- Rates of cement leakage ranged from 2.7 to 26.3%
- A range of adverse effects (including peri-operative or post-operative myocardial infarctions), the occurrence of such serious effects were very low, $< 2\%$.
- An increase in vertebral height, improvement in pain, functional status and quality of life were reported.

Refs for included MSAC Report:

Cohen, J.E., Lylyk, P., Ceratto, R., Kaplan, L., Umansky, F. & Gomori, J.M. (2004), 'Percutaneous vertebroplasty: technique and results in 192 procedures', *Neurological Research*, 26, 41–49.

Cotten, A., Dewatre, F., Cortet, B., Assaker, R., Leblond, D., Duquesnoy, B., Chastanet, P. & Clarisse, J. (1996), 'Percutaneous vertebroplasty for osteolytic metastases and myeloma: effects of the percentage of lesion filling and the leakage of methyl methacrylate at clinical follow-up', *Radiology*, 200, 525–530.

Deramond, H., Depriester, C., Galibert, P. & Legars, D. (1998), 'Percutaneous vertebroplasty with polymethylmethacrylate: technique, indications and results',

Radiologic Clinics of North America, 36, 533–546.

Gangi, A., Guth, S., Imbert, J.P., Marin, H. & Dietemann, J.L. (2003), 'Percutaneous vertebroplasty: indications, technique and results', Radiographics, 23, e10.

Gangi, A., Kastler, B.A. & Dietemann, J.-L. (1994), 'Percutaneous vertebroplasty guided by a combination of CT and fluoroscopy', American Journal of Neuroradiology, 15, 83–86.

Gangi, A., Wong, L.L.S., Guth, S. & Dietemann, J.-L. (2002), 'Percutaneous vertebroplasty: indications, technique, and results', Seminars in Interventional Radiology, 19, 265–270.

Hodler, J., Peck, D. & Gilula, L.A. (2003), 'Midterm outcome after vertebroplasty: predictive value of technical and patient-related factors', Radiology, 227, 662–668.

Khanna, A.J., Reinhardt, M.K., Togawa, D., Stefancin, J., Holman, P. & Lieberman, I. (2004), 73, 'Clinical and functional outcomes of kyphoplasty for vertebral compression fractures', In: Proceedings of the North American Spine Society 19th Annual Meeting, North American Spine Society, Chicago, Illinois.

General comments:

Overall Evidence Level for this guideline, 4 (based on the level of evidence included). However, using the AGREE Instrument to grade the quality of this guideline, is of very high quality. Several components of the AGREE Instrument were clearly addressed. And Included:

1. The overall objective(s) of the guideline should be specifically described.
2. The clinical question(s) covered by the guideline should be specifically described.
3. The patients to whom the guideline is meant to apply should be specifically described.

Stakeholder involvement

4. The guideline development group should include individuals from all the relevant professional groups.

Rigour of development

8. Systematic methods should be used to search for evidence.
9. The criteria for selecting the evidence should be clearly described.
10. The methods used for formulating the recommendations should be clearly described.
11. The health benefits, side effects and risks should be considered in formulating the recommendations.
12. There should be an explicit link between the recommendations and the supporting evidence.
13. The guideline should be externally reviewed by experts prior to publication.

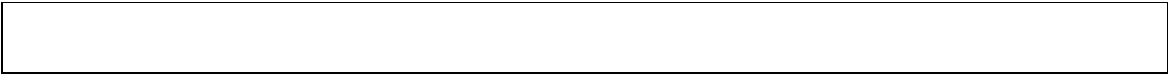
Clarity and presentation

15. The recommendations should be specific and unambiguous.
16. The different options for diagnosis and/or treatment of the condition should be clearly presented.
17. Key recommendations should be easily identifiable.
20. The potential cost implications of applying the recommendations should be considered.

Editorial Independence

22. The guideline should be editorially independent from the funding body.
23. Conflicts of interest of guideline development members should be recorded

Searches: conducted from 1987 to 2004 and included several established medical databases and other sources of evidence that included grey literature.



Prospective cohort study

Shimony, Gilula, Zeller & Brown . Percutaneous vertebroplasty for malignant compression fractures with epidural involvement. Radiology 232[3]. 2004.

Design: Prospective cohort study, evidence level: 2-, conducted in the US

Inclusion criteria

Patients were candidates for PVP if their pain was intractable and related to vertebral body destruction without neurologic symptoms related to compression of the spinal cord or nerve roots.

Patients were divided into 3 groups:

group 1: no epidural involvement and provided a comparison as a control group with the more severely affected groups

group 2: mild epidural involvement but no contact with the spinal cord or nerve roots on the basis of findings at cross-sectional imaging

group 3: moderate epidural involvement, with contact between the tumour and the spinal cord or nerve roots. For patients who had involvement of more than one level, the grading was based on the worst (highest grade) level.

Exclusion criteria

Exclusion criteria included symptomatic spinal cord compression other than local pain, noncorrectable bleeding diathesis, and unstable posterior element fractures.

Population

number of patients = 50.

Interventions

To evaluate safety and effectiveness of performance of percutaneous vertebroplasty (PVP) in patients with malignant compression fractures and involvement of the epidural space. PMMA was used as the bone cement.

Outcomes

Pain level (pre and post PVP):

using a visual pain intensity scale method to assess their pain level on a scale of 0 to 10, with 0 being no pain and 10 indicating the worst pain. When phone calls were made, the visual component was not used only the scale from 1 to 10.

Level of Activity:

Patient activity level and mobility in performance of day-to-day tasks, (including moving around the house, personal care activity, and meal preparation) measures about change or improvement were recorded.

For evaluation of the activity level, the best mobility level that the patients reported in any of the interviews following the procedure, since most patients reported decreased activity was used and mobility level at the last follow-up during the terminal stage of their disease.

Rate and description of Complications:

The safety of the procedure was evaluated by noting any acute post-PVP symptomatic complications and their treatment. Asymptomatic local complications such as leakage of PMMA outside of the vertebral body were not counted for the purposes of this study.

Outcomes were assessed for change in pain level, mobility, and activity, after PVP,

with a follow-up telephone questionnaire.

Follow up

The Follow up calls were made after the procedure at 1 day; 2 weeks; 1, 3, and 6 months; and 1 and 2 years

Results

group 1: n=14 patients

group 2: n= 18

group 3: n= 18

Pain:

A total of 41 (82%) with pain improvement was reported; among all patients, 18 (36%) had complete resolution of pre-PVP pain, 23 (46%) had some pain improvement, 6 (12%) of the patients had no change in pain level 3 (6%) reported increased pain.

Two of the three who reported increased pain after PVP had periods of improvement at earlier follow-up calls and reported increased pain, which may have been related to disease progression, only at their most recent follow-up.

No statistically significant difference between the groups (asymptotic confidence level, $P = 0.46$) using the singly ordered Kruskal-Wallis test.

Mobility and activity level:

Overall, 26 (52%) patients reported improved mobility and activity after PVP (many of these patients had decreased mobility during the advanced stage of their disease near the end of their lives.)

19 (38%) reported no change in mobility

5 (10%) had decreased mobility

Authors note that it is likely that the decreased mobility in these patients was caused by disease progression rather than by the procedure, since all reported some immediate pain relief, with later deterioration.

The three groups were compared with the singly ordered Kruskal-Wallis test, and there was no statistically significant difference between the groups (asymptotic confidence level, $P = 0.25$)

Complications:

Acute or sub-acute complications from the procedure included increased pain or new areas of pain in seven (14%) of 50 patients. None of these required surgery.

0 were in group 1,

3 were in group 2,

4 were in group 3.

A comparison of the number of patients with complications with the number of those without complications among the three groups with the Chi squared test demonstrated no statistically significant difference among the groups ($P = 0.18$).

This was probably due to the small numbers involved.

There were no complications from infection, bleeding, pulmonary embolism, stroke, or cardiac arrest.

General comments

Prevention of spinal cord compression or spinal collapse was not evaluated.

Low sample numbers hindered confidence in stating that PVP is associated with pain relief and increased mobility. However, given the broader body of evidence this study consistently reports similar findings about pain relief and improvement in mobility.

Khanna, Reinhardt, Togawa & Lieberman . Functional outcomes of kyphoplasty for the treatment of osteoporotic and osteolytic vertebral compression fractures. Osteoporos. Int 17[6]. 2006.

Design: prospective case series. 3

Setting: secondary care

Country: US

Inclusion criteria

Patients who had painful osteoporotic or osteolytic vertebral compression fractures.

Exclusion criteria

not stated

Population

211 patients had complete pre-operative and post-operative data.

155 had osteoporosis

56 had multiple myeloma (MM)

Mean age: 69.4 years

Interventions

Kyphoplasty (standard technique – no further details provided)

Patients completed SF-36 and ODI questionnaire pre-op and post-op follow-up visits.

Outcomes

Functional status using:

- SF-36 (included emotional, pain, physical function, social function mental health, and general health sub scores) and
- Oswestry Disability Index (ODI): where a decrease in the ODI is associated with an improvement in functional outcomes.

Changes in pre-op and post-op scores were analysed using the Student T-test.

Follow up

Short-term (3-12 weeks)

Long term (>24 months)

Median follow-up was 12.8 months for MM patients

67.2% of patients were included in the final follow-up.

25 patients were not included due to death.

Results

A statistically significant improvement was reported for: standardised physical component summary, physical functioning, physical-role, pain, vitality, social functioning, mental health and ODI scores (all significant at $p < 0.001$)

General comments

Attrition rate was low: difficult to avoid when the patient population is as unwell and frail as the one included in this study.

Follow-up times included wide variation, making it difficult to assess precisely the respective outcomes.

A comparative randomised study would be ideal to evaluate this intervention compared to no kyphoplasty.

Concluding remarks from authors: Kyphoplasty provided a safe and effective treatment for pain and disability in patients with vertebral compression fractures

secondary to osteoporosis and multiple myeloma. In addition, we found no statistically significant difference with regard to functional outcome between patients with osteoporosis and multiple myeloma.

Retrospective Case Series Studies

Anselmetti, G. & Giovanni Corrao, P. D. M. (2007) Pain Relief Following Percutaneous Vertebroplasty: Results of a Series of 283 Consecutive Patients Treated in a Single Institution. *Cardio Vascular and Interventional Radiology*, 30: 441-447.

Design: Case series study, Evidence level 3

Aim: The aim of this study was to assess if percutaneous vertebroplasty (PVP) could relieve back pain, reduce drug consumption, and improve the mobility of patients with metastases and vertebral compression fractures.

Inclusion criteria

Exclusion criteria

Population

283 patients (50 patients or 17.6% with bone metastases) underwent PVP on 749 vertebrae.

Interventions

Percutaneous Vertebroplasty with polymethyl methacrylate or non acrylic cement.

Outcomes

Pain: evaluated with the pain intensity numeric rating scale (PI-NRS) (0 = no pain; 10 = worst pain) before the procedure and at the end point in September 2004 (follow-up: 1-24 months; median: 7 months) - A reduction of at least two points of the PI-NRS score was considered clinically relevant.

Follow-up

12 months

Results

204 patients were available for evaluation at the end point.
36 had metastatic spinal disease

- Overall results indicated a reduction of the median pain score from 8 at baseline to 1 at the end point ($p < 0.0001$).
- When the sample was divided into subgroups, which included, the cause of vertebral injury (osteoporosis, metastases and other causes), the reduction of the median pain score from baseline to end point was not significantly different, $p = 0.2512$. This was also the case for subgroups such as age, number of fractured or treated vertebrae, and length of follow-up.
- A clinically relevant pain reduction, equivalent to a raw change in PI-NRS score ≤ -2 was observed in 176/205 patients (86%).
- 89/147 patients (61%) gave up a brace support ($p < 0.0001$);
- 117/190 patients (62%) gave up drug therapy.

General comments

Author's conclusions: This study adds evidence that PVP is effective in treating painful vertebral fractures. A significant reduction in drug assumption and significant mobility improvement can also be achieved.

Limitations of the study include the non comparative nature of PV with other comparable procedures. The case series study design means that there will be patient selection biases involved as well as the retrospective approach to collecting data (i.e. patients had to recall their pain responses).

Barragan-Campos, H. M., Vallee, J. N., Lo, D., Cormier, E., Jean, B., Rose, M., Astagneau, P. & Chiras, J. (2006) Percutaneous vertebroplasty for spinal metastases: Complications 298. *Radiology*, 238: 354-362.

Design: Case series, Evidence Level 3

Aim: To retrospectively evaluate complications of percutaneous vertebroplasty (PV) performed with polymethylmethacrylate cement to treat pain in patients with metastases to the spine.

Inclusion criteria

Patients with cancer involving spinal metastases. Spinal metastases included osteolytic, osteoblastic, and mixed lesions.

Exclusion criteria

Patients in whom PV was not suitable

Population

117 patients (38 men [32.5%] and 79 women [67.5%]; mean age, 58.2 years) underwent 159 fluoroscopy-guided PV procedures to treat 304 vertebrae.

Interventions

- Complications were characterized as local or systemic.

Outcomes

Complications were considered early if appearing within 24 hours of PV or late if occurring up to 30 days after PV.

- Technical incidents: Leaks and punctures
- Local complications: as a consequence of cement-related irritation, compression and/or ischemia, and/or needle-induced trauma, radicular pain, neurological deficit, increased pain (at treated site)
- Systemic complications: such as pain in treated vertebra, radicular pain, PE and death

χ^2 or Fisher exact testing was performed for univariate analysis of variables.

Follow Up

- Patients were examined 30 days after the PV
- Clinical complications were evaluated during and after the PV by the same anaesthesiologist. Technical incidents were assessed by the surgeon who performed the PV procedure.

Results

- The primary cancers were breast cancers (45.3%), lung cancers (14.5%), myeloma (7.7%), or other cancers (32.5%).
- T12 was the most treated vertebrae
- The mean duration of hospitalisation was 2.64 days +/-5.4 days.

Technical incidents:

- The anterior or lateral cortex was ruptured in 27 (8.9%) of the vertebra and the posterior wall was ruptured in 107 (35.2%).
- Among the 423 cement leakages identified, 332 (78.5%) were vascular and 91 (21.5%) were nonvascular. Vascular leaks were classified as venous epidural leaks, paravertebral and foraminal plexus leaks, and leaks to the vena cava, while nonvascular leaks included puncture trajectory leaks, paravertebral soft tissue leaks, and discal leaks.

Complications:

- Patients with nonvascular leaks were asymptomatic.
- Eight (6.8%) patients experienced complications, and seven of these complications were symptomatic.
- Among these eight patients, six (5.1%) had local complications (puncture site hematoma in two patients and radicular pain (successfully treated with non-steroidal anti-inflammatory drugs or corticosteroids) in four patients), and two (1.7%) had systemic complications (pulmonary embolism resulting from cement migration through the vena cava). One of the latter patients died.
- Overall, at 30 days after the PV the per procedure and pre-patient morbidity rates were 5.0% (8 out of 159 PV) and 6.8% (8 out of 117 patients) and one death (mortality rate = 0.6%; 1 out of 159 procedures)
- Univariate analyses revealed a significant association between cement migration through the vena cava and pulmonary embolism ($P = 0.001$) but not between foraminal venous leakage and radicular pain ($P = 0.123$).

General comments

Author's Conclusion: "Despite numerous technical incidents (leaks), PV-induced complications were rare, leading to the hypothesis that systemic complications are a consequence of intravascular leakage while local complications are a consequence of cement-related irritation, compression and/or ischemia, and/or needle-induced trauma"

Limitations of the study include the non comparative nature of PV with other comparable procedures. The case series study design means that there will be patient selection biases involved as well as the retrospective approach to collecting data. Nevertheless this study provided some information about the occurrences of complications at one Centre that conducts regular PV procedures.

Health Economic Evaluation

The combined literature search for all the sub-sections of this topic identified 1,532 potentially relevant papers. Twenty-five papers were retrieved and reviewed however none specifically examined the cost-effectiveness of treatments to prevent spinal collapse / MSCC in people with known vertebral metastases. No de novo modelling was undertaken because there was judged to be insufficient clinical evidence establishing a link between treatment and the prevention of spinal collapse / MSCC.

Surgery

Short Summary

The best available evidence about the effectiveness of stabilisation surgery was drawn from retrospective case series studies (Hirabayashi *et al.*2003; Holman *et al.*2005; Jansson *et al.*2006 ; Sundaresan *et al.* 2002; Vrionis *et al.* 2003; Weigel *et al.*1999; Wise *et al.*1999). The results of the studies consistently showed an improvement in pain, functional and ambulation status. Increased survival was associated with tumour types (more favourable types included: breast, kidney, bone marrow, prostate, myeloma or thyroid) and by younger age (Hirabayshi *et al.* 2003; Sundaresan *et al.* 2002), Decreased survival was reported for patients with extra skeletal metastases. The most commonly reported complication was wound infection.

PICO

Population Group	Intervention	comparison	Outcomes
Patients with known vertebral metastases (inc both asymptomatic & symptomatic)	Stabilisation surgery (Intra-lesional debulking)	+/-Intra-lesional debulking to prevent cord compromise	<ul style="list-style-type: none">• Prevention of spinal collapse• Prevention of spinal cord compression• Improvement in pain• Quality of life or performance status• Survival

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

The best available evidence about the effectiveness of stabilisation surgery was drawn from retrospective case series studies (Hirabayashi *et al.*2003; Holman *et al.*2005; Jansson *et al.*2006 ; Sundaresan *et al.* 2002; Vrionis *et al.* 2003; Weigel *et al.*1999; Wise *et al.*1999). The outcomes of these case series studies are presented below.

Pain: Five studies (Hirabayshi *et al.* 2003, Holman *et al.* 2005, Sundaresan *et al.* 2002, Vrionis *et al.* 2003 and Weigel *et al.* 1999) evaluated pain post-operatively; the percentage range of patients that experienced an improvement in pain was 77 - 95%.

Neurological / Functional Status:

- The Frankel Classification was used consistently throughout the studies.
- Ambulation of patients post-operatively from all the studies ranged from 70 to 100%
- Regaining ambulation (after a pre-operative non-ambulatory status) across all studies ranged from 79 to 96%
- An increase in Frankel scores, across included studies, was reported as occurring in 58 to 70% of the study populations
- A decrease in Frankel scores, reported from 2 studies, occurred in \leq 5% of the study populations

From Hirabayshi *et al.* (2003) the following correlations were reported:

- The ambulation time for patients with favourable primary sites was significantly longer than for patients with unfavourable primary sites ($P < 0.0001$). Where favourable sites included: bone marrow, prostate or thyroid.
- For all patients who were able to walk after surgery; significant correlations were found between ambulation time and survival time ($n=33$, $r=0.987$; $P < 0.0001$) was observed.
- For patients with metastatic disease from liver cancer who were able to walk after surgery ($n=9$, $r=0.995$; $P < 0.05$)
- For patients with lung primaries ($n=5$, $r=0.991$; $P < 0.05$)

Survival:

Overall average survival after surgery ranged from 10.6 to 30 months

Associated Factors:

- Univariate analysis demonstrated (Hirabayshi *et al.* 2003) that the site of the primary cancer, postoperative ambulation, and combined adjuvant therapy (chemotherapy and radiotherapy) were associated with prolonged survival.
- Survival was affected by tumour types (more favourable types included: breast, kidney, bone marrow, prostate, myeloma or thyroid) (Hirabayshi *et al.* 2003, Sundaresan *et al.* 2002)
- Longer survival was affected by younger age (Hirabayshi *et al.* 2003, Sundaresan *et al.* 2002)
- Decreased survival was reported for patients with extra skeletal metastases. (Jansson *et al.* 2006 and Weigel *et al.* 1999)
- Lower Frankel scores (less ambulation), pre-operatively indicated a decrease in survival post operatively compared to those who were ambulatory (Holman *et al.* 2005).

Complications:

- Complication rate ranged from 5 to 40% from included studies.
- Most commonly reported complication was wound infection (in Sundaresan *et al.* (2002), 40% of patients with prior RT experienced infections)
- In Wise *et al.* (1999) it was reported that:
 - the higher Frankel grade was associated with an increased risk of complication ($P < 0.05$)
 - when Harrington classifications involving neurologic deficits were present the statistically higher the complication rate ($p < 0.05$)

References

Hirabayashi H, Ebara S, Kinoshita T, Yuzawa Y, Nakamura I, Takahashi J, Kamimura M, Ohtsuka K, Takaoka K (2003) Clinical outcome and survival after palliative surgery for spinal metastases - Palliative surgery in spinal metastases. *Cancer* 97, 476-484.

Holman PJ, Suki D, McCutcheon I, Wolinsky JP, Rhines LD, Gokaslan ZL (2005) Surgical management of metastatic disease of the lumbar spine: experience with 139 patients. *Journal of Neurosurgery-Spine* 2, 550-563.

Jansson KA, Bauer HCF (2006) Survival, complications and outcome in 282 patients operated for neurological deficit due to thoracic or lumbar spinal metastases. *European Spine Journal* 15, 196-202.

Sundaresan N, Rothman A, Manhart K, Kelliher K (2002) Surgery for solitary metastases of the spine - Rationale and results of treatment. *Spine* 27, 1802-1806.

Vrionis FD, Small J (2003) Surgical management of metastatic spinal neoplasms. *Neurosurgical Focus* 15, E12.

Weigel B, Maghsudi M, Neumann C, Kretschmer R, Muller FJ, Nerlich M (1999) *Surgical management of symptomatic spinal metastases - Postoperative outcome and quality of life. Spine* 24, 2240-2246.

Wise JJ, Fischgrund JS, Herkowitz HN, Montgomery D, Kurz LT (1999) Complication, survival rates, and risk factors of surgery for metastatic disease of the spine. *Spine* 24, 1943-1951

EVIDENCE TABLE

Retrospective case series

Hirabayashi H, Ebara S, Kinoshita T, Yuzawa Y, Nakamura I, Takahashi J, Kamimura M, Ohtsuka K, Takaoka K (2003) Clinical outcome and survival after palliative surgery for spinal metastases - Palliative surgery in spinal metastases. *Cancer* 97, 476-484.

Design: Retrospective case series (therapy), evidence level: 3

Country: Japan, setting: Secondary care

Inclusion criteria

Medical records of 107 patients with spinal metastases surgically treated at the Department of Orthopaedic Surgery, Shinshu University School of Medicine, Nagano, Japan

Exclusion criteria

26 patients were unavailable for follow-up review and were excluded from the study.

Population

number of patients = 81

median age of patients at the time of the operation was 59.9 years

Interventions

To examine the effect of surgery for spinal mets.

Surgery included tumour resection and decompression of the spinal cord via an anterior or posterior approach, with or without subsequent stabilisation.

Outcomes

- Overall survival: determined from the date of surgery to death or date of last follow-up
- Factors evaluated as survival variables were:
 - age at surgical treatment,
 - gender,
 - site of primary tumour,
 - presence of distant mets
 - pre and post – operative ambulation
 - urinary disturbance
 - treatment for primary tumour b/f surgery
- Quality of life: Ambulation time was an additional objective variable used for assessment of QOL in patients with postoperative ambulation and was defined as the interval after surgical treatment until walking became impossible.
- Neurological Status: using the Frankel grading system.
- Pain Change (using the Grades of the World Health Organisation classification)

Univariate analysis used the Kaplan–Meier method combined with log rank statistical analysis to test for group differences in survival. Multivariate analysis used the Cox proportional hazards model for variables that had been identified as significant by univariate analysis. The Mann–Whitney U test was used to assess histology and

improvement of ambulatory status after surgery. Spearman P correlation coefficients (r) and regression equations were used to assess ambulation time and survival. Statistical significance was set at a P value < 0.05.

Follow up

- Follow-up data were obtained through routine postoperative clinic visits, letter

surveys, or telephone calls.

- Median observation period of 38.6 months (range, 12.2–96.2 months)

Results

Neurological Status:

- 31 patients were ambulatory preoperatively (Frankel Grade D or E)
- 50 were nonambulatory (Frankel Grade A, B, or C), 27 of whom regained ambulatory ability after surgery
- Of the 31 patients who were ambulatory preoperatively, 1 patient lost the ability to walk after surgery because of carcinomatous pleurisy.
- Overall, 57 of 81 (70%) patients were ambulatory after surgery.
- Authors note: These neurologic outcome data confirmed that failure to ambulate was related specifically to spine issues.

Pain:

- Spinal pain (back pain, radiating pain, or both) was reported in 63 (79%) patients before surgery.

Pre-operatively	Post-operatively
33% reported severe pain	57% reported major relief of pain (two grades)
67% moderate pain	20% reported moderate pain relief (one grade)
	23% reported no change

- Spinal pain and/or paralysis returned in 17 patients because of recurrent or new local spinal metastases.
- Eleven re-operations were performed for nine of these patients who could medically tolerate the procedures
- Re-operation was no longer indicated for the eight remaining patients because local tumor recurrence was a pre-terminal event accompanied by progressive paraplegia.
- Paraplegia ultimately developed in 14 patients (17%) as a result of recurrent (10 patients) or new metastatic spinal disease (4 patients). For these 14 patients, the primary tumor sites were the kidney (5 patients), the breast (3), the GI tract (2), and other sites (4).
- On average, paraplegia developed within 8.4 months (range, 2–37 months) after surgery.
- Survival after onset of recurrent paraplegia was only 3.4 months (range, 0.5–9 months).

Factors affecting survival:

- The median survival duration of all patients was 10.6 months.
- Patients with myeloma, thyroid carcinoma, or prostate carcinoma had significantly longer survival periods than patients with primary tumors in the esophagus, liver, lung, or pancreas ($P < 0.05$)
- Univariate analysis demonstrated that the site of the primary cancer, postoperative ambulation, and combined adjuvant therapy (chemotherapy and radiotherapy) were associated with prolonged survival.

- Age, gender, treatment for the primary malignancy before spinal surgery, preoperative ambulation, preoperative urinary disturbance, synchronous distant metastases, and single adjuvant therapy (chemotherapy or RT alone) did not have a statically significant affect on survival rates.
- Multivariate analysis of the factors associated with significant differences in survival showed that favorable primary sites (bone marrow, prostate, or thyroid) and postoperative ambulation were factors that indicated a significant association with prolonged survival.
- Relative hazards for favorable primary sites was 6.926 (95%CI 3.295 to14.559, $p<0.0001$) and postoperative ambulation was 3.589(95%CI 2.073 to 7.185, $p<0.0001$).

Survival for ambulatory patients (n=57) was significantly longer (median survival of 14.7 months) than for nonambulatory patients (n=24, median survival of 3.6 months) in general, and specifically for patients with prostate, liver, and lung cancer.

Ambulation Status:

- Follow up of the 57 post-op ambulatory was available in 46 patients; overall median survival was 16.5 months (range, 2–106 months) and for ambulation was 13.8 months (range, 0.5–105 months).
- For the 21 patients who were non ambulatory preoperatively the overall median survival was 17.8 months (range, 1.9–106.2 months) and for ambulation was 16.2 months (range, 0.5–105.6 months).
- For the 25 patients who were ambulatory preoperatively the overall median survival was 15.1 months (range, 3.4–81.1 months) and for ambulation was 13.6 months (range, 1.9–77.1 months). No significant differences were noted in survival or ambulation time between the two groups.
- The overall median survival of patients who were non ambulatory postoperatively was 3.6 months (range, 0.5–96 months).
- Thirteen patients were still alive and able to walk after a median observation period of 34.0 months (range, 11.3–78.2 months).
- The remaining 33 patients had died by that time. Their median survival after surgery was 13.0 months (range, 2–106 months) and their median postoperative ambulatory time was 7.0 months (range, 0.5–105 months).
- The longest ambulation time was observed for patients with myeloma (median, 44.1 months) and prostate cancer (22.6 months), followed by patients with carcinoma of the thyroid (21.4 months), lung (14.0 months), and liver (7.9 months).
- Ambulation time for patients with myeloma, thyroid and prostate cancer was significantly longer than that for patients with primary tumors of the liver ($P<0.05$).
- The ambulation time for patients with favourable primary sites was significantly longer than for patients with unfavourable primary sites ($P<0.0001$). Where favourable sites included: bone marrow, prostate or thyroid.

- For all patients who were able to walk after surgery; significant correlations were found between ambulation time and survival time (n=33, r=0.987; P<0.0001) was observed.
 - For patients with metastatic disease from liver cancer who were able to walk after surgery (n=9, r=0.995; P<0.05)
 - For patients with lung primaries (n=5, r=0.991; P<0.05)
- When the correlation coefficient (r) = 1, this represents a strong possible positive relationship.

General comments

The anatomic site of primary cancer and postoperative ambulation were associated with longer survival after palliative surgery for metastatic spinal tumor. If ambulation is present after surgery, it can be preserved until late in remaining life even when the primary tumor is unfavorable. Palliative surgery for spinal metastasis can improve the quality and quantity of life.

Holman PJ, Suki D, McCutcheon I, Wolinsky JP, Rhines LD, Gokaslan ZL (2005) Surgical management of metastatic disease of the lumbar spine: experience with 139 patients. Journal of Neurosurgery-Spine 2, 550-563.

Design: Retrospective case series (therapy), evidence level: 3
Country:US, setting: Secondary care

Inclusion criteria

Patients with suspected metastatic disease exclusively involving the lumbar spine or thoracolumbar junction.

Exclusion criteria

Not stated

Population

139 patients, 166 procedures were performed.
85 males, 54 females, mean age = 55 years
Patients with suspected metastatic disease exclusively involving the lumbar spine or thoracolumbar junction.

Interventions

The approach was selected on the level involved, the distribution of the tumour within anterior, middle and posterior columns and patient's general health.

- Posterior approach with supplemented posterior fixation
- Trans pedicular fixation
- Decortication (of posterior elements) supplemented with allograft.
- Luque rods/rectangles and Galveston rods
- PMMA cement for column reconstruction

Pre-operative data was collected : neurological examination, pain assessment, spinal imaging

Post-operative data collected: serial post-op neuro exams conducted, pain assessment

Outcomes

- neurological function: Frankel Score
- pain assessment: VAS scores
- complications
- survival

Follow up

Evaluations occurred 1, 3, 6 and 12 months post-op.

Results

Neurological function:

Pre-op Frankel Grade	Post-op Frankel Grade (no. of cases)				
	A	B	C	D	E
A					
B					
C			8	26	5
D			4	54	15
E			1	2	23

Of the 112 patients with neural deficits:

- 41% improved at least 1 Frankel grade
 - 18% regained normal neurological function
 - 39 patients could not walk pre-op, 31 (79%) regained the ambulation.
 - 5% of patients were reported as decreasing at least one Frankel grade post operatively
 - Less than 5% became non ambulatory post operatively.
-
- When patients were stratified by operation approach, the Frankel scores were significantly different from pre-op to 1 month post-op. ($p < 0.05$, Wilcoxon signed-rank test)

Pain:

- 133 patients presented with severe pre-op pain.
- Median VAS-pain scores ($n=83$) pre-op, decreased from 7 to 2 (at 1 month) post-op ($p < 0.001$)
 - 40 % reported complete resolution,
 - 54% reported partial improvement.
- In 5% of patients no change in pain scores was reported
- Deterioration in pain was reported by one patient.

Post operative complications:

- 32% of patients experienced a complication.
- In general, these complications included: wound infection, cerebrospinal fluid leakage with and without infection and epidural hematoma.
- Major complications included: acute renal failure, pneumonia, acute respiratory distress syndrome, and bacterial/fungal sepsis.

Survival:

- Median survival rate for all patients included in this study was 14.8 months.
- Survival estimates based on pre-op Frankel grade showed that Frankel grade C was associated with a significant decrease in survival compared with ambulatory groups ($p=0.02$)
- Survival was significantly affected by pre-op weakness ($p=0.01$)
- The presence of extra-spinal metastatic disease strongly correlated with decreased survival ($p=0.002$)

Jansson KA, Bauer HCF (2006) Survival, complications and outcome in 282 patients operated for neurological deficit due to thoracic or lumbar spinal metastases. *European Spine Journal* 15, 196-202.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
 Country: Sweden
 setting: secondary care

Inclusion criteria

a consecutive series of patients operated for spinal metastases from January 1990 to December 2001.

Exclusion criteria -

Population –

282 patients operated for spinal metastases

Interventions

- laminectomy
- posterior stabilisation
- anterior stabilisation

This study reviewed the outcomes of spinal surgical cases in terms of survival, neurological function and complications.

Outcomes

- survival estimated (calculated using Kaplan-Meier curves)
- neurological function, (assessed using FRANKEL classification: 2 weeks post-operatively, then 3, 6, 12 and 24 months)
- complications

Follow up

3, 6, 12 and 24 months after surgery

Results

40% of patients were a primary tumour of the prostate
 15% of patients were a primary tumour of the breast
 some of the other primaries included: kidney, lung, myeloma, colon and GI (usually less than 8 %).

Neurological Function (Frankel Classification):

278 of 282 patients could be assessed post-operatively.

2 week post operatively:

Pre-op status	Post-op status
23 patients with normal motor function pre-op (Frankel E)	23 patients maintained Frankel E
255 with motor deficits	<ul style="list-style-type: none"> ▪ 12 patients worsened post-op ▪ 179 (out of 255) improved at least one Frankel grade
Among 144 who were non-walkers but retained some motor function (Frankel C),	100 could walk (Frankel D-E) at discharge
26 patients had no motor function (Frankel A – B)	10 regained sufficient neurological function to walk during follow-up

Follow-up results:

Frankel Classification	Post-operative : At 3 months	Post-operative : 6 months	Post-operative : 1 year	Post-operative : 2 years
A	3%	3	4	5
B	3	2	1	2
C	14	12	7	7
D	27	22	21	19
E	53	61	67	67
Number alive	166	125	71	43

Survival:

- Of 282 patients, 37 died within 30 days of surgery.
- The 30 day mortality rate was not related to the extent of metastatic disease.
- At 3 months follow-up the survival rate of patients with non-skeletal mets was 0.53
- At 3 months follow-up the survival rate of patients with solitary skeletal mets was 0.81
- The 2 year follow-up survival rate for those with multiple skeletal mets was 0.16
- The 2 year follow-up survival rate for those with solitary skeletal mets was 0.36
- Survival was not related to sex or age.
- Patients who had anterior procedures had a higher survival at 1 and 2 year follow-up than patients who had a procedure from the posterior approach.

Rate of survival	Follow-up Time
0.63	3 months
0.47	6
0.30	12
0.16	24

- Post op survival was not related to pre-op neurological function
- 1 year survival rate was 0.33 for patients who could walk pre-operatively (Frankel D-E) compared to 0.26 for patients who could not (Frankel A-C).

Complications:

- 60 complications in 56 of the 282 (20%) patients were reported.
- 34 wound infections were recorded with 9 requiring operations for wound revision.
- Other complications (affecting 5 or less patients) included: hematoma, wound dehiscence, dural tear, pleural exudate (anterior approach), wrong level decompressed and misplaced screw/hook.

General comments

- Prevention of MSCC: not evaluated. However, could Frankel grades (A, B) be used as a surrogate measure?
- The limits of this study include the lack of a comparative group and biased evaluation.

Sundaresan N, Rothman A, Manhart K, Kelliher K (2002) Surgery for solitary metastases of the spine - Rationale and results of treatment. Spine 27, 1802-1806.

Design: Retrospective case series, evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria

80 consecutive patients with the radiological diagnosis of solitary spinal lesion who underwent surgery for metastatic cancer.

40 patients (50%) had received previous radiation therapy to the operated spinal level. The most common fractionation schedule was 3000 cGy in 200- to 300-cGy fractions over 2 to 3 weeks. All these patients had failed radiation therapy, showing progressive tumour on radiographic studies and neurologic deterioration caused by the tumour. The remaining 40 patients had been referred for surgery because of clinical symptoms and the solitary nature of the tumour.

Exclusion criteria -

Population

number of patients = 80, mean age = 56 years.

Interventions

To assess the effectiveness of surgical treatment of patients who have solitary sites of spine involvement with associated cord compression.

The goal of surgery was 'gross total resection' of the tumour and achievement of spinal stability by instrumentation and fusion.

Techniques of resection included:

- 'en bloc'
- Intra-lesional

Outcomes

- Pain was assessed by using a visual analogue scale with a range from 0 to 10. This was further graded into mild pain (0 to 4), moderate pain (5 to 7), and severe pain (8 to 10).
- Neurologic status was graded on a modified ASIA 14 or Frankel scale. The pre-surgical grade included :
Grades E (36 patients),
D (12 patients),
C (13 patients),
B (19 patients),
A (0 patients).
- Pain relief
- Complications
- Overall survival: Postoperative survival data were computed using Kaplan-Meier curves and comparisons between subgroups were performed using Chi squared analysis.
- Clinical follow-up evaluation was complete in all the patients, and in most patients the cause of death was clearly established. The incidence of local recurrences and systemic relapses were determined, as well as the causes of death.

Follow up

Patients were observed closely until death, or for a minimum of 2 years.

Results

Survival :

Overall median survival was 30 months, with 18% of the patients alive at 5 years.

- The difference in survival was considerable among patients with the various tumour types.
- The longest median and long-term survival was observed for patients with breast and kidney cancer.
- There were no long-term survivors in patients with gastrointestinal cancer or with cancer of an unknown primary site.

- More younger patients were long-term survivors.
- Among the 23 patients younger than 50 years, the 5-year survival rate was 25%.
- Among the remaining 57 patients age 50 years or older, there were 9 (16%) 5-year survivors.
- The long-term term survivors were equally distributed between those with synchronous and those with metachronous presentation of their malignancy.

Neurological Outcomes:

- Of the 36 patients (45%) graded Frankel E, all remained intact.
- Of the 12 patients graded as Frankel D, 6 became neurologically intact postoperatively, whereas 5 retained their overall status.
- One patient lost a Frankel grade, reaching Grade C.
- All the patients with neurologic Grade C improved to grade D.
- Improvement was noted in all the 19 preoperative Grade B patients.
- One patient improved to Grade C, 16 to Grade D, and 2 to Grade E

Pain:

- 52 out of 55 (95%) who presented with pain, demonstrated an improvement.
- Relief was complete in 42 (76%) of the patients
- Incomplete in the remaining 10 patients.
- All forms of pain including mechanical back (instability) pain, tumor-related pain, and radicular pain improved after surgery.

Complications:

40 patients who underwent de novo surgery:

- Complications developed in six patients (15%),
- Complications included excessive bleeding from hypervascular tumors in three patients, wound infection in one patient, loosening of an anterior screw in one patient, and a superficial hematoma requiring drainage in one patient.

Of the 40 patients who had received prior radiation therapy

- 16 (40%) experienced complications,
- Complications included:
 - 10 patients with wound breakdowns,
 - 1 patient with excessive bleeding,
 - 3 patients with instrumentation failures,
 - 1 patient with deep vein thrombosis,
 - 1 patient with radiation-related dysphagia.
 - One of the three patients with instrumentation failure lost a Frankel grade after revision surgery.

- All the wound complications requiring revision surgery occurred in irradiated patients.
- The difference in complication rates between irradiated and non-irradiated patients was statistically significant ($P < 0.03$) – Chi Squared Analysis.

- The factor most responsible for the higher complication rate was the marked increase in wound breakdown and infections in the previously irradiated patients.
- One 30-day mortality occurred in this series: noted as being due to respiratory failure after successfully undergoing surgery for a solitary metastasis to the thoracic spine.

General comments

The study spanned an 11-year period, during which surgical concepts, techniques, and instrumentation were evolving. This could effect the applicability when informing current practice.

The lack of a comparator group makes it difficult to make an unbiased conclusion about the effects of spinal surgery.

Vrionis FD, Small J (2003) Surgical management of metastatic spinal neoplasms. Neurosurgical Focus 15, E12.

Design: Retrospective case series (therapy), evidence level: 3
Country:, setting: Secondary care

Inclusion criteria

Patients with metastatic spine tumours.

Exclusion criteria

Patients with chordomas, primary bone tumors, and non metastatic lesions were excluded

Population

number of patients = 96

Interventions

96 patients with metastatic spine tumors underwent a total of 108 operations
56 male and 40 female patients with a mean age of 53 years

Preoperative evaluation included a neurological examination, MR imaging, and plain x-ray films.

Indications for surgery included evidence of spinal instability (kyphosis, subluxation, or retropulsed bone fragment); evidence of tumour progression (radiographically, clinically, or both) despite previous radiotherapy; neurological deterioration during radiotherapy; medically intractable pain; rapid development of neurological compromise or myelopathy; lack of tissue diagnosis; or radiation-resistant tumour (melanoma, sarcoma, or renal carcinoma).

Procedures included:

- 'en bloc' resection
- Three main approaches have been used in the treatment of metastatic spine tumors: 1) laminectomy; 2) costotransversectomy; and 3) thoracotomy
- Types of Reconstruction:
 - Anterior Reconstruction (with a variety of grafts (autologous or allografts) depending on the size of the defect (fibula, tibia, femoral ring) and goal of fusion. Vascularized fibula, vascularized rib grafts, or a combination of allograft and autograft can also be used)
 - Posterior Reconstruction. With posterior reconstruction, screws (through the pedicles or lateral masses) are preferable to hooks.

Outcomes

- Neurological function
- Pain
- Ambulatory status
- Complications

Follow up

12 months

Results

All patients presented with pain, and 40% exhibited symptoms or signs of myelopathy.

Spinal stabilisation was performed in 71 patients (74%). All but two patients with myelopathy improved neurologically.

Neurological function

No neurological deficits attributable to the surgery itself were reported.

Pain

Pain improved in all but five patients (95%). Pain that did not improve was caused by new metastatic lesions involving a different part of the spine or skeletal system.

Ambulatory status

- Ambulatory status was maintained for at least 3 months post-surgery in 88 (91.6%) of 96 patients.
- At a mean follow-up time of 12 months, 46 (48%) of 96 patients were alive.

Complications

- 5 infections (5.2%) were reported: All patients with infections had previously undergone radiation therapy, and two had undergone previous embolizations.
- All infections occurred after operations performed via a posterior (laminectomy) approach.
- 2 patients had a CSF leak.
- 3 patients (3.1%) had evidence of delayed hardware failure;
- 2 of the 3 required additional revision surgery.
- 1 patient died of a pulmonary embolism in the immediate postoperative period.
- 3 more patients died within 4 weeks after surgery (total 4.1% mortality rate) because of tumor progression.

General comments

Author's conclusions: Surgery is indicated in a select group of patients with metastatic tumors to the spine. A multidisciplinary approach is recommended for patient selection and complication avoidance. Surgical options, including approach, type of reconstruction and extent of resection (including en bloc spondylectomy) need to be addressed for optimal outcomes.

A team consisting of a neurosurgeon and/or an orthopedic spine surgeon/radiation and medical oncologist, pain specialist, thoracic, and plastic surgeon is important for patient selection, tumor access, and ultimate avoidance of complications

Weigel B, Maghsudi M, Neumann C, Kretschmer R, Muller FJ, Nerlich M (1999) Surgical management of symptomatic spinal metastases - Postoperative outcome and quality of life. Spine 24, 2240-2246.

Design: Retrospective case series (therapy), evidence level: 3
Country: Germany, setting: Secondary care

Inclusion criteria

76 patients underwent a total of 86 surgical interventions for symptomatic spinal metastases

Exclusion criteria -

Population

number of patients = 76, mean age = 59 years.

Interventions

The aim of this study was to report on the authors' experience with surgery of spinal metastases and to evaluate surgical outcome and the quality of life of these patients.

Outcomes

- Performance status (Karnofsky score)
- Neurological function (Frankel score)
- Pain (a scale ranging from no pain to mild, moderate, or severe pain. For subjective assessment of the overall results of surgery, the patient or his or her next of kin were asked to select from among the options 1) very satisfied, 2) satisfied, 3) acceptable, or 4) dissatisfied)
- QoL (the time the patient lived at home after spinal surgery, when no further hospitalization for chemotherapy, radiotherapy, rehabilitation, or re interventions was required.)
- Complications
- Survival (represented by Kaplan-Meier curves)

Follow up –

720 days

Results

Neurological function

Neurologic improvement by at least one Frankel grade was observed in 26 of 45 cases (58%) with neurologic deficits:

16 of 26 cases (62%) after anterior surgery,

4 of 8 (50%) after dorsal surgery

5 of 11 (45%) after combined intervention

14 of 20 (70%) non ambulatory patients (Frankel B/C) became ambulatory again (Frankel D).

4 patients experienced segmental sensory loss after surgery; these patients showed deterioration from Frankel Grade E to D.

Overall, 93% of patients were able to walk after surgery.

Pain:

Pain before surgery	Pain after surgery
Spinal pain (back pain and/or radicular pain) was present in all patients before surgery	60% reported much improved pain relief

76% of patients, back pain and/or radicular pain was severe	29% reported moderate improvement
24% it was moderate	11% reported no change
	No patient reported worsening of pain.
	Spinal pain relief was permanent, returning only in patients in whom local tumour recurrence or new metastatic spinal disease developed.

Complications:

- Paraplegia ultimately developed in 18% of patients. Local tumour recurrence occurred in 10 patients and 4 new metastatic spinal disease reported as causing the paraplegia.
- On average, paraplegia developed within 8.4 months with survival after the onset being 3.4 months (ranging from 0.5 to 9 months).
- There were no cases of intraoperative mortality, but two deaths occurred in the immediate postoperative period:
 - One patient died of cardiac infarction 2 days after surgery,
 - One patient died of respiratory failure 7 days after surgery.
- 16 of 86 (19%) surgical interventions were connected with one (12 interventions) or two (4) complications. The most commonly experienced complication was neurological deterioration.

Survival:

Mean postoperative survival time was 13.1 months.

The Kaplan and Meier curve indicates:

- 49% of the patients survived for more than 6 months,
- 24% for more than 1 year,
- 8% for more than 2 years after spinal surgery.

Statistical analysis showed that the length of postoperative survival after initial surgical intervention was significantly associated with an additional two factors:

1. patients younger than 60 years survived significantly longer (P= 0.028) than the patients older than 60 years (20.1 months vs. 6.2 months)
2. patients with no evidence of extra skeletal metastases at initial surgery survived significantly longer (P< 0.0001) than patients with extra skeletal metastases (23.5 months vs. 5.8 months).

Performance Status:

The average postoperative general state of health of all 76 patients was 55% on the Karnofsky Index.

A Karnofsky Index of 10–40% as indicative of a poor state of general health	33% of patients
A Karnofsky Index of 50–70% as indicative of a moderate state	42%
A Karnofsky Index of 80%–90% as reflecting a good state of general health (no patient in this study scored 100%)	25%

The respective survival rates differed statistically significantly (P< 0.0001).

Prevention of SCC:

Not evaluated.

General comments –

The lack of a comparator group makes it difficult to conclude a robust association

between surgery and outcomes listed. The small sample size also affects this conclusion.

Wise JJ, Fischgrund JS, Herkowitz HN, Montgomery D, Kurz LT (1999)
Complication, survival rates, and risk factors of surgery for metastatic disease of the spine. Spine 24, 1943-1951.

Design: Retrospective case series (therapy), evidence level:
Country: United States, setting: Secondary care

Inclusion criteria

80 consecutive patients in whom metastatic disease of the spine was managed operatively.

Surgery was performed in patients with metastatic cancer of the spine who had progressive neurologic deficit before, during, or after radiation therapy; intractable pain unresponsive to conservative treatment; for histologic diagnosis; for a radio resistant tumour; or for spinal instability or vertebral collapse, with or without neurologic deficit.

Exclusion criteria -

Population

number of patients = 80, 38 men and 42 women,
Mean age = 55.6 years

The most common sites of primary tumour were breast, lung, bone marrow, lymph nodes, prostate, and kidney. The site of the primary tumour was identified in all patients except five who had metastatic adenocarcinoma of unknown primary origin.

Interventions

- This study aimed to determine the surgical complication and survival rates of patients with metastatic disease of the spine and risk factors for complication occurrence.
- Surgical approach (anterior, posterior, or combined), procedure (corpectomy, decompression, debulking),
- 88 surgical procedures were performed:
 - 74 patients had a single operation,
 - 5 had primary surgery for metastatic disease of the spine followed by a second operation for noncontiguous metastasis,
 - 1 underwent three additional procedures because of nonunion of an attempted fusion.
 - others were lost to follow up and their surgical procedure was not described.

Outcomes

- Complications (description, rate and interms of the neurological function):
*Early complications were those occurring within the first 30 days after surgery.
Late complications occurred more than 1 month after the initial surgery.
Complications were then assigned to major and minor categories: Major complications were defined as those that significantly altered the expected hospital course (i.e., those requiring unexpected operative intervention or non routine critical care or causing death). Minor complications were defined as those that did not substantially alter hospital course (i.e., urinary tract infection, cellulitis, ileus).*

- Survival

Follow up

The study reviewed cases from January 1993, to December 1996. Follow-up for all patients was performed until November 1997, or time of death.

Results

Complications:

- Overall, complications occurred after 22 of the 88 procedures. Some procedures had multiple postoperative complications.
- If complication rates were calculated by the number of patients, then complications occurred in 20 (25%) of the 80 patients, leaving 60 (75%) with no complications.
- In the 22 procedures 35 postoperative complications occurred:
 - 18 were classified as major (most common were postoperative wound infection and minor urinary tract infection)
 - 17 as minor
 - 27 of the complications occurred in the early postoperative period
 - 8 occurred more than 1 month after surgery but were directly attributable to the surgery.
- There were five deaths that resulted from surgical complications, for a surgical mortality rate of 5.7%

For Harrington Classification

- The occurrence of complications was correlated to the Harrington classification.
- Overall, patients with a higher Harrington classification and neurologic deficits had a higher complication rate.
- The rates of complications, both major and minor, were statistically higher for Harrington classifications involving neurologic deficits ($P < 0.05$).

For Frankel Grade

- Preoperative Frankel grade was also correlated with the occurrence of complications.
- A higher Frankel grade was associated with an increased risk of complication ($P < 0.05$). The small number of patients in the lower Frankel classes affects the statistical association.

Survival:

- Survival time after the diagnosis of primary cancer for all patients averaged 48.8 months (range 4–227 months),
- Survival time after the diagnosis of spinal metastases was 26.0 months (range, 1–107.25 months).

(These times are greater than the amount of time in the study period, because patients were enrolled in the study based on the operative date and not the date of diagnosis)

- The average survival time after surgery of 15.9 months (range, 0.25–55.5 months) reflects the end of the follow-up period November 1, 1997.

(if patients were alive on this date, the date was used as the end point for follow-up. Thus, the follow-up period for these 38 patients may have been longer and thus improved the results, but data past the end of the study period were not included)

- Patients with myeloma survived the longest after diagnosis of spinal metastases—an average of 40.3 months and 28.7 months after surgery.
- Those with adenocarcinoma of unknown primary origin had the shortest

postoperative survival, averaging 5.6 months.

General comments

- Non comparative group prevents clear association between outcomes and intervention being concluded.
- Small sample number also prevents the findings of this study to a wider population.

6.3 Care of the threatened spinal cord in patients with MSCC

Corticosteroids

Short Summary

Evidence for this question comes from a mixture of low quality randomised controlled trials and observational studies. The comparisons evaluated in the studies included: high dose dexamethasone (96 mg) versus no steroidal treatment (Sorenson *et al.* 1994); high dose dexamethasone (100 mg) versus 10 mg dexamethasone as an adjunct to radiotherapy (Vecht *et al.* 1989); high-dose (96mg) versus 16 mg daily (Heimdal *et al.* 1992); and 96 mg versus 16 mg dexamethasone (Graham *et al.* 2006)

Overall there is a limited body of evidence to conclusively report an advantage of high dose corticosteroid dose over a lower dose. There is insufficient evidence of effect of high versus low dose of dexamethasone, as well as high dose versus no steroids and the evidence is lacking for low versus no steroids. Ambulation was an outcome reported across the studies, with some improvement indicated (though not statistically significantly different) for patients on higher doses of dexamethasone (96 or 100mg). With higher doses of dexamethasone, a higher rate of adverse events was consistently reported.

PICO

Population Group	Intervention	Comparison	Outcomes
Patients with suspected/confirmed MSCC <ul style="list-style-type: none">• Pre-treatment• Post-treatment• No treatment	Steroid regimen for pts at presentation (dose, duration and route)	No Steroid	Preserve or improve mobility at presentation Neurology Duration of effect Toxicity

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

Five studies were included for this question, 2 phase III studies, 1 phase II study and 2 observational studies. High dose dexamethasone (a bolus of 96 mg intravenously, followed by 96 mg orally for 3 days and then tapered in 10 days, as an adjunct to radiotherapy) versus no steroidal treatment (Sorenson *et al.* 1994). Initial high dose of dexamethasone (100 mg iv bolus) versus conventional dose dexamethasone (10 mg iv bolus) as an adjunct to radiotherapy (Vecht *et al.* 1989). High-dose (96mg iv bolus tapered in 14 days, as an adjunct to radiotherapy) versus 16 mg daily, in 4 divided iv doses, tapered in 14 days (conventional dose group) (Heimdal *et al.* 1992) and 96 mg versus 16 mg dexamethasone intravenously day 0, continued to day 2 then weaned to 0 by day 15 (Graham *et al.* 2006).

All studies included for this clinical question were small, underpowered and did not adequately report blinding or allocation concealment. Overall there is a limited body of evidence to fully inform the clinical question about the effectiveness of steroid treatment for patients with confirmed or suspected MSCC. There is insufficient evidence of effect of high versus moderate dose of dexamethasone, the evidence is insufficient for high versus no steroids and the evidence is lacking for moderate versus no steroids.

Due to the studies comparing different doses or regimens of dexamethasone it is difficult to report a consistent report with respect to all outcomes. However, with higher doses of dexamethasone, (96 or 100mg) a higher rate of adverse events was consistently reported. Ambulation was an outcome reported across the studies, with improvement indicated for patients on higher doses of dexamethasone.

Loblaw *et al.* (2005), conducted a review that included 4 out of the 5 studies that compared different dose regimens of dexamethasone. Each of these included studies have been appraised and separately reported (Heimdal *et al.* 1992, Vecht *et al.* 1989, Sorenson *et al.* 1994 and Maranzano *et al.* 1996). One out of the five studies that compared different dose regimens of dexamethasone was an update to the Loblaw review (Graham *et al.* 2006). Loblaw *et al.* (2005), was a systematic review, it contained a clearly defined clinical question, conducted a comprehensive systematic literature search and adequately assessed the grade of the evidence included.

The outcomes of each of the studies are describe below:

Mobility

Sorensen *et al.* (1994) randomised patients with MSCC treated with radiotherapy to either high-dose maintenance dexamethasone or no steroids (control group) concluded that high-dose maintenance dexamethasone significantly improved ambulation ($p=0.046$) during one year. At 6 months statistically more patients who were treated with dexamethasone were still ambulatory compared to patients who did not receive steroid treatment. The difference was not significant at 1 year.

When Vecht *et al.* (1989) compared high dose dexamethasone with a low dose, there was no advantage of the high-dose over moderate dose with no change in ambulatory status after treatment in most patients.

A case series study by Maranzano *et al.* (1996) reported that steroids may not be necessary for patients with good motor function. All the patients in this study ($n=20$) regained (or maintained) ambulation after radiotherapy without steroids.

In the phase II study by Graham *et al.* (2006); high dose dexamethasone was compared with a low dose. At entry 67% of patient in the high does group were ambulant and 81% in the low dose group were ambulant. Two to three of six patients in the high dose group and six to nine of nine patients in the low dose group were ambulant at 1 month. No comparisons were statistically significant, but no analysis of 1 month ambulation adjusting for baseline, favoured high dose dexamethasone. Overall, the mean FIS (Functional Improvement Score) at one month for 16 evaluable patients was negative at -1.4 (-3.5 high dose vs -0.2 low dose; $P=0.13$) and not significant.

Neurology

- Vecht *et al.* (1989) showed that patients given the moderate dose or a high dose improved neurologic status (defined as more than one grade difference in a 5-point neurologic score). This difference between the two groups compared in this study was not statistically significant ($p=0.22$, Fisher's exact test, calculated by review authors) but is clinically significant if a difference of this magnitude really exists.
- In the same study bladder dysfunction was significantly ($p < 0.05$) more frequent in the moderate dose group.
- There were no significant differences between both groups during the follow-up period

Duration of effect

- Sorensen *et al.* (1994) reported a trend to a better outcome at 3 months in the group of patients treated with dexamethasone but this is not statically different. (81% vs. 63%, $P =$ not provided),

- At follow-up 6 months after treatment 16 patients (59%) who had been treated with dexamethasone were still ambulatory compared to 10 patients (33%) in the group who had not received dexamethasone therapy ($\chi^2 = 3.850$; $P = 0.05$).
- One year after treatment for spinal cord compression, 8 patients (30%) in the dexamethasone group were alive and ambulatory compared to 6 patients (20%) in the no dexamethasone therapy group ($\chi^2 = 0.711$; $P = 0.40$).
- The median survival was 6 months in both groups, and 3 patients in both groups were still alive at the end of the study (survival > 2 years after spinal cord compression).
- After subgroup analysis, this difference remains the same in breast cancer patients (94% Vs 69%, $0.05 < P < 0.10$) particularly in those with thoracic disease (92% vs. 50%, $P = 0.05$).

The Vecht *et al.* (1989) showed that at entry, 47% of patients could walk in the conventional steroid group and 64% in the high dose group.

- At 24 hours 40% in the conventional group and 64% in the high dose group were able to walk.
- At 1 week 54% patients could walk in the conventional group and 55% patients in the high dose group.

With respect to bladder function at entry there were statistical differences between the 2 groups.

- At 3 hours there was no change in all participants, except 1 deterioration in the high-dose group.
- At 24 hours 1 patient in the low-dose group was improved and 3 pts in the high-dose were deteriorated.
- At 1 week most pts remained unchanged. 5 pts were improved compared with the start (1 vs 4) and 3 pts deteriorated (2 vs 1).

Toxicity

Sorenson *et al.* (1994) reported that three patients (11%) in the high-dose maintenance dexamethasone group had serious adverse effects, including severe psychoses and gastric ulcers requiring surgery.

Heimdal *et al.* (1992) reported the side effects of patients given high and then moderate dose maintenance steroids, showed that more a statistically and clinically significant increase in the number of serious adverse effects in the high-dose group compared with the moderate dose group. Serious adverse effects included ulcers with haemorrhage, rectal bleeding, and gastrointestinal perforations.

Graham *et al.* (2006) reported serious adverse events in the high dose group and included sepsis and death with probable or possible association to steroid treatment (this relationship could not be evaluated accurately because the study design was not set up to demonstrate this).

References:

Graham PH, Capp A, Delaney G, Goozee G, Hickey B, Turner S, Browne L, Milross C, Wirth A (2006) A pilot randomised comparison of dexamethasone 96 mg vs 16 mg per day for malignant spinal-cord compression treated by radiotherapy: TROG 01.05 Superdex study. *Clinical oncology* 18, 70-76.

Heimdal, K., Hirschberg, H., Slettebo, H., Watne, K. & Nome, O. (1992) High incidence of serious side effects of high-dose dexamethasone treatment in patients with epidural spinal cord compression. *Journal of Neuro-Oncology*, 12: 141-144.

Loblaw DA, Perry J, Chambers A, Laperriere NJ (2005) Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. *Journal of Clinical Oncology* 23, 2028-2037.

Maranzano E, Latini P, Beneventi S, et al (1996) Radiotherapy without steroids in selected metastatic spinal cord compression patients: A phase II trial. *Am J Clin Oncol* 19:179-183.

Sørensen, S., Helweg-Larsen, S., Mouridsen, H. & Hansen, H. H. (1994) Effect of high-dose dexamethasone in carcinomatous metastatic spinal cord compression treated with radiotherapy: a randomised trial. *European journal of cancer* 30A: 22-27.

Vecht, C. J., Haaxma-Reiche, H., van Putten, W. L., de, V. M., Vries, E. P. & Twijnstra, A. (1989) Initial bolus of conventional versus high-dose dexamethasone in metastatic spinal cord compression. *Neurology*. 39: 1255-1257.

Evidence Table

Systematic review of combined study designs

Loblaw DA, Perry J, Chambers A, Laperriere NJ (2005) Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group.[see comment]. [Review] [61 refs]. Journal of Clinical Oncology 23, 2028-2037.

Design: Systematic review of combined study designs, Evidence level ranged from 1- to 3;

NOTE: each of the included studies have been appraised separately in tables below. I have included the overview of the included studies which gives context for the recommendations formed by the Cancer Care Ontario group (which are also presented).

References in the review:

Vecht CJ, Haaxma-Reiche H, van Putten WL, et al: Initial bolus of conventional versus high-dose dexamethasone in metastatic spinal cord compression. *Neurology* 39:1255-1257, 1989

Sorensen S, Helweg-Larsen S, Mouridsen H, et al: Effect of high-dose dexamethasone in carcinomatous metastatic spinal cord compression treated with radiotherapy: A randomised trial. *Eur J Cancer* 30A:22-27, 1994

Heimdal K, Hirschberg H, Slettebo H: High incidence of serious side effects of high-dose dexamethasone treatment in patients with epidural spinal cord compression. *J Neurooncol* 12:141-144, 1992

Maranzano E, Latini P, Beneventi S, et al: Radiotherapy without steroids in selected metastatic spinal cord compression patients: A phase II trial. *Am J Clin Oncol* 19:179-183, 1996

Sørensen, S., Helweg-Larsen, S., Mouridsen, H. & Hansen, H. H. (1994) Effect of high-dose dexamethasone in carcinomatous metastatic spinal cord compression treated with radiotherapy: a randomised trial. European journal of cancer (Oxford, England : 1994), 30A: 22-27

Design: Randomised Controlled trial (therapy), evidence level: 1-

Country: Denmark,

Setting: Tertiary care

Aim: To investigate the potential effect of high-dose dexamethasone, as an adjunct to radiotherapy, on gait function in patients with confirmed metastatic spinal cord compression from solid tumours. To record and evaluate the dexamethasone toxicity (secondary).

Inclusion criteria

- Patients with confirmed by myelography +/- MRI spinal cord or cauda equina compression by epidural metastasis from a carcinoma.
- They were stratified before randomisation to breast cancer or other cancer patients, according to their primary tumour and ambulatory or non-ambulatory according to gait function at the time of diagnosis.

Exclusion criteria

Lymphoma, meningeal carcinomatosis, treatment with surgery, previous treatment for epidural metastasis, infectious disease or peptic ulcers

Population

Number of patients = 57 (18 men and 39 women), age range = 25-82 years, mean age = 62 years

Interventions

- Between May 1987 and April 1989 participants were randomized to high dose dexamethasone (27 pts), as an adjunct to radiotherapy, or no steroidal treatment (30 pts).
- The treatment group was given a dose of 96 mg dexamethasone for 4 days, intravenous bolus immediately after the diagnosis and then orally for 3 days, when possible in 4 divided doses, tapered in 10 days.
- Prophylactic medication against ulceration was not performed routinely.
- All patients received a radiation dose of 28 Gy delivered in 7 consecutive days, with the first fraction within 1-20 hours after the diagnosis.

Outcomes

- Gait function
- Walking ability preserved in ambulatory patients and restored within 3 months in non-ambulatory patients was defined as successful treatment result.
- Pain was not recorded systematically

Follow up

Patients were clinically evaluated by the same neurologist who wasn't informed whether or not they had received dexamethasone treatment (single blind RCT), before treatment, after the completion of radiotherapy, at 3 weeks, at 3 months and then every 3 months for 2 years or until death.

Results

Gait function

- There was a trend to a better outcome at 3 months in the group of patients treated with dexamethasone (81% vs. 63%, P = not provided),

- At follow-up 6 months after treatment 16 patients (59%) who had been treated with dexamethasone were still ambulatory compared to 10 patients (33%) in the group who had not received dexamethasone therapy ($X^2 = 3.850$; $P = 0.05$).
- One year after treatment for spinal cord compression, 8 patients (30%) in the dexamethasone group were alive and ambulatory compared to 6 patients (20%) in the no dexamethasone therapy group ($X^2 = 0.711$; $P = 0.40$).

Survival

- Treatment with steroids, as an adjunct to radiotherapy, didn't influence the course of the cancer disease, since there were no differences both in median (6 months vs 6 months) and >2 years survival (11% vs 10%) between the two treatment groups.
- The median survival was 6 months in both groups, and 3 patients in both groups were still alive at the end of the study (survival > 2 years after spinal cord compression).
- After subgroup analysis, this difference remains the same in breast cancer patients (94% Vs 69%, $0.05 < P < 0.10$) particularly in those with thoracic disease (92% vs. 50%, $P = 0.05$).

Toxicity

- Side-effects were observed in 3 (11% Vs 0%, P not provided) of the patients receiving a short course of high-dose dexamethasone. These included: psychosis, gastric ulcer perforation requiring surgery, hypomania.
- 3 (11% Vs 0%, P not provided) more patients stopped treatment because of similar side effects.
- Prophylactic treatment against gastrointestinal ulceration might reduce the frequency of side effects

General comments

- This is a small (53 patients) single blind (neurologist who performed the clinical evaluation) RCT but the only one conducted comparing high dose versus no steroidal therapy.
- The way of randomisation is not reported.
- The inclusion of all randomized (in dexamethasone) patients in the comparison, irrespective of receiving steroids according to the schedule, and the fact that prophylactic medication against ulceration was performed only in patients with a history of peptic ulcers or dyspepsia and not routinely could have influenced the dexamethasone treatment toxicity effects.

Vecht, C. J., Haaxma-Reiche, H., van Putten, W. L., de, V. M., Vries, E. P. & Twijnstra, A. (1989) Initial bolus of conventional versus high-dose dexamethasone in metastatic spinal cord compression. *Neurology.*, 39: 1255-1257.

Design: Randomized Controlled trial (therapy), evidence level: 1-
Country: The Netherlands (Multi-centred study).
Setting: Tertiary care

Aim: To investigate the potential differences in the effect of initial high-dose or conventional dexamethasone, as an adjunct to radiotherapy, on contrast passage following myelography, neurologic function (ambulation and bladder function) and pain relief in patients with confirmed by myelography metastatic spinal cord compression from solid or lympho-reticular malignancies.

Inclusion criteria

- Patients with histologically verified carcinoma or lymphoreticular malignancy, who showed complete obstruction for contrast flow on myelography which was performed on suspicion of metastatic epidural spinal cord compression.
- Patients were stratified during randomisation to carcinomas or lymphoreticular malignancies, according to their primary tumour.

Exclusion criteria

Not reported

Population

Number of patients = 37 (26 men and 11 women), age range = 22 - 87 years, mean age = 61 years

The types of malignancy were equally divided in the treatment arms.

Interventions

- Participants were randomized to initial high (22 pts) or conventional dose dexamethasone (15 pts) as an adjunct to radiotherapy.
- An initial high dose (100 mg dexamethasone iv bolus) immediately after the fluoroscopically confirmation of a complete blockage for contrast flow up to 10 minutes after instilment, was compared with a low-dose (conventional -10 mg iv bolus), both followed by 4mgr 4 times a day orally.
- All patients received a radiation dose of 21 or 30 Gy delivered in 7 or 10 fractions in 10 to 16 days, with the first fraction within 12 hours after the diagnosis.

Outcomes

- Influence of initial bolus iv dose on contrast passage following myelography.
- Pain, scored from 0-10.
- Neurologic function (ambulation and bladder function)

Ambulation, recorded as:

- grade I : walking independently
- grade II : walking with aid
- grade III : walking is impossible, both legs can be lifted from the bed
- grade IV : muscle contractions in legs present, lifting of legs impossible
- grade V : absence of contractions in legs.

Improvement or deterioration denotes at least 1 grade of difference in the above mentioned ambulation grade.

Bladder function, recorded as normal or abnormal (incontinence or catheter-dependent)

Follow up

- Contrast passage following myelography was evaluated fluoroscopically and documented with x-rays 30 minutes after the administration of dexamethasone.
- Patients' pain and neurologic function were clinically evaluated immediately before and at 3 hours, 24 hours and 1 week after dexamethasone administration.

Results

- There were no differences between the two groups on contrast passage, pain, ambulation or bladder function.
- Changes over time in ambulation and bladder function were similar, with no effect of dose on worsening or improving of neurological functions.

Contrast passage

- Within 30 minutes following dexamethasone administration six pts, 3/22 pts in the high-dose group and 3/15 in the conventional-dose group, showed passage of contrast (14% Vs 20%, P not reported)
- Both gravity and time could influence this effect.
- Five of these remained neurological stable and one patient improved.

Pain

- The average pain score of 31/37 pts with pain before the start of the treatment was 5.2 (SD = 2.8) and decreased significantly ($P < 0.001$) to 3.8 at 3 hours 2.8 at 24 hours and 1.4 after 1 week.
- Six patients did not have any pain.
- A substantial and similar effect of dexamethasone on pain within 24 hours was observed in both groups: 67% of patients improved.
- There were no significant differences in pain decrease between both groups.
- The difference at 24 hours was 0.1 (95% confidence interval, -1.6 to +1.8).
- No patient experienced an increase in pain.
- Pain was decreased after 3 hours in 9/17pts in the high-dose group and in 5/12 pts in the conventional dose group (53% Vs 41%, P not reported).
- Pain was decreased after 24 hours in 10/17 pts in the high-dose group and in 10/13 pts in the conventional dose group (59% Vs 77%, P not reported).
- There was a decrease in pain in 11/14 pts in the high-dose group and in 10/11 pts in the conventional dose group (77% Vs 91%, P not reported) after 1 week.

Ambulation

- There was no change in ambulatory status after treatment in most patients.
- No advantage of the high-dose over conventional dose was observed.
- Average ambulation score difference at 24 hours was 0.1 (95% confidence interval, -0.4 to +0.6).
- At entry 14/22 (64%) in high dose group and 7/15 (47%) in the low dose group were ambulatory.
- At 24 hours 14/22 (64%) in high dose and 6/15 (40%) in the low dose group were able to walk.
- At 1 week 11/20 (55%) in high dose and 7/13 (54%) in the low dose group were ambulatory.

Bladder function

- There were clear differences in bladder function before dexamethasone administration between the two groups. Bladder dysfunction was significantly ($p < 0.05$) more frequent in the conventional dose group.
- There were no significant differences between both groups during the follow-up period.
- At 3 hours there was no change in all participants, except 1 deterioration in the high-dose group.
- At 24 hours 1 patient in the low-dose group was improved and 3 pts in the high-dose were deteriorated.
- At 1 week most pts remained unchanged. 5 pts were improved compared with the start (1 vs 4) and 3 pts deteriorated (2 vs 1).

Comparison in MSCC pts after treatment	High-dose dexamethasone therapy (22 pts)	Conventional-dose dexamethasone therapy (15 pts)
Contrast passage 30 minutes after treatment	03/22 (14%)	03/15 (20%)
Pain evaluation after treatment	High-dose dexamethasone therapy (18 pts)	Conventional-dose dexamethasone therapy (13 pts)
Pain improvement after 3 hours	09/17 (53%)	05/12 (41%)
Pain improvement after 24 hours	10/17 (59%)	10/13 (77%)
Pain improvement after 1 week	11/14 (77%)	10/11 (91%)
Pain deterioration	00/00 (00%)	00/00 (00%)
Gait function evaluation after treatment	High-dose dexamethasone therapy (22 pts)	Conventional-dose dexamethasone therapy (15 pts)
Ambulatory at entry	14/22 (64%)	07/15 (47%)
Ambulatory at 24 hours	14/22 (64%)	06/15 (40%)
Ambulatory at 1 week	11/20 (55%)	07/13 (54%)
Improved at 3 hours	00/21	00/14
Improved at 24 hours	02/22	00/15
Improved at 1 week	05/20	01/13
Deteriorated at 3 hours	00/21	01/14
Deteriorated at 24 hours	02/22	02/15
Deteriorated at 1 week	06/20	02/13
Stable at 3 hours	21/21	13/14
Stable at 24 hours	18/22	13/15
Stable at 1 week	09/20	10/13

General comments

- This is small (37 pts) Randomized Controlled Trial, but the only one conducted comparing initial bolus high-dose versus conventional dexamethasone therapy.
- The previous-mentioned way of randomisation is not definitely well conducted and it is not reported who rated the outcomes and if he/she was aware or not of the treatment arm the patients belonged to.
- The exclusion criteria are not mentioned.

- There are obvious differences between two groups concerning both number of participants (22pts vs 15pts) and bladder dysfunction (31% vs 66%).
- The absence of a standard procedure of myelography could have influenced the contrast passage effect.
- The presence of some missing data both in ambulation and pain recording could also influence the results.

Missing data during pain recording (31 pts with pain)	High-dose dexamethasone therapy (18 pts)	Conventional-dose dexamethasone therapy (13 pts)
Pain recording at 3 hrs	01/18 (5.5%)	01/13 (7.7%)
Pain recording at 24 hours	01/18 (5.5%)	00/13 (7.7%)
Pain recording in 1 week	04/18 (22.2%)	02/13 (15.4%)
Missing data during ambulation recording (37 pts)	High-dose dexamethasone therapy (22 pts)	Conventional-dose dexamethasone therapy (15 pts)
Ambulation recording at 3 hrs	01/22 (4.5%)	01/15 (6.6%)
Ambulation recording at 1 week	02/22 (9%)	02/15 (13.3%)

The inclusion of 11 patients with lymphoreticular malignancies in this small study (taking into account the well-known lympho-cytotoxic activity of steroids) as well as some missing data makes this study statistically weak (26 carcinoma pts).

Heimdal, K., Hirschberg, H., Slettebo, H., Watne, K. & Nome, O. (1992) High incidence of serious side effects of high-dose dexamethasone treatment in patients with epidural spinal cord compression. Journal of Neuro-Oncology, 12: 141-144.

Design: Sequential non-randomised prospective comparative study (Nov 1987- Nov 1989) (therapy), evidence level: 2-

Country: Norway,

Setting: Tertiary care

Aim: To record and evaluate the toxicity of high dose dexamethasone therapy in patients with epidural spinal cord compression.

Inclusion criteria

Patients with epidural spinal cord compression due to malignant disease.

Exclusion criteria

- High-dose group: Latent or manifest cardiac failure, serious hypertension, systematic infection, active peptic ulcer disease.
- Low dose group (or conventional dose): Not mentioned

Population

Total number of patients = 66 patients

28 pts (High-dose group) vs 38 pts (Low dose group)

Interventions

- Between November 1987 and November 1988, 28 consecutive pts received immediately after diagnosis a high-dose of 96mg dexamethasone iv bolus tapered in 14 days (high – dose group), as an adjunct to radiotherapy.
- Prophylactic medication against ulceration (antacids or H₂-receptor antagonists orally) was performed routinely to all patients in this group.
- From December 1988, during a 12 months period, 38 consecutive pts received an initial dose of 16 mg dexamethasone daily, in 4 divided iv doses, tapered in 14 days (conventional dose group).
- It is not reported whether pts in normal-dose group received prophylactic medication.
- Most of patients received a radiation dose of 30 Gy in 10 fractions, with the first fraction delivered as soon as possible after the diagnosis.

Outcomes

Number of side effects

Number/rate of serious side effects

Follow up

- Patients were clinically evaluated during the period of their treatment.
- No further information available

Results

- There is a statistically and clinically significant increase ($p = 0.0284$) in the number of serious adverse effects in the high-dose group ($4/28 = 14.3\%$) compared with the normal-dose group ($0/38 = 0\%$).
- Serious adverse effects included ulcers with haemorrhage, rectal bleeding, and gastrointestinal perforations.
- In the high dose group, the incidence of total side effects ($8/28$) were significantly higher than in the conventional dose group ($3/38$, $p = 0.0429$).

Number of side effects

There were 8 events-side effects in 7 pts in the high dose group vs 3 events in 3 pts in the conventional dose group.

Number of serious side effects

Four of the events in the high-dose group were considered as serious vs none of them of the conventional dose group.

Side effects of dexamethasone treatment	High-dose n=28 pts	Conventional- dose n=38 pts	Result
Number of total side effects	08/28 (29%)	03/38 (8%)	p = 0.0429
Gastrointestinal bleeding	1		
Stomach ulcer-fatal bleeding	1		
Rectal bleeding	1		
Gastrointestinal perforation	1	2	
Sigmoid colon	1		
Unknown primary	2	1	
Other side effects			
Pneumonia			
Hyperglycaemia			
Wound infection			
No of serious side effects	04/28 (14.3%)	00/38 (0%)	p = 0.0284
Gastrointestinal bleeding	1		
Stomach ulcer-fatal bleeding	1		
Rectal bleeding	1		
Gastrointestinal perforation	1		
Sigmoid colon			
Unknown primary			

Authors' comments

- High-dose dexamethasone treatment gives an unacceptably high incidence of both side effects and serious side effects and it has been abandoned in their institute's clinical practise in favour of a more standard dose.
- Both prolonged and larger total doses increases the incidence of side effects.
- The serious side effects of dexamethasone treatment tend to occur late in the course of treatment (day 10 to 14).
- Both initial signs and symptoms tend to be masked by the dexamethasone treatment, making the side effects more dangerous.

General comments

- The authors' aim at first was to conduct a prospective observational study evaluating the clinical outcome of high dose steroidal treatment as an adjunct to radiotherapy in patients with spinal cord compression.

Due to high incidence of serious side effects the regimen was abandoned and the study was continued with patients receiving low dose dexamethasone.

- This paper reports the differences in side effects observed between the two parts of the study (part 1: 28 pts received high dose dexamethasone, part 2: 38 pts received normal dose)

- This paper reports finally a sequential non randomised comparison.
- It is not reported in paper whether exclusion criteria were the same for both groups or whether prophylactic treatment was given to pts during both parts of the trial.
- Moreover, concurrent use of NSAID, subnormal number of platelets and severe constipation are factors which might influence the events.
- Although authors reported that there was no significant difference both in the number of ambulatory subjects between the two cohorts and in the ambulatory rate post treatment (ambulatory rate after treatment 57.1% in the high dose vs 57.9% in the normal dose group) none of this data were formally reported.

<p>Maranzano E, Latini P, Beneventi S, et al: Radiotherapy without steroids in selected metastatic spinal cord compression patients: A phase II trial. Am J Clin Oncol 19:179-183, 1996</p>
<p>Design: Case Series, evidence Level 3 Country: Italy</p> <p>Aim: To investigate the feasibility of radiotherapy (RT) without steroids in 20 consecutive patients with metastatic spinal cord compression (MSCC), no neurologic deficits, or only radiculopathy, and no massive invasion of the spine.</p>
<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Patients with early MSCC and no neurological deficits, or only radiculopathy, entered the study of first-line RT without concomitant steroids. • Tumour invading < 50% of spinal cord diameter and extent of compression (max of 2 vertebrae or in cases of nerve root compression, more than 2 vertebral bodies)
<p>Exclusion criteria Where the tumour exceeded size criteria and involved more vertebral bodies that stipulated.</p>
<p>Population 20 patients</p>
<p>Interventions RT: (cobalt 60 or 8 mV photons) was given within 24 h from diagnosis of MSCC (3,4). The regimen was 3 Gy for five consecutive days, for a total dose of 30 Gy in 2 weeks. The target volume encompassed two vertebrae above and below the site of compression or all other proximal vertebrae with osteolysis, and laterally the entire mass revealed by MRI or CT. The reference dose was calculated according to MRI or CT imaging. The median field size was 128 cm² (range, 96 to 360 cm²).</p> <p>Steroid regimen was not reported</p>
<p>Outcomes Response to therapy was assessed 1 month after treatment using parameters:</p> <ul style="list-style-type: none"> • back pain • motor capacity
<p>Follow up Ranged from 2 to 14 months</p>
<p>Results</p> <ul style="list-style-type: none"> • 20 patients receiving RT without corticosteroids remained ambulatory. • 17 of 20 cases (85%, confidence limits 64-95%) achieved relief from back pain (13 of 14 and 4 of 6 taking minor analgesics or narcotics, respectively). Following RT, 1 of the 4 responders in the group using narcotics required only mild analgesics; the other 3 obtained complete relief from pain • All patients (100%) responded; 16 walking patients did not deteriorate and the other 4, who needed support, became ambulatory without motor impairment.
<p>General comments Recognising the toxicity of maintenance steroids (particularly at a high-dose), this case series reported that steroids may not be necessary for patients with good motor function. All the patients in their study (n=20) regained (or maintained) ambulation after radiotherapy without steroids.</p>

Graham PH, Capp A, Delaney G, Goozee G, Hickey B, Turner S, Browne L, Milross C, Wirth A (2006) A pilot randomised comparison of dexamethasone 96 mg vs 16 mg per day for malignant spinal-cord compression treated by radiotherapy: TROG 01.05 Superdex study. *Clinical oncology* 18, 70-76.

Design: Phase II study, evidence level: 1-

Aim: This study focussed on 3 areas:

1. Assessment of the viability of establishing a large randomised trial.
2. Assessment of web technology for clinical trial conduct in Trans-Tasman Radiation Oncology Group (TROG).
3. Evaluation of the several functional outcome measures were more useful in discriminating clinically relevant outcome differences compared with ambulation.

Inclusion criteria

- Patients required evidence from magnetic resonance imaging (MRI) of MSCC and at least one of pain, weakness, sensory symptoms or sphincter disturbance symptoms.
- Prior histological proof of malignancy,
- age older than 16 years,
- Eastern Co-operative Oncology Group (ECOG) performance status less than 4 before the MSCC event, minimum power 1 out of 5,
- estimated minimum survival of 2 months
- written informed consent

Exclusion criteria

Exclusion criteria were prior radiotherapy (defined as being within one vertebral level), prior treatment for MSCC, multi-level MSCC or other central nervous system disease, lymphoma or myeloma histology, definite history of peptic ulceration or cardiac failure, pregnancy and ongoing non-steroidal medication. Patients undergoing surgery were excluded.

Population

- The study started in September 2001 and ended in November 2003 (due to inadequate recruitment).
- 8 institutions in three Australian states were screened for possible participants
- 131 patients were screened but only 20 were recruited. (Ineligibility was dominated by prolonged duration of steroids and previous or coexistent central nervous system disease or therapy.)

Interventions

- Randomisation was conducted using a web interface (Superdex) to select eligible patients for the study and then to allocate study participants to treatments.
- 96 mg or 16 mg dexamethasone intravenously day 0, continued to day 2 then weaned to 0 by day 15.
- Radiotherapy treatment was 30 Gy in 10 fractions.

Outcomes

- Survival
- Adverse events
- Ambulation at 1 month
- Functional indices (Barthel Index, Functional Improvement Measure (FIM) and

Functional Improvement Score (FIS)

- Pain score (visual analogue pain score, possible range 0–10)

Follow up

1 month

Results

For the first 10 days, mean doses received were within 20% of scheduled doses. Beyond this time, a patient randomised to the low-dose arm remained on 12 mg because of neurological decline, thus influencing the mean upwards. Although compliance was satisfactory, there seemed to be a tendency to reduce steroid doses faster than the protocol specification in the high-dose group compared with the low-dose group. Two out of six patients commencing radiotherapy on a Friday did not receive radiotherapy for two consecutive days at the commencement of treatment. Two patients received less than 30 Gy because of general deterioration (n=1) or death (n=1).

Toxicity:

- High Dose Gp: 5 out of 9 patients experienced adverse events
- Low Dose Gp: 4 out of 11 patients experienced adverse events
- (1 patient in the low dose gp was considered likely to be related to the study medication and consisted of staphylococcal sepsis and death at day 9 in a patient in the high-dose group with a history of recent chemotherapy)

Pain:

- High Dose Gp: mean baseline visual analogue pain score = 3.2
- Low Dose Gp: mean baseline visual analogue pain score = 5.8

- Day 0 scores were not statistically different (t test P=0.1).

- First week:

High Dose Gp: mean baseline visual analogue pain score = 2.1

Low Dose Gp: mean baseline visual analogue pain score = 3.2

(P=0.23).

- Days 0–14:

High Dose Gp: mean baseline visual analogue pain score = 2.1

Low Dose Gp: mean baseline visual analogue pain score = 2.9

(P=0.6)

- The pain scores by group over the first week plotted against the analgesic consumption in morphine equivalents.
- Overall pain levels fell rapidly in the first 24 h to half of baseline (mean score 4.8 at day 0 down to 2.7 at day 1).
- Analgesic use seemed to be greater in the low-dose group than the high-dose group over the first week, (not statistically significant after adjusting for baseline (mean 5.6 vs 3.6; t test P=0.14).

Ambulation and Functional Outcome:

- high-dose group: 6 out of 9 patients were ambulant at day 0
- low-dose group: 9 out of 11 low-dose patients were ambulant at day 0.
- Only 80% of patients could be evaluated for functional outcomes at day 28: (6/9 patients in the high-dose group and 10/11 patients in the low-dose group).
- Two to three of six patients in the high dose group and six to nine of nine patients in the low dose group were ambulant at 1 month.
- No comparisons were statistically significant but no analysis of 1 month ambulation adjusting for baseline favoured high dose dexamethasone.

- Overall, the mean FIS (Functional Improvement Score) at one month for 16 evaluable patients was negative at -1.4 (-3.5 high dose vs -0.2 low dose; P=0.13 and not significant).

Survival:

- 2 out of 20 patients died
- 4 patients died before being assessed for ambulation at 1 month.
- Overall median survival = 2.3 months (69 days), with 13% of the patients having 12-month survival.
- Survival was better for breast and prostate compared with other histologies (10.6 vs 2.1 months: hazard ratio (HR) 0.19 [0.06–0.66]; P=0.01),
- Survival was better for time from diagnosis to MSCC greater than 6 months vs less (5.9 vs 1.1 months HR 0.29 [0.11–0.81]; P=0.04) and
- Survival was better for ambulant vs non-ambulant at baseline (5.9 vs 1.0 months HR 0.22 [0.07–0.72]; P=0.01).
- In a multivariate model, histology and baseline ambulation were significant.
- Survival by low dose gp compared with high dose dexamethasone gp was not significant (2.4 vs 2.1 months HR 0.80 [0.31–2.05]; P=0.6).

The hazard ratio in survival analysis is the effect of an explanatory variable on the hazard or risk of an event.

General comments

In Phase II clinical trials, the study drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety. This study was not set up to evaluate the effectiveness of dexamethasone exclusively. It was an under-powered study that provided some data on steroid effectiveness and evaluated the safety of its use. This was captured by the outcomes reported: toxicity, pain, survival and ambulation and function abilities.

Mobilisation

For patients with known MSCC who have had surgery/ RT/ no treatment does 'early' mobilisation give better outcomes (mobility, pain) than 'delayed'?

Short Summary

The West of Scotland Guidelines for Malignant Spinal Cord Compression (2007) have provided evidence for these recommendations.

Observational studies reported the effectiveness of a 'care pathway'. These articles were of low quality. Pease *et al.* (2004) provided limited evidence of an evaluation of a rehabilitation intervention with respect to early mobilisation with a small study sample. Implementation of the care pathway resulted in statically significantly fewer patients being nursed lying flat for the duration of their RT (≥ 5 days) with the majority of patients starting to sit up within one day. There was no significant difference between the groups with respect to patients experiencing altered mobility scores. Farrell *et al.* (1991), also evaluated a rehabilitation intervention as a case study, (n=1). The study evaluated the effectiveness of physiotherapeutic intervention in facilitating transfers in an elderly patient with spinal cord compression. McLinton and Hutchinson (2006) provided a descriptive audit of clinical practices associated with MSCC patients in one regional centre which included a very brief account of mobilisation practices after treatment.

PICO

Population Group	Intervention	Comparison	Outcomes
Patients groups: Patients with known MSCC who have had surgery/ RT/ no treatment	▪ 'early' mobilisation (needs definition see below) – FROM DAY ONE? ▪ how: collars, braces, wheel-chair ▪ frequency	▪ 'delayed' mobilisation ▪ Comparison of different interventions (collars, braces, wheel-chair) ▪ Different frequencies	Improvement in ▪ mobility, ▪ pain (including mechanical pain), ▪ mechanical instability, ▪ neurological issues ▪ Long" term spinal deformity ▪ Level of independence on discharge ▪ DVT rates ▪ Pressure sore incidence ▪ survival

These PICO tables were used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

Pease NJ, Harris RJ, Finlay IG (2004) Development and audit of a care pathway for the management of patients with suspected malignant spinal cord compression.

Physiotherapy. **90**, 27-34. **Evidence Grade: 2-**

- This was an audit study that observed the outcomes of a developed care pathway describing physiotherapeutic options and procedures put in place in one hospital.
- Retrospective data was analysed to report patient characteristics, duration of time spent supine (during RT), and mortality and complication rates. Data collated from two groups of cord compression inpatients. Those managed prior to the use of the care pathway were compared to a second cohort of cord compression inpatients managed since implementation of the care pathway. Cohort before care pathway introduced n= 53. Cohort after care pathway introduced n=95.

- Results indicated that implementation of the care pathway allows earlier mobilisation of appropriate patients leading to a decreased complication rate and a significant increase in patient survival at 60 weeks. Neurological function was not compromised by implementation of the pathway.
- Implementation of the care pathway resulted in statically significantly fewer patients being nursed lying flat for the duration of their RT (≥ 5 days) with the majority of patients starting to sit up within 1 day. With a statistical significant difference between cohorts (before and after care pathways were introduced), $X^2 = 5.33$, $p=0.021$.
- The cohort after the care pathway was introduced showed a statistical significant reduction to the cohort before the care pathway with inpatient deaths, $X^2 = 8.3$, $P=0.0044$.
- A significant initial divergence was observed wrt survival but at 78 weeks no difference was observed.
- No significant difference was observed between the cohorts wrt patients experiencing alteration in mobility scores.
- The level of bias associated with his study is high. The intervention requires a prospective evaluation and greater numbers of patients involved. Ideally a randomised study is required. It would also be valuable to investigate the intervention in different settings.

Farrell, J. C. (1991) Transfer ability in a patient with spinal cord compression: A multiple baseline design. *Physiotherapy Theory & Practice*. 7(1),3943. **Evidence Grade : 3**

A multiple baseline single case study design to assess the effectiveness of physiotherapeutic intervention in facilitating transfers in an elderly patient with spinal cord compression is reported. Training of transfers took place during the first treatment phase, which lasted 8 weeks. Training of walking backwards was commenced during the second treatment phase, which lasted 6 weeks. Specific treatment effects were demonstrated, as the patient's improved ability to transfer observed during the initial treatment phase did not generalise to the other motor activity, i.e. walking backwards. The motor activity of walking backwards only improved during the second treatment phase.

McLinton A, Hutchison C (2006) Malignant spinal cord compression: a retrospective audit of clinical practice at a UK regional cancer centre. *Br.J.Cancer* 94, 486-491.

Evidence Grade : 3

This audit reports data collected retrospectively over a period of 12 months on patients with MSCC referred to the West of Scotland Cancer Centre (n=174). It was carried out to build on the work of the Clinical Resource and Audit Group (CRAG) and to examine current practice for symptom assessment, multiprofessional care and rehabilitation of patients with MSCC admitted to the cancer centre. Areas of concern include poor assessment of pain, the poor ambulatory status of patients on admission and the lack of clear plans for mobilisation and rehabilitation for the majority of patients.

From the case records it was identified that on admission to the cancer centre, the majority of patients (86%) were initially nursed in a supine position on 'bed rest' and 3% remained ambulant. For 11% it was not possible to ascertain from either nursing or medical notes if restrictions were imposed regarding mobility. A plan of incremental movement was documented for 33%; the content of this varied from no plan to a structured plan located in the physiotherapy notes.

References

Farrell, J. C. (1991) Transfer ability in a patient with spinal cord compression: A multiple baseline design. *Physiotherapy Theory & Practice*. 7(1),3943.

McLinton A, Hutchison C (2006) Malignant spinal cord compression: a retrospective audit of clinical practice at a UK regional cancer centre. *Br.J.Cancer* 94, 486-491.

Pease NJ, Harris RJ, Finlay IG (2004) Development and audit of a care pathway for the management of patients with suspected malignant spinal cord compression. *Physiotherapy*. 90, 27-34.

Evidence Tables

Pease, Harris & Finlay . Development and audit of a care pathway for the management of patients with suspected malignant spinal cord compression. *Physiotherapy*. 90[1], 27-34. 2004.

Design: 2- Observational study (retrospective)

Country: Wales

Setting: Tertiary Hospital (Specialist cancer care)

Inclusion criteria

Exclusion criteria

Population

The audits provided data on 53 patients in 1997 and on 95 patients in 1999–2000.

Interventions

Two retrospective audits of management of patients with spinal cord compression were undertaken (Audit 1997).

The first audit was of inpatients admitted to the Oncology Centre with suspected cord compression prior to the introduction of the care pathway. *[During this time patients were nursed supine until completion of their radiotherapy which lasted at least 5 days. Data were collected over a 12-month period (January to December 1997). The data collected (audit 1997) included primary malignancy, level of cord compression, survival from diagnosis of cord compression; duration of time nursed supine, complication rate and mobility on admission and subsequent discharge from the Oncology Centre. Mobility was quantified using an adaptation of the Tomita scale]*

A second identical retrospective audit was undertaken of inpatients managed once the care pathway was in use. Notes of patients admitted over a 14-month period (June 1999–July 2000) were reviewed and data extracted as before (audit 2000).

The Care Pathway:

The care pathway was developed by physiotherapy and medical staff and its implementation audited.

The care pathway flow diagram (see below) was used in conjunction with the care pathway notes.

Outcomes

- 1) Duration spent supine
- 2) Mortality and complication rates
- 3) Mobility

Follow up

Results

- 1) Duration spent supine

The implementation of the care pathway was associated with a reduction in the proportion of patients being nursed flat, providing more opportunity for earlier mobilisation (1997 audit 44/52 (84.6%), 2000 audit 62/95 (65.3%), $\chi^2=5.33$, $P=0.021$).

That is, implementation of the care pathway resulted in significantly fewer patients being nursed lying flat for the duration of their radiotherapy (5 days or more) with the majority of patients starting to sit up within 1 day.

2) Mortality and complication rates

When the two groups are compared, the group managed on the care pathway showed a statistically significant reduction in the proportion of inpatient deaths ($\chi^2=8.3$, $P=0.0044$).

The survival curves for each group (Kaplan–Meier plot), indicated a statistically significant initial divergence of the two audit groups, that is, an improvement in early survival rates ($\chi^2=7.0$, $P=0.0082$, log-rank test). But at 78 weeks there is essentially no difference in survival. Authors note that implementation of the care pathway does not alter overall prognosis but significantly decreases early mortality rates.

3) Mobility

Results show no significant difference due to the use of the care pathway in the proportion of patients maintaining or experiencing alteration in their mobility score (χ^2 -test, $P\geq 0.57$).

It must be noted that reliable data on the patients' mobility were found for only 66% of patients ($n=35$) within the 1997 audit and 84% of patients ($n=80$) in the 2000 audit.

General comments

Authors comments:

Definition of stability: The use of clinical features such as mechanical pain and neurological changes, combined with radiological findings, were found to be the most reliable indicators for assessing spinal stability.

Issues to keep in mind with this study:

A difference between the groups is the number of patients seen in audit 1997 ($n=53$) compared with audit 2000 ($n=95$). It should be noted that the duration of the two audits differed by 2 months. Authors comment that the increased number of patients seen in the second audit may be due to a true increase in the number of patients experiencing malignant spinal cord compression or possibly the heightened awareness of local clinicians so that more patients were referred to the cancer centre.

In order to fully evaluate the effectiveness of the “care pathway” intervention described in this study a prospective study is required. An RCT would definitively evaluate the intervention but given the setting and the type of intervention this could be a logistically very difficult.

6.4 Case selection for definitive treatment of MSCC

Case selection for surgery:

For patients with an established diagnosis of MSCC, what factors predict for successful outcomes (mobility, continence, lack of pain, survival) following surgery?

Short Summary

Evidence of predictive factors for positive outcomes after a surgical intervention was drawn from observational studies, case reports and case series studies. (Cooper *et al.* 1993; Enkaoua *et al.* 1997; Finkelstein *et al.* 2003; Gabriel *et al.* 2004; Gokaslan *et al.* 1998; Harris *et al.* 1996; Hosone *et al.* 2005; Livingston *et al.* 1978; Nanassis *et al.* 1997; North *et al.* 2005; Oda *et al.* 2006; Portenoy *et al.* 1987; Ryken *et al.* 2003; Schoeggl *et al.* 2002; Sinardet *et al.* 2000; Sioutos *et al.* 1995; Sundaresan *et al.* 1995; Tabbara *et al.* 1990; Tokuhashi *et al.* 2005; Tomita *et al.* 2001; Tomita *et al.* 1994; Wang *et al.* 2004; Wise *et al.* 1999; Witham *et al.* 2006).

Several studies stated that a life expectancy of more than three months was an inclusion criterion for the study. Several studies defined the study population by the received treatment, not the diagnosis. In most publications the primary site of the cancer analysed as a distinguishing feature for survival of patients, however, the rank order of cancer types varied, the most consistently reported was the poor prognosis of spinal metastases secondary to lung cancer. The affected vertebral bodies have been identified as a predictor of surgery outcome in a number of studies; however, there was little consistency regarding which area is associated with a poor outcome. There is conflicting evidence regarding the factors age and previous treatment such as radiation therapy. Several authors acknowledged that patients with a poor preoperative performance status often have the worst prognosis but concluded that a substantial number of those may have an improvement in symptoms and quality of life.

The total Tokuhashi score (Tokuhashi *et al.* 2005) which included different risk factors was significantly correlated with survival in a palliative surgery and an excisional surgery group. These factors included performance status, number of extraspinal bone metastases foci, number of metastases in the vertebral body, metastases to the major internal organs, primary site of the cancer and palsy.

Several case series studies reported that even in patients with poor survival prognosis, symptom relief could be achieved after surgery. (Schoeggl *et al.* 2002; Sioutos *et al.* 1995; Livingston & Perrin 1978; Tabbara & Sibley 1990; Harris *et al.* 1996; Cooper *et al.* 1993; Sinardet *et al.* 2000; Tomita *et al.* 1994; Wang *et al.* 2004; Gokaslan *et al.* 1998; North *et al.* 2005; Oda *et al.* 2006). A systematic review of case series (Ryken *et al.* 2003) concluded that “surgical intervention for patients presenting with neurological deficits may experience marked improvement after surgical decompression and fusion, assuming that the individual does not present with complete paraplegia”.

PICO

POPULATION	FACTORS	OUTCOMES
Patients with an established diagnosis of MSCC	For example: 1) grade of malignancy 2) visceral metastases 3) bone metastases 4)Karnofsky performance index	<ul style="list-style-type: none"> • Accuracy of prediction of successful outcomes: • mobility, • continence, • lack of pain • Karnofsky performance index • survival

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary:

Evidence for single predictors was drawn from observational studies, case reports, case series. Only results from patients undergoing surgery were considered, not all patients. Many samples included a wider patient population for example, patients with neoplastic disease. Several studies stated that a life expectancy of more than three months was an inclusion criterion for the surgery study. Several studies defined the study population via the received treatment, not the diagnosis. In most publications the primary site of the cancer analysed as a distinguishing feature for survival of patients (with the rank order of cancer types varying). The most consistent result regarding a poor prognosis is for spinal metastases secondary to lung cancer.

Evidence for single predictors

Pain may be related to a successful outcome:

- Hosone *et al.* (2005) found that patients without pain before surgery survived significantly longer than patients with pain, this factor remained a significant prognostic factor in multivariate analyses.

The site of vertebral bodies involved is related to a successful outcome:

- Livingston and Perrin (1978) reported that the number of satisfactory results (walking and continent) was worst when compression occurred at the T-8 or uppermost lumbar levels.
- Sundaresan *et al.* (1995) reported a median survival duration of 16 months with 46% of patients alive at two years for patients with neoplastic cord compression, excluding patients with chordoma or plasmacytoma the median survival was only 11 months, 36% alive at two years.
- North *et al.* (2005) found that a cervical spinal procedure is a risk factor for reduced survival (HR: 2.0) for patients with spinal metastases.

The number of vertebral bodies involved may be related to a successful outcome:

- Sioutos *et al.* (1995) found statistically significant longer survival for patients with one vertebral body involved compared to multiple involvement. North *et al.* (2005) concluded that surgery extending over two or more spinal segments (HR: 2.73) is a risk factor for reduced survival. Tomita *et al.* (2001) found a significant difference in survival between patients presenting with single or multiple bone metastases.
- Enkaoua *et al.* (1997) stated that the total vertebral body involvement was not associated with the length of survival in a multivariate analysis.

The site of the primary tumour is related to survival:

- Sioutos *et al.* (1995) found a statistically significant difference in survival for lung and breast cancer patients (mean 9.5 vs. 22.5 months) but not for others. Sundaresan *et al.* (1995) showed differential survival but reported no statistical comparison, the reported range was 55 months median survival in colorectal cancer patients, and three months median survival for lung cancer (breast cancer: median: 30 months).
- Enkaoua *et al.* (1997) reported that the type of cancer was predictive of survival in uni- as well as multivariate analyses; the patients with unknown and renal cancer had a poorer prognosis than patients with metastases second to thyroid cancer.
- Gokaslan *et al.* (1998) reported different one year survival rates for renal cell, breast, lung, and melanoma or sarcoma cancer with a range of 65% to 52%.
- Sinardet *et al.* (2000) found poor survival in lung cancer patients, moderate survival for breast, prostate, myeloma and lymphoma cancer patients and the best survival in kidney cancer patients but no significance test was reported.
- Schoeggel *et al.* (2002) showed different median survival according to the site of primary cancer; while the median survival of patients with breast, haematopoietic and

prostate cancer ranged between 32 and 70 weeks, the median survival of patients with unknown primary, colorectal, liver, ovarian, oesophagus, hypernephroma and lung cancer ranged from 15-13 weeks.

- Finkelstein *et al.* (2003) reported that after adjusting for age and gender, the odds of a patient with lung cancer dying at 30 days was 2.65 times greater than the rest of the cohort and after adjusting for (unspecified) confounding factors, lung (HR: 3.17), melanoma, breast, upper gastrointestinal, lower gastrointestinal, renal and prostate tumours had a significantly worse prognosis than the rest of the cohort in an insurance company dataset of almost 1000 patients.
- Wang *et al.* (2004) found a significant difference in patient survival based on the different histological tumour types, with lung cancer and colon cancer patients having poorer survival times than sarcoma, prostate, renal cell, and breast cancer patients.
- North *et al.* (2005) concluded that a primary tumour location other than breast (HR: 0.238) is a risk factor for reduced survival in patients with spinal metastases.
- Hosone *et al.* (2005) divided cancer sites into a group with poor prognosis (survival <20 months: lung, sarcoma, colon, hepatic cell) versus favourable prognosis (survival >20 months: myeloma, thyroid, renal, breast) in a group of surgically treated patients with spinal metastases.
- Oda *et al.* (2006) found substantial differences in survival, e.g. patients with multiple myeloma, oesophagus, thyroid, prostate, breast and ovarian cancer ($\geq 15-23$ months) compared to stomach, unknown, urethra, colon, lung, kidney or rectum cancer (≤ 12 months), however the subgroups consisted often of single patients.
- Nanassis *et al.* (1997) summarised the literature as survival is poorest in patients with spinal tumour secondary to bronchogenic or breast cancer and highest in patients with kidney or prostate cancer and show in their own data that pulmonary carcinoma metastases have the poorest survival time compared to breast, prostate, blood or kidney cancer.
- Tomita *et al.* (2001) found a significant difference in survival when differentiating slow, moderate and rapidly growing primary tumours, however, the sample was not restricted to surgically treated patients.

The site of the primary tumour may be related to the complication rate:

- Wise *et al.* (1999) reported high complication rates for renal, prostate, and bone sarcomas, the lowest complication rates were observed in breast cancer, myeloma, and lymphoma.

The presence of visceral metastases may be related to a successful outcome:

- Tomita *et al.* (2001) reported that visceral metastases to vital organs (no, treatable, untreatable) made a significant difference in survival, however, the sample was not restricted to surgically treated patients. Indirect support comes from literature on the Tokuhashi score (see below).

The preoperative performance status is related to a successful outcome:

- Sioutos *et al.* (1995) found statistically significant longer survival for ambulatory compared to non-ambulatory patients.
- Sundaresan *et al.* (1995) concluded that surgical morbidity was related to the presence of paraparesis.
- Harris *et al.* (1996) stated that preoperative status is an important determinant of outcome, mobile patients do well (not further specified) and that all mobile patients remained mobile regardless of the timing of the surgery.
- Sinardet *et al.* (2000) reported differential results related to the performance status (no improvement in patients with complete motor deficit).
- Schoeggel *et al.* (2002) reported that mobile patients showed more improvement than paralysed or patients only able to slightly flex knees and toes. Wise *et al.* (1999) reported significantly higher complication rates for Harrington classifications involving

neurologic deficits and a higher Frankel grade was associated with a significantly increased complication risk.

- Finkelstein *et al.* (2003) reported that adjusted for confounding factors, there was a significant difference in survival in patients with preoperative neurological deficit (19% higher) and those without a deficit.
- Hosone *et al.* (2005) reported that patients without paresis and patients who walked without support before surgery survived significantly longer than patients with paresis and patients walking with support or unable to walk; only paresis remained a significant predictor in a multivariate analysis.
- Nanassis *et al.* (1997) concluded from the literature and a small case series that prognosis of neurological symptoms depend on pre-surgery deficits; the most unfavourable prognosis is associated with complete paralysis.
- A non-systematic review (Gabriel & Schiff, 2004) stated that the degree of functional disability corresponds with survival.
- A further non-systematic review by Porteney *et al.* (1987) summarise the literature as patients who cannot walk before treatment rarely walk again, while those too weak to walk but not paraplegic have an even chance of walking, and those ambulatory at the start of the therapy are likely to remain so.

The preoperative performance status may be related to the complication rate:

- Finkelstein *et al.* (2003) reported that patients with a preoperative neurological deficit had a 71% higher risk of developing a postoperative wound infection.

The Tokuhashi or Tomita scores are related to survival after surgery:

- The total Tokuhashi score covering different risk factors (performance status, number of extraspinal bone metastases foci, number of metastases in the vertebral body, metastases to the major internal organs, primary site of the cancer, palsy) was significantly correlated with survival in a palliative surgery and an excisional surgery group reported by Tokuhashi *et al.* (2005).
- Enkaoua *et al.* (1997) reported that the Tokuhashi score had a significant effect on the length of survival in both uni- and multivariate analyses.
- Tomita *et al.* (2001) reported that their score was significantly correlated with the survival of patients; however, not all of these were surgically treated.

Age may be related to survival after surgery:

- Enkaoua *et al.* (1997) reported that age was an independent predictor of a poor survival rate. Finkelstein *et al.* (2003) reported that age had a significant influence on the survival at 30 days and the proportional hazard analysis, with each additional year, patients had a 1% increase in the risk of dying.
- Sioutos *et al.* (1995) found no difference in survival between patients younger than 55 compared to patients over 65 overall, this was only the case for renal cancer.
- Wang *et al.* (2004) found no statistically significant difference in patients with spine metastases under or over 65 years of age.

Age may be related to the complication rate and surgical morbidity:

- Sundaresan *et al.*, (1995) found that the complication rate and surgical morbidity was related to the variable age above 65.
- Wise *et al.* (1999) found no significant association between age and the complication rate.
- A history of prior treatment (such as radiation therapy) may be related to a successful outcome
- North *et al.* (2005) concluded that recurrent or persistent disease after primary radiotherapy of the operative site is a risk factor for reduced survival (HR: 2.11).
- Wise *et al.* (1999) reported significantly higher complication rates for patients who had undergone radiation therapy preoperatively. Sundaresan *et al.* (1995) found in a sample of patients with neoplastic cord compression that the complication rate and

surgical morbidity was higher in patients with a history of prior treatment such as radiation therapy compared to de novo operations.

- Wang *et al.* (2004) found no correlation between radiation therapy and the postoperative infection rate in a sample of patients with spine metastases.

Results from studies simultaneously analysing several predictor variables

Specific Factors:

After considering numerous risk factors, North *et al.* (2005) concluded that risk factors for reduced survival were primary tumour location other than breast, surgery extending over ≥ 2 spinal segments, recurrent or persistent disease after primary radiotherapy of the operative site and cervical spinal procedure.

After considering numerous risk factors, North *et al.* (2005) concluded that risk factors for poor ambulation were primary tumour location other than breast, preoperative non-ambulatory status (HR: 11.26), recurrent or persistent disease after primary radiotherapy covering the operative site (HR: 6.72), procedure other than corpectomy (HR: 12.26)

- Hosone *et al.* (2005) identified the type of tumour, paresis, and pain as prognostic factors for survival.
- Finkelstein *et al.* (2003) report that after adjusting for age and gender, the odds of a patient with lung cancer dying at 30 days was greater than the rest of the cohort and after adjusting for (unspecified) confounding factors, lung, melanoma, breast, upper gastrointestinal, lower gastrointestinal, renal and prostate tumours had a significantly worse prognosis than the rest of the cohort.
- Enkaoua *et al.* (1997) reported that age, type of cancer and the Tokuhashi score were independently associated with poorer survival rates; this was not the case for gender, epidural metastases or total vertebral body involvement.
- Sundaresan *et al.* (1995) reported that the complication rate was related to the variables above 65 years old, history of prior treatment and presence of paraparesis.
- Tomita *et al.* (2001) found significant relationships with survival for the variables grade of malignancy of the primary tumour, number and characteristic of visceral metastases to vital organs and bone metastases, however the analyses was based on a sample that did not all receive surgical treatment.

Number of factors

The number of poor prognostic indicators is related to a successful outcome.

- Sioutos *et al.* (1995) concluded that vertebral column disease patients with two or more poor prognostic indicators (preoperative neurological status, anatomic site of primary carcinoma, and number of vertebral bodies involved) have a short life expectancy.
- North *et al.* (2005) concluded that in patients with tumours other than breast cancer, one or more risk factors (extended spinal segments, persistent disease, cervical procedure) increases the risk of death compared to no risk factors; in addition, patients with other cancer than breast neoplasm and none or one risk factor had a better ambulatory prognosis than patients with more risk factors (the number of risk factors was irrelevant for breast cancer).

Other results

Even in patients with poor survival prognosis, symptom relief can be achieved.

- A quarter up to one half of non-ambulatory patients become ambulatory or improves substantially after surgery (0-39%, Schoeggli *et al.*, 2002; 23%, Sioutos *et al.*, 1995; 25% Livingston & Perrin, 1978; 40 – 47%, Tabbara & Sibley, 1990; 47%, Harris *et al.*, 1996; 40-52%, Cooper *et al.*, 1993; 56%, Sinardet *et al.*, 2000; 64%, Tomita *et al.*,

1994; 62-75%, Wang *et al.*, 2004; 76%, Gokaslan *et al.*, 1998; 75-78% North *et al.*, 2005; 80-89%, Oda *et al.*, 2006). A systematic review of relevant case series (Ryken *et al.*, 2003) concludes that surgical intervention for patients presenting with neurological deficits may experience marked improvement after surgical decompression and fusion, assuming that the individual does not present with complete paraplegia. Porteney *et al.* (1987) summarise the literature as patients who cannot walk before treatment rarely walk again, while those too weak to walk but not paraplegic have an even chance of walking, and those ambulatory at the start of the therapy are likely to remain so.

- A high proportion of patients presenting with pain achieves pain relief (38%, Schoeggel *et al.*, 2002; 46%, Sinardet *et al.*, 2000; 70%, Livingston & Perrin, 1978; 84%, Witham *et al.*, 2006; all but 1, Cooper *et al.*, 1993; 90%, Sundaresan *et al.*, 1995; 92% Gokaslan *et al.*, 1998; 96%, Wang *et al.*, 2004; 56%, North *et al.*, 2005). Oda *et al.* (2006) report that pain relief, neurologic function and spinal stability were maintained in 94% of patients. A systematic review of relevant case series (Ryken *et al.*, 2003) concluded that surgical intervention for metastatic spinal disease is beneficial in that it alleviates pain caused by metastases and improves the patient's quality of life.
- A substantial proportion of patients resumes bladder control (80%, Tomita *et al.*, 1994; 60%, Tomita *et al.*, 2001; 49%, Harris *et al.*, 1996; 0% Schoeggel *et al.*, 2002). Oda *et al.* (2006) report that pain relief, neurologic function and spinal stability were maintained in 94% of patients.

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Evidence Tables

Livingston, K.E. & Perrin, R.G. (1978). The neurosurgical management of spinal metastases causing cord and cauda equine compression. J of Neurosurg, 49, 839-843.

Design: Case series, evidence level 3
Country: Canada; Setting: Division of Neurosurgery

Population N=100 consecutive patients with spinal metastases causing cord or cauda equine compression

Predictor variables / preoperative variables statistically analysed -

Subgroups

Pain

Received treatment urgent and extensive laminectomy decompression; dural sac decompressed to beyond equator with as much tumour removal as possible, in particular to decompress nerve roots; rubber catheter extradurally, proximally, distally along the spinal axis to rule out further obstruction; radiation and / or chemotherapy

Follow up 6 months; study period 10 years

Results

FACTOR	OUTCOME and RESULT
Pain (Clinical Scenario)	Pain was relieved in 70% of patients who presented with pain
Involvement (Spinal factor)	The number of satisfactory results (walking and continent) was worst when compression occurred at the T-8 or uppermost lumbar levels
Performance status (Patient factor)	5/20 paraplegic patients showed a satisfactory outcome status (ambulatory and urine continent) [in 3/5 patients was the pathology associated with compression fracture of the vertebral body] Comparison: 58/100 patients were ambulatory postoperatively, 19/100 showed significant improvement in motor function; 40/100 patients had a satisfactory result (ability to walk, urinary continence, survival > 6 months)

Authors' conclusion The widely held view that surgical treatment of cord compression due to spinal metastases is ineffective is not justified; a positive approach and aggressive management can achieve results superior to those generally reflected in the literature.

Portenoy, R. K., Lipton, R. B. & Foley, K. M. (1987). Back pain in the cancer patient: An algorithm for evaluation and management. *Neurology*, 37 (1), 134-138.

Design: Non-systematic review, evidence level 4

Country: USA; Setting: varies

Population 5 possibly relevant studies cited, 3 relevant sentences; patients with epidural spinal cord compression

Predictor variables / preoperative variables statistically analysed

Tumour type, pre-treatment factors

Subgroups

Performance status

Received treatment ?

Follow up ?

Results

FACTOR	OUTCOME and RESULT
Performance status (Patient factor)	Patients who cannot walk before treatment rarely walk again, while those too weak to walk but not paraplegic have an even chance of walking, and those ambulatory at the start of the therapy are likely to remain so.

Authors' conclusion The best hope for a favourable outcome lies in early and accurate diagnosis of epidural tumour in patients with back pain and minimal or no neurologic deficit.

General comments

Tabbara, I.A., Sibley, D.S. & Quesenberry, P.J. (1990). Spinal cord compression due to metastatic neoplasm. South.Med.J, 83.5, 519-523.

Design: Case series, evidence level 3
Country: USA; Setting: Cancer Centre

Population N=73 patients with spinal cord compression and / or metastatic lesions in the vertebral column, all patients had metastatic disease at the time SCC was diagnosed

Predictor variables / preoperative variables statistically analysed -

Subgroups

Paraparesis, paraplegic

Received treatment laminectomy and subtotal removal of the tumour mass (n=40), posterior complete excision of the compressing tumour, radiotherapy, systemic steroid therapy

Follow up range: 2.5 – 24 weeks, retrospective review of 22 year period

Results

FACTOR	OUTCOME and RESULT
Performance status (Patient factor)	47% of patients with paraparesis improved or became ambulatory after surgical decompression and radiotherapy, 17% after surgical decompression alone 40% of paraplegic patients after surgical decompression and radiotherapy improved or had only paraparesis, 25% after surgical decompression alone Paraplegic and paraparetic patients improved in motor function after surgical decompression and radiotherapy, 18% after surgery alone

Authors' conclusion Patients with spinal cord compression should be treated aggressively with immediate surgical decompression followed by radiotherapy

General comments Only results for patients undergoing surgery were extracted; there was no comparison of the subgroups with the total group

Cooper, P.,R., Errico, T.J., Martin, R., Crawford, B. & DiBartolo, T. (1993). A systematic approach to spinal reconstruction after anterior decompression for neoplastic disease of the thoracic and lumbar spine. *Neurosurgery*, 32 (1), 1-8.

Design: Case series, evidence level 3

Country: USA; Setting: Departments of Neurosurgery, Orthopedic surgery, Cardiovascular and thoracic surgery

Population N=33 patients with neoplastic disease of the thoracic and lumbar spine and a life expectancy of at least 4 months

Predictor variables / preoperative variables statistically analysed -

Subgroups

Performance status

Received treatment vertebral body resection, anterior transthoracic or retroperitoneal approach; allograft or methylmethacrylate reconstruction; for some adjuvant radiotherapy

Follow up 30 days, 51 months for individuals, 4 year period

Results

FACTOR	OUTCOME and RESULT
Pain (Clinical scenario)	Radicular or local vertebral pain was ameliorated in all but 1 patient.
Performance status (Patient factor)	2/5 patients who could not stand or walk were ambulatory after surgery, 12/29 patients with lower extremity motor deficit were unchanged, 15/29 were improved, 2/29 were worse after surgery Comparison: 30/33 patients were ambulatory postoperatively, 16/33 patients were intact

Authors' conclusion Correct patient selection for operative therapy and appropriate application of anterior or posterior instrumentation is essential for optimising results; in the majority of patients there has been gratifying pain relief and improvement of neurological deficit.

General comments

Tomita, K., Toribatake, Y., Kawahara, N., Ohnari, H. & Kose, H. (1994). Total en bloc spondylectomy and circumspinal decompression for solitary spinal metastasis. Paraplegia, 3, 36-46.

Design: Case series, evidence level 3

Country: Japan; Setting: Department of Orthopaedic Surgery

Population N=24 patients with solitary metastasis in thoracic or lumbar vertebra

Predictor variables / preoperative variables statistically analysed -

Subgroups

Unable to walk preoperatively (n=11); loss of bladder control (n=10)

Received treatment total en bloc spondylectomy; en bloc corporectomy, en bloc laminectomy, Harrington rod, CD instrumentation, allograft, ceramic hydroxyapatite spacer

Follow up maximum 37 months

Results

FACTOR	OUTCOME and RESULT
Performance status	64% of patients unable to walk preoperatively regained the ability to ambulate
(Patient factor)	Comparison: no patients' neurological condition worsened following surgery, impending paralysis was prevented in 6/6 patients and 7/7 patients recovered fully
	80% with loss of bladder control were continent postoperatively

Authors' conclusion The operation has significant clinical value.

General comments

Sundaresan, N., Sachdev, V.P., Holland, J.F., Moore, F., Sung, M. Paciucci, P.A., Wu, L. Kelligher, K. & Hough, L. (1995). Surgical treatment of spinal cord compression from epidural metastasis. *Journal of Clinical Oncology*, 13 (9), 2330-2335.

Design: Case series, evidence level 3

Country: USA; Setting: Departments of Neurosurgery and Neoplastic Disease

Population N=110 patients with neoplastic cord compression, 50% had undergone prior treatment (e.g. radiotherapy)

Predictor variables / preoperative variables statistically analysed

Age, prior treatment, paraparesis, further variables (not specified)

Subgroups

Pain, chordoma / plasmacytoma, paraparesis, primary tumour sites

Received treatment staged anterior-posterior resection and instrumentation (n=53), anterior resection with instrumentation (n=33), resection only (n=18), posterior resection and instrumentation (n=6)

Follow up minimum 6 months; 2 years

Results

FACTOR	OUTCOME and RESULT
Pain (Clinical Scenario)	For 18/20 people for whom pain was the main reason for surgery, impressive resolution of pain was noted
Primary tumour (Tumour factor)	Colorectal: median survival: 55 months, 2-year survival rate: 17% Chordoma: median survival: 48 months, 2-year survival rate: 84% Kidney: median survival: 44 months, 2-year survival rate: 52% Plasmacytoma: median survival: 36 months, 2-year survival rate: 67% Breast: median survival: 30 months, 2-year survival rate: 50% Sarcoma: median survival: 12 months, 2-year survival rate: 35% Others: median survival: 12 months, 2-year survival rate: 31% Lung: median survival: 3 months, 2-year survival rate: 10%
Chordoma, plasmacytoma (Tumour factor)	The median survival duration was 16 months with 46% alive at 2 years, excluding patients with chordoma or plasmacytoma the median survival was 11 months, 36% alive at 2 years
Prior treatment (Tumour factor)	History of prior treatment: complication rate: 67% De novo surgery: complication rate: 33%
Performance status (Patient factor)	Paraparetic: median survival: 6 months, 2-year survival rate: 19% Ambulatory: median survival: 36 months, 2-year survival rate: 54% Comparison: The overall median survival duration was 16 months, 46% alive at 2 years
OUTCOME	FACTOR and RESULT
Complication rate	The complication rate was clearly related to the variables age > 65, history of prior treatment prior treatment (with radiation and /or chemotherapy), presence of paraparesis

($p < 0.001$, χ^2 test)

Authors' conclusion Long-term survival is feasible in a subset of patients with this aggressive surgical approach; surgical morbidity was related to age, paraparesis and prior treatment.

General comments

Sioutos, P.J., Arbit, E., Meshulam, C. F., Galicich, J.H. (1995). Spinal metastases from solid tumors: Analysis of factors affecting survival. *Cancer*, 76, 1453-1459.

Design: Case series, evidence level 3

Country: USA; Setting: Cancer Center, Neurosurgery service

Population N=109 patients with thoracic spine metastases from solid tumours and epidural compression of the spinal cord

Predictor variables / preoperative variables statistically analysed

neurological status, anatomic site of primary carcinoma, and number of vertebral bodies involved

Subgroups

Number of vertebral bodies, primary carcinoma site, disease extent, age, neurologic deficit; further stratified within

Received treatment anterior transthoracic, anterior transthoracic/retroperitoneal, or posterolateral approach with instrumentation for vertebral body disease and simple laminectomy/ laminectomies for dorsally located epidural metastases; vertebrectomy; radiation treatment

Follow up ?; 14 year chart review

Results

FACTOR	OUTCOME and RESULT
Vertebral bodies number (Spinal factor)	Survival of patients with one vertebral body involved survived longer than patients with multiple vertebral body disease (p=0.027).
Primary tumour (Tumour factor)	Breast: mean survival: 22.5 months, range: 1-88; median: 13 Renal cell: mean survival: 20.9 months, range: 6-84; median: 16 Prostate: mean survival: 16.0, range: 1-47; median: 11 Colon: mean survival: 15.8, range: 2-39; median: 7 Lung: mean survival: 9.5 months, range: 0-28; median: 8 The difference in survival between breast and lung cancer patients was significant (p=0.039).
Disease extent (Tumour factor)	For prostate cancer patients, those with the disease limited to the primary site, thoracic spine, and bone other than spine had longer survival (p=0.005) than patients with disease extended beyond the respective sites
Age (Patient factor)	Patients ≤ 55 years did not survive statistically significantly longer than patients ≥ 65; this was only the case for renal cancer
Performance status (Patient factor)	All ambulatory patients remained ambulatory, 21% regressed later. 23% of nonambulatory were ambulatory at follow-up, 22% of these regressed later; the difference in survival was significant (p<0.001), the difference in survival was also significant when stratified according to primary tumour site (except for colon cancer). The survival was the shortest for patients with sphincter dysfunction
OUTCOME	FACTOR and RESULT
Survival	One negative prognostic factor did not alter the overall survival (compounding weight of prognostic factors). The presence of 2 or 3 factors had a compounding adverse effect on the survival of patients with vertebral column disease: The difference between each category (number of negative prognostic factors) was statistically significant

Authors' conclusion Survival is affected by the preoperative neurological status,

anatomic site of primary carcinoma, and number of vertebral bodies involved. Patients with vertebral column disease and two or more of poor prognostic indicators have a short life expectancy and radical surgery is not recommended.

General comments

Harris, J.K., Sutcliffe, J.C. & Robinson, E. (1996). The role of emergency surgery in malignant spinal extradural compression: assessment of functional outcome. British Journal of Neurosurgery, 10(1), 27-33.

Design: Case series, evidence level 3
Country: UK; Setting: Department of Neurosurgery

Population N=81 patients with malignant extradural spinal compression; patients with vertebral collapse secondary to metastasis without extradural tumours were excluded

Predictor variables / preoperative variables statistically analysed -

Subgroups

Requiring emergency surgery (n=52), mobility, continence, cancer site

Received treatment elective and emergency surgery

Follow up 3 months after surgery

Results

FACTOR	OUTCOME and RESULT
Emergency (Clinical Scenario)	71% of patients with emergency surgery had a good outcome, 32 patients improved functionally 61% of patients with elective surgery had a good outcome, 7 patients improved functionally
Compression site (Tumour factor)	Sacral: 1/1 improved Thoracic: 32/61 improved Thoracolumbar: 3/6 improved Cervical: 1/3 improved Lumbar: 2/9 improved
Performance status (Patient factor)	For patients with functional deficit (incontinence or immobility) emergency surgery was associated with a better outcome (p=0.04) 24% of preoperatively mobile patients with emergency procedure were alive at 3 months follow up; all mobile patients remained mobile 49% of immobile and incontinent patients improved following surgery 47% of incontinent and immobile patients regained the ability to walk

Authors' conclusion Even if the patient is incontinent and immobile, emergency spinal decompression is justified.

General comments not clear what the indications for an emergency were; the discussion states that preoperative functional status is an important determinant of outcome and cites 8 studies

Nanassis, K., Alexiadou-Rudolf, A., Rudolf, J. & Frowein, R.-A. (1997). Surgical indications and prognosis in spinal metastases. *Neurosurg. Rev.*, 20, 99-103.

Design: Review and case series, evidence level 4

Country: Germany; Setting: Department of General Neurosurgery

Population N=45 patients with spinal metastases; 25 studies cited

Predictor variables / preoperative variables statistically analysed -

Subgroups

primary carcinoma site

Received treatment surgery or no surgery, radiation therapy or chemotherapy after surgery

Follow up 4 weeks

Results

FACTOR	OUTCOME and RESULT
Primary tumour (Tumour factor)	Literature: Survival time after surgery is poorest in patients with primary bronchogenic or breast cancer; survival is highest in patients with spinal tumour secondary to kidney or prostate cancer. Literature and original data: Pulmonary carcinoma metastases have the poorest survival time compared to breast, prostate, blood or kidney cancer
Performance (Patient factor)	Literature: Prognosis of neurological symptoms depend on pre-surgery deficits; the most unfavourable prognosis is associated with complete paralysis, improvement can only be expected in 27% of patients (apart from pain relief)
OUTCOME	FACTOR and RESULT
Survival	The prognosis of spinal metastasis depends on the type of primary tumour, the extent of the malignant disease and the duration of symptoms prior to the diagnosis. Furthermore, neurological disturbances and the general condition determine the prognosis.

Authors' conclusion Early diagnosis and adequate therapy may lead to an improved clinical outcome in terms of survival time and quality of life.

General comments The data came primarily from the literature review and few details on the patients in the case series were reported. The prognosis statements appear to relate to a general disease prognosis, not to the prognosis of favourable outcomes of surgery.

Enkaoua, E. A., Doursounian, L., Chatellier, G., Mabesoone, F., Aimard, T. & Saillant, G. (1997). Vertebral metastases: A critical appreciation of the preoperative prognostic Tokuhashi Score in a series of 71 cases. *Spine*, 22(19), 2293-2298.

Design: Case series, evidence level 3

Country: France; **Setting:** Departments of Orthopaedic Surgery and Traumatology, and Surgery

Population N=71 patients with spinal metastases secondary to thyroid, renal and unknown primary tumours

Predictor variables / preoperative variables statistically analysed

Age, gender, presence of epidural metastases, total vertebral body involvement, primary cancer site, high vs. low Tokuhashi preoperative score

Subgroups

primary carcinoma site

Received treatment excisional surgery vs. palliative surgery; anterior transthoracic, anterior transthoracic/retroperitoneal, or posterolateral approach with instrumentation for vertebral body disease and simple laminectomy/ laminectomies for dorsally located epidural metastases; vertebrectomy; radiation treatment

Follow up up to 158 months for single patients

Results

FACTOR	OUTCOME and RESULT
Tumour type (Tumour factor)	<p>Thyroid: patients who died had a mean length of survival of 21 months (range: 0-62); the mean length of survivors was 50 months, range: 9-158 months; 5/7 patients with excisional surgery were still alive at last follow-up</p> <p>Renal: patients who died had a mean length of survival of 13 months, range: 1-45; 4/5 patients with surgery died, 1 was alive 15.6 months after surgery with reasonable performance status</p> <p>Unknown primary tumour: 8/9 patients died, 1 was alive 10 years after surgery with good performance status; patients who died had a mean length of survival of 2.6 months, range: 5 days – 9 months; 4/8 patients died in the hospital during the postoperative period; none underwent excisional surgery</p> <p>The primary cancer site had a major effect on the length of survival: median time to death: unknown site: 2 + - 1 month, renal: 9 + - 4.4 months versus thyroid: 33 + - 7.1 months; the Kaplan-Meier curves of the groups were significantly different (p=0.0005)</p>
Tokuhashi score	<p>The modified Tokuhashi score also had a major effect on the length of survival with a median time to death of 5 + - 1.2 months versus 24 + - 5.8 months; survival curves of patients with high or low Tokuhashi scores were significantly different (p=0.0063).</p>
OUTCOME	FACTOR and RESULT
Survival	<p>Gender, epidural metastases, total vertebral body involvement were not associated with the length of survival</p> <p>In multivariate analyses age (HR=1.04), type of cancer (HR=4.55 / 3.51), modified Tokuhashi score (HR=2.16) were independently associated with poorer survival rates.</p>

Authors' conclusion The Tokuhashi preoperative score is a successful prognostic tool.

General comments Multivariate analyses

Gokaslan, Z.L., York, J.E., Walsh, G.L., McCutcheon, I.E., Lang, F.F., Putnam, J.B., Wildrick, D.M., Swisher, S.G., Abi-Said, D. & Sawaya, R. (1998). Transthoracic vertebrectomy for metastatic spinal tumors. J. Neurosurg., 89, 599-609.

Design: Case series, evidence level 3
Country: USA; Setting: Cancer Centre

Population N=72 patients with metastatic disease involving the thoracic spine, life expectancy > 3 months

Predictor variables / preoperative variables statistically analysed -

Subgroups

Renal vs. breast vs lung cancer, melanoma and sarcoma; patients presenting with pain

Received treatment vertebrectomies, transthoracic approach; tumour embolisation were appropriate; combined sternotomy and anterior neck dissection for lesions at T-1 or T-2; trap door approach (standard anterior neck dissection with partial median sternotomy and anterolateral thoractomy; posterolateral thoracotomy after placement of single-lumen endotracheal tube usually with right hemithorax entry site for T-5-10 lesions; thoracoabdominal approach for T-11 and T-12

Follow up 1 month after surgery, then 3 month intervals for first year, later every 6 months

Results

FACTOR	OUTCOME and RESULT
Pain (Clinical Scenario)	In 23% of patients who presented with pain was complete resolution of pain achieved, pain was significantly improved in 69% and unchanged or worsened in 8% therefore 92% showed completely or greatly reduced pain (p<0.001); analgesic medication usage was significantly reduced postoperatively (p<0.001), 28 patients decreased the class of pain medication by at least one category, 17 patients required pain medication no longer (including 3 patients previously on intravenous or transdermal narcotics)
Tumour Type (Tumour factor)	The 1 year survival rates for renal cell, breast, and lung cancer were 65%, 63% and 55%. The 1 year survival rates for melanoma or sarcoma was 52%
Performance Status (Patient factor)	76% of neurologically impaired patients improved after surgery (p<0.001), 27/35 patients improved at least one Frankel grade, 20/35 patients regained normal function; 52% of ambulatory with weakness regained normal strength, 45% remained ambulatory with weakness; 10/13 non-ambulatory patients regained ambulatory ability after surgery including 3 regaining normal neurological function, 3/13 nonambulatory patients remained nonambulatory.

Authors' conclusion Transthoracic vertebrectomy and spinal stabilisation can improve the quality of life considerably but restoring or preserving ambulation and by controlling intractable spinal pain with acceptable rates of morbidity and mortality.

General comments very detailed

Wise, J., J., Fischgrund, J.S., Herkowitz, H.N., Montgomery, D. & Kurz, L.T. (1999). Complication, survival rates, and risk factors of surgery for metastatic disease of the spine. Spine, 24, 1943-1951.

Design: Case series, evidence level 3

Country: USA; Setting: Department of Orthopaedic Surgery

Population N=80 consecutive patients with metastatic disease of the spine

Predictor variables / preoperative variables statistically analysed

Radiation, Harrington classification, tumour type, Frankel score, tissue type of the primary tumour, surgical approach, number of levels instrumented and/or fused, type of bone graft, preoperative or postoperative chemotherapy, postoperative radiation therapy, age, sex, haemoglobin level, white blood cell count, platelet count, total lymphocyte count, estimated blood loss

Subgroups

Previous radiation treatment, Harrington classification, performance status, tumour type

Received treatment anterior, posterior, or combined decompression and stabilisation

Follow up at least 2 years in most patients

Results

FACTOR	OUTCOME and RESULT
Radiation (Spinal factor)	Patients who underwent radiation therapy preoperatively had a 16% major and 24% minor complication rate, patients without radiation therapy had a 9% major and 7% minor complication rate (p<0.05)
Harrington classification (Spinal factor)	The complication rates were higher for Harrington classifications involving neurologic deficits (p<0.05)
Tumour Type (Tumour factor)	Myeloma: mean survival: 28.7 months; complication rate: 30.8% Soft tissue sarcoma: mean survival: 24.7 months; complication rate: 40% Lymphoma: mean survival: 21.6 months; complication rate: 11.1% Other: mean survival: 21.2 months; complication rate: 0% Bone sarcoma: mean survival: 13.3 months; complication rate: 100% Breast: mean survival: 11.8 months; complication rate: 33.3% Renal: mean survival: 11.3 months; complication rate: 100% Lung: mean survival: 9.3 months; complication rate: 63.6% Prostate: mean survival: 8.1 months; complication rate: 83.3% Unknown: mean survival: 5.6 months; complication rate: 20%
Performance Status (Patient factor)	A higher Frankel grade was associated with an increased complication risk (p<0.05); 24% of patients improved 1 Frankel grade
OUTCOME	FACTOR and RESULT
Complications	No significant association was found between complications and tissue type of the primary tumour, surgical approach, number of levels instrumented and/or fused, type of bone graft, preoperative or postoperative chemotherapy, postoperative radiation therapy, age, sex, haemoglobin level, white blood cell count, platelet count, total lymphocyte count, estimated blood loss

Authors' conclusion Patients must be carefully selected based on expected length of survival, the use of radiation therapy, presence of neurologic deficit, and impending

spinal instability or collapse caused by bone destruction to minimise complications.

General comments

Sinardet, D., Chabane, A., Khalil, T., Seigneuret, E., Sankari, F., Lemaire, J.J., Chazal, J. & Irthum, B. (2000). Evolution neurologique de 152 patients operes de metastases rachidiennes. Neurochirurgie, 46 (1), 4-10.

Design: Case series, evidence level 3
Country: France; Setting: Department of Neurosurgery

Population N=152 patients with spinal metastasis

Predictor variables / preoperative variables statistically analysed -

Subgroups

Pain, sensory disorder, performance status, tumour type

Received treatment Thoraco-lumbar lesions treated using a posterior approach, laminectomy and if necessary an osteosynthesis; cervical lesionsL methylmetacrylate stabilisation; some pre- or postoperative radiotherapy

Follow up 1, 3 months; 4 year study period

Results

FACTOR	OUTCOME and RESULT
Pain (Clinical scenario)	17% of patients in pain became pain free one months after the intervention, 46% of patients reduced their analgesics consumption
Sensory disorder (Spinal factor)	31% of patients with sensory disorder regain normal sensory function
Tumour Type (Tumour factor)	Lung cancer had the least favourable life expectancy (9 months); 50% of breast, prostate, myeloma and lymphoma cancer patients were still alive at the 1 year follow-up and the best survival was seen in kidney cancer with 2/3 of patients still alive after 3 years
Performance Status (Patient factor)	56% of patients with motor deficit improved, 52% of patients who could not walk recovered a gait function; 71% of patients with Frankel grade C recovered gait function; no Frankel grade A patient regained the ability to walk and 4% of grade B patients

Authors' conclusion Surgical decompression is effective in relieving neurological symptoms from spinal metastasis but a complete motor deficit will lack postoperative improvement.

General comments French publication

Tomita, K., Kawahara, N., Kobayashi, T., Yoshida, A., Murakami, H. & Akamaru, T. (2001). Surgical strategy for spinal metastases. *Spine*, 26 (3), 298-306.

Design: Case series, evidence level 3

Country: Japan; Setting: Department of Orthopaedic Surgery

Population N=67 patients with spinal metastasis

Predictor variables / preoperative variables statistically analysed

Grade of malignancy of the primary tumours (slow, moderate, rapid growth), visceral metastases to vital organs (no, treatable, untreatable), bone metastases (solitary / isolated, multiple); Tomita score

Subgroups

Grade of malignancy of the primary tumours, visceral metastases to vital organs (VM), bone metastases (BM), Tomita score, bowel / bladder dysfunction

Received treatment

Follow up

Results

FACTOR	OUTCOME and RESULT
Spinal involvement (Spinal factor)	Single BM: average survival: 34.8 months, range: 1-84, HR: 1 Multiple BM: average survival: 17.9 months, range: 2-57, HR: 1.94 Significant difference between the groups (p<0.05)
Tumour Type (Tumour factor)	Slow growth: average survival period: 40.8 months, range: 5-84, HR: 1 Moderate growth: average survival: 24.2 months, range: 4-84, HR: 1.82 Rapid growth: average survival: 10 months, range: 1-32, HR: 4.08 Significant difference between any two of the three groups (p<0.05)
Tumour Staging (Tumour factor)	No VM: average survival: 36.8, range: 5-84 Treatable VM: average survival: 16.5 months, range: 4-31, HR: 1 Untreatable VM: average survival: 8.7 months, range: 1-24, HR: 1.9 Significant difference between the groups (p<0.05)
Performance Status (Patient factor)	6/10 patients with bowel and bladder dysfunction regained voluntary control after surgery
Prognostic score	Scores 2-3: average survival: 49.9 months, range: 18-84 Scores 4-5: average survival: 23.5 months, range: 7-57 Scores 6-7: average survival: 15 months, range: 5-33 Scores 8-10: average survival: 5.9 months, range: 1-14
OUTCOME	FACTOR and RESULT
Survival	Standardised regression coefficients: -0.405 (grade), -0.416 (VM), -0.199 (BM) Standardised HR of the 7 groups: 1: 1.82: 4.08: 2.16: 4.11: 1.01: 1.97 (slow, moderate, rapid growth; treatable VM, untreatable VM; solitary BM, multiple BM) Survival time and grade correlate -0.492 (P<0.0001) Survival time and VM correlate -0.536 (p<0.0001) Survival time and BM correlate -0.25 (p<0.05) Survival time and prognostic score correlate -0.69 (p<0.0001)

Authors' conclusion This new surgical strategy for spinal metastases based on the prognostic scoring system provides appropriate guidelines for treatment.

General comments multivariate analyses; all analyses included patients that were not surgically treated

Schoegg, A., Reddy, M. & Matula, C. (2002). Neurological outcome following laminectomy in spinal metastases. Spinal Cord, 40, 363-366.

Design: Case series, evidence level 3
Country: Austria; Setting: Department of Neurosurgery

Population N=84 patients suffering from metastases with predominant infiltration of the dorsal epidural parts or patients who could not be operated on via an anterior approach; patients with drop metastasis from CNS tumours were excluded

Predictor variables / preoperative variables statistically analysed -

Subgroups

Pain as indication for surgery, primary carcinoma site, performance status, catheterisation

Received treatment decompressive laminectomy with total or subtotal tumour resection; adjuvant radiotherapy (n=45)

Follow up immediately postoperative, 2, 4 months

Results

FACTOR	OUTCOME and RESULT
Pain (Clinical Scenario)	In patients whose only symptom was pain 38% improved and a clear reduction in analgesic consumption was shown (55% required an increase in pain relief after 2 and 4 months)
Primary tumour (Tumour factor)	Mama: median survival: 70 weeks Haematopoietic tumour: median survival: 60 weeks Prostate: median survival: 32 weeks Unknown primary: median survival: 15 weeks colorectal carcinoma / liver / ovarian cancer / oesophagus, hypernephroma: median survival: 14 weeks bronchus: median survival: 13 weeks
Performance status (Patient factor)	0/5 of paraplegic patients recovered from the paralysis; 22% of patients only able to slightly flex knees or toes regained full mobility; 9/23 patients able to straight leg lifting from supination became mobile with walkers and 3/23 became mobile without assistance All mobile patients remained mobile, 68% showed significant mobility improvement and an increase in walking distance In the cases that began as transaction or paresis with or without pain, 35% improved
Performance status (Patient factor)	None of the patients requiring catheterisation showed improvement

Authors' conclusion The procedures resulted in amelioration of motor function, pain and continence and therefore improved the patients' quality of life.

Ryken, T.C., Eichholz, K.M., Gerszten, P.C., Welch, W.C., Gokaslan, Z.L. & Resnick, D.K. (2003). Evidence-based review of the surgical management of vertebral column metastatic disease. *Neurosurg Focus*, 15 (5), 1-10.

Design: Systematic review of primarily case series, evidence level 3
Country: USA; **Setting:** varies

Population 5 relevant studies on patients with vertebral column metastatic disease

Predictor variables / preoperative variables statistically analysed -

Subgroups

Paraplegia / severe neurological dysfunction

Received treatment laminectomy for decompression; anterior decompression; anterior corpectomy; surgery; not stated

Follow up up to 158 months for single patients

Results

FACTOR	OUTCOME and RESULT
Performance Status (Patient factor)	4 studies in patients who present with paraplegia or severe neurological dysfunction showed little or no improvement, 1 study reported improvement in 5/11 patients

Authors' conclusion Surgical intervention for metastatic spinal disease is beneficial in that it alleviates pain caused by metastases and improves the patient's quality of life and patients presenting with neurological deficits may experience marked improvement after surgical decompression and fusion, assuming that the individual does not present with complete paraplegia.

General comments one of the cited 5 studies is Schoeggel *et al.* (2002)

Finkelstein, J.A. (2003). A population-based study of surgery for spinal metastases. *Journal of Bone and Joint Surgery – British Volume*, 85B.7, 1045-50.

Design: Case series, evidence level 3

Country: USA; Setting: Ontario Health Insurance Plan data

Population N=987 patients undergoing surgery for spinal metastases, a number of exclusion criteria, e.g. benign neoplasms, benign or malignant primary vertebral column tumours, age < 20 years, unknown primary tumour, primary tumour of the spinal cord or CNS

Predictor variables / preoperative variables statistically analysed

Tumour type, gender, preoperative neurological deficit, age

Subgroups

Tumour type, gender

Received treatment decompression / reconstruction surgery

Follow up 30, 90, 365, 1095 days

Results

FACTOR	OUTCOME and RESULT
Primary Site (Tumour factor)	Others: median survival: 716 days Lymphoma: median survival: 716 days Myeloma: median survival: 590.5 days Thyroid: median survival: 587 days Breast: median survival: 346 days Prostate: median survival: 223 days Kidney: median survival: 187.5 days Lower gastrointestinal: median survival: 121 days Lung: median survival: 87 days Melanoma: median survival: 69.5 days Upper gastrointestinal: median survival: 56 days
Gender (Patient factor)	Women had a higher mean and median survival compared with men for every primary type of cancer
Performance status (Patient factor)	Patients with a preoperative neurological deficit had a 71% higher risk of developing a postoperative wound infection
OUTCOME	FACTOR and RESULT
Mortality	Adjusted for age and gender, patients with lung cancer had a greater risk of dying at 30 days following surgery (OR: 2.65) compared to other cancers After adjusting for (unspecified) confounding factors, lung, melanoma, breast, upper gastrointestinal, lower gastrointestinal, renal and prostate tumours had a significantly worse prognosis than the rest of the cohort; patients with lung cancer were 3.17 times more likely to die than the rest of the cohort In an adjusted analysis men had a 48% higher risk of dying compared to women at any time after surgery (analyses without breast and prostate cancer) Adjusted for confounding factors, there was a significant difference in survival in patients with preoperative neurological deficit (19% higher) Age had a significant influence on the survival at 30 days and the proportional hazard analysis, with each additional year, patients had a 1% increase in the risk of dying

Authors' conclusion Surgical morbidity and life expectancy must always be

weighed against anticipated quality of life improvements.

General comments publication used advanced statistical methods, multivariate analyses

Gabriel, K. & Schiff, D. (2004). Metastatic spinal cord compression by solid tumors. *Seminars in Neurology*, 24 (4), 375-383.

Design: Non-systematic review, evidence level 4
Country: USA; Setting: unclear

Population 1 relevant study; patients with metastatic epidural spinal cord compression

Predictor variables / preoperative variables statistically analysed

Degree of functional disability

Subgroups

Ambulation

Received treatment surgery for pain relief and to prevent or restore spinal cord dysfunction

Follow up 12 months

Results

FACTOR	OUTCOME and RESULT
Performance status (Patient factor)	The probability of surviving 12 months was 73% for patients with restored or preserved ambulation following treatment but only 9% for nonambulatory patients

Authors' conclusion The degree of functional disability corresponds with survival.

General comments

Wang, J.C., Boland, PI, Mitra, N., Yamada, Y., Lis, E., Stubblefield, M. & Bilsky, M.H. (2004). Single-stage posterolateral transpedicular approach for resection of epidural metastatic spine tumors involving the vertebral body with circumferential reconstruction: results in 140 patients. J Neurosurg (Spine 1), 3, 287-298.

Design: Case series, evidence level 3
Country: USA; Setting: Cancer Center

Population N=140 consecutive patients undergoing surgery for metastatic spine tumour, 86% with high-grade spinal cord compression

Predictor variables / preoperative variables statistically analysed

Previous radiation therapy

Subgroups

Pain, performance status

Received treatment single-stage posterolateral transpedicular approach to decompress the spine circumferentially and to place instrumentation; autologous bone graft for selected patients

Follow up 3, 6 months or as clinically indicated

Results

FACTOR	OUTCOME and RESULT
Pain (Clinical scenario)	96% of patients with pain reported improvement, no patient's pain was worse after surgery, of the patients with moderate to severe pain, 91% improved to mild or no pain
Tumour Type (Tumour factor)	Colon cancer (3.3 months) and lung (3.6 months) tumours showed significantly worse survival than sarcoma, prostate, renal cell, and breast cancer (7.8-15.4 months); the difference in patient survival based on the different histological tumour types was significant ($p < 0.001$)
Performance status (Patient factor)	62% of patients with motor impairment improved 75% of poor performance status became ambulatory Comparison: 90% of patients had good to excellent performance status
Age (Patient factor)	> 65 years: median survival: 8.2 months ≤ 65 years: 6.4 months Not statistically significant
OUTCOME	FACTOR and RESULT
Complications	There was no significant association between radiation therapy and postoperative infection, radiation therapy within six weeks of surgery did not increase the infection rates

Authors' conclusion The technique achieves pain palliation, neurological preservation and functional improvement while avoiding the morbidity associated with combined approaches

North, R.B., LaRocca, V.R., Schwartz, J., North, C.A., Zahurak, M., Davis, R. & McAfee, P.C. (2005). J Neurosurg: Spine 2, 564-573.

Design: Case series, evidence level 3
Country: USA; Setting: School of Medicine

Population N=61 patients undergoing spinal surgical procedures for metastatic disease

Predictor variables / preoperative variables statistically analysed

Tumour type, sex, age, preoperative ambulatory grade, strength, continence, duration of weakness, duration of pain, myelographic block, radiotherapy or the operative site, indications for the operation, time from diagnosis to surgery, year of surgery, location of compression, number of compressed spinal levels, type of surgery, postoperative radiotherapy

Subgroups

Pain, tumour type, ambulation

Received treatment corpectomy (n=21), corpectomy and placement of posterior instrumentation with or without decompression (n=4), laminectomy (n=24), laminectomy with fusion or placement of instrumentation (n=13), costotransversectomy (n=3), transpedicular approach (n=1); autologous bone graft placement (n=17), methacrylate construct insertion (n=21), instrumentation with anterior distraction constructs (n=15), instrumentation with Kerrison wires and Steinmann pins reinforced with methacrylate (n=10), other instrumentation (n=2); steroid agents (all), external-beam radiation therapy (n=29)

Follow up up to 4 years? Data from 10 year period

Results

FACTOR	OUTCOME and RESULT
Pain (Clinical scenario)	4/12 intractable pain patients (resistant to narcotic therapy) did not lose the intractable pain; pain decreased in 56% patients with pain and increased in 20%
Tumour Type (Tumour factor)	Patients with breast cancer survived a median of 1.7 years experienced the longest survival compared to others (HR: 0.348, p=0.02) Using breast cancer as the reference, the HR were Lung: 5.22, probability value: 0.002 unknown primary: 2.35, p value: 0.13 other diagnoses: 2.59, p value: 0.04
Performance status (Patient factor)	All ambulatory remained so, 7/9 of non-ambulatory patients were able to walk postoperatively (most remained so up to final follow up or death) All 4 paraplegic patients regained normal strength and ambulation, the ability to walk with mechanical aids or minimal lower extremity movement
OUTCOME	FACTOR and RESULT
walking	<ul style="list-style-type: none"> • Risk factors: primary tumour location other than breast, preoperative non ambulatory status (HR: 11.26, p<0.001), recurrent or persistent disease after primary radiotherapy covering the operative site (HR: 6.72, p=0.005), procedure other than corpectomy (HR: 12.26, p=0.02) • No patients with breast cancer lost the ability to walk, even though other risk factors were present in some cases • 5/41 with other primary tumours and ≤1 additional risk factors lost the ability to walk

survival	<ul style="list-style-type: none"> • 7/9 with other primary tumour locations and ≥ 2 other risk factors lost the ability to walk • Risk factors for reduced survival: primary tumour location other than breast (HR: 0.348, $p=0.02$), surgery extending over ≥ 2 spinal segments (HR: 2.73, $p=0.004$), recurrent or persistent disease after primary radiotherapy of the operative site (HR: 2.11, $p=0.03$), cervical spinal procedure (HR: 2.0, $p=0.04$) • Patients with breast cancer had the lowest risk of death • Patients with other tumour types and no risk factor had a moderate risk (median survival: 266 days) • Other tumour types and ≥ 1 risk factor had the highest risk (median survival: 130 days) • Preoperative ambulatory status was marginally associated with survival (HR 2.11, $p=0.15$) • Male sex and survival was marginally associated (HR: 1.856, 0.08) but not significant when stratified by breast cancer
Authors' conclusion	
<p>Prognostic factor scoring system: Status / Risk factor: Outcome</p> <ul style="list-style-type: none"> • Breast cancer: very low probability of losing ability to walk • Other tumour + 0 or 1 risk factors: 72% likely to walk at 1.6 years • Other tumour + 2 or 3 risk factors: 50% likely to walk at 0.15-0.29 years • Breast cancer: 50% survive at 1.7 years • Other tumour + 0 risk factors: 50% survive at 0.73 years • Other tumour ≥ 1 risk factors: 50% survive at 0.36 years • The results support an expanded role for the surgical treatment of metastatic spinal disease. 	
General comments multivariate analysis, numerous risk factors considered	

Hosone, N., Ueda, T., Tamura, D., Aoki, Y., & Yoshikawa, H. (2005). Prognostic relevance of clinical symptoms in patients with spinal metastases. *Clinical Orthopaedics and Related Research*, 436, 196-201.

Design: Case series, evidence level 3
Country: Japan; Setting: referral hospitals

Population N=165 consecutive patients surgically treated with spinal metastases, patients with poor general condition and / or a life expectancy < 3 months were excluded

Predictor variables / preoperative variables statistically analysed

Pain, paresis, walking, cite of primary factor

Subgroups

Poor vs favourable prognosis, pain, paresis, walking

Received treatment

Follow up over 1 year, average: 23.4 months, range: 0.3-140 months

Results

FACTOR	OUTCOME and RESULT
Pain (Clinical scenario)	Patients without pain survived longer than patients with pain (38.2 vs. 19.8 months, p=0.0283)
Tumour Type (Tumour factor)	Myeloma: median survival: 54.2 months Thyroid: median survival: 51.1 months Renal: median survival: 34.2 Breast: median survival: 21.3 Hepatic cell: median survival: 15 months Colon: median survival: 12.9 months Sarcoma: median survival: 10.9 Lung: median survival: 9.9 months
Performance status (Patient factor)	Patients without paresis before surgery survived longer than patients with paresis (29.5 vs. 16.3 months, p=0.0003); patients who walked without support before surgery survived longer than patients walking with support or unable to walk (26.7 vs. 18.3 months, p=0.0077)
OUTCOME	FACTOR and RESULT
survival	The type of primary tumour, paresis, and pain were prognostic factors, while walking status had not prognostic impact in multivariate analyses

Authors' conclusion Histologic type of primary tumour is the strongest prognostic factor, followed by preoperative paresis and pain.

General comments multivariate analysis

Tokuhashi, Y., Matsuzaki, H., Oda, H., Oshima, M. & Junnosuke, R. (2005). A revised scoring system for preoperative evaluation of metastatic spine tumor prognosis. *Spine*, 30 (19), 2186-2191.

Design: Case series, evidence level 3
Country: Japan; Setting: Department of Orthopaedic Surgery

Population N=246 patients with metastatic spinal tumours

Predictor variables / preoperative variables statistically analysed

Tokuhashi score (performance status, number of extraspinal bone metastases foci, number of metastases in the vertebral body, metastases to the major internal organs, primary site of the cancer, plasy)

Subgroups -

Received treatment palliative surgery: posterior decompression and stabilisation, posterior stabilisation alone, laminectomy (n=142), excisional surgery: anterior curettage and stabilisation, combined curettage and stabilisation, en bloc resection and stabilisation (n=22)

Follow up up to 115 months

Results

FACTOR	OUTCOME and RESULT
Tokuhashi score	Total Tokuhashi score is significantly correlated with the survival period: r=0.61 (p<0.01) within the excisional surgery group r=0.53 (p<0.001) within the palliative surgery group

Authors' conclusion The prognostic criteria covered by the total score are useful for pre-treatment evaluation of prognosis.

General comments

Oda, I., Abuni, K., Ito, M., Kotani, Y., Oya, T., Hasegawa, K., Minami, A. (2006). Palliative spinal reconstruction using cervical pedicle screws for metastatic lesions of the spine: a retrospective analysis of 32 cases. *Spine*, 13, 1439-1444.

Design: Case series, evidence level 3

Country: Japan; **Setting:** Department of Orthopaedic Surgery

Population N=32 patients with metastatic tumours in the cervical or upper thoracic spine, life expectancy \geq 3 months

Predictor variables / preoperative variables statistically analysed -

Subgroups

Frankel grade, ambulation, tumour type

Received treatment spinal reconstructive surgery using cervical pedicle screws

Follow up up to 23 months

Results

FACTOR	OUTCOME and RESULT
Tumour Type (Tumour factor)	Ovarium: average survival: 23 months Breast: average survival: 19.8 months Prostate: average survival: 19 months Thyroid: average survival: 18.7 months Esophagus: average survival: 17 months Multiple myeloma: average survival: 15 months Rectum: average survival: 12 months Kidney: average survival: 9.4 months Lung: average survival: 9 months Colon: average survival: 6 months Urethra: average survival: 3 months Unknown: average survival: 4 months Stomach: average survival: 2 months
Frankel (Patient factor)	80% of patients with spinal cord lesions demonstrated neurologic improvement by one or more grades on the Frankel grade, average: 1 grade, range: 0-3 grades
Performance status (Patient factor)	89% of nonambulatory patients due to pain or myelopathy became ambulatory
Combination	Pain relief, neurologic function, spinal stability were maintained throughout the follow-up period in 94% of patients

Authors' conclusion Spinal stability, pain and neurologic function improve after spinal reconstruction using cervical pedicle screws.

General comments some of the sub-samples are n=1

Witham, T., Khavkin, Y.A., Gallia, G.L., Wolinsky, J.P. & Gokaslan, Z.L. (2006). Surgery insight: current management of epidural spinal cord compression from metastatic spine disease. *Nature Clinical Practice Neurology*, 2 (2), 87-94.

Design: Non-systematic review, evidence level 4
Country: USA; Setting: varies

Population 1 relevant study, patients with epidural spinal cord compression from metastatic spine disease

Predictor variables / preoperative variables statistically analysed -

Subgroups

Pain

Received treatment percutaneous vertebroplasty and kyphoplasty

Follow up ?

Results

FACTOR	OUTCOME and RESULT
Pain (Clinical scenario)	In a study with patients with intractable pain secondary to pathologic vertebral body fractures, marked or complete pain relief was achieved in 84%.

Authors' conclusion Surgical techniques for decompression and stabilisation of the spine have improved, leading to improved patient outcomes.

General comments it is possible, though not likely, that the review contains also a relevant statement on neurological deficits which was not extracted (copy unreadable)

Case selection for both surgery and radiotherapy:

For patients with an established diagnosis of MSCC, what factors predict for successful outcomes (mobility, continence, lack of pain, survival) following surgery and/or radiotherapy

Short Summary

This evidence summary is a subset of studies from the evidence body used for case selection for surgery and radiotherapy. These studies examine factors for successful outcomes from surgery and radiotherapy interventions. The evidence included three systematic reviews, one prospective randomised study and several observational studies (Bach *et al.* 1990; Barcena *et al.* 1984; Hill *et al.* 1993, Katagiri *et al.* 2005; Klimo *et al.* 2005, Loblaw *et al.* 2003 Loblaw *et al.* 2005; Martenson *et al.* 1985; Patchell *et al.* 2005). Treatment with surgery and RT, favourable primary tumour, and a favourable ambulatory status after treatment consistently predicted for better survival. In predicting motor function the main factors included surgery and RT as well as a favourable ambulatory status before treatment.

Evidence Summary

Klimo *et al.* (2005) compared results of RT studies with results of surgery studies and found that treatment mode was the only statistically significant factor affecting ambulation success (maintenance or regaining ambulation), which was 1.3 times more likely in patients treated with surgery followed by RT, rather than RT alone. In the subset who were non-ambulatory before treatment, surgical patients were 2 times more likely to regain ambulatory function. However in this group RT as the sole treatment mode was not significantly associated with a decline in rescue rate. Age, gender, primary pathology, lesion distribution in spine did not predict ambulatory success.

The pooled results of the Loblaw *et al.* (2005) for RT suggest that bony compression may be a factor for recovery of ambulation after RT. However this finding is based on a comparison of 9 pooled studies with one single study (see table).

An earlier study by Barcena *et al.* (1984) comparing all treatment modalities used univariate statistical comparisons, the study concluded that tumour biology seemed to have a stronger prognostic significance than neurological grade, myelographic block or tumour location in the spine. The most influential factors for the selection of therapy were the pre-treatment neurological status, the location of the tumour within the spinal canal, and the general medical condition of the patient.. Surgical treatment was considered appropriate in cases with severe but incomplete deficit and posterior compression of the spinal cord. The type of surgical approach – laminectomy vs anterior decompression- was indicated by the posterior or ventral location of the tumour, and individualized for each case. The strongest prognostic factor for patients being treated for spinal metastases was tumour biology, which includes histology, radiosensitivity and response to dexamethasone. The remaining factors had a secondary and complementary prognostic influence.

Evidence from primary studies:

Factors that predict for successful motor function or mobility

Five of the included studies reported the effects of RT and/ or surgery on motor function including two meta-analyses (Klimo *et al.* 2005, Loblaw *et al.* 2005), one small RCT (Patchell *et al.* 2005), and two retrospective cohort studies (Bach *et al.* 1990, Martenson *et al.* 1985).

Multivariate analysis was conducted in one study (Patchell *et al.* 2005) a meta-analysis was conducted in two reviews (Klimo *et al.* 2005, Loblaw *et al.* 2005), and univariate

statistics were reported in the two cohort studies (Bach *et al.* 1990, Martenson *et al.* 1985).

On multivariate analysis Patchell *et al.* (2005) found that maintenance of ASIA and Frankel scores was associated with a surgical procedure rather than RT alone, a stable spine, a lesion at the cervical spine level, and baseline Frankel score. The meta-analysis conducted by Klimo *et al.* (2005) also reported that surgical intervention (\pm RT) rather than RT alone was more successful in the maintenance or recovery of ambulation. In this review the lesion distribution did not predict ambulatory success. A meta-analysis by Loblaw *et al.* (2005) suggested that the presence of bony compression reduced the success of any intervention to achieve the maintenance or recovery of ambulation in ambulant, assisted ambulant and paraparetic patients. The retrospective cohort by Bach *et al.* (1990), although rather dated, also found that surgery and RT together were more successful in restoring gait than surgery or RT alone. Whereas the retrospective study by Martenson *et al.* (1985) reported that the absence of bowel and bladder dysfunction was the main factor predicting gait restoration.

It should be noted that Patchell *et al.* (2005) has been criticised for including 35% (18/51) of patients with spinal instability in the RT only arm, which acts as a confounding factor and tends to bias the findings towards surgery.

Factors that predict improved survival

Survival was assessed in six studies (Bach *et al.* 1990, Hill *et al.* 1993, Katagiri *et al.* 2005, Loblaw *et al.* 2003, Martenson *et al.* 1985 and Patchell *et al.* 2005) with a range of statistical tests.

A multivariate analysis conducted in the RCT by Patchell *et al.* (2005) found that survival was longer in patients treated with surgery (\pm RT) rather than RT alone, in patients with breast cancer, and involvement of the lower thoracic spine. The multivariate analysis in the prospective cohort by Katagiri *et al.* (2005) found a number of factors influencing survival these included: a favourable ECOG performance status, the absence of visceral or cerebral metastases, breast, prostate, or thyroid primary tumours, multiple myeloma, or malignant lymphoma, other carcinomas and sarcomas except hepatocellular, gastric and lung carcinoma, and the absence of multiple skeletal metastases. This study included patients with skeletal metastases. An earlier descriptive but systematic review by Bach (1990) also found that surgery and RT together were better at improving survival than either surgery or RT alone.

The large retrospective cohort by Loblaw *et al.* (2003) reported that survival was dependent on primary cancer site with lymphoma/myeloma, breast and prostate cancers being the most favourable. A small retrospective cohort by Martenson (1985) found that survival was more prolonged in patients with post treatment ambulatory function. The small retrospective study of breast cancer patients (Hill *et al.* 1993) supported this finding.

Other factors

Sphincter function

The only study reporting statistical data on this outcome was the RCT by Patchell (2005). The multivariate analysis found that surgery (\pm RT) rather than RT alone, and baseline Frankel score were significant for restoring sphincter function.

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Barcena A, Lobato RD, Rivas JJ, Cordobes F, de CS, Cabrera A, Lamas E (1984) Spinal metastatic disease: analysis of factors determining functional prognosis and the choice of treatment. *Neurosurgery* **15**, 820-827

Hill, M. E., Richards, M. A., Gregory, W. M., Smith, P., and Rubens, R. D.(1993) Spinal cord compression in breast cancer: A review of 70 cases. *Br.J.Cancer* 68[5], 969-973. 93

Katagiri, H., Takahashi, M., Wakai, K., Sugiura, H., Kataoka, T., and Nakanishi, K.(2005) Prognostic factors and a scoring system for patients with skeletal metastasis. *Journal of Bone and Joint Surgery-British*. Volume. 87B[5], 698-703. 05

Klimo, P., Thompson, C. J., Kestle, J. R., and Schmidt, M. H.(2005) A meta-analysis of surgery versus conventional radiotherapy for the treatment of metastatic spinal epidural disease. *Neuro.-Oncology* 7[1], 64-76. 05.

Loblaw DA, Perry J, Chambers A, Laperriere NJ (2005) Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the cancer care Ontario practice guidelines initiative's neuro-oncology disease site group. *Journal of Clinical Oncology* **23**, 2028-2037.

Loblaw, D A. Laperriere, N J. Mackillop, W J. (2003) A population-based study of malignant spinal cord compression in Ontario. *Clinical Oncology (Royal College of Radiologists)*. 15(4):211-7, 2003

Martenson, J. A., Jr., Evans, R. G., Lie, M. R., Ilstrup, D. M., Dinapoli, R. P., Ebersold, M. J. & Earle, J. D. (1985) Treatment outcome and complications in patients treated for malignant epidural spinal cord compression (SCC). *Journal of Neuro-Oncology*, 3: 77-84.

Patchell, R. A., Tibbs, P. A., Regine, W. F., Payne, R., Saris, S., Kryscio, R. J., Mohiuddin, M., and Young, B. (2005) Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. *Lancet* 366 (9486), 643-648. 05

Stark, R J. Henson, R A. Evans, S J. Spinal metastases. A retrospective survey from a general hospital. *Brain*. 105(Pt 1):189-213, 1982

Evidence tables

Klimo, P., Thompson, C. J., Kestle, J. R., and Schmidt, M. H. A meta-analysis of surgery versus conventional radiotherapy for the treatment of metastatic spinal epidural disease. *Neuro.-Oncology* 7[1], 64-76. 05.

Design: Meta-analysis

Aim: Aim of the meta-analysis was to critically and analytically review and compare the existing surgical and radiotherapy literature for the treatment of metastatic epidural spinal cord compression.

Inclusion criteria Prospective or retrospective cohort studies of adult participants with symptomatic metastatic spinal epidural disease who were treated either with surgery (with radiation pre- or post-operatively or not at all) or with radiation alone and followed up.

Surgical papers had to employ circumferential spinal cord decompression, reconstruction and stabilization. The radiation series had to contain the cumulative dose and schedule. In addition confounding was controlled by requiring certain demographic information: age, gender, site of primary disease, site of spinal disease. Surgical papers required the approach used, and any previous radiation, surgery or adjuvant therapy. For radiation papers any other treatments were required.

Exclusion criteria None reported

Population 28 studies

Interventions RT vs. surgery

Outcomes

Primary outcome ambulatory status

Secondary outcomes included: pain control, sphincter function, survival, local recurrence, complications.

Follow up -

Results

Surgical interventions:

24 articles between 1984 and 2002 were identified for the surgical interventions. 999 patients and 1020 treated spinal lesions.

Average age 56.4 years, 52% male.

Lesion location:

Thoracic spine 68%; cervical spine 11%; lumbosacral spine 21%

More than 50% of the primary tumours were from breast, renal and lung cancers.

17 papers (360 patients) had previous conventional EBRT

4 papers (28 patients) had previous decompressive laminectomy

10 papers (206 patients) had post-operative radiation therapy

Surgical approaches were classified as anterior (trans thoracic, retroperitoneal); posterior (laminectomy, transpedicular, costotransversectomy, lateral extracavitary); and combined.

Anterior 556 occasions (55%)

Posterior 395 occasions (39%)

Combined 68 occasions (6%)

Radiotherapy

4 articles between 1980 and 2002 were identified. 543 patients and 578 treated spinal lesions.

Average age 62.5 years, 49% male.

Lesion location:

Thoracic spine 68%; cervical spine 6%; lumbosacral spine 33%

Almost 70% of the primary tumours were from breast, lung and prostate cancers.

OUTCOME OF INTEREST	INTERVENTION	COMPARISON	OVERALL RESULT
Ambulation Success	Surgery N=999 Before 615 ambulatory After 843 ambulatory	Radiation N=543 Before 278 ambulatory After 357 ambulatory	Meta-analysis RR=1.28 [95%CI, 1.20-1.37; P<0.001] Favours surgery
	Cumulative success rate (effect size 0.85)	Cumulative success rate (effect size 0.64)	Overall Cumulative success 0.805 [95% CI, 0.758-0.852] Test for heterogeneity significant (p<0.001)
Independent factors: Age, gender, primary pathology, lesion distribution within the spine (at study level)	Not significant predictors of ambulatory success		Meta-regression Multivariate analysis
Treatment mode	When radiation was the only mode then success rate declined significantly.		Cumulative success rate (-0.243; 95%CI, -0.365 to -0.121; p<0.001)
Treatment mode	When radiation was the only mode then success rate declined significantly.		Meta-regression Univariate analysis Cumulative success rate (-0.205; 95%CI, -0.296 to -0.113; p<0.001)
Ambulation Rescue	Surgery N=999 Before 384 non-ambulatory After 228 regained ambulation	Radiation N=543 Before 265 non-ambulatory After 79 regained ambulation	Meta-analysis RR=1.99 [95%CI, 1.63-2.44; P<0.001] Favours surgery
	Cumulative rescue rate	Cumulative rescue rate	Overall Cumulative

	(effect size 0.58)	(effect size 0.26)	rescue 0.53 [95% CI, 0.431-0.621] Test for heterogeneity significant (p<0.001)
Treatment mode	When radiation was the only mode then treatment mode was not significantly associated with a decline in rescue rate.		Meta-regression Multivariate analysis Cumulative rescue rate (-0.353; 95%CI, -0.805 to 0.100; p<0.127)
Treatment mode		When radiation was the only mode then success rate declined significantly.	Meta-regression Univariate analysis Cumulative success rate (-0.318; 95%CI, -0.523 to -0.113; p<0.002)

Definitions

Ambulation success = the proportion of patients that maintained or regained the ability to ambulate after treatment

Rescue rate is the proportion of patients who regained ambulatory function

Cumulative success rate = effect size of pooled surgical and/or radiation studies

Author conclusions

“The results indicate that all patients with newly diagnosed metastatic spinal disease should be carefully evaluated for surgery as a primary treatment modality. Ambulatory function seems to be preserved and regained at a greater rate with surgery than with radiation. It also appears that surgery is superior at relieving pain and recovering sphincter function. However, the decision to pursue surgery must be tempered with the realization that significant morbidity and mortality exist. Patient selection is of utmost importance.”

General comments –

Methodology

Included studies were retrospective or prospective cohorts, although no quality assessment was reported. Significant heterogeneity was present on pooling the studies, even though studies were selected to control for as many potential covariates as possible. The main differences reported by the authors between the surgical and radiation papers were in the distributions of primary tumour types and the high frequency of prior radiation therapy in the surgical patients. Meta-regression was used to examine the relationship of covariates.

Loblaw DA, Perry J, Chambers A, Laperriere NJ (2005) Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the cancer care Ontario practice guidelines initiative's neuro-oncology disease site group. *Journal of Clinical Oncology* **23**, 2028-2037.

Design: Systematic review

Aim: This systematic review describes the diagnosis and management of adult patients with a suspected or confirmed diagnosis of extradural malignant spinal cord compression (MSCC).

Inclusion criteria

Exclusion criteria

Population RT 6 studies, surgery 17 studies

Follow up NA

Results

RT for patients without bony compression or spinal instability

Two retrospective studies and a pooled analysis of ambulatory outcomes of patients with and without bony compression suggest that the presence of bony compression is a negative predictive factor for achieving ambulation (see table).

No studies were found that address spinal instability.

The findings of the pooled analysis of studies with and without bony compression are suggestive of a better response to RT for ambulatory, assisted ambulatory and paraparetic patients who do not have bony compression, although no confidence interval was provided for the data of the single study. It is less clear whether paraplegic patients with no bony compression benefit from RT, since the 11.1% of PPL in the single study are within the confidence interval of the pooled results from the studies with bony compression.

It was also reported that patients with bony compression, particularly those with mild to moderate paraparesis, treated with RT are less likely to recover ambulation compared with paretic patients without bony compression (Chi² 7.64, P < 0.01).

Symptoms for MSCC include sensory changes, autonomic dysfunction, and back pain; however, back pain was not predictive of MSCC. A randomized study detected higher ambulation rates in patients with MSCC who received high-dose dexamethasone before radiotherapy (RT) compared with patients who did not receive corticosteroids before RT (81% v 63% at 3 months, respectively; P = .046). There is no direct evidence that supports or refutes the type of surgery patients should have for the treatment of MSCC, whether surgical salvage should be attempted if patient is progressing on or shortly after RT, and whether patients with spinal instability should be treated with surgery.

Author conclusions:

Patients with symptoms of MSCC should be managed to minimize treatment delay. MRI is the preferred imaging technique. Treatment for patients with

MSCC should consider pre-treatment ambulatory status, co-morbidities, technical surgical factors, the presence of bony compression and spinal instability, potential surgical complications, potential RT reactions, and patient preferences.

General comments - Evidence level:

This review is systematically conducted. It sets out clear clinical questions, systematically searches for relevant evidence, broadly outlines inclusion and exclusion criteria of included studies, grades the included evidence and summarises either descriptively or by statistically pooling the raw data where possible. The methodology of this review is of high quality but this is superseded by the evidence level of the included studies, which is low.

An important factor omitted is the detailed inclusion criteria required for case series studies. There are numerous studies in the evidence body and only a select number are included. Further information would have explained inclusion further.

Loblaw DA; Perry J; Chambers A; Laperriere NJ. Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. (2005) *J Clin Oncol* 23(9):2028-2037

Design: Systematic review of combined study designs, evidence level: 3 (observational studies)

Country: international

Aim: What are the indications for RT in the Management of MSCC?

Inclusion criteria

Studies: retrospective and prospective case series studies and one cross sectional study

Patients:

1. patients with bony compression or spinal instability
2. patients with sub-clinical cord compression (results not reported; not in PICO)

Exclusion criteria

Patients with intramedullary or leptomeningeal cord compression are not considered in this report.

Population

Adult patients with confirmed diagnosis of extradural malignant spinal cord compression (MSCC).

Interventions

Radiotherapy as primary treatment

Outcomes

Rate (and ability) of retaining or regaining ambulation

Note: For the purposes of this systematic review, ambulatory refers to patients who are able to walk with or without assistance and who may be mildly paraparetic; paretic refers to patients who are non-ambulatory and paraparetic; and paraplegic

refers to those patients who have only a flicker of or no muscle movement.

Results

The results from 2 retrospective reviews and a pooled analysis of ambulatory outcomes of patients with and without bony compression (studies listed in reference list below) imply that the presence of bony compression is a negative predictive factor for achieving ambulation after RT.

Loblaw *et al* 2005 reports studies that included patients without bony compression treated with RT:

patients who are ambulatory, have ambulatory rates of 100%,
ambulatory with assistance, have ambulatory rates of 94%,
paraparetic, or have ambulatory rates of 60%,
paraplegic have ambulatory rates of 1%,

Compared to studies of patients where bony compression is not excluded, retain or regain ambulation (with or without assistance):

patients who are ambulatory, have ambulatory rates of 92%
ambulatory with assistance, have ambulatory rates of 65%
paraparetic, or have ambulatory rates of 43%
paraplegic have ambulatory rates of 14%

Patients with bony compression, particularly those who have mild to moderate paraparesis, who are treated with RT were less likely to recover ambulation compared with paretic patients without bony compression (χ^2 7.64, $P \leq .01$).

Loblaw *et al* 2005 report that no studies were identified that specifically addressed spinal instability. Despite the lack of evidence, 3 studies reported that spinal instability to be a surgical indication.

General comments

Opinions Of The Neuro-Oncology Cancer Disease Site Group - Cancer Care Ontario Evidence Based Guideline Program (Experts have developed the recommendations for the clinical guideline based on the evidence presented in the Loblaw 2005 systematic review.)

References of Included Studies:

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Maranzano E, Latini P, Beneventi S, et al (1998) Comparison of two different radiotherapy schedules for spinal cord compression in prostate cancer. *Tumori* 84:472-477

Pigott KH, Baddeley H, Maher EJ (1994) Pattern of disease in spinal cord compression on MRI scan and implications for treatment. *Clin Oncol (R Coll Radiol)* 6:7-10

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Barcena A, Lobato RD, Rivas JJ, Cordobes F, de CS, Cabrera A, Lamas E (1984) Spinal metastatic disease: analysis of factors determining functional prognosis and the choice of treatment. *Neurosurgery* 15, 820-827

Design: Predates systematic review methods, analysis of a series of studies of surgical and radiotherapy treatment for spinal metastases.

Country:, setting:

Aim:

To establish simple criteria to improve the choice of treatment in patients with spinal metastases.

Inclusion criteria: Studies were selected for comparison of two “homogeneous” therapy groups with a uniform distribution of prognostic variables (pre-therapy neurological status, incidence of radiosensitive tumours, etc)

Exclusion criteria: Studies with imprecise definitions of either the materials and methods or results.

Population number of patients = 31 studies (2300 patients)

Interventions:

Surgical group – 19 studies of surgical treatments as the main therapy (majority were laminectomy). Most patients also received radiotherapy.

Nonsurgical group – 12 studies with patients receiving radiotherapy as the main treatment

Outcomes Factors influencing functional prognosis

Follow up

Results

Tumour biology

Probability of therapy success rate for all treatments by tumour cell type was statistically significant in 13 studies ($P < 0.001$). However for functional outcomes

there was no correlation between tumour type and treatment mode (radiotherapy or surgery and radiotherapy) in 7 studies. The authors report that these data show that high tumour radiosensitivity is significantly related to low aggressiveness, both local and systemic, and favourable prognosis and that the contrary is true for radioresistant tumours.

Neurological grade at time of treatment

Success rates by neurological grade for surgery and radiotherapy or radiotherapy alone were not statistically significantly different with the exception of paraplegic patients ($p < 0.05$), where surgery and radiotherapy were more beneficial (10 studies).

Completeness of myelographic block

The degree of myelographic block did not correlate with the neurological grade between the two treatment modalities (2 studies). However the completeness of block did influence the results of therapy (from 2 studies): no block vs complete block 37% pooled success rate ($P < 0.02$) favouring no block.

Tumour topography

The location of the tumour within the spinal canal influences the surgical prognosis (3 studies). There is a positive correlation ($p < 0.01$) between the location of the extradural metastatic deposit and response to laminectomy. A posterior location has a significantly better prognosis than anterior compression ($p < 0.005$). However in a very small series of patients who failed to improve by laminectomy and/or radiotherapy, the anterior approach was more successful (too small a sample to measure significance).

The presence of vertebral collapse (3 studies) did not influence prognosis significantly after laminectomy ($p > 0.9$). However the authors state that this finding should be viewed with caution because laminectomy does not necessarily alleviate anterior cord compression caused by vertebral collapse, and may increase spinal instability.

Relative influence of prognostic factors on choice of treatment

Definitions:

Neurological grade:

- I able to walk
- II capable of some movement but unable to walk
- III complete functional cord transaction

Neurological grade

For all therapies response of radiosensitive (4 studies) vs. radioresistant (3 studies) tumours were significantly different for patients with neurological Grades II and III, than Grade I (better response for grade I). See table below.

When these findings were compared to the pre-therapeutic neurological grade, it was found that tumour biology had a stronger prognostic significance than neurological grade.

OUTCOME OF INTEREST	INTERVENTION	COMPARISON	RESULT
Response to all therapies	Radiosensitive tumours	Radioresistant tumours	
Neurological grade I	67% success	73% success	$p > 0.5$
Neurological	63% success	35% success	$p < 0.01$
			$p < 0.001$

grade II	34% success	2% success	p<0.01
Neurological	54%	39%	
grade III			
Total			

Another analysis comparing extreme prognostic factors on success rates obtained by all therapies for factors related to tumour biology (neurological grade III and radioresistance vs myelographic block, anterior or posterior compression, no block), and factors not related to tumour biology (neurological grade III vs. myelographic block, anterior or posterior compression) found that the influence of extreme factors on the final prognosis was not statistically different unless tumour biology was taken into account.

The authors concluded that tumour biology seems to have a stronger prognostic significance than neurological grade, myelographic block or tumour location in the spine.

General comments – No table of the characteristics of individual studies or a quality assessment were provided. Some of the statistical tests were relatively weak in comparison to what is available nowadays, e.g., no confidence intervals were provided. However this work was completed before the methodology for evidence synthesis was developed.

Patchell, R. A., Tibbs, P. A., Regine, W. F., Payne, R., Saris, S., Kryscio, R. J., Mohiuddin, M., and Young, B. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial.[see comment]. *Lancet* 366[9486], 643-648. 05.

Design: RCT

Level1-

Country:USA, setting: Multi-institutional

Aim: To determine the value of surgery in the management of Metastatic epidural spinal cord compression (MESCC) by comparing the efficacy of direct decompressive surgery plus postoperative radiotherapy with that of radiotherapy alone in a randomised trial.

Inclusion criteria Patients at least 18 years old with a tissue-proven diagnosis of cancer (not of CNS or spinal column origin) and MRI evidence of MESCC were eligible for the study. Patients also had to have at least one neurological sign or symptom (including pain) and not have been totally paraplegic for longer than 48 h before study entry. The MESCC had to be restricted to a single area, which could include several contiguous spinal or vertebral segments. Patients also had to have a general medical status good enough to be acceptable surgical candidates and an expected survival of at least 3 months.

Exclusion criteria Patients with a mass that compressed only the cauda equina or spinal roots and those with multiple discrete compressive lesions were excluded (unless they had one area of compression and multiple non-compressive lesions). Patients with certain radiosensitive tumours (lymphomas, leukaemia, multiple myeloma, and germ-cell tumours) were excluded, as were patients with pre-existing or concomitant neurological problems not related directly to their MESCC (e g., brain metastases). Additionally, patients with previous MESCC and those who had received spinal radiation such that they were unable to receive the study dose were excluded.

Population number of patients = 101 (50 surgery followed by radiotherapy (RT), 51 RT alone)

Interventions Radiation group: RT started within 24 hours after randomization. 30Gy given in 10 fractions of 3Gy. Treatment was delivered to a port including one vertebral body above and below the visible lesion.

Surgery group: Operated on within 24 hours of randomisation. No operative techniques or fixation devices were specified. The aim was to provide immediate direct circumferential decompression of the spinal cord. A variety of approaches were used according to tumour location and patient circumstances. Stabilization of tumours in all locations was performed if spinal instability was present; cement (methyl methacrylate), metallic rods, bone grafting, or other fixation devices were used.

Outcomes

The primary endpoint of the study was the ability to walk after treatment. A patient was deemed ambulatory if he or she could take at least two steps with each foot unassisted (4 steps total), even if a cane or walker was needed. We assessed ambulatory status in two ways, and both methods were pre-specified. The combined ambulatory rate was the percentage of patients who maintained or regained the ability to walk immediately after completion of radiotherapy and quantified the initial success rate of treatment. Ambulatory time after treatment was a measure of long-term success.

Secondary endpoints were urinary continence, changes in Frankel functional scale scores and American Spinal Injury Association (ASIA) motor scores, and use of

corticosteroids and opioid analgesics. Corticosteroid use was assessed by calculating and comparing mean daily dexamethasone equivalent doses. Pain relief was assessed by calculating and comparing mean daily morphine equivalent doses. Survival time after treatment was also recorded. All time dependent endpoints were measured from the day of randomisation until death or last follow up.

Follow up Patients had neurological assessments before treatment, weekly during radiotherapy, and within 1 day after completion of treatment. Patients then had regular study follow-up assessments every 4 weeks until the end of the trial or death. Patients were also reassessed at any time they had symptoms suggestive of neurological progression.

Results

Ambulation:

The combined post-treatment ambulatory rate in the surgery group was 84% (42/50) and 57% (29/51) in the radiation group.
p value 0.001 with an odds ratio of 6.2 (95% CI 2.0–19.8) favouring surgery

Patients in the surgery group retained the ability to walk for significantly longer than did those in the radiation group (median 122 days vs 13 days, $p=0.003$). Multivariate analysis showed surgery ($p=0.0017$) and pretreatment Frankel score ($p=0.0008$) to be associated with longer ambulatory time.

In the subgroup of patients who could walk at study entry, 94% (32/34) in the surgery group continued to walk after treatment compared with 74% (26/35) in the radiation group ($p=0.024$). Patients in the surgical group were able to walk for a median of 153 days compared with 54 days in the radiation group (odds ratio 1.82 [95% CI 1.08–3.12] $p=0.024$

32 patients (16 in each group) entered the study unable to walk; of these, ten patients (62%) in the surgery group regained the ability to walk compared with three patients (19%) in the radiation group ($p=0.012$). Additionally, non-ambulatory patients treated with surgery walked for a median of 59 days compared with a median of 0 days for patients in the radiation group ($p=0.04$).

Multivariate analyses

Multivariate analyses were based on a Cox regression model. The covariates used were treatment group, age, sex, primary tumour type, spinal level involved, predominant position of metastasis in vertebra, stability of spine, Frankel and ASIA scores at study entry, length of time motor symptoms associated with cord compression were present before treatment, and length of time between diagnosis of the primary tumour and development of cord compression. All these analyses were pre-specified.

Multivariate analysis showed surgery ($p=0.0017$) and pretreatment Frankel score ($p=0.0008$) to be associated with longer ambulatory time.

Multivariate analysis showed surgery ($p=0.0048$), Frankel score ($p=0.016$), and breast primary tumour ($p=0.029$) to be associated with longer ambulatory times.

Surgical treatment resulted in significant differences in maintenance of continence, muscle strength (ASIA scores), functional ability (Frankel scores), and increased survival time (Table 2 of

paper).

General comments –

A possible limitation of the study was patient selection bias. The patient population studied consisted of those patients for whom surgery would be “regarded as a realistic treatment option”. Patients with very radiosensitive tumours, multiple areas of spinal cord compression, or total paraplegia for longer than 48 h were excluded. Therefore, the results of this trial cannot be used to justify surgery in all patients with MSCC and apply only to patients comparable to those included in this study.

Byrne (2006) has commented on this RCT and a commentary by Loblaw (2005). It was noted that the outcomes reported by the RT group were significantly worse than those reported elsewhere. Loblaw concluded that the ambulatory outcome of paraparetic patients treated with RT who have bony compression was worse than those without bony compression. This may explain the worse outcomes of RT reported by Patchell because 36% of patients randomised to RT had spinal instability. Many investigators use spinal instability as a criterion for surgery. It would be useful to know whether the reported benefit of surgery would be found if patients with mechanical instability were analysed separately.

References:

Byrne TN, Borges LF, Loeffler JS. Metastatic epidural spinal cord compression: update on management. [Review] *Seminars in Oncology*. 33(3):307-11, 2006

Loblaw DA, Perry J, Chambers A, Laperriere NJ (2005) Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the cancer care Ontario practice guidelines initiative's neuro-oncology disease site group. *Journal of Clinical Oncology* **23**, 2028-2037.

Katagiri, H., Takahashi, M., Wakai, K., Sugiura, H., Kataoka, T., and Nakanishi, K. Prognostic factors and a scoring system for patients with skeletal metastasis. *Journal of Bone and Joint Surgery-British.*(2005). 87B[5], 698-703. 05.

Design: Prospective cohort (July 1992 – Dec 1999)
Country: Japan, setting: Not stated

Level 2+

Aim:

To determine prognostic factors from clinical features obtained at presentation, and create a prognostic model for patients with bone metastases.

Inclusion criteria All patients with skeletal metastases who had treatment either surgical or non-surgical.

Exclusion criteria Malignant lymphoma of bone without an extraosseous lesions; solitary plasmacytoma;

Population number of patients = 350, 199 (57%) male and 151 (43%) female. Mean age 59 years (14 to 88).

Lung cancer most common 82/350 (23%)

Breast cancer 64/350 (18%)

Prostate cancer 28/350 (8%)

Multiple myeloma 24/350 (7%)

Interventions 247 (71%) treated non-surgically (2 palliative care, 27 had chemotherapy, 94 had RT alone, 126 had combined RT and chemotherapy) 101 treated by surgery: 56 had internal fixation or endoprosthetic replacement; 37 had decompression and instrumentation; 1 had endoprosthetic replacement and spinal instrumentation; 6 had resection without reconstruction; amputation in one.

Outcomes

Prognostic factors listed in results.

Follow up 24 months (24 patients lost to follow-up). Mean follow-up 13 months (2 weeks to 88 months) for those who died; 39 months (1 to 142) for survivors.

Results

Axial bone metastases in 222 (63%) of patients

Appendicular bone metastases in 41 (12%)

Appendicular and axial bone metastases in 87 (25%)

On multivariate analysis site of primary tumour, ECOG performance status 3 or 4, visceral or cerebral metastases, previous chemotherapy, multiple skeletal metastases were found to be significant, independent prognostic factors for survival.

Factor (1 st factor as reference)	P value	Hazard ratio (95%CI)
Gender (F, M)	0.423	0.891 (0.672 to 1.181)
Age (>60 yr, <60 yr)	0.727	1.050 (0.800 to 1.378)
Performance Status (0 to 2.0, 3 to 4)	0.008	1.495 (1.112 to 2.008)
Neurological deficits (absent, present)	0.953	1.009 (0.743 to 1.372)
Primary site		
Group1 (reference)		
Group2	<0.001	2.479 (1.699 to 3.619)
Group3	<0.001	5.189 (3.665 to 7.346)

Remaining primary disease (absent, present)	0.16	1.304 (0.901 to 1.887)
Visceral or cerebral metastases (absent, present)	<0.001	2.217 (1.697 to 2.897)
Previous chemotherapy (absent, present)	0.017	1.538 (1.081 to 2.190)
Disease free interval before skeletal metastases (absent, present)	0.15	1.343 (0.899 to 2.006)
Location of skeletal metastases		
Appendicular (reference)		
Axial bone	0.221	1.354 (0.834 to 2.200)
Appendicular and axial	0.504	1.204 (0.698 to 2.078)
Multiple skeletal metastases (absent, present)	0.048	1.404 (1.004 to 1.964)
Pathological fracture (absent, present)	0.288	1.155 (0.885 to 1.508)

Group 1: breast, prostate, thyroid, multiple myeloma, malignant lymphoma

Group 2: carcinoma and sarcoma other than groups 1 and 3

Group 3: Hepatocellular, gastric and lung carcinoma.

Significant prognostic factors and scores

A prognostic score was developed using the regression coefficients of the multivariate model. The score was calculated by summing all the scores for individual factors. Each patient was scored from 0 to 8, and divided into nine groups according to prognostic score.

Prognostic factor	Score	
Primary lesion	Rapid growth	3
	Slow growth	0
	Moderate growth	2
Visceral or cerebral metastases.	2	
Performance status (ECOG) 3 or 4	1	
Previous chemotherapy	1	
Multiple skeletal metastases.	1	

Rapid growth: hepatocellular, gastric and lung carcinoma

Moderate growth: other carcinoma and sarcoma

Slow growth: breast, prostate, thyroid, multiple myeloma, malignant lymphoma

Survival

Overall survival rate of entire group:

0.66 at 6 months
 0.48 at 12 months
 0.33 at 24 months
 0.23 at 36 months

Survival by prognostic scores are shown in the table below:

Prognostic score	Survival at 6 mths	12 mths	24 mths
0 to 2	0.979 (0.950 to 1.000)	0.891 (0.828 to 0.955)	0.753 (0.663 to 0.843)
3 to 5	0.706 (0.633 to 0.78)	0.488 (0.406 to 0.570)	0.278 (0.202 to 0.353)
6 to 8	0.313 (0.224 to 0.401)	0.109 (0.049 to 0.169)	0.023 (0.000 to 0.053)

General comments –

Author conclusions:

General comments:

The authors state that the finding of previous chemotherapy as a prognostic factor does not indicate that chemotherapy makes survival worse. The reasons for this are that patients in an advanced state of disease at diagnosis are given chemotherapy, and those with previous chemotherapy have fewer options when skeletal metastases occur. Disease free interval from primary cancer to skeletal metastases did not influence survival.

The scoring system can be used to determine the optimal treatment for patients with pathological fractures or epidural compression.

Definitions

Performance status (PS) used ECOG scale. Two categories used were PS 0 to 2 and 3 to 4.

Limitations

Patient sample with skeletal metastases. Not clear how many patients had spinal metastases only.

Imaging studies with radiography and scintigraphy were conducted in all patients to assess spread of bone metastases. MRI used in 165 patients for skeletal metastases. Histology not reported.

Bach, F., Larsen, B. H., Rohde, K., Borgesen, S. E., Gjerris, F., Boge-Rasmussen, T., Agerlin, N., Rasmusson, B., Stjernholm, P., and Sorensen, P. S. Metastatic spinal cord compression. Occurrence, symptoms, clinical presentations and prognosis in 398 patients with spinal cord compression. Acta Neurochir.(Wien.) 107[1-2], 37-43. 90.

Design: Retrospective cohort (1979-1985)

Level 3

Country:Denmark, setting: Hospital

Aim: To elucidate the occurrence, initial symptoms, symptom development, treatment modalities and prognosis of patients suffering from spinal cord or cauda equine compression (SCC) secondary to cancer

Inclusion criteria: All patients admitted with SCC during the specified dates in Eastern Denmark. Confirmed diagnosis of SCC.

Exclusion criteria none reported

Population number of patients = 398, average age 63 years (range 14-84); 260 male (65%) 138 female (35%)

Main primary tumours were: prostate (19%), lung (18%), breast (14%), kidney (10%)

Interventions

- Decompressive laminectomy (105 pts, 31%)
- Laminectomy with additional radiotherapy (RT). (91 pts, 26%)
- RT alone given as a single posterior field, with at least one adjacent vertebra above and below the spinal block. Doses were 20-45Gy in 5-20 fractions during 6-28 days. (149 pts, 43%)
- Surgery if the patient had no known primary tumour, or if previous RT for epidural metastases at the same spinal level.
- A few patients did not receive any specific therapy.
- Corticosteroids were not administered consistently. 42% of patients

Outcomes

Motor function

Survival

Sphincter function

Follow up Not reported

Results

Factors

Motor function

“Pre-treatment motor deficits seem to be the most important determinant for motor function after treatment. A total of 79% of patients able to walk before treatment remained ambulatory, whereas only 21% of non-ambulatory paraparetic patients and 6% of paralytic patients regained walking ability.” A higher proportion of patients treated with laminectomy followed by RT (59% improved) seemed to respond better than those treated with laminectomy (46% improved) or RT alone (35% improved). However when pre-treatment motor function was taken into account, no significant differences were observed.

A further analysis is provided by Sorensen (1990):

Sorensen (1990) reporting on the same data found no significant differences in the distribution of treatment modalities between the groups of pre-treatment ambulatory, non-ambulatory, and paralytic patients ($P= 0.12$, Ch^2). In ambulatory patients before intervention no treatment modality was found to be superior

($p=0.62$, Ch^2); this was also the case for non-ambulatory and paralytic patients. However, a comparison of all non-ambulatory patients treated with RT vs. laminectomy and RT found better gait restoration for the combined treatment group $P = 0.05$, Ch^2).

When assessing improvement vs. unchanged vs. worse in motor and sphincter function Sorensen reported that the combination treatment of laminectomy and RT was significantly superior to RT alone ($P=0.001$, Ch^2) but not to laminectomy alone.

When assessing the treatment response to these outcomes by primary tumour type no significant differences were found ($P= 0.54$, Ch^2)

Survival

Average survival was 3.1 months (range 0.4-70.8 months).

Patients with breast, prostate and kidney cancers survived longer than those with lung cancer. The number of long-term survivors (> 12 months after diagnosis of epidural metastases) were:

20 with breast cancer (45% of those with br ca)

23 with prostate cancer (38%)

8 with lymphoma/myeloma (17%)

3 with lung cancer (5%)

Sorensen reported that survival of patients who had laminectomy followed by RT (0.4-70.8 months) was significantly longer than any other group ($P=0.004$, Lee-Desu statistic; RT alone 0.0-39.8 months; laminectomy alone 0.0-61.3 months).

However, tumour type is the major determinant for survival length after diagnosis of MSCC with breast cancer patients surviving a mean of 14 months, prostate 11.7 months, lymphoma/myeloma 8.6 months, kidney 8.5 months, lung 3.0 months and other cancers 6.3 months.

Sphincter function

“No major changes were seen in the number of patients with normal sphincter function or in the number needing a catheter after treatment.”

General comments –

An associated paper contains further analyses that have been included in this table:

Sorensen S et al. Metastatic epidural spinal cord compression. Results of treatment and survival. *Cancer* 65:1502-1508 (1990)

Hill, M. E., Richards, M. A., Gregory, W. M., Smith, P., and Rubens, R. D. Spinal cord compression in breast cancer: A review of 70 cases. *Br.J.Cancer* 68[5], 969-973. 93.

Design: Retrospective cohort (1976-1990)
Country: London UK, setting: One hospital

Level 3

Aim: To look for risk factors which might assist in the early detection of cord compression, and to assess determinants of functional outcome and survival following cord compression.

Inclusion criteria all records of patients with spinal cord or cauda equina compression secondary to breast cancer at Guy's Hospital.

Diagnostic criteria were sensory symptoms, weakness, sphincter disturbance or a combination of these in association with demonstrable neurological signs and at least one abnormal radiological investigation corresponding to the site of compression.

Exclusion criteria: Patients with neurological deficits due to nerve root compression, limb girdle plexopathy, peripheral neuropathy or epidural compression of non-metastatic origin.

Population number of patients = 70; median age at diagnosis 51 years (range 30-80).

Interventions:

Surgical decompression if the patient was sufficiently well, had rapidly progressive signs or the site had been irradiated previously (21 cases, 30%). Radiotherapy was given if patients had more slowly progressive symptoms or signs at previously non-irradiated sites (43 cases, 61%). 6 cases received neither of these treatments.

Outcomes

Ambulation
Survival
Time to SCC

Follow up Not reported.

Results

Median interval between diagnosis of breast cancer and development of cord compression was 42 months (range 16 days to 25 years)

Median age of onset SCC 54 years.

Radiological evidence of bone metastases in 65 (93%) patients at one or more skeletal sites before onset of neurological symptoms, 46 had spinal metastases.

Commonest symptom at time of SCC was motor weakness (96%) followed by pain (94%), sensory disturbance (79%) and sphincter disturbance (61%). Before treatment 31 (45%) were ambulant.

Ambulation and functional outcomes

23/24 (96%) of patients receiving either RT or surgery maintained the ability to walk after treatment.

13/29 (45%) who were unable to walk regained this ability after treatment.

In the majority of cases sphincter control, pain and sensory symptoms either improved or remained stable following treatment. No differences in functional outcomes were observed between treatment groups.

Survival

Median survival following diagnosis of SCC was 4 months (range 0-56 months). No difference in survival was observed between treatment modalities. Survival of 6 patients receiving supportive care only was poor (4-52 days, median 12 days).

Patients able to walk at the start of treatment survived longer than those unable to walk, but the difference was not statistically significant ($p=0.11$).

Survival of patients able to walk after treatment was statistically significantly longer than those not able to walk ($p=0.001$), this was not dependent on

treatment modality.

Time to SCC

Time from diagnosis of primary tumour was the other significant predictor of survival. Those developing SCC after 3 years had improved survival ($p < 0.04$). This is covered in topic 5 A.

No other factors predicted survival including number of metastatic sites.

Martenson, J. A., Jr., Evans, R. G., Lie, M. R., Ilstrup, D. M., Dinapoli, R. P., Ebersold, M. J. & Earle, J. D. (1985) Treatment outcome and complications in patients treated for malignant epidural spinal cord compression (SCC). *Journal of Neuro-Oncology*, 3: 77-84.

Design: Retrospective cohort (1980-1981)
Country: USA, setting: One hospital

Level 3

Aim: To provide evidence for early diagnosis and treatment of SCC as an emergency leads to an improved outcome, and the impact of successful treatment on survival.

Inclusion criteria Biopsy proven malignant tumour. 96% (62 patients) had myelography confirmation of an epidural mass, the remainder had back pain, sensory loss and LE weakness (5 patients).

Exclusion criteria Patients with prior RT treatment and unable to receive treatment to the entire tumour; patients with no tissue diagnosis; patients who received treatment at other centres.

Population number of patients = 66 with 67 episodes of SCC. 22 females, 44 males. Median age 61 years (17 to 78 years). Most common primary tumours were prostate cancer, breast cancer, lung, multiple myeloma, renal cell carcinoma.

Neurological impairment was assessed (standard criteria from "Clinical examinations in neurology" 1971, Aronson, A et al.) and patients divided into 3 groups based on motor function at initiation of treatment.

Group 1	Ambulatory	35 cases (52%)
Group 2	Non-ambulatory	29 cases (43%)
Group 3	Paraplegic	3 cases (4%)

Interventions:

Radioresponsive tumours from 46 (67%) patients were treated with RT (lymphoma, small cell lung, testicular, multiple myeloma). Total doses varied between 1750 and 4200 rads in 5-23 fractions over 5-47 days. 4 of these patients also had decompressive laminectomy.

Less radioresponsive tumours from 21 (31%) patients were treated with initial decompressive laminectomy (prostate, breast, non-small cell lung, renal cell carcinoma, adenocarcinoma, others). In 17 (81%) of these postoperative RT was given.

Steroids were given in 94% of cases.

Outcomes Survival, ambulation, bowel and bladder dysfunction.

Follow up 19.8 months or until death. Four patients died before completion of treatment.

Results

Ambulation

Primary RT and surgical treatment were equally effective. 64% (27/42) of RT group and 57% (12/21) of surgery group were ambulatory after treatment. (No statistical test reported).

100% of group 1 for motor function were ambulatory post treatment.
24% (4/17) RT patients and 27% (3/11) surgical patients in group 2 regained the ability to walk.

None of group 3 patients regained ambulation.

Group 1 vs group 2 $p < 0.001$ (chi squared test).

Primary RT and surgical treatment appeared equally effective for groups 1 and 2 when comparing the less radioresponsive tumours, however the sample was small and no statistical test was reported.

Patients who were ambulatory following treatment had a high probability of remaining so (87% at 1 year and 73% at 2 years).

Bowel and bladder dysfunction (BBD)

Bowel and bladder dysfunction was significantly more common in group 2 (21/28, 75%) than group 1 (10/32, 31%) patients. ($p < 0.001$).

A significantly higher proportion of patients with BBD (20/34, 59%) were non-ambulatory at completion of treatment in comparison to patients without BBD (3/29, 14%), ($p < 0.001$).

Within each motor function subgroup the presence of BBD did not predict a significantly higher probability of worse outcomes (no data provided).

Survival

Median survival of the entire group was 72 days.

Survival of ambulatory patients at completion of treatment was significantly better than non-ambulatory patients ($p < 0.03$).

General comments –

The definitions of ambulatory status for groups 1 and 2 were referenced in the article.

The effects of other non-treatment related factors such as tumour histology were not investigated.

Author conclusions:

“Effective treatment of MSCC is associated with improved survival, with significantly better survival in patients who are ambulatory following treatment.

Bowel and bladder dysfunction is a poor prognostic sign but likely to be a covariate of pre-treatment motor function”.

Stark, R J. Henson, R A. Evans, S J. Spinal metastases. A retrospective survey from a general hospital. *Brain*. 105(Pt 1):189-213, 1982

Design: Retrospective cohort (1968 to 1978), evidence level 3

Country:UK, setting: One hospital

Aim:

To estimate prognosis for immediate and long-term outcomes, and correlate with patient characteristics to provide a guide for the best form of treatment.

Inclusion criteria Patients diagnosed with cancer and had spinal metastases with a neurological deficit. Histological confirmation. Patients had cauda equine compression, myelopathy, or radicular compression.

Exclusion criteria Patients with pain only or a deficit ascribed to limb girdle plexuses or peripheral nerves. Lymphoma and haematological malignancies.

Population number of patients = 131
Most common tumour lung carcinoma.
18 patients site of primary not known.
Ratio male to female 66:65

Interventions

Surgical decompression
RT
Surgery followed by RT
RT then surgery
Symptomatically

Outcomes

Analyses conducted by primary diagnosis:

Group 1 bronchus

Group 2 breast

Group 3 other known primary sites: (3A= 16 cases; 3B= 17 cases)

3A kidney, rectum, colon, pancreas, liver, teratomas, testis, mesotheliomas, leiomyosarcomas

3B bladder, prostate, cervix, melanoma, seminoma of testis, salivary cylindroma

Group 4 primary site undetermined

Follow up

Results

Breast cancer was the only group (2) where the probability of being ambulant post treatment was greater than at presentation.

Factors affecting outcome:

Site of primary tumour

Severity of neurological signs, there was a trend for better outcome when the initial deficit was less severe.

Findings from different treatment modes did not favour one type of treatment:

Treatment of cord or cauda equine compression by surgery or RT resulted in improvement in 37% and 33% respectively, 20% and 23% could walk at 6 mths.

Exclusion of primary tumour type from the analysis did not alter the results.

There were no statistically significant differences between surgery or RT groups when all patients were analysed together.

Conclusion

Severe neurological deficit on presentation is associated with a less frequent response to treatment and poor long-term outlook.

Loblaw, D A. Laperriere, N J. Mackillop, W J.

A population-based study of malignant spinal cord compression in Ontario.

Clinical Oncology (Royal College of Radiologists). 15(4):211-7, 2003

Design: Retrospective cohort from population cancer registry (Jan 1990 – Dec 1995)

Level 3

Country:Canada, setting: Ontario hospitals

Inclusion criteria Episodes of MSCC were identified on the basis of analysis of diagnostic codes and procedure codes recorded in computerized hospital separation records from all Ontario hospitals, and radiotherapy treatment records from all Ontario cancer centres. For the purposes of this study, ICD Code 336, corresponding to

myelopathy or spinal cord compression, was accepted as diagnostic of MSCC, except for subcategories 336.0, 336.2, and 336.8, which correspond to myelopathies that are not directly cancer related. Patients with ICD 198.3 corresponding to a secondary malignant neoplasm to brain or spinal cord, and 198.4 'secondary to cerebral or spinal cord meninges' were also accepted as having a spinal cord compression, if they received radiotherapy to the spine, underwent surgical decompression (CCP 160), and did not receive radiotherapy to the brain within 1 month of the diagnosis of ICD 198.3 or ICD 198.4.

Exclusion criteria Subcategories 336.0, 336.2, and 336.8, which correspond to myelopathies that are not directly cancer related.

Population number of patients = 3458 with at least one admission for MSCC

Interventions RT (60.2%), surgery (16.1%) or neither (23.7%)

Outcomes Survival

Follow up Not reported.

Results

Survival

Median survival after first admission with MSCC was 2.9 months.

8.4% were alive at 3 years.

The median survival of untreated cases was approximately 1 month, compared to 3 months overall.

Table 3 in the article shows that survival was strongly dependent on primary cancer site. Survival at 1 year was less than 10% for melanoma, colorectal and lung cancers, and more than 20% for lymphoma, myeloma, prostate and breast cancers. At 3 years survival was less than 10% for most cancers with the exception of lymphoma and myeloma.

Clinical Evidence for case selection for radiotherapy

For patients with an established diagnosis of MSCC, what factors predict for successful outcomes (mobility, continence, lack of pain, survival) following radiotherapy?

Short Summary

The evidence identified is variable in quality (Graham *et al.* 2006; Helweg-Larsen *et al.* 2000; Kim *et al.* 1990; Kovner *et al.* 1999; Huddart *et al.* 1997; Loblaw *et al.* 2005; Maranzano *et al.* 1991, 1992, 1997, 2005; Rades *et al.* 2007a, 2007b, 2008). Most studies reported on the most common factors to influence post treatment RT for patients with MSCC. There was general agreement between them for ambulatory status before RT, absence of visceral metastases and a favourable histology to improve survival. Fewer factors were reported for the effects on motor function however a favourable histology and ambulatory status before treatment were the most common.

PICO

POPULATION	FACTORS	OUTCOMES
Patients with an established diagnosis of MSCC	For example: 1) grade of malignancy 2) visceral metastases 3) bone metastases 4) Karnofsky performance index	Accuracy of prediction of successful outcomes: mobility, continence, lack of pain Karnofsky performance index Survival Unsuccessful outcomes: complete paraplegia death within 30 days

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

The evidence identified is variable in quality, including a small RCT, prospective and retrospective case series studies. Most studies focused on pre and post treatment motor function and survival.

Two RCTs were relevant to this question, and comparisons were made between different RT fractions (Maranzano *et al.* 2005) and different dexamethasone doses with RT (Graham *et al.* 2006). Neither of the interventions being compared had any effect on the outcomes of interest.

The majority of patients had breast or prostate cancer, reflecting the prevalence of these carcinomas. Exceptions were three small studies: the prospective study by Maranzano *et al.* (1997) that recruited patients with a poor prognosis; Maranzano *et al.* (1992) breast cancer patients only; Huddart *et al.* (1997) prostate cancer patients only.

Most studies reported on the most common factors to influence post treatment RT for MSCC. There was general agreement between them for ambulatory status before RT, absence of visceral metastases and a favourable histology to improve survival. Fewer factors were reported for the effects on motor function however a favourable histology and ambulatory status before treatment were the most common. Some studies reported other statistically significant factors. Those that differed in not supporting some of these

findings or reporting other factors were studies of particular subgroups e.g. patients with a poor prognosis, breast cancer, prostate cancer.

Although motor function especially ambulation was assessed in the majority of studies, a range of instruments were used. The Tomita scale I-IV or I-IV was the most common, other tools included the Barthel Index (Graham *et al.* 2006) or were not specified (Helweg-Larsen *et al.* 2000; Kovner *et al.* 1999). Some studies conducted multivariate and univariate analyses. Only the findings from multivariate analyses of these studies are reported here. Several studies only conducted univariate analyses. Studies that provided only descriptive data with no statistical analysis were excluded. A table of identified factors is located at the end of this document.

Summary of Results:

Factors that predict for successful motor function or mobility

Six of the included studies reported the effects of RT on motor function including three small prospective cohort studies (Helweg-Larsen *et al.* 2000; Kim 1990 *et al.*; Kovner *et al.* 1999), and three retrospective cohort studies (Huddart *et al.* 1997; Rades *et al.* 2007a, Rades *et al.* 2007b).

Multivariate analyses were conducted in four studies (Rades *et al.* 2007 a and b; Huddart *et al.* 1997, Kim *et al.* 1990) however not all the component statistics were reported.

On multivariate analysis, improved motor function was associated with a favourable tumour type (myeloma/lymphoma) and a longer interval to develop motor deficits of more than 7 days in the elderly subgroup (Rades *et al.* 2007b) and 14 days for those with oligometastases (Rades *et al.* 2007a). Being ambulatory before RT was also statistically significant for the elderly subgroup (Rades 2007b), this was also reported in a smaller study by Kim *et al.* (1990). It was not possible to rank these factors.

On univariate analysis Kovner *et al.* (1999) found that ambulatory status post RT was statistically significantly associated with improving motor function. In contrast Helweg-Larsen *et al.* (2000) reported that ambulatory function at diagnosis and a favourable tumour type were significant factors.

One retrospective study of prostate cancer patients (Huddart *et al.* 1997) found on multivariate analysis that no hormone treatment prior to RT, a single site of compression and age less than 64 years predicted a better neurological outcome.

Duration of response

The duration of motor capacity was assessed in the four prospective studies by Maranzano *et al.* (2005, 1997, 1992, 1991). A favourable histology was found to significantly influence the duration of response in two studies (Maranzano *et al.* 2005, 1991). In the smaller study of patients with a poor prognosis (Maranzano *et al.* 1997) neither pre-treatment walking capacity nor histology influenced the duration of response. However in the small study of breast cancer patients post treatment walking capacity improved the duration of response.

Factors that predict improved survival

Actuarial survival was assessed by Kaplan-Meier survival curves for periods of up to 3 years in three studies (two retrospective cohorts Rades *et al.* 2006, 2007a; and one RCT Maranzano *et al.* 2005); up to 80 months by one small prospective cohort (Helweg-Larsen 2000); up to one year in four studies (one retrospective cohort Rades *et al.* 2007b; and three prospective cohorts Maranzano *et al.* 1997, 1992, 1991). Survival where a time course was not reported was assessed in 3 small studies (one RCT

Graham *et al.* 2006; one prospective cohort Kovner 1999; and one retrospective cohort Huddart *et al.* 1997).

On multivariate analysis from 3 retrospective cohorts by Rades *et al.* (2006, 2007a, 2007b) it may be possible to rank prognostic factors by their relative risks. The factors are described below:

- No visceral metastases was the strongest prognostic factor for survival in the large retrospective cohort and smaller subgroup of elderly patients (Rades *et al.* 2006, 2007b). The differences in relative risks were not statistically significant.
- Ambulatory status before RT was the next strongest prognostic factor for elderly patients (Rades *et al.* 2007b), with a statistically significantly higher relative risk than for the whole cohort (Rades *et al.* 2006) and for patients with oligometastases (Rades *et al.* 2007a).
- The absence of bone metastases was the next strongest prognostic factor for survival in the large cohort and smaller subgroup of elderly patients (Rades *et al.* 2006, 2007b). Again the differences in relative risks were not statistically significant.
- Type of tumour was the next strongest factor (Rades *et al.* 2006, 2007b)

There were no statistically significant differences in relative risks between the largest cohort (Rades *et al.* 2006) and subgroup of elderly patients (Rades *et al.* 2007b) for time of developing motor deficits > 14 days, and type of primary tumour. The interval from tumour diagnosis to MSCC was measured at different time points.

There were no statistically significant differences in relative risks between the largest study (Rades *et al.* 2006) and the subgroup of patients with oligometastases (Rades *et al.* 2007a) for ambulatory status, time of developing motor deficits > 14 days, and type of primary tumour. The only additional factor to improve survival in patients with oligometastases was long course RT.

To summarize the studies by Rades *et al.* (2006, 2007a, 2007b) results found that the absence of visceral metastases was the strongest prognostic factor influencing survival from survival curves to 3 years. The absence of bone metastases and favourable tumour type (breast, prostate, myeloma/lymphoma) were the next strongest factors. A longer interval to diagnosis of MSCC, a longer time to develop motor deficits and being ambulatory before RT were significant to a lesser degree. The effect of ambulatory status after treatment on survival was not reported in this study.

Absence of visceral metastases > absence of bone metastases and tumour type > interval to diagnosis and development of motor deficits or ambulatory before RT.

In the elderly subgroup ambulatory status before RT was the second strongest factor after visceral metastases to influence survival up to 1 year. Long course RT was also found to influence survival in patients with oligometastases.

The other smaller studies conducting multivariate analyses were Kovner (1999 prospective cohort) and Huddart *et al.* (1997 retrospective cohort). Kovner supported the Rades *et al.* findings in that the absence of visceral metastases improved survival. However ambulatory status after treatment was also statistically significant. Pre-treatment ambulatory status was significant on univariate analysis but became non significant on multivariate analysis.

The study of prostate cancer patients (Huddart *et al.* 1997) reported no hormone treatment prior to RT, a single site of compression and a haemoglobin \leq 12g as significant factors for survival. Ambulatory status was not significant in this small cohort.

The very small RCT by Graham *et al.* (2006) reported statistically significant hazard ratios favouring tumour type (breast and prostate vs others), and being ambulant pre-treatment. These also support the Rades findings.

The remaining studies reported results of Kaplan-Meier log rank tests (Maranzano *et al.* 2005 RCT, Helweg-Larsen *et al.* 2000 prospective cohort, Maranzano *et al.* 1997, 1992, 1991 prospective cohorts). The strongest of these (Maranzano *et al.* 2005 RCT) supported the Rades findings of being ambulatory before treatment and a favourable histology being highly significant. This study also found that being ambulatory post RT was also highly statistically significant. The smaller prospective cohorts all reported being ambulatory before and after treatment as significant factors with the exception of the breast cancer study (Maranzano *et al.* 1992) where only post treatment ambulatory ability was significant. A favourable histology was found not to be significant for patients with a poor prognosis (Maranzano *et al.* 1997), the only statistically significant factors for these patients were being ambulatory pre and post treatment.

Rades *et al.* (2008) developed a scoring system to predict the probability of a patient surviving \geq 6 months after RT. The system included 6 factors which were considered for the survival score. The 6 significant factors were: type of primary tumor; interval between tumor diagnosis and MSCC; presence of other bone metastases at the time of RT; visceral metastases at the time of RT; pretreatment ambulatory status and time to develop motor deficits before RT. The system was able to confirm survival for specific patient groups/disease characteristics, however, due to the retrospective nature of this study the prospective predictive capacity of the system was not evaluated. When patient survival for those receiving short-course RT was compared with patients receiving long-course RT for each of the patient groups, no statistically significant difference in the survival of the patients in Groups A (P = 0.90), B (P =0.47), and C (P =0.73), whereas survival was significantly better after long-course RT compared with short-course RT in Groups D (P =0.011) and E (P =0.002).

Pain relief

Few studies reported this outcome (Maranzano *et al.* 2005- descriptive statistics only, Maranzano *et al.* 1991, Helweg-Larsen *et al.* 2000). Only the latter two small prospective studies reported any statistics. Pain relief was improved if there was no sensory disturbance in the legs at diagnosis (Helweg-Larsen *et al.* 2000), and when there was myelographic block then post treatment pain relief occurred more frequently in those with a partial block rather than complete block.

Other outcomes

Local control

Long course RT was a statistically significant factor for maintaining local control in all 3 studies by Rades *et al.* (2006, 2007a, 2007b). The absence of visceral metastases was also significant in the large cohort (Rades *et al.* 2006).

Myelographic block

Complete myelographic block significantly diminished response to RT and had a negative influence on prognosis in comparison to partial block (Maranzano *et al.* 1991).

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Rades D, Fehlaue F, Schulte R, Veninga T, Stalpers LJ, Basic H, Bajrovic A, Hoskin PJ, Tribius S, Wildfang I, Rudat V, Engenhardt-Cabilic R, Karstens JH, Alberti W, Dunst J, Schild SE (2006) Prognostic factors for local control and survival after radiotherapy of metastatic spinal cord compression. *Journal of Clinical Oncology* **24**, 3388-3393

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Evidence Tables:

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Design: RCT (1998 – 2002)

Level 1-

Country: Italy

setting: Multicentre

Aim: Hypofractionated radiotherapy (RT) is often used in the treatment of metastatic spinal cord compression (MSCC). This randomized trial was planned to assess the clinical outcome and toxicity of two different hypofractionated RT regimens in MSCC

Inclusion criteria MSCC diagnosed by MRI or CT, and clinical features, short life expectancy < 6 months

Exclusion criteria spinal instability, vertebral body collapse causing cord or nerve root compression, previous irradiation in same area

Population 300 randomized 276 (92%) assessable

Patients well balanced for age, gender, performance status, ambulatory status, histology (data not reported).

99 (36%) had favourable histology:

Prostate	39/276 (14%)
Breast	28/276 (10%)
Myeloma	19/276 (7%)
Small cell lung	8/276 (3%)
Lymphoma	6/276 (2%)

177 (64%) had unfavourable histology:

Non-small cell lung	177/276 (28%)
Colorectal	25/ 276 (9%)
Kidney	22/276 (8%)
Gastric	11/276 (4%)
Head and neck	7/276 (2.5%)
Liver	7/276 (2.5%)
Bladder	6/276 (2%)
Sarcoma	6/276 (2%)
Melanoma	3/276 (1.5%)
Uterine	3/276 (1.5%)
Other	14/276 (5%)

Site of MSCC

Location in spine	Location of metastases
Cervical 8%	Spine (26%) 72/276
Thoracic 50%	Multiple bone metastases 113/276 (41%)
Lumbar 23%	Bone and visceral metastases 91/276 (33%)
Sacral 7%	
Cervicothoracic 1%	
Thoracolumbar 6%	
Lumbosacral 2%	

Interventions:

Short course (8 Gy x 2 days) vs. split course RT (5 Gy x 3; 3 Gy x 5).

Outcomes

Ambulation

Motor performance (Tomita I to IV):

I ability to walk without support

II ability to walk with support

III inability to walk

IV paraplegic

Bladder function – need of catheter

Pain: no pain; pain controlled with minor analgesics; pain requiring narcotics

Response criteria:

Responders- recovery or maintenance of walking ability, sphincter function.

3 categories for back pain- complete, partial, non-response

Survival

Pain relief

Follow up -1 month after RT, then monthly for 1 year.

Median follow-up 33 months (range 4-61mths)

Results*RT response*

A total of 276 (92%) patients were assessable; 142 (51%) treated with the short-course and 134 (49%) treated with the split-course RT regimen.

There was no significant difference in response, duration of response, survival, or toxicity found between the two arms. When short- versus split-course regimens were compared, after RT 56% and 59% patients had back pain relief, 68% and 71% were able to walk, and 90% and 89% had good bladder function, respectively.

Survival

Median survival was 4 months and median duration of improvement was 3.5 months for both arms.

Survival time was significantly associated with walking ability pre and post treatment and favourable histology.

Percent probability of survival (Kaplan-Meier):

Patient group N=276	1 year	2 years	3 years	Median survival (months)	P
<i>Pre-treatment status:</i>					
Walking n=184	15%	10%	5%	5	
Non-walking n=92	10%	6%	0%	3	0.025
<i>Post-treatment status:</i>					
Walking n=193	18%	10%	6%	5	
Non-walking n=83	5%	0%	0%	2	0.0001
<i>Histology:</i>					
Favourable n=96	30%	30%	8%	6	
Unfavourable n=180	5%	5%	2%	3	0.0001

Pain relief

Achieved in 157 patients (56.9%; 95%CI 51.1 - 62.7)
Complete response in 92 (33.3%; 95%CI 27.7 - 38.9)
Partial response in 65 (23.6%; 95%CI 18.6 - 28.6)

Motor function

Responders 192 (69.6%; 95%CI 63.9 - 75.3)
Grade I 93% maintained function
Grade II 88% maintained function
Grade III 35% regained motor ability
Grade IV None of the 17 paraplegics improved

The median duration of motor capacity improvement was independent of the patient's walking capacity. Only primary tumour type influenced the median duration of motor capacity improvement which was 6 months for favourable histologies and 3 months for unfavourable histologies (P= 0.0001).

Median duration of improvement in motor capacity:

Patient group	% of responders	Median duration of improvement (months)	P value
Post treatment walking	70	4	
Pre-treatment status:			
Walking	91	4	
Non-walking	28	3	
Histology:			
Favourable	76	6	
Non-favourable	66	3	0.0001

Sphincter dysfunction

29 patients had sphincter dysfunction:
Response rate 89%
4 (14%) regained control
4 (2%) of those with good bladder control worsened
The remainder maintained bladder control

General comments –

Authors conclusions

Both hypofractionated RT schedules adopted were effective and had acceptable toxicity. However, considering the advantages of the short-course regimen in terms of patient convenience and machine time, it could become the RT regimen of choice in the clinical practice for MSCC patients

Graham, P. H., Capp, A., Delaney, G., Goozee, G., Hickey, B., Turner, S., Browne, L., Milross, C. & Wirth, A. (2006) A pilot randomised comparison of dexamethasone 96 mg vs 16 mg per day for malignant spinal-cord compression treated by radiotherapy: TROG 01.05 Superdex study. *Clinical oncology (Royal College of Radiologists (Great Britain))*, 18: 70-76.

Design: RCT (Sept 2001-Nov 2003)

Level 1-

Country: Australia, setting: 8 recruiting centres in 3 Australian states.

Aim:

One of the objectives was to determine which of several functional outcomes were more useful in discriminating clinically relevant outcome differences compared with ambulation.

Inclusion criteria Histological proof of malignancy, MRI, and at least one of pain, weakness, sensory symptoms, sphincter disturbance. Eastern Co-operative Oncology Group (ECOG) performance status of less than 4 before MSCC, minimum survival of 2 months.

Exclusion criteria Prior RT within one vertebral level, prior treatment for MSCC, multi-level MSCC or other CNS disease, lymphoma or myeloma histology, peptic ulceration, cardiac failure, patients undergoing surgery.

Population number of patients = 130 patients screened, 38 eligible and only 20 were randomised. Mean age 66 years (41-81). 14/20 (70%) were male.

11/20 (55%) had breast or prostate cancers.

15/20 (75%) were ambulant.

Interventions Radiotherapy – dose 30Gy in 10 fractions. One arm received 96mg iv dexamethasone, the other arm 16 mg for 2 days, then reduced to 0mg by day 15.

Outcomes

Ambulation at 1 month

Functional indices of the Barthel Index, Functional Improvement Measure (FIM), Functional Improvement Score (FIS), pain score.

Follow up At 1 month and at death.

Results

Survival

Median survival 2.3 months.

Survival was better for breast and prostate compared with other histologies:

10.6 vs 2.1 months; Hazard ratio 0.19 (0.06-0.66, p=0.01)

ambulant vs non-ambulant at baseline 5.9 vs 1.0 months HR 0.22 (0.07-0.72, p=0.01)

In a multivariate analysis histology and baseline ambulation were significant.

Survival by low or high dose dexamethasone was not significant.

Rades D, Fehlaue F, Schulte R, Veninga T, Stalpers LJ, Basic H, Bajrovic A, Hoskin PJ, Tribius S, Wildfang I, Rudat V, Engenhart-Cabilic R, Karstens JH, Alberti W, Dunst J, Schild SE (2006) Prognostic factors for local control and survival after radiotherapy of metastatic spinal cord compression. *Journal of Clinical Oncology* **24**, 3388-3393

Design: Retrospective consecutive cohort (1992-2005) Level 3

Country: UK, Germany, Netherlands, Bosnia, setting: Multicentre

Aim: To evaluate potential prognostic factors for local control and survival after radiotherapy of metastatic spinal cord compression (MSCC).

Inclusion criteria RT for MSCC, motor deficits of lower extremities due to MSCC of thoracic or lumbar spine, no prior RT to index sites, confirmation of MSCC by CT or MRI, dexamethasone given from 1st day of treatment for at least one week.

Exclusion criteria None reported

Population number of patients = 1852, 40% female, 53% ≤ 64 years

Cohort of unselected consecutive patients treated at contributing centres during the specified time period.

Characteristic	% of patients
ECOG performance	
1-2	52
3-4	48
Type of primary tumour	
Breast ca	21
Prostate ca	19
Myeloma / lymphoma	13
Lung ca	17
Other tumours	30
Other bone metastases	
Yes	53
No	47
Visceral metastases	
Yes	38
No	62
Ambulatory status	
Ambulatory	63
Non-ambulatory	37
Radiation schedule	
Short course RT	42
Long course RT	58
Interval from tumour diagnosis to MSCC (months)	50
≤ 15 months	50
> 15 months	
Time to develop motor deficits before RT	
1-14 days	56
> 14 days	44

Interventions:**Short course vs. long course RT**

Short course was the standard regime for UK, Netherlands and Bosnia, and long course the standard regime for Germany.

Short course: 1x8Gy in 1 day or 5x4Gy in 1 week

Long course 10x3Gy in 2 weeks, 15x2.5Gy in 3 weeks or 20x2Gy in 4 weeks

Outcomes:

Motor function 5 point scale (Tomita)

Grade 0 normal strength

Grade 1 ambulatory without aid

Grade 2 ambulatory with aid

Grade 3 not ambulatory

Grade 4 paraplegia

ECOG performance status 1 to 2 vs. 3 to 4

Survival assessed at 1, 2 and 3 years.

Multivariate analyses of prognostic factors (Cox proportional hazards model) $P < 0.0045$ as significant. Significant univariate prognostic factors ($P < 0.0045$) included in multivariate analysis.

Prognostic factors: age, gender, ECOG, primary tumour, number of vertebra involved, other bone or visceral metastases, time from tumour diagnosis to MSCC, ambulatory status, time to develop motor deficits before RT.

Follow up: Motor and ambulatory status evaluated before RT and up to 24 months after. Median follow-up 7 months (0-110)

Results

Definitions:

Local control of MSCC defined as no recurrent motor deficits as a result of progressive or recurrent MSCC in the previously irradiated spinal region.

Recurrence of MSCC defined as recurrence of motor deficits if RT had improved motor function or progression of motor deficits if RT resulted in no change.

Improvement in motor function defined as a change of at least one point.

Factors for local control after RT

Univariate analysis:

Improved local control of MSCC was associated with a favourable histology (breast, prostate, myeloma/lymphoma), absence of visceral metastases, long course RT.

No significant association for:

Age ≤ 64 years v ≥ 65 years

Gender

Number of involved vertebrae 1-2 v ≥ 3

Other bone metastases

Interval from tumour diagnosis to MSCC, (months)

Ambulatory status before RT (ambulatory vs. non-ambulatory)

Time to develop motor deficits before RT (days) 1-14 v > 14 days

Multivariate analysis:

Absence of visceral metastases and long course RT maintained significance.

Factor for better	Univariate P	Multivariate analysis
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local control	value
Type of tumour	
Breast	RR 1.09 (95%CI 0.97, 1.21)
Prostate	P 0.14
Myeloma/lymphoma	
v	
Other tumours	<0.001
Visceral metastases at time of RT	
Yes	RR 2.64 (95% CI 1.76, 3.90)
No	<0.001 P <0.001
Radiation schedule	
Short course	RR 0.54 (95% CI 0.45, 0.65)
Long course	<0.001 P <0.001

Survival

Univariate analysis:

Improved survival measured at 1, 2 and 3 years was significantly associated with female sex, better performance status, favourable histology, involvement of 1 to 2 vertebrae, absence of other bone metastases at the time of RT, a longer interval between tumour diagnosis and MSCC (> 15), being ambulatory before RT, slower development of motor deficits before RT (p<0.001)

Survival was not associated with age (≤64 or ≥ 65), or radiation schedule.

Multivariate analysis:

Favourable histology, absence of other bone metastases and absence of visceral metastases at the time of RT, a longer interval between tumour diagnosis and MSCC (Breast, Prostate, Myeloma/lymphoma, Lung vs. Other tumours), being ambulatory before RT, and slower development of motor deficits before RT maintained significance.

Gender, performance status and number of involved vertebrae were not associated with survival.

General comments –

Author conclusions:

Better local control of MSCC was significantly associated with the absence of visceral metastases at the time of RT and with long course RT.

Survival may be influenced by several prognostic factors. For patients with visceral metastases or other bone metastases at the time of RT, primary tumours other than breast cancer, prostate cancer and myeloma/lymphoma, inability to walk before RT, a short interval between tumour diagnosis and MSCC (<15 months), and rapid development of motor deficits before RT (1-14 days), data suggest the survival prognosis is poor.

Rades D, Veninga T, Stalpers LJ, Basic H, Rudat V, Karstens JH, Dunst J, Schild SE (2007) Outcome after radiotherapy alone for metastatic spinal cord compression in patients with oligometastases. *Journal of Clinical Oncology* **25**, 50-56

Design: Retrospective cohort (1992-2005)

Level 2 +

Country: Not stated, setting: Multicentre

Aim: To investigate outcome and prognosis of metastatic spinal cord compression (MSCC) patients with oligometastatic disease treated with radiotherapy alone.

Inclusion criteria Patients with metastatic involvement of 3 or fewer vertebrae, lack of further bone or visceral metastases, motor deficits from MSCC, no prior spinal RT, confirmation of MSCC by CT or MRI, administration of dexamethasone from day 1 of RT for at least 1 week.

Exclusion criteria Presence of other metastases from abdominal ultrasound, chest X ray, CT, bone scanning, whole spine MRI

Population number of patients = 521 Consecutive series from each centre.

Interventions RT

Short course RT 8Gy in 1 day or 5 x 4Gy in 1 week

Long course RT 10 x 3Gy in 2 weeks, 15 x 2.5Gy in 3 weeks, or 20 x 2Gy in 4 weeks

Outcomes

Motor function 5 point Tomita scale, improvement defined as change of at least 1 point

Survival assessed at 6 months, 1, 2 and 3 years.

Follow up 1 and 3 months after RT, then at 6 monthly or when motor function deteriorated.

Median follow-up 12 months (range 2-96 months) for entire cohort, for survivors 14 months (range 6-96 months).

32 patients lost to follow-up within 12 months

171 deaths during follow-up median 9 months (range 2-61).

Results

Motor function

Improved motor function in 40% (207/521)

No further progression in 54% (279/521)

Deterioration in 7% (35/521) of patients.

Fifty-eight (54%) of 107 non-ambulatory patients became ambulatory

388 (94%) of 414 ambulatory patients remained ambulatory

Improved functional outcome was significantly associated with tumour type and slower development of motor deficits (> 14 days). Local control at 1, 2, and 3 years was 92%, 88%, and 78%, respectively. Improved local control was significantly associated with long-course radiotherapy.

Functional improvement was not associated with:

Gender

Age ≤ 64 years v ≥ 65 years

Radiation schedule short or long course

The authors report a trend was observed for an interval between tumour diagnosis and MSCC more than 15 months and ambulatory status. However, these were not independently associated with improved functional outcome.

Factor for improved functional outcome	Estimate (95% CI)	Multivariate analysis P<0.007 significant
Type of tumour:		
Breast	-0.01 (-0.65 to 0.63)	P 0.985
Prostate	-0.34 (-0.89 to 0.21)	P 0.222
Myeloma/lymphoma	-2.61 (-3.40 to -1.83)	P <0.001
Lung	0.03 (-0.66 to 0.71)	P 0.941

Other tumours		
Time of developing motor deficits before RT, days		
1-7	0.55 (0.09 to 1.00)	P 0.018
8-14	2.55 (1.94 to 3.17)	P <0.001
>14		

Survival

Survival at 1, 2, and 3 years was 71%, 58%, and 50%, respectively.

Better survival was significantly associated with tumour type, ambulatory status, slower development of motor deficits, and long-course radiotherapy.

Univariate analysis

Better survival at 6 months, 1, 2 and 3 years was significantly associated with favourable tumour type (myeloma/lymphoma, breast cancer), a longer interval between tumour diagnosis and MSCC (> 15 months), ambulatory status, slower development of motor deficits (>14 days), long course RT (p<0.001).

There was no association between age or gender for survival on univariate analysis.

Multivariate analysis

The following prognostic factors maintained significance:

Tumour type: RR 1.1 (95%CI 1.07, 1.32) P <0.001,
 ambulatory status: RR 0.47 (95% CI 0.34, 0.67) **P <0.001**,
 slower development of motor deficits : RR 0.66 (95% CI 0.54, 0.80) **P <0.001** ,
 long course RT (RR 0.63 (95% CI 0.47, 0.86) P = 0.004.

The interval between tumour diagnosis and MSCC lost significance: RR 0.87 (95% CI 0.75, 1.03) P =0.092 NS

During follow-up 120/521 (23%) of patients died without experiencing progression of motor deficits during irradiation or recurrence of MSCC after RT. These 120 patients remained oligometastatic for a limited period of time and died after a median of 9 months (range 4 to 61 months) due to metastatic disease.

Further analyses

Patients who developed motor deficits slowly (onset > 14 days before initiating treatment) were further analyzed. In this subgroup (302/521, 58%), the best results were observed for myeloma/lymphoma and breast cancer patients. No patient had progression of motor deficits. One hundred percent (myeloma/lymphoma) and 99% (breast cancer) of patients were ambulatory after radiotherapy. One-year local control was 100% and 98%, 1-year survival was 94% and 89% respectively.

General comments –

This paper is about a subset of patients from the earlier larger study of 1800 patients. Definitions:

Local failure of MSCC defined as a recurrence of motor deficits resulting from MSCC in the previously irradiated spinal region, if RT improved motor function, or as progression of motor deficits, if RT did not change motor deficits.

Time to local failure measured from the end of RT.

Author conclusions:

Given the limitations of a retrospective review, improved outcome of patients with oligometastatic MSCC was associated with myeloma/lymphoma and breast cancer, slower development of motor deficits, and a more prolonged course of radiation. The study suggests that surgical intervention may not be needed in oligometastatic patients, in particular in those patients with favourable radiosensitive tumours and slow development of motor deficits.

Rades D, Hoskin PJ, Karstens JH, Rudat V, Veninga T, Stalpers LJ, Schild SE, Dunst J (2007) Radiotherapy of metastatic spinal cord compression in very elderly patients. *International Journal of Radiation Oncology, Biology, Physics* **67**, 256-263

Design: Retrospective cohort (1992-2005)

Level 3

Country: Not stated, setting: Multicentre

Aim: Owing to the aging of the population, the proportion of elderly patients receiving cancer treatment has increased. This study investigated the results of radiotherapy (RT) for metastatic spinal cord compression (MSCC) in the very elderly, because few data are available for these patients.

Inclusion criteria MSCC with motor deficits of the lower extremities due to MSCC of the thoracic or lumbar spine, no previous RT to involved sites, confirmation of MSCC by CT or MRI, administration of dexamethasone for at least 1 week.

Exclusion criteria None reported

Population number of patients = 308 patient records aged > or =75 years

Interventions

short-course (treatment time 1-5 days, n=176) or long-course RT (2-4 weeks, n=132)

Outcomes

Motor function 5 point Tomita scale, improvement defined as change of at least 1 point
Evaluated before RT and 1, 3, and 6 months after RT.

Survival assessed at 6 months and 1 year

Multivariate analyses of prognostic factors (Cox proportional hazards model) $P < 0.0045$ as significant. Significant univariate prognostic factors ($P < 0.0045$) included in multivariate analysis.

Prognostic factors for functional outcome, local control of MSCC, and survival: gender, ECOG performance status (2 vs. 3-4), primary tumour, number of vertebra involved, other bone or visceral metastases, time from tumour diagnosis to MSCC (≤ 18 vs. > 18 months), ambulatory status (ambulatory vs. non-ambulatory), time to develop motor deficits before RT (1-7 vs. 8-14 vs. > 14 days).

Follow up Until death. Survivors median follow-up 13 months (6-72 months)

Results

Definitions:

Local control of MSCC defined as no recurrent motor deficits as a result of progressive or recurrent MSCC in the previously irradiated spinal region.

Motor function

Improvement of motor deficits occurred in 25% (78/308) of patients.

No further progression of MSCC in 59% (182/308)

16% (48/308) had motor function deterioration

Of 129 non-ambulatory patients 35 (27%) regained the ability to walk after RT.

Effects of prognostic factors on functional outcomes:

Improved functional outcome was significantly associated with ambulatory status, a slower development of motor deficits before RT (> 7 days).

The authors reported a trend for favourable tumour type (myeloma/lymphoma) and the interval between tumour diagnosis and MSCC, although statistical significance was not achieved in the former.

Factor for improved functional outcome	Estimate (95% CI)	Multivariate analysis P<0.0045 significant
Type of tumour:		
Breast	-0.50 (-1.45 to 0.45)	P 0.302
Prostate	+0.11 (-0.67 to 0.89)	P 0.781
Myeloma/lymphoma	-1.36 (-2.41 to -0.30)	P <0.012
Lung	0.36 (-0.58 to 1.31)	P 0.451
Unknown primary	1.50 (0.38 to 2.61)	P 0.008
Other tumours (reference)		
Interval to develop motor deficits before RT, days		
1-7	2.46 (1.71 to 3.20)	P <0.001
8-14	0.58 (0.03 to 1.20)	P 0.061
>14 (reference)		
Ambulatory status before RT		
Ambulatory	-1.20 (-1.92 to -0.48)	P <0.001
Non-ambulatory (reference)		

Improved functional outcome was significantly associated with ambulatory status and slower development of motor deficits before RT (interval to develop motor deficits > 7 days).

A strong trend was observed for a longer interval between tumour diagnosis and MSCC and for a favourable tumour type (myeloma/lymphoma).

RT schedule had no impact on motor function.

Local control

The local control rate for the entire cohort was 94% at 6 months and 92% at 12 months after RT. The radiation schedule was the only statistically significant prognostic factor associated with local control on univariate analysis, favouring long course RT (P<0.001).

Survival

The 1-year survival rate was 43%.

Univariate analysis

On univariate analysis better survival was associated with better performance status, longer interval from tumour diagnosis to MSCC, tumour type (breast, prostate, myeloma/lymphoma), the absence of other bone metastases and visceral metastases, ambulatory status before RT, and slower development of motor deficits. Gender, number of involved vertebrae and radiation schedule were not associated with survival.

Multivariate analysis

On multivariate analysis a longer interval from tumour diagnosis to MSCC, a favourable tumour type, the absence of other bone metastases and visceral metastases, ambulatory status and slower development of motor deficits maintained significance. Performance status lost significance.

Actuarial overall survival after RT (measured at 6 and 12 months)	Univariate P <0.0045 significant	Multivariate analysis (overall survival) P <0.0045 significant
Type of tumour:		
Breast		
Prostate		
Myeloma/lymphoma		RR 1.13 (95%CI 1.04, 1.22)
Lung		P <0.005
Unknown primary		(stated in text as significant)
Other tumours	<0.001	
ECOG performance		
2	<0.001	RR 1.03 (95% CI 0.66, 1.61)
3-4		P =0.911 NS
Ambulatory status before RT:		
Ambulatory		RR 1.96 (95% CI 1.30, 2.94)
Non-ambulatory	<0.001	P 0.001
Other bone metastases at RT		
No		RR 1.57 (95% CI 1.15, 2.25)
Yes	0.003	P 0.004
Visceral metastases at RT		
No		RR 5.64 (95% CI 4.02, 7.97)
Yes	<0.001	P <0.001
Interval from tumour diagnosis to MSCC (mths)		
≤ 18		RR 0.76 (95% CI 0.65, 0.89)
> 18	<0.001	P =0.001
Time of developing motor deficits before RT, days		
1-7		RR 0.56 (95% CI 0.45, 0.69)
8-14	<0.001	P <0.001
> 14		
Radiation schedule		
Short course		
Long course	0.256	NS

The survival rate of 31 patients with all 6 favourable prognostic factors was 100% at 6 months and 86% at 12 months after RT.

In patients with 3 prognostic factors (no visceral metastases, ambulatory status, interval to develop motor deficits before RT > 7 days) survival rates were 97% at 6 months and 83% at 12 months.

In patients with visceral metastases, non-ambulatory status and an interval to developing motor deficits <7 days, no patients survived > 5 months after RT.

Conclusions:

Improved functional outcomes were associated with ambulatory status and slower developing motor deficits. Improved local control resulted from long-course RT. Improved survival was associated with a longer interval from tumour diagnosis to MSCC, tumour type (breast/prostate cancer, myeloma/lymphoma), lack of visceral or other bone metastases, ambulatory status, and a slower development of motor deficits.

General comments –

This paper is about a subset of patients from the earlier larger study of 1800 patients.

Author conclusions:

Short- and long-course RT are similarly effective in patients aged > or =75 years regarding functional outcome and survival. Long-course RT provided better local control. Patients with better expected survival should receive long-course RT and others short-course RT. The criteria for selection of an appropriate regimen for MSCC in very elderly patients should be the same as for younger individuals.

Maranzano E, Latini P, Perrucci E, Beneventi S, Lupattelli M, Corgna E (1997) Short-course radiotherapy (8 Gy x 2) in metastatic spinal cord compression: an effective and feasible treatment. *International Journal of Radiation Oncology, Biology, Physics* **38**, 1037-1044

Design: Prospective cohort (1993-1995)

Level 2

+

Country:Italy, setting: Single Oncology Centre

Aim: To evaluate the clinical outcome and toxicity of a short-course regimen of radiotherapy (RT) in selected metastatic spinal cord compression (MSCC) patients

Inclusion criteria

Patients with MSCC and a suspected bad prognosis were enrolled.

1. Metastatic spinal cord compression diagnosed by magnetic resonance imaging (MRI) or computed tomography (CT), or evidence of clinical myeloradiculopathy and X-ray osteolysis in patients with progressive neoplastic disease.
2. No previous irradiation of treated area.
- 3a. Presence of unfavorable histologies or less radio-responsive primary tumors (non small cell lung, kidney, gastrointestinal and head and neck carcinomas, melanoma, sarcomas) with or without clinical evidence of neurological deficit; or
- 3b. Presence of favorable histologies or more radio-responsive tumors (breast and prostate carcinomas, myeloma, lymphomas and seminoma) in patients with plegia or paresis and/or low performance status (PS ECOG 2-3), and/or a short life expectation.
4. Informed consent.

Exclusion criteria None stated.

Population number of patients = 53 consecutive patients.

The study population comprised 33 men and 16 women with a median age of 67 years (range, 41-79 years).

Lung, prostate and gastroenteric carcinomas (five gastric and four colon cancers) were the most common histologies (32 cases, 65%). Others were bladder and uterus carcinomas,

lymphoma and melanoma (two, one, one and one cases, respectively).

Location of disease was mainly in the thoracic and lumbar spine (51% and 33%, respectively).

In 48 of 49 (98%) cases MSCC was localized at one level.

Only in one patient with kidney cancer were there two levels of compression (thoracic and lumbar) both simultaneously treated with RT alone.

Interventions

The majority of patients (92%) were treated with RT alone, others (8%) underwent surgery and RT for doubtful diagnosis or for necessity of stabilization. Emergency RT was started within 24 h from diagnosis and usually given by posterior fields from a 4-8 MV linear accelerator. Two vertebral bodies above and below the involved vertebrae and the entire paravertebral mass were included in the treatment portal. Radiotherapeutic regimen was one single fraction of 8 Gy repeated after 1 week in responders or stable patients, for a total dose of 16 Gy.

Outcomes

1. Back pain before and after RT dividing patients into three groups: (a) no pain; (b) pain requiring minor analgesics; (c) pain controllable with narcotics.
2. Ambulatory status before and after RT grading according to this classification: Group I-ability to walk without support; Group II-ability to walk with support; Group III-inability to walk; Group IV-plegia (Tomita).
3. Bladder function before and after RT evaluating the need for an indwelling catheter.
4. Post-treatment survival.
5. Duration of response.
6. Acute and late toxicity.

Follow up During treatment, each patient was evaluated on the day of RT and contact was maintained by telephone, in case of problems, for the first 4 weeks. Follow-up continued once a month for one year, and four times per year until death.

Results

Forty nine of 53 (92%) patients who entered the trial were evaluable. The remaining four (8%) -who died 2-10 days from the start of RT-are not evaluable for early death. RT alone. The

remaining four (8%) underwent surgery and post-operative RT for doubtful diagnosis or necessity of stabilization (three and one cases, respectively).

Median follow up was 25 months (range, 6-34 months).

Motor function

At the time of diagnosis eight (16%) patients did not complain of motor weakness, 15 (3 1%) were able to walk with support, 20 (41%) were unable to

walk and six (12%) were paraplegics. All but two ambulant patients maintained the function (all group I and 87% group II).

Ten of 20 (50%) non-ambulant patients regained motor ability (three passed to group I and seven to group II).

Recovery of gait was verified in six cases with favorable histologies (prostate carcinoma, myeloma and lymphoma), and in another four with unfavorable ones (lung, gastroenteric and bladder carcinomas). None of six (0%) paraplegics regained the ability to walk; therefore, total motor function response rate was 63%.

Bladder dysfunction

Urinary dysfunction was found in only 9 of 49 (18%) cases, four with favorable and five with unfavorable histologies.

Four of 9 (44%) patients with urinary retention recovered function, two with favorable histologies (both with prostate cancer) and two with unfavorable ones (gastric and liver carcinomas). Only 1 of 40 (2%) patients with good bladder function required an indwelling catheter after RT, while the others maintained the ability; therefore, urinary capacity was recovered or maintained in 43 of 49 (88%) cases.

Survival

Median survival of the whole group was 5 months and probability of surviving 1 year was 30%. Comparing pre-treatment walking and non-walking patients median survival was seven and 3 months with 1 year probability of survival of 36% versus 11%, respectively ($p < 0.02$).

Another dramatic difference in median survival was recorded for those who could and could not walk after treatment (8 and 2 months, respectively). The probability of surviving 1 year was 36% for post-treatment ambulatory and 0% for non-ambulatory patients ($p < 0.0001$). Examining survival in relation to primary tumor type, found a median survival time of 7 months in favourable histologies (prostate and breast carcinomas, myeloma and lymphoma) and 3 months for unfavorable ones. This difference was not statistically significant ($p = 0.1$).

Seven of 49 (14%) patients had MSCC as the only site of metastasis, 21 (43%) also had other bone metastases and the remaining 21 (43%) presented other metastatic sites apart from bone. Median survival of the three groups were 6, 7 and 3 months, respectively, with no statistically significant differences.

There was agreement between length of survival and duration of response; generally, patients died from systemic progression of disease rather than relapse in the irradiated spine. Median duration of improvement in the whole group was 7 months. Neither pretreatment walking capacity, nor histology of primary tumor significantly influenced duration of response.

No responders had ambulatory and/or sphincter dysfunctions caused by in-field relapse of disease. Three of 33 (9%) responders without pain or with pain controlled by minor analgesics developed back pain requiring high dose narcotics with a 4-to 13-month interval from RT.

They underwent a second RT course at different dose schedules (8 Gy in 1 fraction, 2 Gy to 8 Gy or 2 Gy to 30 Gy) without reaching pain intensity reduction. Nevertheless, all three cases were able to walk and preserved the capacity.

Maranzano E, Latini P, Checcaglini F, Ricci S, Panizza BM, Aristei C, Perrucci E, Beneventi S, Corgna E, Tonato M (1991) Radiation therapy in metastatic spinal cord compression. A prospective analysis of 105 consecutive patients. *Cancer* **67**, 1311-1317

Design: Prospective cohort (1986-1989)

Level 2+

Country: Italy, setting: Single Oncology Centre

Aim: Analysis of RT alone for MSCC

Inclusion criteria MSCC treated with RT as the major intervention

Exclusion criteria

Population number of patients = 130 consecutive patients, 12 excluded because treated with surgery in addition. Thirteen (11%) early death patients were not evaluable. 105 evaluable patients, 57 women and 48 men median age 60 years (30-80 years).

Interventions

Twelve patients (9.2%) underwent surgery plus RT, and 118 (90.8%) received RT alone.

Chemohormonal potentially responsive tumors were also treated with chemotherapy or hormonal therapy.

Outcomes

Definitions:

Responders include PR and CR for back pain; improvement by at least 1 functional group to at least group II (motor function); normal bladder control (autonomic dysfunction).

Motor function (Tomita I – IV)

Pain relief- use of narcotics and analgesics- complete (CR) and partial response (PR)

Sphincter function – use of catheter

Myelographic block

Survival

Follow up. Response to treatment at 1 month. Median follow-up 15 months (4-38 months).

Results

Motor function

Treatment response depended primarily on the degree of motor dysfunction and secondly on histological type.

In cases with motor dysfunction, 48.6% (35/72) improved, and in 33 of 105 (31.4%) patients without motor disability (Groups I and II) there was no deterioration.

Radiosensitivity of tumour (histological type) was only important in paraparetic patients (Groups III and IV) in predicting response to RT.

The median duration of improvement was 8 months. The probability of duration of response at 1 year for patients with breast, lung, and prostate carcinomas and myeloma was 49%, 17%, 36% and 50% respectively. There was a significant difference between breast and lung tumours ($P < 0.05$) reflecting the radiosensitivity of the tumour.

Survival

Median survival time was 7 months (2-38 months) with a 36% probability of survival for 1 year.

A median of 10 months for walking and 1 month for non-walking patients, post treatment.

When analyzed by pre-treatment ambulatory status, median survival was 9 and 4

months for walking and non-walking patients.

Median survival for tumour type was:

Breast 12 months

Prostate 8 months

Lung 4 months

Others 3 months

Myelomas 7 months

One year survival probability was significantly better in post-treatment walking than non-walking patients (47% vs 7%, $P < 0.0001$); in pre-treatment ambulatory than non-ambulatory patients (42% vs 30% $P < 0.04$)

Sphincter function

Forty percent (6/15) of patients with autonomic dysfunction responded to RT.

Back pain

Response among patients with back pain was 80% (80/100). Differences were noticed in response for patients with complete or partial myelographic block (14/24 (58.3%) and 40/48 (83.3%) respectively, $p < 0.02$).

Myelographic block

Complete myelographic block significantly diminished response to RT.

In patients with complete or partial block post-treatment analysis showed improvement in motor capacity in 27.3% (6/22) and 65.6% (21/32) symptomatic cases respectively ($P < 0.005$).

A complete myelographic block had a negative influence on prognosis.

Vertebral collapse

Vertebral collapse did not influence response or survival.

General comments –

Author conclusions:

The most important prognostic factor in MSCC is early diagnosis and early therapy.

Maranzano E, Latini P, Checcaglini F, Perrucci E, Aristei C, Panizza BM, Ricci S (1992) Radiation therapy of spinal cord compression caused by breast cancer: report of a prospective trial. *International Journal of Radiation Oncology, Biology, Physics* **24**, 301-306

Design: Prospective cohort (1986-1990)

Level 2+

Country: Italy, setting: Single Oncology Centre

Aim: Prospective analysis of breast cancer patients with MSCC

Inclusion criteria Diagnosed MSCC from breast cancer

Exclusion criteria Patients who died at the start of RT (n=5) from other complications

Population number of patients = 56 consecutive patients

Age 57 years, range 32-85 years.

Metastatic sites	Number	%	Motor capacity	Number	%
None	2	4	Group I	21	38
Vertebral bone only	13	23	Group II	9	16
Bone	19	34	Group III	23	41
Bone and other sites:	22	39	Group IV	3	5
Lung	10				
Liver	5				
Nodes	4				
Soft tissue	2				
Brain	1				

Interventions RT alone. Emergency radiation therapy was administered using a split-course regimen: 5 Gy for 3 days, stopped for 4 days and, only in responders, a further 3 Gy for 5 days (time dose fractionation 68). All patients received steroids plus chemotherapy and/or hormonal therapy.

Outcomes

Ambulation (Tomita (I – IV)

Survival

Back pain

Urinary dysfunction

Follow up Median follow-up 22 months (4-52 months)

Results

Response and survival were assessed on the basis of pre-treatment and post treatment walking capacity, presence of vertebral body collapse or osteolysis, presence of other metastatic sites apart from bone and chemotherapy and/or hormonal therapy.

Ambulation

Of 35 cases with motor dysfunction at the time of diagnosis, 21 (60%) regained the ability to walk and another five (14%) who were able to walk with support at diagnosis did not deteriorate.

All 21 cases without motor deficits before treatment maintained good motor performance after radiation therapy.

Response to therapy was better in pre-treatment walking (Groups I and II) than in non-walking patients (Groups III and IV) (97% vs 69%; $p < 0.02$, Fisher's exact test).

Duration of response

Median duration was 12 months for all cases, 15 months for post treatment walking patients and 2 months for non-walking patients.

Probability of duration of response at 1 year was 59% and 10% for post treatment walking and non-walking patients, respectively ($p < 0.0001$ log rank test).

Survival

Median survival was 13 months (range 2-37 months) with 29% surviving for 3 years.

One year survival probability was 66% for post treatment walking and 10% for post treatment non-walking patients, respectively ($p < 0.0001$) (Kaplan-Meier log rank test).

Pre-treatment motor capacity, type of vertebral injury, presence of other metastases or associated systemic therapy did not significantly affect survival.

Back pain

In 89% of patients with back pain the pain disappeared or lessened.

Sphincter function

Four of 6 cases (67%) with urinary dysfunction responded to radiation therapy.

Pre-treatment and post treatment ambulatory status were the most important prognostic factors.

General comments -

Helweg-Larsen, S., Sorensen, P.S., Kreiner, S., Prognostic Factors In Metastatic Spinal Cord Compression: A Prospective Study Using Multivariate Analysis Of Variables Influencing Survival And Gait Function In 153 Patients, *Int. J. Oncology Biol. Phys.*, (2000) 46:1163-1169

Design: Prospective cohort (3.5 years data)

Level 2+

Country:, setting:

Aim: The aim of the present study was to analyze the prognostic significance of various clinical and radiological variables on the post-treatment ambulatory function and survival.

Inclusion criteria A diagnosis of spinal cord compression due to metastatic disease

Exclusion criteria Patients who underwent laminectomy due to unknown malignant disease or due to earlier radiation therapy in the affected area were excluded from this study

Population number of patients = 153 consecutive patients during a 3.5 year period.

75 women median age 64 years (36–88 years)

78 men with a median age of 71 years (26–92 years)

The site and histology of the primary tumor was breast carcinoma in 56 patients (37%), prostatic carcinoma in 43 (28%), non–small cell lung cancer in 18 (12%), small cell lung cancer in 9 (6%), and other solid tumors in the remaining 27 (17%) patients.

Motor function

n

Total paralysis

43

No gait function	31
Walk with assistance	19
Unaided gait	60

Sensibility (pain)	n
Normal perception	34
Slight disturbances	84
Total lack of perception	35

Compression site	n, (%)
Lumbosacral	44 (29%)
Thoracic	102 (67%)
Cervical	7 (4%)

Interventions

All patients were irradiated with 6 MV photon beams administered in two parallel opposing anterior and posterior fields encompassing one normal vertebra above and distal to the epidural block. Total dose was 28 Gy, given in fractions of 4 Gy on 7 consecutive days. Five patients underwent a supplementary laminectomy within 2 weeks after radiation therapy because of progression of symptoms during radiation therapy.

Outcomes

The prognostic significance of five variables on gait function and survival time after treatment was analyzed.

Follow up The patients were followed with regular neurological examinations by the same neurologist for a minimum period of 11 months or until death.

Results

Definitions:

Sensory disturbance – disturbance of pain sensibility in legs, 3 categories

Ambulatory function – 4 categories

The type of the primary tumor had a direct influence on the interval between the diagnosis of the primary malignancy and the occurrence of spinal cord compression ($p < 0.0005$), and on the ambulatory function at time of diagnosis ($p = 0.016$). There was a clear correlation between the degree of myelographic blockage and gait function ($p = 0.000$) and between gait function and sensory disturbances ($p = 0.000$). The final gait was dependent on the gait function at time of diagnosis ($p < 0.0005$). Survival time after diagnosis depended directly on the time from primary tumor diagnosis until spinal cord compression ($p = 0.002$), on the ambulatory function at the time of diagnosis ($p = 0.018$), and on the ambulatory function after treatment.

Influence of primary tumour type

The histological type of the primary tumor influenced the interval between the diagnosis of the primary malignancy and the occurrence of spinal cord compression, as well as the ambulatory function at time of diagnosis of intraspinal metastases. Tumours with a low speed of dissemination, reflected by a long period from diagnosis of the primary cancer until occurrence of spinal cord compression, will tend to have longer survival

after treatment of spinal cord compression irrespectively of the tumour type. Conversely, a primary tumour that causes metastatic spinal cord compression with abolished gait function shortly after the cancer diagnosis predicts a pure treatment response and short survival independent of the tumour type.

The relationship between tumour type and ambulatory function at the time of the diagnosis of spinal cord compression is shown below. Patients with lung cancer had the most severe affection of gait function and more than 50% were totally paralyzed in the legs. Conversely, 59% of breast cancer patients were ambulatory when the diagnosis of spinal cord compression was confirmed.

Primary tumour	Ambulatory function at diagnosis				Total
	Paralytic	Paretic	Gait with assistance	Unaided gait	
Breast	6	11	6	33	56
Prostate	17	10	4	12	43
Others	6	5	6	10	27
Lung	14	5	3	5	27
Total	43	31	19	60	153

$P = 0.003$ (Chi^2) (statistical tests included assessment of effect modification and confounding).

Correlation of clinical variables and treatment response

The final gait was not dependent on the gait function at time of diagnosis ($p < 0.0005$), but sensory disturbances at time of diagnosis were also shown to have a direct prognostic importance regarding the final gait function ($p = 0.01$). None of the patients with normal sensation in the legs remained paralyzed after radiotherapy, whereas 60% of the patients without sensation in the legs were paralyzed after treatment for spinal cord compression.

However, the analysis also showed that this effect of loss of sensibility on the final gait is confounded by gait function at time of diagnosis. The conditional relationship between loss of sensibility and gait function after treatment given gait function at diagnosis was somewhat weaker than what appeared in the marginal relationship shown in Table 4 of the paper.

Gait function was not a modifier since the conditional relationship was homogeneous across the four different subgroups of gait function at diagnosis.

Survival

The median survival of the whole group after the diagnosis of spinal cord compression was 3.6 months; 1-year survival probability was 20.9%.

Survival time after diagnosis depended directly on the time from primary tumor diagnosis until spinal cord compression ($p = 0.002$), on the ambulatory function at the time of diagnosis ($p = 0.018$), and in particular on the ambulatory function after treatment.

The effect of the pretreatment ambulatory function on survival was modified by the post-treatment ambulatory function, in the sense that pretreatment ambulatory function can not be shown to have any separate direct prognostic effect on survival if the final gait function is taken into account, except cases where patients have fully recovered gait function. In the latter case, where gait function has improved, the chances of survival increase with the degree of recovery of ambulatory function ($p = 0.002$).

There was a large difference in survival between groups of post-treatment walking patients (median survival 7.9 months), and post-treatment non-walking patients (median survival 1.2 months). The median survival of pre-treatment walking patients was 7.0 months compared to 1.5 months for patients without gait function prior to treatment ($p = 0.001$). However, this result is highly confounded when testing and controlling for endpoint gait function before death. This test result yields no evidence of correlation if patients in the endpoint examination had disturbed or no gait function. Whereas in the group of patients with normal gait in the endpoint examination, the survival time was long in those patients who were non-ambulatory before treatment and had regained normal gait compared to patients who were ambulatory both before and after therapy.

General comments –

An earlier study by the same author (Helweg-Larsen, S., Clinical Outcome in Metastatic Spinal Cord Compression: A Prospective Study of 153 patients, *Acta Neurol. Scand.*, (1996) 94: 269-275) on the same patient population reported that there was no statistically significant relationship between ambulatory outcome and collapse of the vertebral body in initially paralyzed patients.

Kovner F, Spigel S, Rider I, Otremsky I, Ron I, Shohat E, Rabey JM, Avram J, Merimsky O, Wigler N, Chaitchik S, Inbar M (1999) Radiation therapy of metastatic spinal cord compression. Multidisciplinary team diagnosis and treatment. *Journal of Neuro-Oncology* **42**, 85-92.

Design: Prospective cohort (1985-1994)

Level 2 +

Country: Israel, setting: Single hospital centre, multidisciplinary team approach

Aim: To evaluate the effectiveness of a multidisciplinary approach to spinal cord compression (SCC) in accordance with prospective protocol, providing a uniform approach to diagnosis, decision making concerning optimal treatment modality in any particular case of SCC, treatment performance and evaluation of treatment results.

Inclusion criteria SCC diagnosed by CT myelography, MRI and histology if patients did not have a previous malignancy.

Exclusion criteria Not stated

Population number of patients = 79

The median age of the patients (48 females and 31 males) was 60 years (range 23–87). Twenty five (32%) also had visceral metastases. See table 1 of paper for patient characteristics and numbers.

Interventions

Seventy-nine patients received a 30 Gy radiation dose to a compression-causing mass and course of high dose dexamethasone. Three fractions of 5 Gy and 5 fractions 3 Gy each were delivered by Co60 or 8 MV photon beam in 12 days

Outcomes

Definitions:

Ambulatory patients could either walk independently or with the assistance of

some device (e.g. a walker) or another person. A motor deficit could be present or absent among ambulatory patients who could have ataxia, heaviness or weakness in the legs.

Pain as well as sensory and sphincter disturbances could be present in patients of both ambulatory and non-ambulatory patients

Therapeutic outcome was expressed in terms of ambulation. Changes in variables such as pain, sensory disturbances and sphincter function were also assessed.

Treatment outcome was evaluated by ambulatory status. Changes in other neurologic motor, sensory and autonomic disturbances were also evaluated.

Follow up

Results

Treatment resulted in some improvement in almost all groups of symptoms in 45–63% of all cases, but to a lesser extent (20%) in paraplegia. There was no worsening of radicular pain or of sensory and sphincter disturbance after treatment, and local pain worsened in 2.5% of the cases.

Motor function

Deterioration of motor function in non-ambulatory patients was observed in 2–3% of cases, there was a 10% deterioration among patients who were ambulatory before treatment but who had some degree of motor deficit, such as motor weakness or paresis.

Ambulation

The ambulation status of patients after completion of treatment is presented in Table 3. Of those patients who were ambulatory before treatment, 90% remained ambulatory afterwards, but the condition of the remaining 10% deteriorated despite treatment, and they became non-ambulatory. One-third of the patients who were non-ambulatory before treatment became ambulatory after treatment, and 50% of non-ambulatory patients with some kind of paresis regained ambulation after treatment. Fourteen percent of paraplegic patients became ambulatory after treatment. See table 3 for treatment results according to ambulatory status

Survival

The overall mean survival of all patients was 8.9 months, median 2 months (range 1 week to 70 months). Survival was longer for ambulatory patients than non-ambulatory after radiation. It was also increased for patients whose symptoms improved after treatment (pain, motor deficit, and sensory and autonomic disturbances) than those whose symptoms did not improve. Patients benefiting from RT survived 4–19 months, compared with those who did not respond 0.5–1.5 months.

Median survival of patients with SCC caused by lymphoma was 14 months, caused by cancer 1–5 months. Differences in survival between patients with malignancies of unknown origin and known malignancies were not statistically significant.

Univariate statistical analysis (Student's *t*-test) revealed three factors significantly

correlating with survival (Table 5). The ability to walk before treatment ($p = 0.03$) and the ability to walk after treatment ($p = 0.001$), positively affected survival. The presence of visceral metastases reduced survival ($p < 0.001$).

Multivariate statistical analysis (Cox proportional hazard) showed two independent prognostic factors for survival: the ability to walk after treatment ($p = 0.004$) and visceral metastases ($p = 0.037$).

See Table 5 for univariate analysis of possible prognostic factors for survival.

Summary abstract

Seventy-two percent of the patients were non-ambulatory at diagnosis. The first symptom was motor deficiency in only 33% of them while in all other cases it was pain. Ambulation capability was the main prognostic factor of treatment outcome; 90% of patients who were ambulatory before treatment remained so while 33% of the non-ambulatory patients regained their ability to walk. The grade of motor disturbance was also an important variable: among the non-ambulatory patients, 50% of the paretic but only 14% of the plegic ones became ambulatory. Overall, 51% of the study patients were ambulatory after undergoing radiation. The ambulatory state after treatment was the main predictor for survival.

Kim RY, Spencer SA, Meredith RF, Weppelmann B, Lee JY, Smith JW, Salter MM (1990) Extradural spinal cord compression: analysis of factors determining functional prognosis--prospective study. *Radiology* **176**, 279-282.

Design: Prospective cohort (April 1987-December 1988)

Level 2+

Country:USA, setting: Single centre

Factors for functional prognosis in Extradural SCC

Inclusion criteria Diagnosis of ESCC confirmed with myelography in 53 patients, with computed tomography (CT) in 39 patients, and with magnetic resonance (MR) imaging in six patients.

Exclusion criteria Six patients were excluded from analysis owing to death during treatment.

Population number of patients = 65 recruited, 59 for analysis (6 deaths) 43 men and 22 women median age 63.5 years (range, 18-87 years).

Most common primary tumour: lung (27%) followed by prostate (19%), unknown primary tumour (12%), breast cancer (10%), kidney (8%); non-ambulatory (78%)

Most frequent sites of spinal cord compression were the thoracic spine in 43 patients (73%), followed by the lumbosacral spine in 14 patients (24%) and the cervical spine in two patients (3%).

Neck or back pain in 50/59 (85%) cases

Motor weakness in seven (12%) cases

Sphincter dysfunction two (3%) cases

Average duration of pain prior to diagnosis of ESCC was 6 weeks

Interventions Initiation of emergency radiation therapy except in patients

without a diagnosis of cancer and in those who had previously undergone radiation treatment to the spinal cord. High dose dexamethasone. When the location of the ESCC was established, radiation treatment was started immediately at the site of the compression, encompassing one or two vertebral bodies above and below it.

Thirty-two patients received 3,000 cGy in 10 fractions; 14 patients received 3,000 cGy in nine fractions with three initial high dose fractions of 400 cGy; five patients received 2,000 cGy in five fractions; and three patients who had previously undergone radiation treatment and were not candidates for laminectomy received 3,000 cGy in 15 fractions. Of the six patients who underwent decompression laminectomy, three patients underwent the procedure prior to treatment, and three underwent the procedure during radiation therapy.

Outcomes

Motor function:

Grade 1 normal

Grade 2 weak but ambulatory

Grade 3 non-ambulatory but able to resist gravity

Grade 4 non-ambulatory and unable to resist gravity

Grade 5 paraplegic

Survival

Follow up Motor function was assessed at the end of radiation treatment and 1 and 6 months after treatment.

Results

Effect of prognostic factors on improvement in motor function

	p value	
	Univariate analysis	Multivariate analysis
Pre treatment motor function	0.001	0.0058
Degree of spinal cord block	0.009	0.3774
Radiosensitivity of tumour	0.048	0.0710
Radiation dose schedule	Not significant	Not done

Motor function

The pretreatment motor function grade and post treatment ambulatory status correlated well (P<0.001, Table). All 13 patients with grade 1 or 2 motor function before treatment remained ambulatory. Of the 31 patients with grade 3 or 4 motor function (non-ambulatory) before treatment, 11 (35%) were able to walk after treatment. However, only one of 15 (7%) patients with level 5 motor function (paraplegic before treatment) was able to walk after treatment.

Motor function improved in 4/6 (67%) patients with breast cancer, 6/16 (38%)

patients with lung cancer, 2/11 (18%) patients with prostate cancer, and 1/5 (20%) patients with kidney cancer. Improvement occurred in 11 of the 27 (41%) patients with primary tumours considered to be more sensitive to radiation (breast cancer, lung cancer, multiple myeloma, and lymphoma) but in only three of the 21 (14%) patients with primary tumours considered to be less sensitive to radiation (liver cancer, kidney cancer, prostate cancer, malignant melanoma, and sarcoma) (P=0.048).

In the multivariate analysis of pre-treatment motor function, degree of spinal cord block, and radiosensitivity of tumor, pre-treatment motor function was a significant factor in determining improvement in motor function (P = 0.0058) (Table). Degree of spinal cord block and radiosensitivity of tumor were not significant independent factors after adjustment for other factors.

Survival

Median survival in ambulatory patients was 3.63 months; in non-ambulatory patients, 1.79 months.

Summary

The prognostic significance of pre-treatment motor function, degree of spinal cord block, radiosensitivity of tumour, and radiation dose schedule were determined with multivariate analysis. Only pre-treatment motor function was found to be a significant factor in determining functional prognosis (P = .0058).

Huddart RA, Rajan B, Law M, Meyer L, Dearnaley DP (1997) Spinal cord compression in prostate cancer: treatment outcome and prognostic factors. *Radiotherapy and Oncology* **44**, 229-236.

Design: Retrospective cohort (1984-1992)

Level 3

Country:UK, setting: Single Cancer Centre

Aim: To assess treatment outcome and prognostic factors in patients with prostate cancer.

Inclusion criteria Spinal cord compression and prostate cancer identified from patient records. Most had a histological diagnosis of prostate cancer. Confirmation of SCC from myelography (\pm CT) (42%) or MRI (47%), otherwise X-ray and clinical features.

Exclusion criteria None stated

Population number of patients =69

Functional assessment of patients was made retrospectively with 5 point modified Tomita scale.

SCC was present at the initial diagnosis of prostatic cancer in 13 patients and 17 patients had received no hormone treatment prior to diagnosis.

At presentation 40 (58%) patients were non-ambulant and 52% (36) were catheterised.

Abnormal bowel function 25%

Paraplegia in 7 (10%)

Most had extensive bone metastases at presentation.

24/65 (38%) had vertebral collapse at the site of cord compression

See table outlining patients characteristics, not reproduced here.

Interventions

A radiotherapy dose of 20 Gy in five fractions over 1 week (n = 10) or 28-30 Gy in nine to ten fractions over 2 weeks (n = 37) (prescribed to spinal cord depth).
A minority who were judged to have the best prognosis received higher dose radiotherapy, i.e. doses of 35-40 Gy in 15-20 fractions (n = 10).
Fourteen patients underwent surgery.

Outcomes

Motor function: See Details outlined in table supplied in paper
Neurological deterioration.
Urinary and bowel function.
Survival

Follow up Grading performed prior to RT, and 7 days, 12 weeks, 6 months, 1 year and 2 years after RT.

Results

Motor function

Following treatment 36 (52%) patients had a functional improvement of motor power by at least one grade, stable in 22 (32%), and a deterioration in 8 (11%).
25/40 (63%) non-ambulant patients became ambulant, whilst 7 (25%) of ambulant patients became unable to walk.

Overall after treatment:

21/28 (75%) became ambulant

23/32 (71%) of paraparetic (grade 4) and 2/7 paraplegic (grade 5) patients were able to walk

77% of patients who had eventual improvement had some improvement in power within 7 days.

Neurological deterioration

Following treatment of spinal cord compression 20/69 (29%) patients had subsequent neurological deterioration with a median time to relapse of 238 days (range 47-1215 days). This consisted of further cord compression at the same site in 8 patients or a new site in five patients.

The remaining cases were due to base of skull metastases (1), CVA (1) or an indeterminate cause (1). Overall this represented an actuarial risk of 45% at 2 years and 75% at 5 years of developing a further episode of spinal cord compression. There was no significant difference between these patients and those who had no progression of presenting factors including haemoglobin, the number of lesions evident by bone scan, hormonal status or method of diagnosis. Despite worse clinical features patients diagnosed by MRI did not have more episodes of neurological deterioration (29 versus 32%, $P = 0.79$), though their period at risk was shorter.

There was no significant difference in the rate of relapse of SCC at the initial site with radiation dose with relapse occurring in 7/54 patients receiving 30 Gy or less and 1/11 patients receiving over 30 Gy ($P = 0.51$), though this observation could be confounded by other factors.

Bladder function

10/39 (35%) of catheterized patients were able to have the catheter removed.

On multivariate analysis no prior hormone treatment, single sites of disease and age under 65 years were predictive of a better neurological outcome (Table).

Survival

The overall median survival was 115 days (range 5-2016 days) with 25% of all patients surviving for 2 years.

On univariate and multivariate analysis hormonal status prior to treatment had a significant impact on survival (Table). Patients receiving no hormone therapy prior to presentation of cord compression had a median survival of 627 days (range 46-1552 days). On multivariate analysis other significant factors which were predictive of better survival were single site of compression and a haemoglobin > 12 g. Although surgery and increased radiation dose appeared as prognostic factors on univariate analysis they disappeared from the multivariate model.

Summary of findings:

- On multivariate analysis a single level of compression, no previous hormone therapy and a young age (<65 years) predicted for better neurological outcome.
- When these factors were included an increased radiation dose (>30 Gy) or the addition of surgery did not improve the functional outcome.
- Following initial recovery; there was a 45% risk of developing a further episode of cord compression at the same or new site by 2 years with a median time to progression of 236 days (range 47-1215 days).
- The median survival was 115 days (range 5-2016 days) with 25% of patients surviving for 2 years.
- Patients with no prior hormone therapy had a median survival of 627 days (range 46-1516 days).
- Other predictors of improved survival on multivariate analysis were a single site of compression and a haemoglobin over 12 g.

Rades, D., Dunst, J. & Schild, S. E. (2008) The first score predicting overall survival in patients with metastatic spinal cord compression. *Cancer*, 112: 157-161

Design: retrospective case series, evidence 3

Country: germany

Aim: This study presents a scoring system that allows for the adequate prediction of the probability of a patient surviving ≥ 6 months after RT.

Synopsis: Rades *et al.* (2008) developed a scoring system to predict the probability of a patient surviving ≥ 6 months after RT. The system included 6 factors which were considered for the survival score. The 6 significant factors were: type of primary tumor; interval between tumor diagnosis and MSCC; presence of other bone metastases at the time of RT; visceral metastases at the time of RT; pretreatment ambulatory status and time to develop motor deficits before RT. The system was

able to confirm survival for specific patient groups/disease characteristics, however, due to the retrospective nature of this study the prospective predictive capacity of the system was not evaluated. When patient survival for those receiving short-course RT was compared with patients receiving long-course RT for each of the patient groups, no statistically significant difference in the survival of the patients in Groups A ($P = 0.90$), B ($P = 0.47$), and C ($P = 0.73$), whereas survival was significantly better after long-course RT compared with short-course RT in Groups D ($P = 0.011$) and E ($P = 0.002$).

Inclusion criteria

The scoring system was based on the retrospective analysis of 1852 patients treated with RT for MSCC published in an earlier study published by the same group of authors

Exclusion criteria**Population**

The score is based on the retrospective analysis of 1852 patients treated with RT for MSCC

Interventions

- The scoring system was based on the retrospective analysis of 1852 patients treated with RT for MSCC published in an earlier study published by the same group of authors. In that analysis, 11 potential prognostic factors were investigated with respect to survival after RT on both univariate and multivariate analysis. In the multivariate analysis, 6 prognostic factors were found to be significant with regard to overall survival. These 6 factors were considered for the survival score presented in the current study. The 6 significant factors were as follows: type of primary tumor (breast cancer vs prostate cancer vs myeloma/lymphoma vs lung cancer vs other tumors); interval between tumor diagnosis and MSCC (≤ 15 months vs > 15 months); presence of other bone metastases at the time of RT (no vs yes); visceral metastases at the time of RT (no vs yes); pretreatment ambulatory status (non-ambulatory vs ambulatory) and time to develop motor deficits before RT (faster [1–14 days] vs slower [> 14 days]).
- A separate score was calculated for each of the 6 significant prognostic factors (i.e., the 6-month survival rate [given as the percentage] was divided by 10). The 6-month survival rates and the separate scores for each of the 6 prognostic factors were provided in the paper (but not reproduced here).
- The total scores ranged from 20 to 45 points. Five groups were formed according to the total score based on the 6-month survival rates for each score. 20 to 25 points (214 patients, Group A), 26 to 30 points (387 patients in Group B), 31 to 35 points (401 patients, Group C), 36 to 40 points (402 patients, Group D), and 41 to 45 points (448 patients, Group E).

Outcomes

The 5 groups were compared for survival using the Kaplan-Meier method. The Kaplan-Meier curves were compared using the log-rank test. The difference was considered significant with $P < .05$.

Results

- The 6-month survival rates were:
Group A: 4% for patients with a total score of 20 to 25 points,
Group B: 1% for patients with a score of 26 to 30 points,
Group C: 48% for patients with a score of 31 to 35 points,
Group D: 87% for patients with a score of 36 to 40 points,
Group E: 99% for patients with a score of 41 to 45 points.

- The 1-year survival rates for the 5 groups were 0%, 6%, 23%, 70%, and 89%, respectively.
- The difference between the 5 groups was statistically significant ($P < .001$).
- Subgroup analyses revealed that the differences between Groups A and B ($P < .001$), Groups B and C ($P < .001$), Groups C and D ($P < .001$), and Groups D and E ($P < .001$) were statistically significant.
- When patient survival for those receiving short-course RT was compared with patients receiving long-course RT for each of the patient groups, no statistically significant difference in the survival of the patients in Groups A ($P = 0.90$), B ($P = 0.47$), and C ($P = 0.73$), whereas survival was significantly better after long-course RT compared with short-course RT in Groups D ($P = 0.011$) and E ($P = 0.002$).

General comments

This study has limitations which include, the retrospective observation, the lack of data wrt patient numbers in the long and short dose fractionation groups, clarification about why patients in groups D and E (who have very good prognosis) did not receive surgery.

6.6 Surgery for MSCC

What surgical technique is the most effective in treating patients with known MSCC in terms of the following outcomes: long term deformities; overall survival; symptom control (pain control, continence, ambulation, sphincter function, neurological function - ASIA /Frankel grades); rate of revision surgery – further interventions (depending on prior surgery); QoL; Economics (cost of surgery and rehab); complication/safety

Short Summary

The evidence included for this question ranges from moderate to low quality. Very few reports exist on comparative interventions. Most report on retrospective analysis of a case series (Chen *et al.* 2007; Harris *et al.* 1996; Jansson *et al.* 2006; Klimo *et al.* 2003, 2004; Kwok *et al.*, 2006; Lewandrowsky *et al.* 2004; Loblaw *et al.* 2005; Prasad & Schiff 2005; Senel *et al.* 2007; Shehadi *et al.* 2007 Witham *et al.* 2006) but there is one prospective non comparative study (Mannion *et al.* 2007) and one RCT (Patchell *et al.* 2005). Klimo *et al.* (2005) conducted an indirect comparative, meta-analysis (which included uncontrolled studies with diverse study populations) of surgery versus conventional radiotherapy for the treatment of metastatic spinal epidural disease.

There is consistent evidence that laminectomy alone in case of ventral compression is associated with poor outcomes. Anterior, posterior or combined decompression with immediate stabilisation have been shown to provide improved patient outcomes, when compared with historical reports of RT, decompressive laminectomy without stabilisation or combined RT and laminectomy. The evidence indicates that in appropriately selected patients surgery should be the initial treatment of choice, as it is usually able to maintain ambulation, provides pain relief, provides a significant chance of recovery of neurologic function, acceptable peri-operative morbidity and mortality and prevention of late neurologic deterioration. Overall complications are higher for vertebral body resection compared to laminectomy. The rate of complications is significantly increased in patients who have received RT before surgery than in patients who received surgery first. Surgical complications included wound infection and failure of fixation that required additional surgery.

A meta-analysis by Klimo *et al.* (2005) compared the effect of surgery versus conventional radiotherapy on the ambulatory status of people with metastatic spinal epidural disease. Surgery involved decompression of the spinal cord circumferentially, followed by reconstruction and stabilisation, with radiation given either pre-operatively, post-operatively, or not at all. This review reported that, compared with conventional radiotherapy, surgery improved ability to walk for people with metastatic cancer in the spine. The study conducted an indirect comparison between observational studies of RT and surgery. Although providing insight into the effects of RT compared to surgery, the extent of bias associated with this kind of comparison, requires conclusions be considered with caution. Mannion *et al.* (2007) conducted a prospective non-comparative study that evaluated the long term outcomes of patients with MSCC who received decompression surgery with fixation followed by radiotherapy. Median survival was 13 months, significant improvements were reported for ambulation, continence and in SF36 quality of life scores as well as pain. Patchell *et al.* (2005) reported a randomised trial that evaluated the efficacy of direct decompressive surgery plus postoperative radiotherapy compared to radiotherapy alone in patients with MSCC. Significantly more patients in the surgery group than in the radiotherapy group were ambulant after treatment. Patients treated with surgery plus RT retained the ambulation significantly longer than did those with radiotherapy alone. Significantly more patients in the surgery group regained ambulation than patients in the radiotherapy group. The use

of opioid analgesics was significantly reduced in the surgical group. Patient selection for this study has some influence on results reported (as suggested by Loblaw A. 2004 and Maranzano and Trippa 2007) and therefore, the results of this trial cannot be used to justify surgery in all patients with MSCC and apply only to patients comparable to those included in the Patchell *et al.* (2005) study.

PICO

Population Group	Intervention	Comparison	Outcomes
Patients with known MSCC	<ul style="list-style-type: none"> • Laminectomy • Laminectomy plus fusion • Laminectomy plus mechanical support • Anterior surgery – corporectomy and instrumented anterior fusion • 360 front and back • Bone graft • Cages • Endoscopic surgery • Vertebroplasty in combination with laminectomy (transpedicular supplementation) 	<ul style="list-style-type: none"> • Evaluations compared with each other (if possible) • Results from interventional studies with no comparison • RT 	<ul style="list-style-type: none"> • long term deformities • overall survival • symptom control: pain control, continence, ambulation, sphincter function • rate of revision surgery – further interventions (depending on prior surgery) • QoL • complication/safety • Economics – cost of surgery and rehab

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

The evidence resulting from these studies is of low to moderate quality. The studies included in the review have a high degree of consistency; with consensus that laminectomy alone in case of ventral compression is infrequently used due to poor outcomes. Anterior, posterior or combined decompression with immediate stabilisation have been shown to provide improved patient outcomes when compared with historical reports of radiotherapy, decompressive laminectomy without stabilisation or combined radiotherapy and laminectomy. Surgery is often considered after failure of radiation and chemotherapy to achieve tumour control. The evidence indicated that in appropriately selected patients surgery should be considered as initial therapy, as it provides effective pain relief, improved chance of recovery of neurologic function, acceptable peri-operative morbidity and mortality and prevention of late neurologic deterioration

A systematic review which included one RCT and observational studies reports no direct evidence to support or refute the type of surgery patients should have for the treatment of MSCC. (Loblaw *et al.* 2005)

Laminectomy has been only proven to help if the compression is posterior. In anterior spinal cord compression there is loss of spinal ability when the posterior elements are removed, leading to neurological deterioration. Anterior decompression allows for total removal of the pathological vertebral body and tumour mass. Bone grafting is not used because the bed is often too diseased to support the graft and post-operative RT will reduce the chance of graft acceptance. (Prasad & Schiff 2005) This is supported by Patchell *et al.* (2005) who conducted a randomised trial evaluating the efficacy of direct decompressive surgery in patients with MSCC. The original study design planned for a sample size of 200 patients. However, after an interim analysis, the study was stopped

because the criterion of a predetermined early stopping rule was met. 101 patients were entered into the study. The percentage of patients able to walk after treatment was significantly ($p = 0.001$) higher in surgical patients (84%) than in the radiotherapy alone patients (57%). Patients treated with surgery also retained the ability to walk significantly longer than those with radiotherapy alone (median 122 days versus 13 days, $p = 0.003$). 32 patients (16 in each treatment group) entered the study unable to walk; patients in the surgery group regained ambulation in a significantly greater proportion than patients in the radiation alone group (62% versus 19%, $p = 0.01$). The need for corticosteroids and opioid analgesics was significantly lower in the surgical group, and muscle strength and functional status were also maintained for significantly longer in patients treated with surgery. Survival times were also significantly longer in the surgery group (median, 126 days versus 100 days, $p = 0.033$). This study suggested that patients in the surgery plus radiotherapy survive longer and continue to walk for a longer proportion of the time they are alive (126 days of survival with 122 days ambulation) compared to radiotherapy only patients who don't live as long and are not walking for very long (100 days survival with 13 days ambulation).

Mannion *et al.* (2007) conducted a prospective non comparative study that evaluated the long term outcomes of patients with MSCC who received decompression surgery with fixation followed by radiotherapy. Patients were selected from a wider patient population as suitable for surgery. The patient suitability depended on: severity of paraparesis: MRC grade ≥ 3 , pain suggesting instability; primary tumour type; prognosis ≥ 6 months and extent of disease: intra and extra vertebral, presence of other mets. The Median survival was 13 months, with 56% of patients surviving at 1 year; 28% of patients surviving at 3 years. With respect to ambulatory, 68% of patients were ambulant pre-operatively; of the remaining 32% not ambulant – 50% could walk post operatively. 80% of patients were ambulant post-operatively – median follow up 3 months. 6% of patients had wound infection and 6% experienced instability or collapse post operatively. Only 3 % had neurological deterioration. Overall continence was 92% of patients continent post-operatively with median follow up of 3 months. Overall the SF-36 questionnaire which included components assessing : Physical function; role limitation (how does a patient feel their condition is impacting their role in life); bodily pain indicated a significant improvement post surgery. Pain scores indicated a significant improvement (that is, a reduction) reported between pre-operative function and post-operative at 3 months with further improvement at median 1 year follow up.

A systematic review of the management of MSCC patients reports similar improvements in neurological function following RT alone or laminectomy with or without RT. The laminectomy series had the added disadvantage of associated surgical morbidity and mortality. If a posterior decompressive procedure was performed in conjunction with a stabilisation procedure functional outcomes were better. After anterior approaches, functional improvement has a mean of 75% and a mortality rate largely unchanged. (Witham *et al.* 2006)

Evidence from a systematic review of mixed study designs (controlled and uncontrolled studies) (Klimo *et al.* 2003) reported the outcomes for patients who received posterior decompressive laminectomy. The results showed that 14 to 58% of patients who underwent a posterior decompressive laminectomy were ambulatory post-surgery. With an overall mean of 30% of patients having the ability to walk after the surgery, i.e. gait maintained, improved or regained as a result of laminectomy. Not shown in the review but broadly described, is the considerable non-neurological complications that follow laminectomy, specifically wound infection/dehiscence and spinal instability with up to 11% incidence of non- neurological complications reported in one study. The efficacy of laminectomy alone compared with radiation alone and with laminectomy followed by radiation was also reported, with 8 controlled cohort studies investigated the efficacy of laminectomy alone with radiation alone and with laminectomy followed by radiation. The

efficacy of decompressive laminectomy with internal fixation (eg. pedicle screws) and fusion was also reported from 6 studies. In one study, out of 134 patients treated with either a laminectomy (111 patients) or laminectomy with stabilization (23 patients), 75 patients who had had laminectomy with stabilisation reported better post treatment ambulatory status (92 compared with 57%), sphincter function, and pain control, and less recurrent neurological dysfunction.

Klimo *et al* (2003) also reported the findings of Circumferential Spinal Cord Decompression (where approaches included anterior (transthoracic or retroperitoneal) or posterior, including posterolateral trajectories (laminectomy, transpedicular, costotransversectomy, or lateral extracavitary) and reconstruction and immediate stabilization of the spinal column.) 17 uncontrolled cohort studies or case series studies were included. 72 to 98% of patients were ambulatory after treatment, with an overall crude mean of 86%. 0 to 94%, non-ambulatory patients regained ambulatory function, either with assistance or independently, with an overall crude mean of 57%. Mortality rates were reported for all 17 studies, this ranged from 0% to 31% of patients dying within 30 days of the operation. The crude mean of these rates = 5.7%. Morbidity data was available for 15 studies, this ranged from 7.7 to 65% of patients experiencing a complication within 30 days of the operation. This rate was the number of complications divided by the number of patients in the study (therefore, overestimates may arise if one patient suffered more than one complication). The crude mean rate from these rates = 31.8%.

A meta-analysis to compare the effect of surgery versus conventional radiotherapy on the ambulatory status of people with metastatic spinal epidural disease was conducted by Klimo *et al.* (2005). Overall the comparative analysis conducted was indirect, included uncontrolled studies and therefore was greatly influenced by bias which would require conclusions to be considered with caution. This meta-analysis found that, compared with conventional radiotherapy, surgery improved ability to walk for people with metastatic cancer in the spine. The authors concluded that surgery should be the primary treatment, with radiation as adjuvant therapy.

A retrospective case series of 30 patients who have undergone anterior column reconstruction with structural cortical allografts in combination with anterior or posterior instrumentation reports a median survival was 14 months. 93% of the allografts were radiographically incorporated as early as 6 months after surgery in spite of adjuvant chemotherapy and RT. Postoperative complications can often be successfully managed. 14 (46%) patients had intraoperative or postoperative complications. 2 patients underwent revision surgery for local recurrence. There were no allograft infections, fractures or collapse. (Lewandrowsky *et al*, 2004)

A retrospective case series study of 282 consecutive patients with thoracic or lumbar metastasis provides evidence that important improvement of function can be gained by surgical treatment but complication rate was high as was mortality from disease within the first months of surgery. Between 10-20% of the patients did not benefit from the surgical treatment and some of those will have been worsened by complications and increased pain (Jansson *et al* 2006)

A retrospective case series of 81 patients with malignant extradural spinal compression concludes that even if the patient is incontinent and immobile, emergency spinal decompression leads to better outcome. A greater proportion of patients which have undergone emergency surgery rather than electively (within 24 hours) showed functional improvement (61.5% versus 25%). Overall, 70% of patients were mobile post-operatively. (Harris *et al* 1996)

Unsystematic reviews of RCTs and cohort studies conclude that various posterolateral approaches allow adequate anterior and posterior decompression and the ability to reconstruct and stabilise with acceptable peri-operative risk. Anterior, posterior or combined decompression with immediate stabilisation have been shown to provide improved patient outcomes in terms of ambulatory status, sphincter function and pain control when compared with historical reports of RT, decompressive laminectomy without stabilisation or combined RT and laminectomy. Laminectomy is no more effective than RT in relieving pain and preserving and regaining neural function. Laminectomy should only be used for disease isolate to the dorsal spine without evidence of concomitant instability. This is a reasonable surgical option in patients who cannot tolerate a more extensive approach or who have multilevel disease. (Klimo *et al.* 2004; Kwok *et al.*, 2006)

Insertion of ghost screws and acrylic cement is reported in a series of 7 patients, with good neurological outcomes and high rate of pain control (Senel *et al.* 2007)

Chen *et al.* (2007) evaluated postoperative outcomes and survival rates of non-small cell lung cancer patients surgically treated for symptomatic spinal metastasis. The study reported that 68% of patients regained the ability to walk, and overall 74% of patients were able to walk after surgery. Median survival was 8.8 months. 61% of patients survived more than 6 months and 32% survived more than 1 year. For patients surviving more than 6 months, 89% were ambulatory. The authors highlighted that for an aggressive disease such as advanced metastatic lung cancer, "it is worthwhile to aggressively treat patients with symptomatic spinal cord compression".

Shehadi *et al.* (2007) assessed the outcomes of patients who have had spinal surgery due to metastatic breast cancer. Both Anterior (38% of 87 patients) and Posterior approaches (35% of 87 patients) were included. 87% were ambulatory pre-operatively and 98% were ambulant post operatively. 85% of patients maintained or improved Frankel scores from pre-operative to immediate post-operative time point and up to 1 year. A significant difference between the pre-operative median VAS score (6) and the post operative median score (2) was reported, $p < 0.001$. The post-operative median score was significantly lower at all time points. The pre-operative median analgesic score was 4 and dropped to 3 at discharge. It remained at this point for time points: 1, 3 6 months and 1 years. This was a significant reduction for all post operative time points when compared to pre-operative scores, $p < 0.05$. The median length of stay was 11 days. 39% of patients experienced 39 complications (26% were major and 24% were minor). Instrument failure was the most common reason for complication reason. Combined-staged surgical approach had the most major complications (38% occurring in this group). When a multivariate analyses was conducted to determine risk factors for major early complications, the only significant factor = instrumentation of ≥ 5 spinal levels, (RR=7.2, 95%CI 1.5-35.5, $P=0.01$). 20 patients had tumour recurrence; 7 local, 10 distant 3 had both. Re-treatment which included surgery in 11 patients and RT on 9. Median survival interval after original breast cancer diagnosis = 80 months. Survival rate after date of primary breast cancer diagnosis was 96% at 1 year, 81% at 3 years, 69% at 5 years. Median survival time after spinal surgery = 21 months. Survival rate after patients' first spinal surgery was 62% at 1 year, 33% at 3 years, 24% at 5 years.

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Kwok, Y., Tibbs, P.A., Patchell, R.A. (2006) Clinical Approach to metastatic epidural spinal cord compression. *Hematology – Oncology Clinics of North America*, 20, 1297-1305

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Patchell, R.A., Tibbs, P.A., Regine, W.F., Payne, R. (2005) Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial, *Lancet*, 366:643-48

Prasad, D., Schiff, D. (2005) Malignant Spinal Cord Compression. *Lancet Oncol.* (2005) 6:15-24

Ratliff, J.K., Cooper, P.R.(2003) Metastatic spine tumours, *Southern Medical Journal* 97, 246-253

Senel, A., Kaya, A.H., Kuroglu, E., Celik, F., (2007) Circumferential stabilisation with ghost screwing after posterior resection of spinal metastases via transpedicular route. *Neurosurgical Review*, 30:131-137

Shehadi, J. A., Sciubba, D. M., Suk, I., Suki, D., Maldaun, M. V. C., McCutcheon, I. E., Nader, R., Theriault, R., Rhines, L. D. & Gokaslan, Z. L. (2007) Surgical treatment strategies and outcome in patients with breast cancer metastatic to the spine: a review of 87 patients. *European Spine Journal*, 16: 1179-1192.

St Clair S.F., McLain, R.F. (2006) Posterolateral spinal cord decompression in patients with metastasis: an endoscopic assisted approach. *Surgical Technology international*, 15: 257-66

Witham, T.F., Khavkin, Y.A., Gallia, G.L. Wolinsky, J.P., Gokaslan, Z.L. (2006) Surgery insight: current management of epidural spinal cord compression from metastatic spine disease. *Nature Clinical Practice Neurology*, 2006, 2 (2) 87-94

Evidence Tables

Table: Evidence Summary: Main Outcomes

Reference	Intervention	Evidence Grade	Outcome: Survival	Outcome: Complication	Outcome: Rate of Revision surgery/Recovery
Chen, Y. J., Chang, G. C., Chen, H. T., Yang, T. Y., Kuo, B. I., Hsu, H. C., Yang, H. W. & Lee, T. S. (2007) Surgical results of metastatic spinal cord compression secondary to non-small cell lung cancer. <i>Spine</i> , 32: E413-E418.	combined anterior and posterior procedures (anterior corpectomy, reconstruction with methylmethacrylate, and posterior instrumentation).	retrospective case series, evidence grade 3	<p>Survival / Analysis of Prognostic Factors for Survival:</p> <ul style="list-style-type: none"> • Patients surviving >6 months, 89% (17 of 19) were ambulatory. • One patient developed a symptomatic tumor recurrence at the previous level of decompression. • 3 patients developed new symptomatic spinal cord compression due to noncontiguous metastasis (all these patients received decompressive surgeries again). • Post-surgery, 11 patients received 	<p>Postoperative complications</p> <ul style="list-style-type: none"> • wound infection was the most common complication (With 8 complications in total; 5 were surgery-related) • No intraoperative mortality, but 2 deaths occurred in the immediate postoperative period. 	Not reported

Reference	Intervention	Evidence Grade	Outcome: Survival	Outcome: Complication	Outcome: Rate of Revision surgery/Recovery
			<p>chemotherapy and 13 patients received gefitinib treatment.</p> <ul style="list-style-type: none"> • Median survival = 8.8 months • 61% (19 of 31) of the patients survived for more than 6 months, • 32% (10 of 31) survived for more than 1 year. • 6 patients are still alive. <ul style="list-style-type: none"> • A log-rank test and Cox proportional hazards model indicated that better preoperative performance status, postoperative ambulatory status, and improvement in ambulatory status after surgery all had statistically significant associations with 		

Reference	Intervention	Evidence Grade	Outcome: Survival	Outcome: Complication	Outcome: Rate of Revision surgery/Recovery
			longer survival.		
Harris, J.K., Sutcliffe, J.C. & Robinson, E. (1996). The role of emergency surgery in malignant spinal extradural compression: assessment of functional outcome. British Journal of Neurosurgery, 10(1), 27-33	Emergency or elective surgery and decompression <ul style="list-style-type: none"> • Laminectomy • Laminectomy and fusion • Anterior corpectomy and fusion 	retrospective case series; evidence level 3	not reported	not reported	not reported

Reference	Intervention	Evidence Grade	Outcome: Survival	Outcome: Complication	Outcome: Rate of Revision surgery/Recovery
Jansson, K.A., Bauer H.C.F. (2006) Survival, complications and outcome in 282 patients operated for neurological deficit due to thoracic or lumbar spinal metastases, Eur Spine Journal , 200615:196-202	Posterior decompression and stabilisation; posterior stabilisation with rods (hooks, screws, pedicle screws) augmentation with methyl methacrylate; anterior decompression with reconstruction of the vertebral body (bone cement)	retrospective case series; evidence level 3	a total of 37/282 (13%) died within 30 days. The rate of survival was 0.63 at 3 months , 0.47 at 6 months, 0.30 at 1 year , 0.16 at 2 years and 0.005 at 5 years. The 30 day mortality was not related to the extent of metastatic disease, but the 3 months survival rate was 0.50 for patients with non-skeletal metastases, compared to 0.81 for those with a solitary skeletal metastasis.	a total of 60 complications recorded in 56/282 patients (20%). Systemic complications were often associated with death. 49/282 had local complications and 34 wound infections of which 9 were operated with wound revision.	a total of 29/282 patients were re-operated during follow-up 17 at the same level (due to local progression of disease at previously decompressed site and /or failure of stabilisation),. Median time to re-operation was 3 (0.4-9) years. 12 patients with epidural compression at a new spinal level were re-operated after only 0.7 (0.3-10) years.
Klimo, P., Jr., Kestle, J. R. & Schmidt, M. H. (2003) Treatment of metastatic spinal epidural disease: a review of the literature. <i>Neurosurgical</i>	Posterior Decompressive Laminectomy Circumferential Spinal Cord Decompression	Systematic review of evidence obtained from ≥ 1 properly designed randomized controlled trial and evidence obtained from well-designed,	Decompressive Laminectomy <i>Not reported</i> Circumferential Spinal Cord Decompression Mortality Mortality rates were reported for all 17 studies, this ranged	Posterior Decompressive Laminectomy non-neurological complications that follow laminectomy, specifically wound infection/dehiscence and spinal instability (up to 11% incidence of non- neurological	Not reported

Reference	Intervention	Evidence Grade	Outcome: Survival	Outcome: Complication	Outcome: Rate of Revision surgery/Recovery
<i>Focus, 15: E1.</i>		controlled trials w/o randomisation, such as nonrandomised cohort studies, case-control studies, quasi-experimental studies and randomised controlled trials. Evidence level ranged from 1- to 3	from 0% to 31% of patients dying within 30 days of the operation. The crude mean of these rates = 5.7%	<p>complications in Findlay GF (1984).</p> <p><i>Efficacy of laminectomy alone compared with radiation alone and with laminectomy followed by radiation:</i></p> <ul style="list-style-type: none"> •No detailed analysis of the results of these studies was reported <p><i>Decompressive laminectomy with internal fixation (eg. pedicle screws) and fusion:</i></p> <ul style="list-style-type: none"> •In a study by Sherman and Waddell (1986) reported that out of 134 patients treated with either a laminectomy (111 patients) or laminectomy with stabilisation (23 patients), 75 patients who had had 	

Reference	Intervention	Evidence Grade	Outcome: Survival	Outcome: Complication	Outcome: Rate of Revision surgery/Recovery
				<p>laminectomy with stabilisation reported better post treatment ambulatory status (92 compared with 57%), sphincter function, and pain control, and less recurrent neurological dysfunction.</p> <p>Circumferential Spinal Cord Decompression Morbidity data was available for 15 studies, this ranged from 7.7 to 65% of patients experiencing a complication within 30 days of the operation. The crude mean rate from these rates = 31.8%</p> <p>Complications were further described by surgical, hardware or medical, rates were generally low,</p>	

Reference	Intervention	Evidence Grade	Outcome: Survival	Outcome: Complication	Outcome: Rate of Revision surgery/Recovery
				however, surgical complications due to wound infection etc. had the highest rate of complication, ranging from 1 to 45% of patients, with a crude mean rate of 8.69 % of patients experiencing this complication	
Klimo, P., Dailey, A.T., Fessler, R.G. (2004) Posterior surgical approaches and outcomes in metastatic spine disease. Neurosurgery Clinics of North America 15: 425-435	Posterior decompressive laminectomy, vertebrectomy, anterior approaches	Unsystematic review of RCTs, prospective cohort studies and retrospective case series; evidence level 4	Not reported	Not reported	Not reported
Klimo P, Thompson C J, Kestle J R, Schmidt M H.	Surgery involved decompression of the spinal cord circumferentially,	The comparison between radiotherapy	The one-year survival in the surgical studies (n=502) ranged from 12% to 62%, with an	Complications and local recurrences No significant treatment-related	One radiation article described patients that developed local recurrences. 2.4%

Reference	Intervention	Evidence Grade	Outcome: Survival	Outcome: Complication	Outcome: Rate of Revision surgery/Recovery
(2005) A meta-analysis of surgery versus conventional radiotherapy for the treatment of metastatic spinal epidural disease. Neuro-Oncology 7(1): 64-76	<p>followed by reconstruction and stabilisation, with radiation given either pre-operatively, post-operatively, or not at all.</p> <p>Studies of radiotherapy had to report the cumulative radiation dose and schedule. Most of the included studies involved standard external beam radiation therapy (usually 2,800 to 3,200 c Gy total dose divided over 7 to 12 days).</p>	and surgery was indirect and based on uncontrolled observational studies 2-	<p>average of 41%</p> <p>For the radiation articles (n=397), the rate was 20% to 28%, with an average of 24%</p> <p>The most significant factor that determined post-treatment survival was the primary histology.</p> <p>Although the survival statistics vary among the papers, in general, patients with breast and renal cancer have a more favourable survival prognosis than those with lung cancer and sarcoma.</p>	<p>complications were reported in the radiation studies.</p> <p>Within the surgical papers, 63 patients died within 30 days of their operation (6.3%).</p> <p>233 complications (23%) occurred within the following categories defined previously: medical, 100; neurologic, 19; hardware, 18; and surgical, 96.</p>	<p>patients developed local recurrences.</p> <p>81 patients described in nine surgical papers also developed local recurrences for an incidence of at least 8%</p> <p>Ambulatory rescue</p> <ul style="list-style-type: none"> Ambulation “rescue” rates from the surgical papers were generally greater than those calculated in the radiation papers. Of 384 surgical patients who were non-ambulatory before treatment, 228 regained the ability to walk. In the radiation studies, of 265 patients who were non ambulatory before treatment, 79 became ambulant. People receiving surgery were twice as likely to regain

Reference	Intervention	Evidence Grade	Outcome: Survival	Outcome: Complication	Outcome: Rate of Revision surgery/Recovery
					ambulatory function compared with those undergoing radiotherapy (crude RR 1.99, 95% CI: 1.63, 2.44, P<0.001), but there was significant heterogeneity (Q=480.9, df = 27, P<0.001) which, when controlled for, meant that the differences between treatments were not statistically significant.
Lewansrowsky , K.U., Hecht, A.C., DeLaney, T.F., Chapman, P.A., Horniceck, F.J., Pedlow, F.X. (2004) Anterior spinal arthrodesis with structural I cortical allografts and instrumentation for spine tumour	Anterior vertebral reconstruction with fresh frozen cortical bone allografts, in combination with anterior or posterior instrumentation.	retrospective case series; evidence level 3	overall median survival period 14 months (range 7 months-5 years). Patients with chordoma had the best overall median survival time.	14 out of 30 patients (46%) have experienced intraoperative or postoperative complications. These include wound breakdown in 3 cases, stabilisation failure in 2, superficial wound infections in 4, excessive haemorrhage in 6, postoperative respiratory failure in 1, intraoperative vascular/visceral	Not reported

Reference	Intervention	Evidence Grade	Outcome: Survival	Outcome: Complication	Outcome: Rate of Revision surgery/Recovery
surgery. Spine, vol. 29, 10:1150-59				injury in 2 and cerebrospinal fluid leak in 2 patients. Adjuvant RT and chemotherapy did not appear to be related to clinical complications. Four operations were necessary for treatment of complications: 2 for wound revision, 2 for infection. 2 patients underwent revision surgery for local recurrence.	
Loblaw, <i>et al.</i> (2005) Systematic Review of the Diagnosis and Management of Malignant Extradural Spinal Cord Compression. Journal of Clinical Oncology	Six general types of cervical laminoplasty; Surgery plus RT; RT alone; vertebral body resection; laminectomy	Systematic review of RCTs, population based studies, prospective cohort studies, cross-sectional studies, retrospective case series; evidence level 3		surgery is associated with significant morbidity and mortality: 0-54% 30 day postoperative complication rates and 0-13% postoperative mortality rates reported in the reviewed literature. Overall complications are higher for	

Reference	Intervention	Evidence Grade	Outcome: Survival	Outcome: Complication	Outcome: Rate of Revision surgery/Recovery
23:2028-2037				vertebral body resection (10-54%) vs laminectomy (0-10%). The rate of complications is increased in patients who received RT before surgery 32%, vs. 12 % in patients who received surgery first (p<0.05)	
Mannion, R. J., Wilby, M., Godward, S., Lyratzopoulos, G. & Laing, R. J. C. (2007) The surgical management of metastatic spinal disease: prospective assessment and long-term follow-up. British Journal of Neurosurgery, 21: 593-598.	Surgical Types included anterior approach and type of fixation (vertebrectomy and fixation) compared to posterior approach and type of fixation use (laminectomy and fixation, laminectomy only (intradural), vertebrectomy and fixation, occipito-cervical fusion.) Fixation was with pedicle screws or halo jacket.	prospective non comparative study Evidence grade 2-	The Median survival was 13 months, with 56% of patients surviving at 1 year; 28% of patients surviving at 3 years.	6% of patients had wound infection and 6% experienced instability or collapse post operatively. Only 3 % had neurological deterioration.	Morbidity: 6% of patients had wound infection and 6% experienced instability or collapse post operatively. Only 3 % had neurological deterioration.

Reference	Intervention	Evidence Grade	Outcome: Survival	Outcome: Complication	Outcome: Rate of Revision surgery/Recovery
Patchell, R.A., Tibbs, P.A., Regine, W.F., Payne, R. (2005) Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial, Lancet, 2005, 366:643-48	Direct decompressive surgery followed by RT, compared to RT alone	RCT: Evidence level 1+	Increased survival time reported for the surgery grp. 30 day mortality rates were 6% in the surgery group and 14 % in RT grp, (p=0.32)	4 patients reported with surgical complications: wound infection and 1 with failure of fixation that required additional surgery.	Not reported
Prasad, D., Schiff, D. (2005) Malignant Spinal Cord Compression. Lancet Oncol 2005; 6:15-24	Laminectomy; anterior decompression (thoracotomy and retroperitoneal dissection); RT (from 6 included studies)	Expert review 3	mean post-operative survival 271 days.	51% of patients with spinal cord compression had vertebral collapse and 25% of patients treated with laminectomy sustained major neurological deterioration associated with surgery.	92% of patients had a stable spine as a result of surgery

Reference	Intervention	Evidence Grade	Outcome: Survival	Outcome: Complication	Outcome: Rate of Revision surgery/Recovery
Ratliff, J.K., Cooper, P.R.(2003) Metastatic spine tumours, Southern Medical Journal 97, 246-53	Surgery – not specified any further	Expert Review Evidence level 4	overall patient survival will depend on primary malignancy, degree of systemic spread and tumour biology. Median survival of at least 1 year after surgery is reported in many series. Considerable diminished survival presents in certain malignancies, such as metastatic colon carcinoma or metastatic melanoma with spinal involvement, where median survival is less than 4 months.	<ul style="list-style-type: none"> • Severe complications include perioperative neurologic deterioration, wound breakdown, significant blood loss and mortality. • Major and minor complication may occur in up to 30% of patients. • Pulmonary, cardiac and gastro-intestinal complications, along with cerebrospinal fluid leakage are common. Instrumentation failures may occur. • The use of high dose steroids, RT and chemotherapy increase complication rates. • Perioperative mortality should be 	

Reference	Intervention	Evidence Grade	Outcome: Survival	Outcome: Complication	Outcome: Rate of Revision surgery/Recovery
				<p>expected less than 5%.</p> <ul style="list-style-type: none"> Wound complications after RT in laminectomy have been reported in 28% of patients, and an increase from 12 to 32% was reported in patients treated with RT before decompression and stabilisation. Surgery performed within 7 days of beginning RT results in a wound complication rate of 46%. 	
Senel, <i>et al.</i> (2007) Circumferential stabilisation with ghost screwing after posterior resection of spinal metastases via	posterior transpedicular laminectomy/corpectomy, circumferential stabilisation using ghost screws and acrylic cement.	Case reports : Evidence Level 3	1 patient died 1 month postoperative of pulmonary embolism. Overall survival not reported	Not reported	Not reported

Reference	Intervention	Evidence Grade	Outcome: Survival	Outcome: Complication	Outcome: Rate of Revision surgery/Recovery
transpedicular route. Neurosurgical Review, 30:131-137					
Shehadi <i>et al.</i> (2007). Surgical treatment strategies and outcome in patients with breast cancer metastatic to the spine: a review of 87 patients. <i>European Spine Journal</i> , 16: 1179-1192.	Surgical Techniques included: Anterior approach Posterior approach Combined anterior-posterior simultaneous Anterior or posterior portion of staged procedure	retrospective case series, Evidence Grade 3	Survival <ul style="list-style-type: none"> • Median survival interval after original breast cancer diagnosis = 80 months • Survival rate after date of primary breast cancer diagnosis was 96% at 1 year, 81% at 3 years, 69% at 5 years. • Median survival time after spinal surgery = 21 months. • Survival rate after patients' first spinal surgery was 62% at 1 year, 33% at 3 years, 24% at 5 years. 	Length Of Stay and Complications <ul style="list-style-type: none"> • Median LOS = 11 days • 33% required post op rehabilitative services. • 39% of patients experienced 39 complications (26% were major and 24% were minor) • 34 complication were early, 5 complications were classed as late. (1 patient died within 24hours of surgery) • Instrument failure was the most common complication reason • Combined–staged surgical approach 	Tumour recurrence <ul style="list-style-type: none"> • Median overall duration of follow up = up to 13 months • 20 patients had tumour recurrence; 7 local, 10 distant 3 had both. • Re-treatment which included surgery in 11 patients and RT on 9.

Reference	Intervention	Evidence Grade	Outcome: Survival	Outcome: Complication	Outcome: Rate of Revision surgery/Recovery
				<p>had the most major complications (38% occurring in this group)</p> <ul style="list-style-type: none"> • When a multivariate analyses was conducted to determine risk factors for major early complications, the only significant factor = instrumentation of \geq 5 spinal levels, (RR=7.2, 95%CI 1.5-35.5, P=0.01) 	
St Clair S.F., McLain, R.F. (2006)Posterolateral spinal cord decompression in patients with metastasis: an endoscopic assisted approach.	Laminectomy and posterolateral decompression; vertebrectomy; bone graft and titanium cage; posterior spinal fusion with bone graft and pedicle screw instrumentation; intralesional	Case reports; evidence level 3	18 months for one patient who died of subsequently developed intracranial metastases. Not reported for the other 2 patients outside the follow-up period.	the article reports no respiratory complications (pneumonia, atelectasis)	Not reported

Reference	Intervention	Evidence Grade	Outcome: Survival	Outcome: Complication	Outcome: Rate of Revision surgery/Recovery
Surgical Technology international, 15: 257-66	vertebrectomy with posterolateral endoscopic decompression.				
Witham, T.F., Khavkin, Y.A., Gallia, G.L. Wolinsky, J.P., Gokaslan, Z.L. (2006) Surgery insight: current management of epidural spinal cord compression from metastatic spine disease. Nature Clinical Practice Neurology, 2 (2) 87-94	<ul style="list-style-type: none"> • Outcomes were reported for: • RT alone (20 studies), • Laminectomy with or without RT (27 studies) • Posterior decompression and stabilisation (16 studies) • Vertebral body resection and stabilisation (18 studies). • Studies reporting on circumferential surgical decompression with concomitant spinal cord stabilisation, vertebroplasty, kyphoplasty. 	Partly - Systematic review of RCTs, prospective cohort studies and retrospective case series; evidence level 3	<p>Mean values across included studies listed:</p> <p>Laminectomy with or without RT: 6% mortality rate</p> <p>Posterior decompression and stabilisation: 5% mortality rate</p> <p>Vertebral body resection and stabilisation: 10% mortality rate</p>		

Symptom Outcomes:

Study details and Citation	Symptom Ambulation	Other Functions (eg. Neurological Function Motor, sphincter control, continence, ROM)	Pain
<p>A retrospective case series of 25 patients who have undergone single stage posterolateral transpedicular decompression for MSCC (Blisky <i>et al.</i> 2000)</p>	<ul style="list-style-type: none"> • Functional status was assessed (ECOG) and all patients who were fully ambulatory before the surgery (0-2) remained so (0-1). • Ten patients who were bedridden more than 50% of the time or who were completely disabled (3-4) improved to ambulatory status (0-2) and 4 patients did not improve. 	<ul style="list-style-type: none"> • Patients who were neurologically intact before the surgery remained neurologically normal; five patients improved a grade to become neurologically intact (ASIA grade D to E). • Patients with significant neurologic deficit before the surgery (ASIA grade C) did not fare as well. • The two patients who worsened in this group had the acute onset of myelopathy and high grade spinal cord compression. 	<ul style="list-style-type: none"> • pain relief was reported to have been immediate and durable. • 15 patients with severe back or radicular pain rated their pain as mild after the surgery, and two others improved to moderate pain status. No patient developed recurrent mechanical back pain or loss of fixation.
<p>A retrospective case series study that evaluated postoperative outcomes and survival rates of non-small cell lung cancer patients surgically</p>	<p>Performance Score/Ambulation</p> <ul style="list-style-type: none"> • Neurologic improvement by at least one Frankel grade was reported in 25 of 31 cases 		

Study details and Citation	Symptom Ambulation	Other Functions (eg. Neurological Function Motor, sphincter control, continence, ROM)	Pain
treated for symptomatic spinal metastasis. Chen <i>et al.</i> (2007)	(80%). <ul style="list-style-type: none"> • 5 patients showed no improvement, and one patient showed deterioration from Frankel grade B to A. • Overall, 74% of patients (23 of 31) were able to walk after surgery. • 17 of 25 (68%) non-ambulatory (Frankel B/C) patients became ambulatory (Frankel D/E) again. 		
In a retrospective case series study the following intervention were evaluated: Anterior decompression, angular correction, fusion with anterior plate fixation; corpectomy, discectomies and acrylic implants. (Ferch at al 2004)			<ul style="list-style-type: none"> • cervical pain scores were similar before and after surgery
A retrospective case series that evaluated the outcomes of emergency or elective surgery and decompression (Harris <i>et al.</i> 1996)		<ul style="list-style-type: none"> • patients with functional deficit (incontinence or immobility) emergency surgery was associated with a stat significantly better outcome ; 71% of patients with 	

Study details and Citation	Symptom Ambulation	Other Functions (eg. Neurological Function Motor, sphincter control, continence, ROM)	Pain
		<p>emergency surgery had a good outcome, 32 patients improved functionally; 61% of patients with elective surgery had a good outcome, 7 patients improved functionally</p> <ul style="list-style-type: none"> • 24% of preoperatively mobile patients with emergency procedure were alive at 3 months follow up; • All mobile patients remained mobile; 49% of immobile and incontinent patients improved following surgery; 47% of incontinent and immobile patients regained the ability to walk 	
A case series study evaluated the outcomes of posterior decompression and stabilisation; posterior	The ability to walk was retained at 1 and 2 years of follow-up.	<ul style="list-style-type: none"> • 23 patients with normal motor function preoperatively (Frankel E) retaining this 	

Study details and Citation	Symptom Ambulation	Other Functions (eg. Neurological Function Motor, sphincter control, continence, ROM)	Pain
<p>stabilisation with rods (hooks, screws, pedicle screws) augmentation with methyl methacrylate; anterior decompression with reconstruction of the vertebral body. (Jansson, <i>et al.</i> 2006)</p>		<p>function postoperatively.</p> <ul style="list-style-type: none"> • 12/255 with motor deficits worsened postoperatively • 179 improved at least one Frankel grade. • Among 144 patients who were non-walkers but retained some motor function (Frankel C) 100 could walk at discharge (D-E). • 10/26 patients who had no motor function (A-B) regained sufficient neurological function to walk during follow-up 	
<p>A meta-analysis to compare the effect of surgery versus conventional radiotherapy on the ambulatory status of people with metastatic spinal epidural disease. Surgery involved decompression of the spinal cord circumferentially, followed by reconstruction and</p>	<ul style="list-style-type: none"> • People receiving surgery were 1.3 times more likely to be ambulatory after treatment: • 85% surgery versus 64% radiotherapy (crude RR 1.28, 95% CI: 1.20, 1.37, P<0.001). • Significant heterogeneity was present in the meta-analysis for this outcome (Q=164.6, df =27, 	<p>Sphincter function</p> <ul style="list-style-type: none"> • Of the 131 patients within the surgical articles, 65 (50%) were incontinent preoperatively compared with 22 (17%) postoperatively. • In the radiation studies, 	<ul style="list-style-type: none"> • Although this outcome was reported frequently across studies, the assessment was quite crude with no distinction between the type of pain (axial vs. radicular), and improvement was simply a dichotomous variable (i.e., yes/no). • Only one paper (Gokaslan et al

Study details and Citation	Symptom Ambulation	Other Functions (eg. Neurological Function Motor, sphincter control, continence, ROM)	Pain
<p>stabilisation, with radiation given either pre-operatively, post-operatively, or not at all. (Klimo <i>et al</i> 2005)</p>	<p>P<0.001).</p> <ul style="list-style-type: none"> Age, gender, primary pathology and lesion distribution did not statistically significantly influence these findings. 	<p>82 out of 397 patients (21%) were incontinent prior to radiation compared with 61 patients post-radiation (15%).</p> <ul style="list-style-type: none"> Overall rescue rate (for the sphincter function) with surgery was 66% compared with 26% with radiation. 	<p>1998) reported this outcome in a comprehensive manner. Out of the 72 patients who underwent a thoracotomy for vertebral metastases, 65 presented with pain. Complete resolution was achieved post-treatment in 15 patients (23%), significant improvement in 45 (69%), and no change or worsening in five (8%). Gokaslan <i>et al</i> (1998) also recorded and classified the type of analgesics used by patients both preoperatively and postoperatively. 28 patients were able to decrease their class of analgesic use by at least one category.</p> <ul style="list-style-type: none"> The review authors recorded the percentage of patients within each study that had any improvement in pain after their primary treatment. Within the surgical studies, the average percentage of patients that experienced an improvement in pain was 90% (71%–100%)

Study details and Citation	Symptom Ambulation	Other Functions (eg. Neurological Function Motor, sphincter control, continence, ROM)	Pain
			compared with 70% (54%–83%) within the radiation studies.
An unsystematic review comparing the outcomes of posterior laminectomy plus RT and direct decompressive surgery with maximal debulking . (Kwok <i>et al.</i> 2006)	Fewer than 50% of patients treated with RT alone will remain ambulant and even fewer will regain the ability to walk. However, retrospective studies suggest that RT was as effective as posterior laminectomy plus RT and showed no benefit of surgery in terms of pain relief, ambulation or sphincter function. In preliminary uncontrolled studies using direct surgical decompression results have been promising, with ambulatory rates higher than 75%. In several series even about 50% of patients who were non-ambulatory preoperatively regained ambulence		
Outcomes of studies reporting on posterior decompressive laminectomy, vertebrectomy, anterior approaches. It was an unsystematic review of the evidence. (Klimo <i>et al</i> 2004)	<ul style="list-style-type: none"> • Posterior decompressive laminectomy with internal fixation provides a better outcome in terms of ambulatory status, sphincter function compared to laminectomy only. 	<ul style="list-style-type: none"> • Posterior decompressive laminectomy with internal fixation provides a better outcome in terms of 	<ul style="list-style-type: none"> • Laminectomy is no more effective than RT in relieving pain • Posterior decompressive laminectomy with internal fixation provides a better

Study details and Citation	Symptom Ambulation	Other Functions (eg. Neurological Function Motor, sphincter control, continence, ROM)	Pain
	<ul style="list-style-type: none"> • Costotransversectomy: adequate anterior decompression was achieved in all reported patients. Patients who were ambulatory remained so after surgery. 	<ul style="list-style-type: none"> • sphincter function compared to laminectomy only. • Laminectomy is no more effective than RT in preserving and regaining neural function 	<ul style="list-style-type: none"> • outcome in terms of pain control when compared to laminectomy only. • Costotransversectomy: adequate anterior decompression was achieved in all reported patients pain was improved in 75% of patients after surgery.
<p>In a retrospective study comparing anterior decompression with spinal fusion versus laminoplasty in. (Masaki <i>et al.</i>, 2007)</p>		<ul style="list-style-type: none"> • 59 patients surgical outcome of ASF (anterior decompression with spinal fusion) was superior to the surgical outcome of laminoplasty. • Elderly patients treated with laminoplasty showed an especially poor surgical outcome. The hyper mobility of vertebrae at the cord compression level is a risk factor for poor outcome after 	

Study details and Citation	Symptom Ambulation	Other Functions (eg. Neurological Function Motor, sphincter control, continence, ROM)	Pain
		laminoplasty. <ul style="list-style-type: none"> • ASF should therefore be the first choice of treatment for patients with ossification of the posterior longitudinal ligament and a hyper mobile cervical spine. • When laminoplasty is used for such cases the addition of posterior instrumented fusion is desirable for stabilising the spine and decreasing damage to the cord 	
In a retrospective case series evaluating the effectiveness of corpectomy; corpectomy and placement of posterior instrumentation with or without decompression; laminectomy; laminectomy with fusion or placement of instrumentation; costotransversectomy; transpedicular approach; autologous bone graft	<ul style="list-style-type: none"> • Patients who have undergone surgery, 97% of patients (59/61) were ambulatory postoperatively – 52 were ambulatory on admission and 7 regained ambulatory function. • Most patients who survived 6 months remained ambulatory (81%), as did 66% of those alive at 1.6 years. • The number of patients who 		Pain relief was achieved in 8 patients

Study details and Citation	Symptom Ambulation	Other Functions (eg. Neurological Function Motor, sphincter control, continence, ROM)	Pain
(North <i>et al.</i> , 2005)	<p>could walk unaided increased from 14 to 22 (Frankel grade E)</p> <ul style="list-style-type: none"> Patients who could walk only for minimal distance decreased from 14 to 9 (Frankel grade D). 		
An RCT comparing surgery plus RT vs. RT alone (Patchell <i>et al.</i> 2005)	<ul style="list-style-type: none"> Reported post-treatment ambulatory rates were significantly different (surgery group was 84%(42/50) and 57% (29/51) in RT alone group Significantly more patients in the surgery group regained the ability to walk compared to patients in the radiotherapy group Patients treated with surgery also retained the ability to walk significantly longer than did those with radiotherapy alone (median 122 days vs. 13 days, p=0.003). Of those patients who had the ability to walk at study entry 94% (32/34) in the surgery group preserved the function compared to 74% (26/35) in the RT grp. (p=0.024). 	Surgical treatment resulted in significant differences in maintenance of continence, muscle strength (ASIA score), functional ability (Frankel scores).	In the surgery group, the median mean daily morphine equivalent dose was significantly lower than the radiation group (indicated the level of pain in the RT group).

Study details and Citation	Symptom Ambulation	Other Functions (eg. Neurological Function Motor, sphincter control, continence, ROM)	Pain
<p>Observation study evaluating the long term outcomes of patients with MSCC who received decompression surgery with fixation followed by radiotherapy. Mannion <i>et al.</i> (2007)</p>	<p>68% of patients were ambulant pre-operatively; of the remaining 32% not ambulant – 50% could walk post operatively. 80% of patients were ambulant post-operatively – median follow up 3 months</p>	<p>Urinary continence:</p> <ul style="list-style-type: none"> • 86% of patients were continent pre-operatively (with an additional 4 patients continent post-op) • Overall continence = 92% of patients continent post-operatively– median follow up 3 months. • Of the 9 incontinent patients pre-operatively, 6 regained continence post-operatively. <p>Quality of Life Components of SF-36 included Physical function; role limitation (how does a patient feel their condition is impacting their role in life); bodily pain.</p> <ul style="list-style-type: none"> • Physical function: A significant difference 	<p>Visual analogue pain scores and Roland Morris back pain scores indicated a significant difference of improvement (that is, a reduction) reported between pre-operative function and post operative at 3 months with further improvement at median 1 year follow up.</p>

Study details and Citation	Symptom Ambulation	Other Functions (eg. Neurological Function Motor, sphincter control, continence, ROM)	Pain
		<p>of improvement was reported between pre-operative function and post operative at 3 months with further improvement at median 1 year follow up.</p> <ul style="list-style-type: none"> • Role limitation: A significant difference of improvement was reported between pre-operative function and post operative at 3 months with further improvement at median 1 year follow up. • Bodily Pain: A significant difference of improvement was reported between pre-operative function and post operative at 3 months with further improvement at median 1 year follow 	

Study details and Citation	Symptom Ambulation	Other Functions (eg. Neurological Function Motor, sphincter control, continence, ROM)	Pain
		<p>up.</p> <ul style="list-style-type: none"> • A median survival analysis was conducted for patients who returned a complete SF-36 data set (n=18), it indicated that survival was longer in this group of patients than in the group as a whole (18 months compared to 13 months). 	
<p>A meta-analysis evaluating the outcomes of different types of cervical laminoplasty. (Ratliff and Cooper 2003)</p>	<ul style="list-style-type: none"> • Recovery of walking of previously non-ambulatory patients may be achieved in 50% of patients. • Addition of decompressive laminectomy to RT did not contribute to improvement. • Addition of stabilisation via anterior or posterior approaches achieved improvement in 70% of patients. <p>Patients who deteriorate during RT may manifest poor recovery, with 77% of patients unchanged</p>	<ul style="list-style-type: none"> • Results indicated that cervical range of motion (ROM) decreased substantially after laminoplasty (mean decrease 50%, range 17-80%) reported as compared to the Hirabayashi laminoplasty technique. • Progressive loss of cervical ROM and final ROM is similar in 	<ul style="list-style-type: none"> • Pain control: isolated pedicle screw stabilisation achieved nearly 90% improvement in VAS pain scores at 1 month after surgery. • Similar results are reported in more aggressive anteroposterior combined approaches, with over 90% of patients achieving improvement in pain control after decompression and stabilisation.

Study details and Citation	Symptom Ambulation	Other Functions (eg. Neurological Function Motor, sphincter control, continence, ROM)	Pain
	after surgery.	<p>patients who underwent laminoplasty and those who underwent laminectomy and fusion.</p> <ul style="list-style-type: none"> • Neurologic deficit: postoperative neurologic function depends on preoperative status. • Patients with severe deficit of long-standing duration may not achieve improvement even with adequate decompression and fusion. <p>Assessment of operative outcomes varies in different series making comparison difficult.</p> <p>In properly selected patients 70-80% may achieve improvement in neurologic function.</p>	Multiple series report reduction in pain control medication.

Study details and Citation	Symptom Ambulation	Other Functions (eg. Neurological Function Motor, sphincter control, continence, ROM)	Pain
Retrospective Case series study. (Shehadi <i>et al.</i> 2007)		Overall continence was 92% of patients continent post-operatively with median follow up of 3 months. Overall the SF-36 questionnaire which included components assessing : Physical function; role limitation (how does a patient feel their condition is impacting their role in life); bodily pain indicated a significant improvement post surgery.	Pain scores indicated a significant improvement (that is, a reduction) reported between pre-operative function and post-operative at 3 months with further improvement at median 1 year follow up.
A case report (of 3 patients) on endoscopic assisted posterolateral decompression was evaluated. (St Clair, and McLain 2006)	<ul style="list-style-type: none"> patients reported as ambulant after surgery 	<ul style="list-style-type: none"> patients reported as neurologically intact after surgery 	<ul style="list-style-type: none"> patients reported as pain free after surgery
A systematic review of the management of MSCC patients (Witham <i>et al.</i> , 2006)		<ul style="list-style-type: none"> After anterior approaches, functional improvement has a mean of 75% A mean of 36% patients with improved 	Pain relief was achieved in a high percentage (mean 88%) with a mean mortality rate comparable to laminectomy alone (5%).

Study details and Citation	Symptom Ambulation	Other Functions (eg. Neurological Function Motor, sphincter control, continence, ROM)	Pain
		neurological function and 17% worsened following RT alone	

Evidence Tables (for individual studies)

Study Identification:	Bilsky, M.H., Boland, P., Lis, E., Raizer, J.J. (2000) Single stage posterolateral transpedicle approach for spondylectomy, epidural decompression and circumferential fusion of spinal metastases. Spine, 25. 25[17] 2240-49					
Design:	retrospective case series; evidence level 3					
Country / Setting:	USA					
Population:	25 undergoing PTA, out of 104 patients with MSCC					
Intervention:	posterolateral transpedicular approach for anterior and posterior surgical decompression and spinal fusion.					
Outcomes:	Pain relief, neurologic symptoms; ASIA scale					
Follow-up:						
Results:	The posterolateral transpedicular approach provides a wide surgical exposure to decompress and instrument the anterior and posterior spine. This technique avoids morbidity associated with anterior approaches and provides immediate stability.					
OUTCOME OF INTEREST	COMPARISON	RESULT				
Long term deformities:	not reported					
Overall survival:	not reported					
Symptom control: pain relief was immediate and durable. 15 patients with severe back or radicular pain rated their pain as mild after the surgery, and two others improved to moderate pain status. No patient developed recurrent mechanical back pain or loss of fixation.	Postoperative pain assessment	Preoperative pain assessment				
	Mild	Moderate	Severe			
	2	3	15			
	Moderate		3			
	Severe					
Patients who were neurologically intact before the surgery remained neurologically normal; five patients improved a grade to become neurologically intact (ASIA grade D to E).	Postoperative score	Preoperative score				
Patients with significant neurologic deficit before the surgery (ASIA grade C) did not fare as well. The two patients who worsened in this group had the acute onset of myelopathy and high grade spinal cord compression.	A	B	C	D	E	
			1			
	B		1			
	C		1			
	D			1	1	
	E			5	15	
Functional status was assessed (ECOG) and all patients who were fully ambulatory before the surgery (0-2) remained so (0-1). Ten patients who were bedridden more than 50% of the time or who were completely disabled (3-4) improved to ambulatory status (0-2) and 4 patients did not improve.	Postoperative score	Preoperative score				
Rate of revision surgery/ recovery: not reported		0	1	2	3	4
QOL: not reported	0	1			1	
Economics: not reported	1		5	3	3	2
Complications/safety:	2				2	2
	3					
	4				1	2

Chen, Y. J., Chang, G. C., Chen, H. T., Yang, T. Y., Kuo, B. I., Hsu, H. C., Yang, H. W. & Lee, T. S. (2007) Surgical results of metastatic spinal cord compression secondary to non-small cell lung cancer. *Spine*, 32: E413-E418.

Design: retrospective case series, evidence grade 3
Country: Taiwan

Aim: To evaluate postoperative outcomes and survival rates of NSCLC patients surgically treated for symptomatic spinal metastasis.

Synopsis: Chen *et al.* (2007) evaluated postoperative outcomes and survival rates of non-small cell lung cancer patients surgically treated for symptomatic spinal metastasis. The study reported that 68% of patients regained the ability to walk, and overall 74% of patients were able to walk after surgery. Median survival was 8.8 months. 61% of patients survived more than 6 months and 32% survived more than 1 year. For patients surviving more than 6 months, 89% were ambulatory. The authors highlighted that for an aggressive disease such as advanced metastatic lung cancer, "it is worthwhile to aggressively treat patients with symptomatic spinal cord compression".

Inclusion criteria

Any symptomatic metastatic spinal cord compression (thoracic or lumbar spine) secondary to non-small cell lung cancer (NSCLC) who underwent palliative surgery with the indication for surgery being neurologic progression due to spinal cord compression.

Exclusion criteria

Population

A retrospective analysis of hospital records and radiographs was conducted: 31 patients with symptomatic metastatic spinal cord compression (thoracic or lumbar spine) secondary to NSCLC underwent palliative surgery.

Interventions

- 37 surgical procedures were performed in the 31 patients.
- The choice of surgical approach was dependent on the preoperative tumour location in the first 3 (10%) patients with the method of combined anterior and posterior procedures (anterior corpectomy, reconstruction with methylmethacrylate, and posterior instrumentation).
- Surgical method was changed to a posterolateral transpedicular approach (PTA) in the remaining 28 (90%) patients.
- All patients underwent posterior spinal instrumentation after adequate decompression.
- Local radiotherapy, systemic chemotherapy, and targeted therapy were provided to patients post-operatively.
- Posterolateral Transpedicular Surgical Approach: see details supplied in paper.

Outcomes

- Patient Characteristics
- Performance Score/Ambulation
- Survival
- Analysis of Prognostic Factors for Survival: The factors considered for inclusion in analyses were age (≥ 65 vs. < 65 years), tumor type (adenocarcinoma vs. non-adenocarcinoma), preoperative and postoperative ambulatory status (Frankel A +

- B+ C, non-ambulatory vs. Frankel D+ E, ambulatory), preoperative Eastern Cooperative Oncology Group performance status (0, 1 vs. 2, 3, 4), and postoperative adjuvant therapy (with vs. without).
- Postoperative complications
- Follow-up times ranged from 15 to 30 months.

Results

Patient Characteristics

- Patients Age ranged from 20 to 81 years
- Majority of tumors (19) presented in the thoracic spine; 8 in the lumbar spine, and 4 in the thoracolumbar spine.
- The most common histological type was adenocarcinoma (24 patients)
- The predominant tumor component was anterior (vertebral body and anterior epidural space) in 12 patients; and circumferential in 19 patients.

Performance Score/Ambulation

- Neurologic improvement by at least one Frankel grade was reported in 25 of 31 cases (80%).
- 5 patients showed no improvement, and one patient showed deterioration from Frankel grade B to A.
- Overall, 74% of patients (23 of 31) were able to walk after surgery.
- 17 of 25 (68%) non-ambulatory (Frankel B/C) patients became ambulatory (Frankel D/E) again.

Survival / Analysis of Prognostic Factors for Survival:

- Patients surviving >6 months, 89% (17 of 19) were ambulatory.
- One patient developed a symptomatic tumor recurrence at the previous level of decompression.
- 3 patients developed new symptomatic spinal cord compression due to noncontiguous metastasis (all these patients received decompressive surgeries again).
- Post-surgery, 11 patients received chemotherapy and 13 patients received gefitinib treatment.
- Median survival = 8.8 months
- 61% (19 of 31) of the patients survived for more than 6 months,
- 32% (10 of 31) survived for more than 1 year.
- 6 patients are still alive.
- A log-rank test and Cox proportional hazards model indicated that better preoperative performance status, postoperative ambulatory status, and improvement in ambulatory status after surgery all had statistically significant associations with longer survival.

Postoperative complications

- wound infection was the most common complication (With 8 complications in total; 5 were surgery-related)
- No intraoperative mortality, but 2 deaths occurred in the immediate postoperative period.

General comments

Retrospective study provides limited evidence of effectiveness, without a comparative group. The patient numbers are low.

Study Identification:	Harris, J.K., Sutcliffe, J.C. & Robinson, E. (1996). The role of emergency surgery in malignant spinal extradural compression: assessment of functional outcome. British Journal of Neurosurgery, 10(1), 27-33						
Design:	retrospective case series; evidence level 3						
Country / Setting:	UK; Department of Neurosurgery						
Population:	81 patients with malignant extradural spinal compression; patients with vertebral collapse secondary to metastasis without extradural tumours were excluded; 49 male, 32 female; median age 65, mean 60.0, range 15-86; 3 patients with two separate episodes at different sites; location: cervical spine 3 (3.6%), thoracic 64 (76.2), thoraco-lumbar 6 (7.1%), lumbar 9 (10.7%), sacral 2 (2.4%); 19 patients were mobile pre-operatively, 43 patients were continent						
Intervention:	Emergency or elective surgery and decompression						
Outcomes:	functional outcome: mobility and bladder function						
Follow-up:	3 months						
Results:	Even if the patient is incontinent and immobile, emergency spinal decompression leads to better outcome. A greater proportion of patients which have undergone emergency surgery rather than electively (within 24 hours) showed functional improvement (61.5% versus 25%). Overall, 70% of patients were mobile post-operatively.						
Long term deformities: not reported							
Overall survival: not reported							
Symptom control: For patients with functional deficit (incontinence or immobility) emergency surgery was associated with a better outcome ($p=0.04$) ; 71% of patients with emergency surgery had a good outcome, 32 patients improved functionally; 61% of patients with elective surgery had a good outcome, 7 patients improved functionally 24% of preoperatively mobile patients with emergency procedure were alive at 3 months follow up; all mobile patients remained mobile; 49% of immobile and incontinent patients improved following surgery; 47% of incontinent and immobile patients regained the ability to walk							
<u>Post-operative functional outcome (good outcome=functional improvement, or preservation of mobility and continence)</u>							
		Improve d	Unchang ed	Deteriorat ed	Good outcome		
Emergency surgery		32	19	1	71.2%		
Elective surgery		7	18	3	60.7%		
Overall		39	37	4	67.5%		
<u>Comparison of pre-operative functional status with post-operative functional outcome according to the surgical approach (number in brackets indicate procedures performed as an emergency)</u>							
		Preoperative			Post-operative		
		Total	Mobile and continent	Immobile and incontinent	Good outcome	Poor outcome	Other outcome
Laminectomy	66	12 (4)	29 (19)	45 (31)	18 (10)	3 (2)	
Laminectomy and fusion	12	4 (3)	5 (5)	7 (5)	4 (2)	1 (1)	

Anterior corpectomy and fusion	2	1	1 (1)	2 (1)	0	0
Rate of revision surgery/ recovery: not reported						
QOL: not reported						
Economics: not reported						
Complications/safety: not reported						

Study Identification:	Jansson, K.A., Bauer H.C.F. (2006) Survival, complications and outcome in 282 patients operated for neurological deficit due to thoracic or lumbar spinal metastases, Eur Spine Journal , 200615:196-202
Design:	retrospective case series; evidence level 3
Country / Setting:	Sweden; Dept. of Orthopaedics
Population:	282 consecutive patients with thoracic or lumbar metastasis; 69% men, 31% women; mean age 66 (range 23-93)
Intervention:	Posterior decompression and stabilisation; posterior stabilisation with rods (hooks, screws, pedicle screws) augmentation with methyl methacrylate; anterior decompression with reconstruction of the vertebral body (bone cement);
Outcomes:	Survival; ambulation, motor function - Frankel grades
Follow-up:	3 months postoperative; yearly after that
Results:	Important improvement of function can be gained by surgical treatment but complication rate was high as was mortality from disease within the first months of surgery. Between 10-20% of the patients did not benefit from the surgical treatment and some of those will have been worsened by complications and increased pain.
OUTCOME OF INTEREST RESULT	COMPARISON
Long term deformities: not reported	
Overall survival: a total of 37/282 (13%) died within 30 days. The rate of survival was 0.63 at 3 months , 0.47 at 6 months, 0.30 at 1 year , 0.16 at 2 years and 0.005 at 5 years. The 30 day mortality was not related to the extent of metastatic disease, but the 3 months survival rate was 0.50 for patients with non-skeletal metastases, compared to 0.81 for those with a solitary skeletal metastasis.	
Symptom control: 23 patients who had normal motor function preoperatively (Frankel E) retained this function postoperatively. 12/255 with motor deficits worsened postoperatively and 179 improved at least one Frankel grade. Among 144 patients who were non-walkers but retained some motor function (Frankel C) 100 could walk at discharge (D-E). 10/26 patients who had no motor function (A-B) regained sufficient neurological function to walk during follow-up. The ability to walk was retained at 1 and 2 years of follow-up.	
Rate of revision surgery/ recovery: a total of 29/282 patients were re-operated during follow-up 17 at the same level (due to local progression of disease at previously decompressed site and /or failure of stabilisation),. Median time to re-operation was 3 (0.4-9) years. 12 patients with epidural compression at a new spinal level were re-operated after only 0.7 (0.3-10) years.	
QOL: not reported	
Economics: not reported	
Complications/safety: a total of 60 complications recorded in 56/282 patients (20%). Systemic complications were often associated with death. 49/282 had local complications and 34 wound infections of which 9 were operated with wound revision.	

Klimo, P., Jr., Kestle, J. R. & Schmidt, M. H. (2003) Treatment of metastatic spinal epidural disease: a review of the literature. *Neurosurgical Focus*, 15: E1.

Inclusion/Exclusion Criteria: not reported in the review

Population

Patients with metastatic spinal epidural disease

Interventions

- Posterior Decompressive Laminectomy
- Circumferential Spinal Cord Decompression

Outcomes

- “Success” defined as the proportion of patients who were ambulatory after treatment
- “Rescue” defined as the proportion of non-ambulatory patients who regained ambulatory function, either with assistance or independently
- Mortality and morbidity are defined as occurrence of death or complication within 30 days of the operation.
- Morbidity: is the number of complications divided by the number of patients in the study (therefore, overestimates may arise if one patient suffered more than one complication)
 - Surgical complications could include wound infection, hematomas, cerebrospinal fluid leaks.
 - Hardware complications could include broken screws and graft migration/dislodgement.
 - Medical complications were those that were not directly related to the surgery, and could include pneumonia, myocardial infarction, deep venous thrombosis/pulmonary embolism.
 - Patients who suffered new neurological deficits were considered to have neurological complications.
 - Local recurrence and pseudarthrosis were not counted as complications.
 - Pain improvement

Results

Posterior Decompressive Laminectomy

- The evidence on decompressive laminectomy consists of 13 uncontrolled cohort studies.
- Recorded outcomes usually include ambulatory status before and after treatment, pain relief, and treatment related complications.
- 14 to 58% of patients who underwent a posterior decompressive laminectomy were ambulatory post-surgery. With an overall mean of 30% of patients having the ability to walk after the surgery, i.e. gait maintained, improved or regained as a result of laminectomy.
- Not shown in the review but broadly described, is the considerable non-neurological complications that follow laminectomy, specifically wound infection/dehiscence and spinal instability (up to 11% incidence of non- neurological complications in Findlay GF (1984).

Efficacy of laminectomy alone compared with radiation alone and with laminectomy followed by radiation:

- 8 controlled cohort studies investigated the efficacy of laminectomy alone with radiation alone and with laminectomy followed by radiation.
- No detailed analysis of the results of these studies was reported apart from a narrative report that “laminectomy was viewed as a procedure with minimal neurological benefit and significant morbidity”, and from this evidence, clinical practice should include radiation as the primary treatment.

Decompressive laminectomy with internal fixation (eg. pedicle screws) and fusion:

- In a study by Sherman and Waddell (1986) reported that out of 134 patients treated with either a laminectomy (111 patients) or laminectomy with stabilization (23 patients), 75 patients who had had laminectomy with stabilization reported better post treatment ambulatory status (92 compared with 57%), sphincter function, and pain control, and less recurrent neurological dysfunction.
- This review reports that these findings are supported by further 6 studies. No detail about these studies are reported in the review.

Circumferential Spinal Cord Decompression

Approaches included anterior (transthoracic or retroperitoneal) or posterior, including posterolateral trajectories (laminectomy, transpedicular, costotransversectomy, or lateral extracavitary) and reconstruction and immediate stabilization of the spinal column.

- There is a substantial body of evidence evaluating Circumferential Spinal Cord Decompression (17 studies reported) but it is low quality and comes from uncontrolled cohort studies or case series studies. However, these studies did provide more detail on outcomes of circumferential decompression compared to laminectomy studies.
- The results (of individual studies) reported in the review were listed in a table and the range of results are presented wrt outcome.

Success:

From 16 studies the range of success was, 72 to 98% of patients were ambulatory after treatment, with an overall crude mean of 86%

Rescue:

From 15 studies the range of rescue was 0 to 94%, of non-ambulatory patients who regained ambulatory function, either with assistance or independently, with an overall crude mean of 57%

Mortality

Mortality rates were reported for all 17 studies, this ranged from 0% to 31% of patients dying within 30 days of the operation. The crude mean of these rates = 5.7%

Morbidity

Morbidity data was available for 15 studies, this ranged from 7.7 to 65% of patients experiencing a complication within 30 days of the operation. This rate was the number of complications divided by the number of patients in the study (therefore, overestimates may arise if one patient suffered more than one complication). The crude mean rate from these rates = 31.8%

Complications were further described by surgical, hardware or medical, rates were generally low, however, surgical complications due to wound infection etc. had the highest rate of complication, ranging from 1 to 45% of patients, with a crude mean rate of 8.69 % of patients experiencing this complication.

Further details:

This review did provide details about the following included studies:

(1) One case series study described the results of 80 patients who had solitary metastatic spinal lesions. Depending on the anatomical and radiological findings on the extent of the tumor, the researchers used a variety of approaches: an anterior approach was used in 32 patients, a strictly posterior or posterolateral approach was used in eight, and a combined antero-posterior approach was used in 40.

- Preoperatively, 48 patients (60%) were ambulatory and 55 (69%) experienced a

severe pain.

- Postoperatively, 78 (98%) were ambulatory, including 94% of those who were initially non ambulatory.
- Pain was improved in 95%, with 76% reporting complete relief.
- Overall survival duration was 30 months, with considerable range among the various tumor types. Patients with breast and renal cell carcinoma had a median survival duration of 36 months compared with 15 and 12 months for gastrointestinal and cancer of unknown primary carcinoma, respectively.

(2) Another case series study reported their results with trans-thoracic vertebrectomy in 72 patients. Pain was improved in 92% of patients, and 93% were able to walk postoperatively.

- Of the 13 patients who were non ambulatory preoperatively, 10 regained ambulatory ability after surgery, with three of them regaining normal function. The 1-year survival rate for the entire cohort was 62%.
- Overall, the data seem to indicate that neurological outcomes are far superior compared to decompressive laminectomy and/or radiation.

(3) In a retrospective case series of 25 patients who had undergone single stage posterolateral transpedicular decompression for MSCC, pain relief was reported to have been immediate and durable.

- 15 patients with severe back or radicular pain rated their pain as mild after the surgery, and two others improved to moderate pain status.
- No patient developed recurrent mechanical back pain or loss of fixation.
- Patients who were neurologically intact before the surgery remained neurologically normal; five patients improved a grade to become neurologically intact (ASIA grade D to E). Patients with significant neurologic deficit before the surgery (ASIA grade C) did not fare as well. The two patients who worsened in this group had the acute onset of myelopathy and high grade spinal cord compression.
- Functional status was assessed (ECOG) and all patients who were fully ambulatory before the surgery (0-2) remained so (0-1). Ten patients who were bedridden more than 50% of the time or who were completely disabled (3-4) improved to ambulatory status (0-2) and 4 patients did not improve

General comments

This review conducted systematic searches and described the search terms.

The quality of the evidence was assessed and the definitions of the different classes of evidence denoting quality and strength of treatment recommendations were also described. Inclusion/exclusion criteria not reported and used.

Outcome measures were pre-specified and some evaluation of pooled estimates were reported. However, no detail of analysis was described and a more narrative summary was presented. In some sections, outcomes are described with only a broad description of the results for several studies included and no detail (about study protocol or results) presented.

Study Identification:

Klimo, P., Dailey, A.T., Fessler, R.G. (2004) Posterior surgical approaches and outcomes in metastatic spine disease. *Neurosurgery Clinics of North America* 15: 425-

	435
Design:	Unsystematic review of RCTs, prospective cohort studies and retrospective case series; evidence level 4
Country / Setting:	international
Population:	Patients with MSCC enrolled in 55 reported studies
Intervention:	Studies reporting on posterior decompressive laminectomy, vertebrectomy, anterior approaches,
Outcomes:	
Follow-up:	Majority of studies included in the review had long-term follow-up
Results:	<p>Laminectomy is no more effective than RT in relieving pain and preserving and regaining neural function. Laminectomy should only be used for disease isolate to the dorsal spine without evidence of concomitant instability</p> <p>Postoperative decompressive laminectomy with internal fixation provides a better outcome in terms of ambulatory status, sphincter function and pain control. This is a reasonable surgical option in patients who cannot tolerate a more extensive approach or who have multilevel disease.</p> <p>Various posterolateral approaches allow adequate anterior and posterior decompression and the ability to reconstruct and stabilise with acceptable peri-operative risk</p>
Long term deformities:	not reported
Overall survival:	not reported
Symptom control:	
	<p><u>Direct posterior trajectories:</u></p> <p><i>Laminectomy</i> is no more effective than RT in relieving pain and preserving and regaining neural function. Before surgery 80% of patients were non-ambulatory and 56% has sphincter dysfunction. Overall, mobility increased to 45% immediately after surgery but decreased to 33% and 25% to 2 and 4 month follow-up respectively. Postoperative sphincter dysfunction decreased to 38% but then increased to 46% at 2 months and 51% at 4 months. None of the plegic patients had any improvement.</p> <p><i>Posterior decompressive laminectomy with internal fixation</i> provides a better outcome in terms of ambulatory status, sphincter function and pain control. Comparative laminectomy only, patients who underwent internal fixation had better ambulatory status at 6 months (92% vs 57%), sphincter function (63% vs 31%) and pain control (55% vs 32%). Postoperative RT did not improve the results in either group.</p> <p><u>Posterolateral trajectories:</u></p> <p><i>Transpedicular approach</i> out of the 18 patients with preoperative neurological deficit 10 showed improvement the single most common reported complication was cerebrospinal fluid leak and 4 patients were reported to have suffered migrations of the methylmethacrylate graft or pins.</p> <p><i>Costotransversectomy:</i> adequate anterior decompression was achieved in all reported patients. Patients who were ambulatory remained so after surgery and pain was improved in 75% of patients. No perioperative deaths, neurological injuries or wound complications were reported. However, the authors recommend this method to be used only in patients with extensive bone disease, non-contiguous spinal involvement, visceral metastases or other contraindications for transcavity procedures, as well as in extremely old patients.</p>
Rate of revision surgery/ recovery:	not reported

QOL: not reported

Economics: cost of surgery and rehab not reported

Complications/safety: reported above

Klimo P, Thompson C J, Kestle J R, Schmidt M H. (2005) A meta-analysis of surgery versus conventional radiotherapy for the treatment of metastatic spinal epidural disease. *Neuro-Oncology* 7(1): 64-76

NOTE: the appraisal of this review has been conducted by Centre for Reviews and Dissemination (CRD) and was accessed through DARE database, where additions have been made by the NICE reviewer it has been noted.

For Centre for Reviews and Dissemination Appraisal refer to:

A meta-analysis of surgery versus conventional radiotherapy for the treatment of metastatic spinal epidural disease. [Abstract number: 12005009537] Database of Abstracts of Reviews of Effects, available <http://www.crd.york.ac.uk/crdweb/> [31 January 2007] Abstract of: A meta-analysis of surgery versus conventional radiotherapy for the treatment of metastatic spinal epidural disease. Klimo P, Thompson C J, Kestle J R, Schmidt M H. *Neuro-Oncology* (2005) 7(1): 64-76

Design: Retrospective or prospective cohort studies were eligible for inclusion.

Overall evidence level: 3 (Designated by NICE Reviewer)

Aim: To compare the effect of surgery versus conventional radiotherapy on the ambulatory status of people with metastatic spinal epidural disease.

Results

Ambulatory success (Refer to CRD Appraisal)

Ambulatory rescue (Refer to CRD Appraisal)

Pain (As described by NICE reviewer)

- Although this outcome was reported frequently across studies, the assessment was quite crude with no distinction between the type of pain (axial vs. radicular), and improvement was simply a dichotomous variable (i.e., yes/no).
- Only one paper (Gokaslan *et al* 1998) reported this outcome in a comprehensive manner. Out of the 72 patients who underwent a thoracotomy for vertebral metastases, 65 presented with pain. Complete resolution was achieved post-treatment in 15 patients (23%), significant improvement in 45 (69%), and no change or worsening in five (8%). Gokaslan *et al* (1998) also recorded and classified the type of analgesics used by patients both preoperatively and postoperatively. 28 patients were able to decrease their class of analgesic use by at least one category.
- The review authors recorded the percentage of patients within each study that had any improvement in pain after their primary treatment. Within the surgical studies, the average percentage of patients that experienced an improvement in pain was 90% (71%–100%) compared with 70% (54%–83%) within the radiation studies.

Sphincter function (bladder function) (As described by NICE reviewer)

- Of the 131 patients within the surgical articles, 65 (50%) were incontinent preoperatively compared with 22 (17%) postoperatively.
- In the radiation studies, 82 out of 397 patients (21%) were incontinent prior to radiation compared with 61 patients post-radiation (15%).
- Overall rescue rate (for the sphincter function) with surgery was 66% compared with 26% with radiation.

Survival (As described by NICE reviewer)

- Survival was difficult to assess within this body of evidence because it was inconsistently reported.
- The most consistent means of presenting survival data is the 12-month mortality rate, which was readily available in nine surgical articles and two radiation articles.
- The one-year survival in the surgical studies (n=502) ranged from 12% to 62%, with

an average of 41%

- For the radiation articles (n=397), the rate was 20% to 28%, with an average of 24%
- The most significant factor that determined post-treatment survival was the primary histology.
- Although the survival statistics vary among the papers, in general, patients with breast and renal cancer have a more favourable survival prognosis than those with lung cancer and sarcoma.

Complications and local recurrences (As described by NICE reviewer)

- No significant treatment-related complications were reported in the radiation studies. Within the surgical papers, 63 patients died within 30 days of their operation (6.3%).
- 233 complications (23%) occurred within the following categories defined previously: medical, 100; neurologic, 19; hardware, 18; and surgical, 96.
- One radiation article described patients that developed local recurrences. 2.4% patients developed local recurrences.
- 81 patients described in nine surgical papers also developed local recurrences for an incidence of at least 8%

General comments (NICE Reviewer)

This review conducted a systematic search of the literature for evidence about the effectiveness of surgery compared to radiotherapy. Quality assessment of included studies was not reported (other than describing the types of studies included). Overall the comparative analysis conducted was indirect, included uncontrolled studies and therefore it is greatly influenced by bias. Conclusions that the authors have drawn need to be considered/used with caution.

Study Identification:	Kwok, Y., Tibbs, P.A., Patchell, R.A. (2006) Clinical Approach to metastatic epidural spinal cord compression. Hematology – Oncology Clinics of North America, 20, 1297-1305
Design:	unsystematic review of RCTs, prospective cohort studies and retrospective case series; evidence level 4
Country / Setting:	international
Population:	patients diagnosed with MSCC enrolled in 29 studies
Intervention:	Laminectomy; laminectomy plus postoperative RT; anterior decompression (thoracotomy and retroperitoneal dissection); posterior decompressive and maximal debulking surgery and stabilisation
Outcomes:	Ambulatory status; continence; pain relief
Follow-up:	Majority of studies included in the review had long-term follow-up
Results:	If operable, patients with MSCC should undergo maximal tumour resection and stabilisation followed by postoperative radiotherapy. Although patients have short survival risks of paraplegia can be minimised.
OUTCOME OF INTEREST RESULT	COMPARISON
Long term deformities:	
Overall survival: not reported	
Symptom control: fewer than 50% of patients treated with RT alone will remain ambulant and even fewer will regain the ability to walk. However, retrospective studies suggest that RT was as effective as posterior laminectomy plus RT and showed no benefit of surgery in terms of pain relief, ambulation or sphincter function. In preliminary uncontrolled studies using direct surgical decompression results have been promising, with ambulatory rates higher than 75%. In several series even about 50% of patients who were non- ambulatory preoperatively regained ambulance.	
Rate of revision surgery/ recovery: not reported	
QOL: not reported	
Economics: cost of surgery and rehab not reported	
Complications/safety: not reported	

Study Identification:	Lewansrowsky, K.U., Hecht, A.C., DeLaney, T.F., Chapman, P.A., Horniceck, F.J., Pedlow, F.X. (2004) Anterior spinal arthrodesis with structural I cortical allografts and instrumentation for spine tumour surgery. Spine, vol. 29, 10:1150-59
Design:	retrospective case series; evidence level 3
Country / Setting:	USA
Population:	30 patients with MSCC; 18 women, 12 men; median age 47 (range 17-76)
Intervention:	Anterior vertebral reconstruction with fresh frozen cortical bone allografts, in combination with anterior or posterior instrumentation.
Outcomes:	Overall survival, complications/revision rate
Follow-up:	
Results:	Anterior column reconstruction with structural cortical allografts proved to be a reliable technique in patients with MSCC. Median survival was 14 months. 93% of the allografts were radiographically incorporated as early as 6 months after surgery in spite of adjuvant chemotherapy and RT. Postoperative complications can often be successfully managed. 14 (46%) patients had intraoperative or postoperative complications. 2 patients underwent revision surgery for local recurrence. There were no allograft infections, fractures or collapse.
OUTCOME OF INTEREST RESULT	COMPARISON
Long term deformities:	
Overall survival: overall median survival period 14 months (range 7 months-5 years). Patients with chordoma had the best overall median survival time.	
Symptom control: not reported	
Rate of revision surgery/ recovery:	
QOL: not reported	
Economics: not reported	
Complications/safety: 14 patients (46%) have experienced intraoperative or postoperative complications. These include wound breakdown in 3 cases, stabilisation failure in 2, superficial wound infections in 4, excessive haemorrhage in 6, postoperative respiratory failure in 1, intraoperative vascular/visceral injury in 2 and cerebrospinal fluid leak in 2 patients. Adjuvant RT and chemotherapy did not appear to be related to clinical complications. Four operations were necessary for treatment of complications: 2 for wound revision, 2 for infection. 2 patients underwent revision surgery for local recurrence.	
General comments: -	

Study Identification:	Loblaw, D.A., Perry, J., Chambers, A., Laperriere, N.J. (2005) Systematic Review of the Diagnosis and Management of Malignant Extradural Spinal Cord Compression. <i>Journal of Clinical Oncology</i> 23:2028-2037
Design:	Systematic review of RCTs, population based studies, prospective cohort studies, cross-sectional studies, retrospective case series; evidence level 3
Country / Setting:	International
Population:	MSCC patients
Intervention:	Six general types of cervical laminoplasty; Surgery plus RT; RT alone; vertebral body resection; laminectomy
Outcomes:	Survival, ambulation, complication rate
Follow-up:	Not reported for individual studies
Results:	There is not direct evidence that supports or refutes the type of surgery patients should have for the treatment of MSCC, whether surgical salvage should be attempted of patient is progressing on RT and whether patients with spinal instability should be treated with surgery.
OUTCOME OF INTEREST RESULT	COMPARISON
Long term deformities:	
Overall survival: not a significant difference in survival between groups (p=0.08) studied in the Patchell RCT.	
Recovery rate:	
Symptom control – ambulation: Patients undergoing surgery in addition to RT are more likely to retain and maintain ambulatory status longer than patients treated with RT alone (p=0.006)	
Rate of revision surgery/ recovery - further interventions (depending on prior surgery): not reported	
QOL: not reported	
Economics: - cost of surgery and rehab: not reported	
Complications/safety: surgery is associated with significant morbidity and mortality: 0-54% 30 day postoperative complication rates and 0-13% postoperative mortality rates reported in the reviewed literature. Overall complications are higher for vertebral body resection (10-54%) vs laminectomy (0-10%). The rate of complications is increased in patients who received RT before surgery 32%, vs. 12 % in patients who received surgery first (p<0.05)	
General comments: trials analysed for survival data might have been too small and insufficiently powered to detect difference in survival data.	
This review was not really helpful for this question, as the main focus of this review are clinical symptoms, optimal investigations for diagnosis, role of corticosteroids and indications for RT. Surgery is tangential and not particularly well addressed in relation to this PICO	

Study Identification:	Patchell, R.A., Tibbs, P.A., Regine, W.F., Payne, R. (2005) Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial, <i>Lancet</i> , 2005, 366:643-48
Design:	RCT; evidence level 1-
Country / Setting:	USA, departments of neurosurgery and radiation oncology
Population:	101 patients, tissue-proven carcinoma and MSCC, randomised – within strata, by permuted blocks, to surgery (n=50) or RT (n=51)
Intervention:	<p>Direct decompressive surgery followed by RT, compared to RT alone</p> <p><i>Details about surgical interventions used:</i></p> <ul style="list-style-type: none"> • <i>The aim of surgery was to provide immediate direct circumferential decompression of the spinal cord. The operation was tailored for each patient depending on the level of the spine involved and the patient's circumstances.</i> • <i>In general, for anteriorly located tumours the approach in the cervical spine was anterior, and in the thoracic and lumbar spine, depending on the tumour location, the approach was through a transversectomy or anterior approach. For laterally-located tumours, a lateral approach was used, and for posteriorly-located tumours, a laminectomy was done and any other posterior elements involved were removed. Stabilisation of tumours in all locations was performed if spinal instability was present; cement (methyl methacrylate), metallic rods, bone grafting, or other fixation devices were used.</i>
Outcomes:	Ability to walk, urinary continence, muscle strength and functional status, need for corticosteroids and opioid analgesics, survival time
Follow-up:	Median 102 days surgery grp (0-1940); 93 days RT grp. (0-1117 days)
Results:	Direct decompressive surgery plus postoperative radiotherapy is superior to treatment with radiotherapy alone. Patients treated with surgery had significantly better outcomes: significantly more patients in the surgery group than in the radiotherapy group were able to walk after treatment and retained the ability to walk significantly longer. Of those patients unable to walk pre-operatively, significantly more patients in the surgery group regained the ability to walk compared to patients in the radiotherapy group. Surgical treatment resulted in significant differences in maintenance of continence, muscle strength (ASIA score), functional ability (Frankel scores) and increased survival time. The need for corticosteroids and opioid analgesics was significantly reduced in the surgical group.

Long term deformities: not reported

Overall survival: Increased survival time reported for the surgery grp. 30 day mortality rates were 6% in the surgery group and 14 % in RT grp, (p=0.32)

Symptom control: pain control, continence, , sphincter function, neurological function - ASIA /Frankel grades

The combined post-treatment ambulatory rate in surgery group was 84%(42/50) and 57% (29/51) in RT alone grp. (odds ratio 6:2 [95%CI 2.9-19.8] p=0.01). 32 patients entered in the study were unable to walk; significantly more patients in the surgery group regained the ability to walk compared to patients in the radiotherapy group (10/16, 62% vs. 3/16, 19%, p=0.01). Patients treated with surgery also retained the ability to walk significantly longer than did those with radiotherapy alone (median 122 days vs. 13 days, p=0.003). Of those patients who had the ability to walk at study entry 94% (32/34) in the surgery group preserved the function compared to 74% (26/35) in the RT grp. (p=0.024).

Surgical treatment resulted in significant differences in maintenance of continence, muscle strength (ASIA score), functional ability (Frankel scores). At 30 days patients in the surgery grp. maintained or improved their pre-treatment ASIA score at a significantly higher rate than RT grp. patients (86% vs. 60%, p=0.0064).

Frankel scores at or above study entry were higher in surgery grp (91% vs. 61%, p=0.0008)

Rate of revision surgery/ recovery: further interventions (depending on prior surgery): not reported

QOL: not reported explicitly

Economics: cost of surgery and rehab not reported as such, but the analysis shows that surgery did not result in prolonged hospitalisation, median hospital stay was 10 days in both the surgery (2-51 days) and RT (0-41) group, p=0.86.

Complications/safety: 4 patients reported with surgical complications: wound infection and 1 with failure of fixation that required additional surgery.

<p>Mannion, R. J., Wilby, M., Godward, S., Lyratzopoulos, G. & Laing, R. J. C. (2007) The surgical management of metastatic spinal disease: prospective assessment and long-term follow-up. British Journal of Neurosurgery, 21: 593-598.</p>
<p>Design: prospective cohort study, evidence grade 2- Country: UK</p> <p>Aim: To evaluate the long term outcomes of patients with MSCC who received decompression surgery with fixation followed by radiotherapy.</p>
<p>Inclusion criteria Patients were selected from a wider patient population as suitable for surgery. The patient suitability depended on: severity of paraparesis: MRC grade \geq 3, pain suggesting instability; primary tumour type; prognosis \geq 6 months and extent of disease: intra and extra vertebral, presence of other mets.</p>
<p>Exclusion criteria Patients who did not meet the above criteria</p>
<p>Population 62 patients participated were included</p>
<p>Interventions</p> <ul style="list-style-type: none"> • Primary treatment: Patients underwent surgical decompression surgery (decompress the neural elements) and to confirm tissue diagnosis • Secondary treatment: Fixation for an unstable spine. • Surgical Types included anterior approach and type of fixation (vertebrectomy and fixation) compared to posterior approach and type of fixation use (laminectomy and fixation, laminectomy only (intradural), vertebrectomy and fixation, occipito-cervical fusion.) Fixation was with pedicle screws or halo jacket. • 85% were posterior approach and 15 % were anterior approach • Patients were followed for 10 years prospectively.
<p>Outcomes</p> <ul style="list-style-type: none"> • Survival • Ambulation (pre and post-operatively reported as ability to walk independently, with or without walking aids. • Urinary continence: pre and post-operatively reported as patients with voluntary control over micturition and not requiring a catheter (indwelling or intermittent) • Quality of life (29% of patients responded to a pre and post-operative SF-36 questionnaire, reported visual analogue pain scores and Roland Morris back pain scores)
<p>Results 62 patients participated were included, median age 62 years. Most common tumour type was breast, 26% Most common vertebral site was the thoracic region, 58% Most common presenting symptom was axial back pain (at the level of disease), 84% and 53% experiencing paraparesis.</p> <p>Survival:</p> <ul style="list-style-type: none"> • 56% of patients survived at 1 year; 28% of patients survived at 3 years Median survival = 13 months. • 2 patients died within 1 month of surgery, 5 patients died within 3 months (of this

5; one group were elderly and did not tolerate surgery and another group were younger patients with aggressive tumour growth)

- Majority of patients surviving at 3 months were ambulant and maintained continence.

Morbidity:

6% of patients had wound infection and 6% experienced instability or collapse post operatively. Only 3 % had neurological deterioration.

Ambulation:

- 68% of patients were ambulant pre-operatively; of the remaining 32% not ambulant – 50% could walk post operatively.
- 80% of patients were ambulant post-operatively – median follow up 3 months.

Urinary continence:

- 86% of patients were continent pre-operatively (with an additional 4 patients continent post-op)
- Overall continence = 92% of patients continent post-operatively– median follow up 3 months.
- Of the 9 incontinent patients pre-operatively, 6 regained continence post-operatively.

Quality of Life

Components of SF-36 included Physical function; role limitation (how does a patient feel their condition is impacting their role in life); bodily pain.

- Physical function: A significant difference of improvement was reported between pre-operative function and post operative at 3 months with further improvement at median 1 year follow up.
- Role limitation: A significant difference of improvement was reported between pre-operative function and post operative at 3 months with further improvement at median 1 year follow up.
- Bodily Pain: A significant difference of improvement was reported between pre-operative function and post operative at 3 months with further improvement at median 1 year follow up.
- A median survival analysis was conducted for patients who returned a complete SF-36 data set (n=18), it indicated that survival was longer in this group of patients than in the group as a whole (18 months compared to 13 months).

Visual analogue pain scores and Roland Morris back pain scores indicated a significant difference of improvement (that is, a reduction) reported between pre-operative function and post operative at 3 months with further improvement at median 1 year follow up.

General comments

Limitations include the bias involved with non random patient selection for treatment, as well as the lack of a comparative group. Caution with interpretation of the QoL results is required because as the results represent those of a select patient group and are not representative.

No information was provided about the radiotherapy that patients received, that is, how long after surgery did they receive it, what RT regimen they received and what the possible difference in effect would be post op/pre RT VS post op/post RT.

Study Identification:	Prasad, D., Schiff, D. (2005) Malignant Spinal Cord Compression. Lancet Oncol 2005; 6:15-24
Design:	Systematic Review of RCTs prospective cohort studies and retrospective case series; evidence level 3
Country / Setting:	international
Population:	patients diagnosed with MSCC
Intervention:	Laminectomy; anterior decompression (thoracotomy and retroperitoneal dissection); RT
Outcomes:	Ambulatory status; continence; complications; pain relief
Follow-up:	Majority of studies included in the review had long-term follow-up
Results:	Patients with MSCC treated with radical direct decompressive surgery and post-operative RT remain ambulatory and continent for the rest of their lives. Laminectomy has been only proven to help is the compression is posterior. In anterior spinal cord compression there is loss of spinal ability when the posterior elements are removed, leading to neurological deterioration. Anterior decompression allows for total removal of the pathological vertebral body and tumour mass. Bone grafting is not used because the bed is often to diseased to support the graft and post-operative RT will reduce the chance of graft acceptance.
OUTCOME OF INTEREST RESULT	COMPARISON
<p>Long term deformities: 51% of patients with spinal cord compression had vertebral collapse and 25% of patients treated with laminectomy sustained major neurological deterioration associated with surgery.</p> <p>Overall survival: mean post-operative survival 271 days.</p> <p>Recovery rate: 92% of patients had a stable spine as a result of surgery</p> <p>Symptom control: 82% of patients improved after surgery in terms of pain relief and ambulation.</p> <p>Rate of revision surgery/ recovery: not reported</p> <p>QOL: not reported</p> <p>Economics: cost of surgery and rehab not reported</p> <p>Complications/safety: not reported</p>	
General comments: this study is not really helpful in answering the question, as its main focus is on epidemiology and pathophysiology, clinical features and general therapeutic aspects: use of corticosteroids, RT and surgery. Very little in this review is dedicate to the comparison of various surgical approaches.	

Study	Ratliff, J.K., Cooper, P.R.(2003) Metastatic spine tumours, Southern Medical Journal 97, 246-53
Design:	Expert opinion / unsystematic review; evidence level 4
Country	International
Population:	patients with MSCC
Intervention:	surgery
Outcomes:	Pain control, neurologic deficit, survival, complications
Follow-up:	n/a
Results:	Surgical treatment of MSCC remains controversial. Modern surgical techniques provide options for decompression and immediate stabilisation. Laminectomy alone in case of ventral compression is seldom used due to poor outcomes. Anterior, posterior or combined decompression with immediate stabilisation have been shown to provide improved patient outcomes when compared with historical reports of RT, decompressive laminectomy without stabilisation or combined RT and laminectomy. Surgery is often contemplated after failure of radiation and chemotherapy to achieve tumour control. In properly selected patients surgery should be considered as initial therapy, as it provides excellent pain relief, significant chance of recovery of neurologic function, acceptable perioperative morbidity and mortality and prevention of late neurologic deterioration.
	<p>Long term deformities: not reported. Transient neurologic deficits ranging from quadriparesis form cord ischemia to foot drop form nerve root retraction are reported in several series.</p> <p>Overall survival: overall patient survival will depend on primary malignancy, degree of systemic spread and tumour biology. Median survival of at least 1 year after surgery is reported in may series. Considerable diminished survival presents in certain malignancies, such as metastatic colon carcinoma or metastatic melanoma with spinal involvement, where median survival is less than 4 months.</p> <p>Symptom control: Pain control: isolated pedicle screw stabilisation achieved nearly 90% improvement in VAS pain scores at 1 month after surgery. Similar results are reported in more aggressive anterioposterior combined approaches, with over 90% of patients achieving improvement in pain control after decompression and stabilisation. Multiple series report reduction in pain control medication. Neurologic deficit: postoperative neurologic function depends on preoperative status. Patients with severe deficit of long-standing duration may not achieve improvement even with adequate decompression and fusion. Assessment of operative outcomes varies in different series making comparison difficult. In properly selected patients 70-80% may achieve improvement in neurologic function. Recovery of walking of previously non-ambulatory patients may be achieved in 50% of patients. Addition of decompressive laminectomy to RT did not contribute to improvement. Addition of stabilisation via anterior or posterior approaches achieved improvement in 70% of patients. Patients who deteriorate during RT may manifest poor recovery, with 77% of patients unchanged after surgery.</p> <p>Rate of revision surgery/ recovery: not reported</p> <p>QOL: not reported</p> <p>Economics: not reported</p> <p>Complications/safety: severe complications include perioperative neurologic</p>

deterioration, wound breakdown, significant blood loss and mortality. Major and minor complication may occur in up to 30% of patients. Pulmonary, cardiac and gastrointestinal complications, along with cerebrospinal fluid leakage are common. Instrumentation failures may occur. The use of high dose steroids, RT and chemotherapy increase complication rates. Perioperative mortality should be expected less than 5%. Wound complications after RT in laminectomy have been reported in 28% of patients, and an increase from 12 to 32% was reported in patients treated with RT before decompression and stabilisation. Surgery performed within 7 days of beginning RT results in a wound complication rate of 46%. Wound infections are uncommon in anterior transthoracic approaches.

Blood loss may be significant in surgical decompression and stabilisation of spinal malignancies. (2-100 ml – range 50-31,000 ml). Perioperative embolisation did not correlate with decreased blood loss, although empirically embolisation appeared to decrease intraoperative blood loss.

General comments: -

Study Identification:	Senel, A., Kaya, A.H., Kuroglu, E., Celik, F., (2007) Circumferential stabilisation with ghost screwing after posterior resection of spinal metastases via transpedicular route. Neurosurgical Review, 30:131-137
Design:	Case reports; evidence level 4
Country / Setting:	Turkey
Population:	7 patients with MSCC; 4 women, 3 men, mean age 62.4 (range 55-70 years)
Intervention:	posterior transpedicular laminectomy/corpectomy, circumferential stabilisation using ghost screws and acrylic cement.
Outcomes:	Neurological function, pain control
Follow-up:	Mean 12 months (range 2-24 months)
Results:	
OUTCOME OF INTEREST	COMPARISON
RESULT	
Long term deformities: not reported	
Overall survival: 1 patient died 1 month postoperative of pulmonary embolism. Overall survival not reported	
Symptom control: patients who were neurological intact were able to self-mobilise rapidly and those with preoperative neurological deficit were mobilised early with support. One of 2 patients who had severe paraparesis at presentation exhibited improvement after surgery and only showed slight paraparesis at the 2month follow-up. The Karnofsky score preoperatively and at last follow-up ranged from 50-70% and 70-100% respectively.	
Rate of revision surgery/ recovery: not reported	
QOL: not reported	
Economics: not reported	
Complications/safety: not reported	
General comments: -	

Shehadi, J. A., Sciubba, D. M., Suk, I., Suki, D., Maldaun, M. V. C., McCutcheon, I. E., Nader, R., Theriault, R., Rhines, L. D. & Gokaslan, Z. L. (2007) Surgical treatment strategies and outcome in patients with breast cancer metastatic to the spine: a review of 87 patients. *European Spine Journal*, 16: 1179-1192.

Design: retrospective case series, Evidence Grade 3
Country: US

Aim: To assess the outcomes of patients who have had spinal surgery due to metastatic breast cancer.

Inclusion criteria

Patients had to be medically stable enough to undergo spinal surgery and to have at least one of the criteria:

1. Obvious spinal deformity with intractable pain
2. Retropulsed bone or disc fragment in the spinal canal causing significant spinal compression
3. Prior irradiation of the site or progressive spinal involvement with cord compression.
4. medically intractable mechanical, local or radicular pain.

Exclusion criteria

Patients with end-stage disease with <3 months survival, absence of biomechanical instability, significant spinal deformity or major neurological deficit as well as patients who did not consent to participate.

Population

87 patients met the inclusion criteria, and had 125 spinal operations

Interventions

Surgical Techniques included:

- Anterior approach (38% of 87 patients)
- Posterior approach (35% of 87 patients)
- Combined anterior-posterior simultaneous (6%)
- Anterior or posterior portion of staged procedure (21%)

Instrumentation of all procedures

Incidence of any instrumentation (92%)

Incidence of PMMA usage (60%)

(Further details of fixation can be obtained from study)

Outcomes

- Post operative neurological function
- Post operative pain
- Length of stay post op (LOS also included time spent on rehab service)
- Complications (early = within the first 30 days post-op, late >30 days post-op)
- Tumour recurrence
- Survival

- Follow-up: time of discharge, 1, 3, 6 months and 1 year after surgery. Median overall duration of follow up = up to 13 months
- Comparisons b/w pre op and post op Frankel grade, VAS pain scores , pain medication usage

Results

Post operative neurological function

- 87% were ambulatory pre op and 98% were ambulant post op.
- Of the 11 patients (13%) not ambulant pre op, 4 were alive 3 months post op and

3 regained ambulation.

- 85% of patients maintained or improved Frankel scores from pre op to immediate post op time point and up to 1 year.

Post operative pain

- A significant difference between the Pre op median VAS score (6) and the post op median score (2) was reported, $p < 0.001$. The post op median score was significantly lower at all time points.
- Pre op median analgesic score = 4 and dropped to 3 at discharge. It remained at this point for time points: 1, 3 6 months and 1 years. This was a significant reduction for all post op time points when compared to pre op scores, $p < 0.05$.

LOS and Complications

- Median LOS = 11 days
- 33% required post op rehabilitative services.
- 39% of patients experienced 39 complications (26% were major and 24% were minor)
- 34 complication were early, 5 complications were classed as late. (1 patient died within 24hours of surgery)
- Instrument failure was the most common complication reason
- Combined–staged surgical approach had the most major complications (38% occurring in this group)
- When a multivariate analyses was conducted to determine risk factors for major early complications, the only significant factor = instrumentation of ≥ 5 spinal levels, (RR=7.2, 95%CI 1.5-35.5, P=0.01)

Tumour recurrence

- Median overall duration of follow up = up to 13 months
- 20 patients had tumour recurrence; 7 local, 10 distant 3 had both.
- Re-treatment which included surgery in 11 patients and RT on 9.

Survival

- Median survival interval after original breast cancer diagnosis = 80 months
- Survival rate after date of primary breast cancer diagnosis was 96% at 1 year, 81% at 3 years, 69% at 5 years.
- Median survival time after spinal surgery = 21 months.
- Survival rate after patients' first spinal surgery was 62% at 1 year, 33% at 3 years, 24% at 5 years.

General comments

Study Identification:	St Clair S.F., McLain, R.F. (2006)Posterolateral spinal cord decompression in patients with metastasis: an endoscopic assisted approach. Surgical Technology international, 15: 257-66
Design:	Case reports; evidence level 3
Country / Setting:	USA
Population:	3 patients with MSCC
Intervention:	Laminectomy and posterolateral decompression; vertebrectomy; bone graft and titanium cage; posterior spinal fusion with bone graft and pedicle screw instrumentation; intralaminar vertebrectomy with posterolateral endoscopic decompression.
Outcomes:	Neurologic function
Follow-up:	1 year; 18 months; 5years;
Results:	Endoscopic assisted posterolateral decompression has been beneficial in the 3 reported cases. Postoperative morbidity was minimal, even in patients with known lung pathology. Neurological recovery and maintenance have been excellent in each case.
OUTCOME OF INTEREST RESULT	COMPARISON
Long term deformities: reported as absent	
Overall survival: 18 months for one patient who died of subsequently developed intracranial metastases. Not reported for the other 2 patients outside the follow-up period.	
Symptom control: patients reported as neurologically intact, ambulant and pain free.	
Rate of revision surgery/ recovery: not reported	
QOL: not reported coherently	
Economics: not reported directly: inpatient times reported averaged 4.6 days and ICU days have averaged 1/3 day per patient, lower than in traditional surgical approaches.	
Complications/safety: the article reports no respiratory complications (pneumonia, atelectasis)	
General comments: -	

Study Identification:	Witham, T.F., Khavkin, Y.A., Gallia, G.L. Wolinsky, J.P., Gokaslan, Z.L. (2006) Surgery insight: current management of epidural spinal cord compression from metastatic spine disease. Nature Clinical Practice Neurology, 2006, 2 (2) 87-94				
Design:	Systematic review of RCTs, prospective cohort studies and retrospective case series; evidence level 3				
Country / Setting:	international				
Population:	5536 patients diagnosed with MSCC reported in 81 studies				
Intervention:	Studies reporting on circumferential surgical decompression with concomitant spinal cord stabilisation, vertebroplasty, kyphoplasty				
Outcomes:	Neurological function, Ambulatory status				
Follow-up:	Majority of studies included in the review had long-term follow-up				
Results:	Patients treated with a combination of surgery followed by RT can remain ambulatory longer and those who are not ambulatory at presentation have a better chance of regaining ambulatory function.				
OUTCOME OF INTEREST RESULT	COMPARISON				
Long term deformities:	not reported				
Overall survival:	not reported				
Recovery rate:	not reported				
Symptom control:	neurological function and ambulatory status:				
	Neurological function following RT reveals a mean of 36% patients improved and 17% worsened. This result is similar to those obtained in a series of trials of laminectomy with or without RT which resulted in improved neurological function in a mean of 42% and worsened function in a mean of 13%. Laminectomy series had the added disadvantage of associated surgical morbidity and mortality of 6%. If a posterior decompressive procedure was performed in conjunction with a stabilisation procedure functional outcomes were better. If the stabilisation procedure was subsequent to posterior decompression a mean motor improvement of 64% was reported. Pain relief was achieved in a high percentage (mean 88%) with a mean mortality rate comparable to laminectomy alone (5%). Functional improvement after anterior approaches have a mean of 75% and a mortality rate largely unchanged 10%.				
Results of treatment			Functional outcome		Pain improved
Method	No of studies	Patient s	improved	worse	
RT alone	20	1396	36%	17%	
Laminectomy with or without RT	27	2355	42%	13%	
Posterior decompression and stabilisation	16	1010	64%		88%
Vertebral body resection and stabilisation	18	775	75%		84%

Rate of revision surgery/ recovery: not reported

QOL: not reported

Economics: cost of surgery and rehab not reported

Complications/safety: mortality reported above

General comments: this is a review of clinical presentation, diagnostic work-up and general management of MSCC; it is not evident which studies are pertaining to the surgical management. Also, patient characteristics are not reported in sufficient detail.

6.5 The Role of Scoring Systems

The following issues were covered:

1. The validity of Tomita and Tokuhashi scoring systems
2. Identification of gaps in these systems
3. Assessment of systems currently described in the literature that address the gaps in the established systems.

Short Summary

Overall the quality of the evidence for this topic was poor, accumulated from case series or expert opinion studies.

1. The validity of Tomita and Tokuhashi scoring systems

The scoring system of Tokuhashi (1990) may be useful for the selection of patients for treatment. Three studies all used different cut-offs but demonstrated a correlation of the total score with survival (Enkaoua *et al.* 1997; Huch *et al.* 2005; Ulmar *et al.* (2007a). Several publications (Bünger *et al.*, 1999; Enkaoua *et al.*, 1997; Ulmar *et al.*, 2007a, Tokuhashi *et al.*, 1990) reported favourable results for the Tokuhashi (1990) system, although this has since been revised by the authors (Tokuhashi *et al.* 2005). Tokuhashi and colleagues have repeatedly reported data to support their 2005 revision of the scoring system (Tokuhashi *et al.* 2002; Tokuhashi *et al.*, 2005; Huch *et al.* 2005 and Ulmar *et al.* 2007a) applied the Tomita system and did not replicate its proposed usefulness.

2. Identification of gaps in these systems

Several publications (Bünger *et al.*, 1999; Clar, 2004; Enkaoua *et al.*, 1997; Tokuhashi *et al.* 2002, 2005; Tomita *et al.* 2001) suggested a revision of the scoring system developed by Tokuhashi *et al.* (1990). This evidence suggests it may be useful to differentiate the primary site of the cancer further which is now incorporated in the revised Tokuhashi system (Tokuhashi *et al.* 2005). Furthermore, the studies suggested it may be useful to further differentiate the treatment options for patients with a life expectancy of more than six months. (Enkaoua *et al.* 1997 and Tokuhashi *et al.* 2005).

3. Assessment of systems currently described in the literature that address the gaps in the established systems.

The revised scoring system of Tokuhashi *et al.* (2002, 2005) may be useful for the selection of patients for treatment. Other evidence about scoring systems comes from several studies suggesting a combination of established scoring systems with other modifications. (Bartanusz & Porchet, 2003); Bartels *et al.* (2007); (Bilsky *et al.* 2007); Chow *et al.* (2006); Clar (2004); Day *et al.* (1998) Katagiri *et al.* (2005) ; Kluger *et al.* (1997); Ulmar *et al.* (2005 and 2007b)

Evidence Summary

Overall the quality of the evidence for this topic was poor, accumulated from case series or expert opinion studies. There were no randomised trials or complete diagnostic accuracy studies. In several studies the scoring system were evaluated, however, a new dataset would be needed to validate a newly developed system. Patients included in the studies had: bones metastases, tumourous osteolyses of the spine, +/-metastatic spinal cord compression.

Overall results consistently reported the following findings:

A. What is the validity of Tomita and Tokuhashi scoring systems?

- Several publications have reported favourable results for the Tokuhashi (1990) system (which been revised)

- Tokuhashi and colleagues have repeatedly reported data to support their 2005 revision of the scoring system.

B. What are the gaps in these systems?

Several publications including one by the original author suggested a revision of the scoring or a revision of the use of the Tokuhashi (1990)

C. Are there systems currently described in the literature that address the gaps in the established systems?

There are other proposed approaches although no other system that addresses treatment options (apart from the revision proposed by Tokuhashi)

A. What is the validity of Tomita and Tokuhashi scoring systems?

The scoring system of Tokuhashi (1990) may be useful for the selection of patients for treatment

- Tokuhashi *et al.* (1990) present data in a simple test evaluation study that shows a correlation of the total score and survival and differential survival for three cut-offs. Ulmar *et al.* (2007a) also reported favourable results for the Tokuhashi system (but suggested that this may be due to the application of the Karnofsky status). Enkaoua *et al.* (1997) also report favourable results in a test evaluation study; however, the authors applied a different cut-off and suggested a change in the scoring. Huch *et al.* (2005) did not find the Tokuhashi system useful although this could also be due to study design problems.

The validity of the Tomita *et al.* (2001) scoring system is unclear.

- Tomita *et al.* (2001) showed in a confirmatory prognostic study different average survival periods for the proposed score categories. Ulmar *et al.* (2007a) in a simple test evaluation study applied the Tomita system and did not replicate its proposed usefulness. Huch *et al.* (2005) from the same research group as Ulmar *et al.* did not find the Tomita system useful although this could also be due to study design problems.

B. What are the gaps in these systems?

The evidence indicates that it may be useful to differentiate the primary site of the cancer further as proposed in the revised Tokuhashi system.

- Tokuhashi *et al.* (2002 and 2005) suggested and validated a revision of the scoring or the use of the Tokuhashi *et al.* (1990); both publications use a 15 point system that differentiates six primary cancer sites. Enkaoua *et al.* (1997) also criticised the original scoring, in particular the equal treatment of renal and tumours of unidentified sites.

It may be useful to further differentiate the treatment options for patients with a life expectancy of more than six months. (The statement is an evidence level 4 evidence – expert opinion, as none of the relevant publications reported empirical results on a comparison between the original Tokuhashi system and a modified version addressing the gap)

- A simple test validation study by Bünger *et al.* (1999) suggested a more differentiated treatment approach for patients with a life expectancy of more than six months. Tomita *et al.* (2001) pointed out that the original Tokuhashi system only differentiated between excisional or palliative procedures while more aggressive and more recently suggested surgery procedures, such as total en bloc spondylectomy, should also be considered. Tokuhashi *et al.* (2005) reported that for patients in the score group 9 to 11 (in a 0 to 15 point system) excisional surgery can be an option even if for the majority of patients palliative surgery is more appropriate.

It may be useful to discuss patient preferences when intermediate results occur.

- Clar (2004) suggested in a non-systematic review to discuss patient preferences when intermediate results occur; although Tokuhashi *et al.* (1990) was cited, the proposed system differed in further aspects. Tokuhashi *et al.* (2002) also concluded that patients' goals should be considered when selecting surgical procedures (but this is not part of the scoring system).

C. Are there systems currently described in the literature that address the gaps in the established systems?

- The revised scoring system of Tokuhashi *et al.* (2002, 2005) may be useful for the selection of patients for treatment
- Tokuhashi *et al.* (2002 and 2005) presented data from test evaluation studies supporting the new 15 point system; some overlap between patients may have occurred. Ulmar *et al.* (2005) applied the revised (15 point) system and did find it useful for the prognostication of survival, however different cut-offs were applied in this dataset.
- It may be useful to combine the established scoring systems with other published suggestions.
- Several publications have suggested modifications or alternatives although none have been replicated in another publication by a different author group and directly compared to the original so it is difficult to formulate a more specific evidence statement from the identified literature. The statement is an evidence level 4 statement as although some empirical studies have suggested modifications, due to the reasons outlined above the validity remains unclear and it seems more appropriate to classify these as published expert opinions.)
- A simple test validation study by Büniger *et al.* (1999) suggested combining the Tokuhashi *et al.* (1990) scoring with a system proposed by Tomita *et al.* (1984) and suggested a more differentiated treatment approach for patients with a life expectancy of more than 6 months; no validation data for the new system were provided.

Indirect support comes from these studies (none of these suggested a combination, all published alternatives):

- Tomita *et al.* (2001) set out to address a gap in the original Tokuhashi system but the validity of the Tomita system remains unclear.
- Kluger *et al.* (1997) present affirmative data for an algorithm to decide the treatment strategy for patients with spinal neoplasms (elements: Narrowed spinal canal, unstable vs. stable free spinal canal, survival prognosis from enhanced diagnostic results (MRI, bone scan, myelography).
- A non-systematic review (Bartanusz & Porchet, 2003) suggested the decision tree: 1.Has the spinal metastasis already been irradiated?; 2. Is the spinal segment stable; 3. What is the motor performance status?; 4. Is the primary tumour known? to decide upon the mode of primary treatment.
- A non-systematic review by Clar *et al.* (2004) suggested different areas, a reduction in the number of assessed areas and to discuss patient preferences when intermediate results occur.
- Chow *et al.* (2006) validated the system suggested by the Dutch Bone Metastases Study Group and their own Rapid Response Radiotherapy Program; however, both systems appear to only predict survival rather than providing clear treatment recommendations.
- Katagiri *et al.* (2005) successfully distinguish three patient groups but no predictions were made about the survival nor were specific treatment options proposed and the number of patients with spinal metastases amongst the bone metastases patients was unclear.

- Day *et al.* (1998) proposed a modification of the Tokuhashi score but failed to show a significant difference in survival between two groups distinguished by the scores.
- Bartels *et al.* (2007) validated a new model in order to predict survival of MSCC patients. However, analyses indicated limited confidence in the predictive capacity, in its current form. The model therefore requires further validation, and possible modification.
- The NOMS framework, was developed to address the decision making process of whether to irradiate or operate on patients with cervical spine tumours (Bilsky *et al.* 2007). The NOMS framework was applied to a group of patients in one Oncology Centre, the issues included in NOMS were described in a narrative manner, and it was not clearly validated using a techniques used in other studies that have validated other scoring systems i.e. with different data sets.
- A retrospective case series study by Ulmar *et al.* (2007b), evaluated the validity of the original and modified prognostic score of Tokuhashi *et al.* (1990 and 2005) against a modified predictive model. The study analysed the correlation between predicted and real survival. It showed that the original and modified Tokuhashi scores indicated a significant predictive value, however, the modifications made indicated the highest reliability between predicted and real survival.

Overall question: Case selection for treatment – The role of scoring systems

- Scoring systems may be useful for the selection of patients for treatment.
 - Several authors advocate scoring systems and appear to routinely apply these to help with clinical decisions (e.g. Bünger *et al.*, 1999; Clar2004; Enkaoua *et al.*, 1997; Katagiri *et al.*, 2005; Ulmar *et al.*, 2007a; Tokuhashi *et al.*, 1990; 2002; 2005).
- It may be useful to use scoring systems as a quantitative rating scale rather than a classification system with distinct categories or to use the cut-offs more flexible.
- Clar(2004, non-systematic review) suggested to use the scoring system as a quantitative scale rather than using the scale to categorise patients into three distinct and qualitatively different groups with differential treatment consequences.
- Further publications could be used to indirectly substantiate this suggestion:
 - Several authors (Tomita *et al.*, 2001; Tokuhashi *et al.* 1990; 2002; 2005) have shown that their promoted scale scores and life expectancy are correlated. Treatment indications are stronger for scores in the lower third and upper third of the scores (Tokuhashi 1990) and the life expectancy varies greatly in the group with intermediate results (Tokuhashi, 2002).
 - In a sample of breast cancer patients Ulmar *et al.* (2005) reported better predictions when the cut-off scores for the intermediate group are moved one point.
 - Tomita *et al.* (2001), although also promoting a system with clear cut-offs, show in their data that some patients received other treatments as indicated by their scores.
- Algorithms may be a useful alternative to scoring systems.
 - Bartanusz & Porchet (2003) suggested a decision tree in order to find the appropriate treatment option for each person; this non-systematic review presented no empirical data for the suggested decision tree.
 - Gasbarrini *et al.* (2004) suggested after analysing a case series a sequential algorithm for treatment decisions, no direct empirical evaluation of the algorithm was provided.

Ulmar *et al.* (2007a) did not investigate a gap but discuss whether the scoring systems of Tokuhashi and Tomita are superfluous as only the Karnofsky Index appeared to predict actual survival when the other predictors are statistically controlled. The authors cite a French publication that has suggested cut offs of >70% and <40% (Narzarian,

Guigui, & Gouvernet, 1997). However, no direct comparisons were reported. In the interim report by Huch *et al.* (2005) the same author group did not find the Karnofsky index useful (dividing patients into 3 groups according to the Karnofsky score) for the prognosis of survival but this could also be due to the problematic design feature of the study. A case series (Jansson & Bauer, 2006) divided the preoperative sample into walkers and non-walkers according to the Frankel score and concluded that the post-operative survival was not related to the preoperative neurological function; the study formulated no predictions about the survival or treatment consequences.

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Evidence Tables

Tokuhashi, Y., Matsuzaki, H., Toriyama, S., Kawano, H. & Ohsaka, S. (1990). Scoring system for the preoperative evaluation of metastatic spine tumor prognosis. *Spine*, 15 (11), 1110-1112.

Design: Test evaluation / epidemiological study, evidence level 3
Country: Japan; Setting: Department of Orthopaedic Surgery

Population N=64 patients with spinal metastasis

Test items

General condition (performance status), number of extraspinal bone metastases foci, number of metastases in the vertebral body, metastases to the major internal organs, primary site of the cancer, spinal cord palsy

Scoring

0, 1 or 2 scores for 6 areas (primary cite of cancer: lung, stomach = 0; kidney, liver, uterus = 1; others, unidentified, thyroid, prostate, breast, rectum = 2), maximum total score of 12

Life expectancy prognosis / Treatment consequences

0-5 scores: palliative operation (securing support),
9-12: excisional surgery (securing support and prolonging life)

Received treatment 53 cases treated palliatively, 11 excisionally treated (the score did not decide upon treatment)

Follow up at least 12 months

Results

OUTCOME	RESULT
Survival	Scores 0-5: average survival: 3 months or less Scores 6-8: average survival: 12 months or less Scores 9-12: average survival: 12 months or more
Correlation total score and survival	$r = 0.65$ ($p < 0.01$)

Author's conclusion. An excisional operation should be performed on those cased who scored more than 9 points, while a palliative operation is indicated for patients scoring less than 5 points.

General comments Test score and received treatment may be intercorrelated, and treatment and outcome (survival) may not be independent.

Kluger, P., Korge, A. & Scharf, H.-P. (1997). Strategy for the treatment of patients with spinal neoplasms. Spinal Cord, 35, 429-436.

Design: Algorithm evaluation study, evidence level 3

Country: Germany; Setting: Orthopaedic Clinic

Population N=154 patients with tumorous osteolyses of the spine

Test items

Narrowed spinal canal, unstable vs stable free spinal canal, survival prognosis from enhanced diagnostic results (MRI, bone scan, myelography)

Scoring

algorithm

Life expectancy prognosis / Treatment consequences

Group 1: < 6 months: no further operation; temporary aids, nursing at home

Group 2: 6-24 months: vertebrectomy, alloplastic vertebral body replacement; temporary aids, nursing at home

Group 3: > 24 months: vertebrectomy, autogeneic vertebral body replacement; individual aids, rehabilitation in hospital

Received treatment according to algorithm; exclusive posterior approach (n=104), secondary anterior procedure with alloplastic replacement of the vertebral body (n=20), additional anterior approach with autogeneic vertebral body replacement (n=12), posterior transpedicular biopsy alone (n=18)

Follow up at 30 days; up to 80 months

Results

OUTCOME	RESULT
Survival	Group 1: mean survival 13.9 months, range: 0.5-56 Group 2: mean survival 18.2, range: 0.25-48 Group 3: mean survival 41.7 months, range: 11.8-80.4

Author's conclusion. The treatment of patients with tumorous osteolyses of the thoracic and lumbar spine treated according to the proposed algorithm underline the unequivocal advantages of initially posterior procedures..

General comments The received treatment depended on the preliminary diagnosis, the treatment and outcome (survival) may not be independent.

Enkaoua, E. A., Doursounian, L., Chatellier, G., Mabesoone, F., Aimard, T. & Saillant, G. (1997). Vertebral metastases: A critical appreciation fo the preoperative prognostic Tokuhashi Score in a series of 71 cases. Spine, 22(19), 2293-2298.

Design: Test evaluation study, evidence level 3

Country: France; Setting: Department of Orthopaedic Surgery and Traumatology

Population N=85 patients with vertebral metastases

Test items

Tokuhashi (1990)

Scoring

Tokuhashi (1990), median as cut-off: scores 0-7 vs 8-12

Life expectancy prognosis / Treatment consequences

Tokuhashi (1990)

Received treatment patients with single metastases received excisional surgery, multiple metastases were treated palliatively to restore stability, to reverse neurological compromise and / or pain relief

Follow up up to 62 months for single patients

Results

OUTCOME	RESULT
Survival	Scores 0-7: median time to death: 5.3 (+ - 1.2) months Scores 8-12: median time to death: 23.6 (+ - 5.8) months
Survival curve	Comparison of length of survival and preoperative score of both groups is significant (p=0.0063)
Multivariate analysis	The modified Tokuhashi score was independently associated with a poorer survival rate
Other	The survival of patients with tumours of unknown primary sites was 2 months, the survival of those with renal tumours 8.6 months

Author's conclusion. The Tokuhashi score is a successful prognostic tool; the rating of unknown primary tumours should be reduced to 0.

General comments Test score and received treatment may be correlated, and treatment and outcome (survival) may not be independent. The authors state that Tokuhashi (1990) give 1 point to renal cancers and unknown primary tumour, but the original states 2 points.

Day, G.A., McPhee, I.B., Swanson, C., Tomlinson, F.H., McCombe, P. & Coyne, T. (1998). Outcomes following treatment of metastatic spine tumors. Bulletin – Hospital for Joint Diseases, 57, 11-15.

Design: Case series (scoring system applied to all), evidence level 3
Country: Australia; Setting: Spine Unit

Population N=57 consecutive patients with metastatic spine tumours

Test items

Modified Tokuhashi (1990): Involvement of the major organs, Disseminated skeletal metastases, Severe cord compromise, Contiguous vertebral body disease more than 2 bodies

Scoring

1 point for each prognostic factor

Life expectancy prognosis / Treatment consequences

Scores 2-4: Radiotherapy / chemotherapy

Scores 0-2: Surgery

Received treatment as outlined above; 29 received surgery

Follow up 60 weeks

Results

OUTCOME	RESULT
Survival	Surgery: mean survival: 30 weeks No surgery: mean survival: 16 weeks
Survival curve	The difference between the groups was not statistically significant

Author's conclusion Patients with severe cord compromise at presentation are instructed that surgery will not significantly improve outcomes on average; operating on patients who have a low serum albumin and lymphocyte count as well as preoperative radiotherapy and steroids is not indicated due to the substantial complication rate.

General comments Test score and received treatment are interdependent, and treatment and outcome (survival) may not be independent. The authors present also a detailed algorithm that starts with the diagnosis.

Bünger, C. Laursen, M., Hansen, E.S., Neumann, P., Bjarke, F., Høy, K. & Helmig, P. (1999). A new algorithm for the surgical treatment of spinal metastases. *Current Opinion in Orthopedics*, 10, 101-105.

Design: Test validation / epidemiological study, evidence level 3
Country: Denmark; Setting: Department of Orthopaedic Surgery

Population N=unclear patients with spinal metastasis

Test items

Tokuhashi (1990);
Tomita (1984)

Scoring

Tokuhashi (1990);
Tomita (1984);
Combination of Tokuhashi (1990) and Tomita (1984)

Life expectancy prognosis / Treatment consequences

Combination of Tokuhashi and Tomita system; treatment modification: patients with Tokuhashi 0-4 (Tomita 1-7): are treated with laminectomy;
Tokuhashi 5-8 (Tomita 1-7): posterior decompression, stabilisation and reconstruction; Tokuhashi 9-12 (Tomita 1-3): En bloc resection with vertebrectomy and 360° reconstruction
Tomita 4-6: Intralesional vertebrectomy and 360° reconstruction
Tomita 7: Posterior decompression and stabilisation
all groups: treated with radiation therapy

Received treatment as suggested by score

Follow up at least 644 days

Results

OUTCOME	RESULT
Survival	Tokuhashi scores 0-4: mean survival rate 99 days; Tokuhashi scores 6-8: mean survival rate 175 days Tokuhashi scores 9-12: 644 days Patients who died within 3 months had a mean score of 5.2; patients dying after 3 to 6 months 6.8; patients dying after 6 months had a mean score of 8.2

Author's conclusion The use of the Tokuhashi score facilitates good clinical practice. Tokuhashi system is a reliable tool for estimating life expectancy. For patients with long life expectancy the Tokuhashi (1990) and the Tomita (1984) systems should be combined.

General comments Reports 1998 conference data. Test score and treatment, and treatment and outcome (survival) may not be independent. The study does not report data to validate Tomita (1984) or their modification.

Tomita, K., Kawahara, N., Kobayashi, T., Yoshida, A., Murakami, H. & Akamaru, T. (2001). Surgical strategy for spinal metastases. *Spine*, 26 (3), 298-306.

Design: Test evaluation / prognostic study, evidence level 3
Country: Japan; Setting: Department of Orthopaedic Surgery

Population N=67 patients with spinal metastasis

Test items

Primary tumour (slow, moderate, rapid growth), visceral metastases (no, treatable, untreatable), bone metastases (solitary/isolated, multiple)

Scoring

Derived from hazard ratios; Primary tumour: 1, 2, 4; Visceral metastases: 0, 2, 4; Bone metastases: 1, 2; total score range: 2-10

Life expectancy prognosis / Treatment consequences

2-3: long-term local control; wide or marginal excision;

4-5: middle-term local control; marginal or intralesional excision

6-7: short-term palliation; palliative surgery

8-10: terminal care; supportive care

Received treatment not reported

Follow up maximum 5 years

Results

OUTCOME	RESULT
Survival	Scores 2-3: average survival: 49.9 months, range: 18-84 Scores 4-5: average survival: 23.5 months, range: 7-57 Scores 6-7: average survival: 15 months, range: 5-33 Scores 8-10: average survival: 5.9 months, range: 1-14
Correlation total score and survival	-0.69 ($p < 0.0001$)
Other	The correlations of the 3 prognostic factors and survival time were for malignancy of primary organs: -0.492 ($p < 0.0001$), for visceral metastases to vital organs: -0.536 ($p < 0.0001$) and -0.250 ($p < 0.05$) for bone metastases

Author's conclusion The surgical strategy system provides appropriate guidelines for treatment in all patients with spinal metastases.

General comments Test score and treatment, and treatment and outcome (survival) may be interrelated. Further data in the publication show that the treatment consequences were not strictly adhered to (the variation of scores was higher than suggested in the system).

Tokuhashi, Y. (2002). Surgery for metastatic spine tumor. *Jpn J Neurosurg (Tokyo)*, 11, 446-452.

Design: Test evaluation / epidemiological study, evidence level 3

Country: Japan; Setting: Department of Orthopaedic Surgery

Population N=117Patients with metastatic spine tumour

Test items general condition (performance status), number of extraspinal bone metastases foci, number of metastases in the vertebral body, metastases to the major internal organs, primary site of the cancer, severity of the spinal cord palsy

Scoring 0, 1 or 2 scores for 5 areas, primary site of the cancer is scored 0 to 5 (0: lung, stomach, esophagus, bladder, osteosarcoma, pancreas, 1: gallbladder, unidentified, 2: others, 3: kidney, uterus, 4: rectum, 5: thyroid, prostate, breast, carcinoid tumour); maximum total score 15

Life expectancy prognosis / Treatment consequences

0-8 score: predicted prognosis up to 6 months

9-11: 6 months or more

12-15: 1 year or more

Received treatment 110 patients treated with posterior decompression and stabilisation as palliative procedure for thoraco-lumbar metastases, 7 treated with en bloc spondylectomy as excisional procedure

Follow up 10 years, 6 months

Results

OUTCOME	RESULT
Survival	Survival periods ranged from 10 days to 10 years, 6 months. Patients with scores 0-5: 96% survived up to 6 months; 4% survived between 6 months and 1 year. 6-8: 61% survived up to 6 months, 27% survived up to 1 year, 12.2% survived 1 year or more. 9-11: 29% patients survived only up to 6 months, 33% survived between 6 months and 1 year and 38% survived 1 year or more. 12-15: 1 patient survived only up to 6 months, 16 patients (94%) survived 1 year or more.
Consistency predicted survival and survival	The consistency was 78.7%. Score 0-8: 79.5%, score 9-11: 71.1%, 12-15: 94.1%
Correlation total score and survival	$r = 0.55$ ($p < 0.0001$)

Author's conclusion Proper operative indications should be applied and surgical procedures have to be selected in consideration of the patients' goals and within the limits of their life expectancy.

General comments Japanese language publication, only abstract, tables and figures were used. It is possible that there is overlap in patients described in Tokuhashi *et al.* (1990). Test score and received treatment may be correlated, and treatment and outcome (survival) may not be independent

Bartanusz, V. & Porchet, F. (2003). Current strategies in the management of spinal metastatic disease. *Swiss Surgery*, 9, 55-62.

Design: Non-systematic review; evidence level 4

Country: Switzerland; Setting: Department of Neurosurgery (author affiliation)

Population N=- Patients with spinal metastatic disease

Test items

1. Has the spinal metastasis already been irradiated?;
2. Is the spinal segment stable;
3. What is the motor performance status?;
4. Is the primary tumour known?

Scoring

Decision tree;

2 categories: patients with uncontrolled neoplastic disease presenting visceral dissemination and/or multiples spinal metastases vs patients with unknown tumour or controlled primary disease presenting with a solitary spinal metastasis; ultimately this should differentiate patients with a life expectancy of more vs less than 3 months

Life expectancy prognosis / Treatment consequences -

Received treatment -

Follow up -

Results

OUTCOME	RESULT
	No data presented

Author's conclusion It is important to clearly identify those patients who can benefit from surgery.

General comments The publication does not cite the Tokuhashi or Tomita or scoring systems in general.

Clar, H. E. (2004). Operatives oder konservatives Behandlungskonzept bei spinalen Metastasen. *Klinikerarzt*, 33(5), 149-152.

Design: Non-systematic review, evidence level 4
Country: Germany; Setting: Neurosurgery Clinic (author affiliation)

Population N=- patients with spinal metastasis

Test items

simplified Tokuhashi (1990): 5 areas (Karnowsky general condition, tumour progress, risk factors, spinal compression, neurological symptoms);
in addition patient preferences

Scoring

0, 1 or 2 scores for 5 areas with a maximum total score of 10

Life expectancy prognosis / Treatment consequences

0-4 scores: conservative therapy,
7-10: surgery;
use as continuous scale (the higher the score, the more aiming at curative (surgery) rather than palliative care);
intermediate scores: patient preferences should be discussed with the patient

Received treatment -

Follow up -

Results

OUTCOME	RESULT
	No data presented

Author's conclusion A score system is helpful; the primary question is from which therapy does the individual patient profit the most.

General comments German language publication.

Gasbarrini, A., Cappuccio, M., Bandiera, M.S., Terzi, S., Barbanti Brodano, G. & Boriani, S. (2004). Spinal metastases: treatment evaluation algorithm. *European Review for Medical and Pharmacological Sciences*, 8, 265-274.

Design: Case series (all undergoing same algorithm), evidence level 3
Country: Italy; Setting: Orthopaedic and traumatology department

Population N=182 patients with spinal metastases from a solid tumour (patients with plasmacytoma and lymphoma excluded)

Test items

Is the patient operable, Does the tumour respond to adjuvant therapies (assessed at multiple time points), Frankel score, Is there acute and ingravescent spinal cord damage, Is there a single metastasis only, Pathological fracture evaluation, Are there hypervascularised tumours / metastases from renal cell carcinoma and from sarcoma, Is en bloc removal easy to perform

Scoring

algorithm, sequential decision process; multidisciplinary input (anaesthetist, radiotherapist, oncologist)

Life expectancy prognosis / Treatment consequences

Adjuvant therapies (CHT, RXT...), pain relief, emergency surgery, resection of the lesion, decompression and stabilisation, en bloc resection or debulking

Received treatment 79 were treated with decompression and stabilisation, 64 with intralesional resection (debulking), 27 had an en bloc resection (vertebrectomy, corporectomy, sagittal resection, posterior resection)

Follow up 81 months

Results

OUTCOME	RESULT
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No data on comparison to other algorithm / different procedure

Author's conclusion The treatment options for metastatic spinal disease has increased, it has become clear that effective implementation of these treatments can only be achieved by a multi-disciplinary approach.

General comments

Katagiri, H., Takahashi, M., Wakai, K., Sugiura, H., Kataoka, T. & Nakanishi, K. (2005). Prognostic factors and a scoring system for patients with skeletal metastasis. *The Journal of Bone and Joint Surgery – British Volume*, 87B.5, 698-703.

Design: Prognostic study, evidence level 3 (case series level)
Country: Japan; Setting: Division of Orthopaedic Oncology

Population N=350 consecutive patients with skeletal metastases

Test items

Site of primary lesion, performance status, presence of visceral or cerebral metastases, any previous chemotherapy, multiple skeletal metastases

Scoring

Primary lesion 0, 2 or 3 according to speed of growth, visceral or cerebral metastases 2; all other areas 1 point; possible range 0-8

Life expectancy prognosis / Treatment consequences

-

Received treatment 71% non-surgical (palliative alone, chemotherapy, radiotherapy alone, combined chemotherapy and radiotherapy), 29% surgery (internal fixation or endoprosthetic replacement, posterior decompression and instrumentation, endoprosthetic replacement and spinal instrumentation, resection without reconstruction, amputation)

Follow up at least 2 years, mean: 13 months for deceased, 39 for survivors

Results

OUTCOME	RESULT
Survival	Scores 0-2: survival rate of more than 80% at 12 months; survival rate 0.98 at 6 months; 0.75 at 24 months Scores 3-5: survival rate of 30-70% at 12 months, survival rate 0.71 at 6 months; 0.28 at 24 months Scores 6-8: survival rate less than 20% at 12 months, survival rate 0.31 at 6 months; 0.02 at 24 months
Survival curves	The survival curves of the three groups are significantly different (p<0.0001)

Author's conclusion The scoring system can be used to determine the optimal treatment for patients with pathological fractures or epidural compression.

General comments The number of patients with spinal metastases is unclear. Test score and received treatment may be intercorrelated, and treatment and outcome (survival) may not be independent

Huch, K., Cakir, B., Ulmar, B., Schmidt, R., Puhl, W. & Richter, M. (2005). Prognose, operative Therapie und Verlauf bei zervikalen und hochthorakalen Tumorosteolysen. Z.Orthop.Ihre Grenzgeb., 143 (2), 213-218.

Design: Test validation study and case series, evidence level 3
Country: Germany; Setting: Department of Orthopaedic surgery and spinal cord injury

Population N=14 patients with tumour osteolysis

Test items

Tokuhashi (1990)
Tomita (2001)
Karnofsky-Index

Scoring

Tokuhashi (1990)
Tomita (2001)
Karnofsky Performance status 10-40% = 0, 50-70% = 1, 80-100% = 2

Life expectancy prognosis / Treatment consequences

Tokuhashi (1990), Tomita (2001)

Received treatment surgery with modular rod-screw implant system for the posterior instrumentation of the occipito-cervical, cervical and cervicothoracic spine; comotherapy or radiotherapy

Follow up

up to 3 years possible

Results

OUTCOME	RESULT
Survival	6 survivors: Tokuhashi score: 6.8 (+ - 1.6, CI: 6.0-7.7), mean survival 9.8 months 8 deceased: Tokuhashi score 8.5 (+ - 1.1, CI: 7.9-9.1), mean survival 11.5 months Tokuhashi score 0-5: both patients still alive after approximately 3 and 7 months Tokuhashi score 6-7: one patient died around 3, one just before 6 months, two around 9, one at 32 months, and three patients were still alive after 3 / 15 months Tokuhashi score 8-12 : two patients died at 3 or 4 months, one at 27 months Tomita score 2-3: one patient died at 4, one at 8 months and two were still alive at 12 or 17 months Tomita score 4-5: one patient died at 3, one at 27 and one at 32 months, one was still alive at 4 months Tomita score 6-7: one patient died at 5 and one at 8 months, two patients were still alive 3 months or 15 months Tomita score 8-10: one patient still alive at 1 month Karnofsky index 1: two patient died at 5 or 5 months, two at 8 or 9 months, and one at 32 months, the survivors were still alive at 4, 12, 16 or 17 months Karnofsky index 2: one patient died at 3 months, one at 22 months, the survivors were still alive at 2 and 3 months
Correlation total score and survival	In the patients who died the correlation was 0.11 with the Tokuhashi score

Author's conclusion The time of survival appeared to be difficult to estimate by a scoring system.

General comments German language publication. The scores were not used to select patients for surgery. The publication is at best an intermediate report, with only few patients and too short observation periods.

Ulmar, B., Richter, M., Cakir, B., Mucbe, R., Puhl, W. & Huch, K. (2005). The Tokuehashi score: Significant predictive value for the life expectancy of patients with breast cancer with spinal metastases. *Spine*, 30 (19), 2222-2226.

Design: Test validation study, evidence level 3
Country: Germany; Setting: Department of Orthopaedic surgery and spinal cord injury

Population N=55 consecutive patients with vertebral metastases secondary to breast cancer

Test items

Tokuhashi (2005)

Scoring

Tokuhashi (2005)

Life expectancy prognosis / Treatment consequences

Scores 0-5: predicted survival \leq 3 months; palliative group

Scores 6-8: predicted survival \leq 12 months

Scores 9-15: predicted survival $>$ 12 months

Alternatively: Scores 0-4: group 1 (predicted survival $<$ 3 months)

Alternatively: Scores 5-8: group 2 (\leq 12 months)

Received treatment surgery for spine fusion for reduction of pain or for neurological deficits

Follow up maximum 132.2 months, median 16.2

Results

OUTCOME	RESULT
Survival	Mean survival 27.2 (+ - 28.6), range: 0.8-132.2; median: 16.2 Scores 0-5: mean survival: 11.5 months (+ - 17.2); range: 0.8-49.4; median: 5.0 Scores 6-8: mean survival: 21.5 months (+ - 18.4); range 1.9-64.9, median: 14.8 Scores 9-15: mean survival: 38.9 months (+ - 36.7); range: 2.7-132.2; median: 25.6 Scores 0-4: mean survival: 2.9 months (+ - 2.0) Scores 5-8: mean survival: 21.7 months (+ - 18.4)
Prognostication / survival curve	The prognostication of the survival interval was significant ($p < 0.0103$) for the original system; the modification showed a higher significance ($p < 0.0001$)

Author's conclusion The modified Tokuhashi score supports decision making based on reliable estimators of life expectancy in patients with breast cancer and spinal metastases.

General comments Test score and received treatment may be intercorrelated, and treatment and outcome (survival) may not be independent

Tokuhashi, Y., Matsuzaki, H., Oda, H., Oshima, M. & Junnosuke, R. (2005). A revised scoring system for preoperative evaluation of metastatic spine tumor prognosis. *Spine*, 30 (19), 2186-2191.

Design: Test evaluation / epidemiological study, evidence level 3
Country: Japan; Setting: Department of Orthopaedic Surgery

Population N=246 patients with metastatic spinal tumours

Test items General condition (performance status), number of extraspinal bone metastases foci, number of metastases in the vertebral body, metastases to the major internal organs, primary site of the cancer, palsy (Frankel)

Scoring

0, 1 or 2 scores for 5 areas, primary site of the cancer is scored 0 to 5 (see Tokuhashi 2002) with a maximum total score of 15

Life expectancy prognosis / Treatment consequences

0-8 scores: less than 6 months life expectancy; conservative or palliative surgery
9-11: up to 1 year life expectancy; palliative surgery or in case of single lesions only and no metastases to the major internal organ excisional surgery
12-15: 1 year or more; excisional surgery

Received treatment decisions based on oncologist opinion and preoperative prognostic score; 142 patients treated with palliative surgery (posterior decompression and stabilisation, posterior stabilisation alone, laminectomy), 22 treated with excisional surgery (anterior curettage and stabilisation, combined curettage and stabilisation, en bloc resection and stabilisation), 82 treated conservatively (radiation, chemotherapy, hormonal therapy, only analgesics). Surgery was not suggested for patients with predicted survival of \leq six months, with a poor general condition, who responded well to oral narcotic analgesics, showed marked effects of radiotherapy, had ultra-rapid palsy progression (complete motor paralysis 2-3 days after onset) or had lost the inclination to live. Conservative therapy was given priority in patients with multiple metastases.

Follow up 115 months

Results

OUTCOME	RESULT
Survival	Survival periods ranged from 10 days to 115 months (mean survival after treatment = 8.7 months, SD=12.3) Scores 0-8: 85% survived up to 6 months; Score 9-11: 73% survived 6 months or more; Score 12-15: 95% survived 1 year or more Respective numbers for a prospectively followed subgroup (N = 118) were 89%, 79% and 88%
Correlation total score and survival	$r = 0.57$ ($p < 0.0001$); the correlations within the treatment group were 0.61, 0.53 and 0.62
Kaplan-Meier curves of score groups	The mean survival amongst the three score cut-of groups differed significantly ($p < 0.01$)

Author's conclusion. The total scores from the revised scoring system were useful for the pre-treatment evaluation of metastatic spinal tumour prognosis irrespective of treatment modality or local extension of the lesion.

General comments Received treatment depended in parts on the score, and treatment and outcome (survival) may not be independent. It is possible that there is overlap in patients described in Tokuhashi (2002) and Tokuhashi *et al.* (1990), only some results for a subgroup of non-overlapping patients are presented.

Jansson, K-A & Bauer, H.C.F. (2006). Survival, complications and outcome in 282 patients operated for neurological deficit due to thoracic or lumbar spinal metastases. Eur Spine J, 15, 196-202.

Design: Case series, evidence level 3
Country: Sweden; Setting: Department of Orthopaedics

Population N=282 consecutive patients with thoracic or lumbar spinal metastasis

Test items

Frankel classification: A: complete paraplegia, B: no motor function, C: motor function useless, D: slight motor function deficit, E: no motor deficit

Scoring

A-C: non-walkers
D-E: walkers

Life expectancy prognosis / Treatment consequences

-

Received treatment 212 patients received posterior decompression and stabilisation, posterior stabilisation with rods (hooks, pedicle screws, mixed; CD, Isola, Synergy or USS implant; augmentation with methyl methacrylate), bone cement for anterior reconstruction, Z-plates or Synergy rods for instrumentation

Follow up 3 months postoperatively, later once yearly

Results

OUTCOME	RESULT
Survival	Scores A-C: 0.26 survival rate at 1 year Scores D-E: 0.33 survival rate at 1 year
Neurological function	Score A-B: 38% walked during follow up Score A-D: 5% worsened postoperatively, 70% improved Score C: 36% walked at discharge (new Frankel: D-E) Score E: 100% retained normal motor function (still E)

Author's conclusion. The post-operative survival was not related to the preoperative neurological function.

General comments Received treatment depended in parts on the score, and treatment and outcome (survival) may not be independent. No attempts were made to predict survival and compare it with actual survival, only the actual survival was recorded; no treatment consequences were formulated either.

Chow, E., Harris, K. & Fung, K. (2006). Successful validation of a survival prediction model in patients with metastases in the spinal column. *Int. J. Radiation Oncology Biol. Phys.*, 65 (5), 1522-1527.

Design: Test evaluation study, evidence level 3
Country: Canada; Setting: Cancer Centre

Population N=231 patients with metastases in the spinal column

Test items

Dutch model: Karnofsky Performance Score (KPS), primary tumour site, visceral involvement;
RRRP model: Primary cancer site, site of metastases, KPS, Edmonton Symptom Assessment Scale (ESAS) fatigue score, ESAS appetite score, ESAS shortness of breath score;
NRF method: Number of risk factors (non breast cancer, sites of metastases other than bone only, KPS≤50, fatigue score 4-10, appetite score 8-10, shortness of breath score 1-10

Scoring

Dutch model: KPS 10-40=0, 50-70=1, 80-100=2; Other cancer=1, lung=1, prostate=2, breast=3; present visceral involvement= 0, absent=1; total score range: 0-6
RRRP model: 0-7 partial scores (items were weighted according to survival prediction scores), total score range: 0-32
NRF method: 0-3 risk factors vs 4 vs 5-6

Life expectancy prognosis / Treatment consequences -

Received treatment not reported

Follow up 3, 6, 12 months, median: 44.9 months

Results

OUTCOME	RESULT
Survival	The median survival was 7 months, range: 0-70 Dutch model score 0-3: median survival: 4.4 months (95% CI: 3.5-6.2) Dutch model score 4-5: median survival: 12.2 months (95% CI: 9.6-16.0) Dutch model score 6: median survival: 51.3 months (95% CI: 19.7-62.3) RRRP model score 0-13: median survival: 3 months (95% CI: 2.3-3.8) RRRP model score 14-19: median survival: 1.2 months (95% CI: 0.8-2.2) RRRP model score 20-32: median survival: 0.6 months (95% CI: 0.3-0.9) NRF method score 0-3: median survival: 12.2 months (95% CI: 10.2-16) NRF method score 4-5: median survival: 3.3 months (95% CI: 2.3-4.5) NRF method score 6: median survival: 1.6 months (95% CI: 1.1-4.3)
Survival probability	Dutch model score 0-3: 63% at 3 months, 42% at 6 months, 30% at 12 months Dutch model score 4-5: 88% at 3 months, 74% at 6 months, 62% at 12 months Dutch model score 6: 100% at 3, 6 and 12 months

	RRRP model score 0-13: 91% at 3, 78% at 6, 61% at 12 months RRRP model score 14-19: 67% at 3, 46% at 6 months, 42% at 12 months RRRP model score 20-32: 44% at 3, 22% at 6 months, 9% at 12 months NRF method score 0-3: 92% at 3 months, 77% at 6 months, 62% at 12 months NRF method score 4-5: 53% at 3 months, 31% at 6 months, 25% at 12 months NRF method score 6: 40% at 3 months, 18% at 6 months, 9% at 12 months
Survival curves	The Dutch model led to significant separation of survival curves (p<0.0001). The RRRP model led to significant separation of survival curves (p<0.0001). The NRF method led to significant separation of survival curves (p<0.0001).
Calibration	R ² was 0.90 for the Dutch model and 0.86 for the RRRP model (predicted survival probability plotted against fraction of patients surviving past 3, 6 and 12 months)
<p>Author's conclusion The Dutch and the RRRP model were successfully validated, the Dutch model is easier to administer.</p> <p>General comments The publication gave little information about the performed treatments. The test score and received treatment may be correlated, and treatment and outcome (survival) may not be independent. The publication does not cite the Tokuhashi or Tomita system.</p>	

Ulmar, B., Naumann, U., Catalkaya, S., Mucbe, R., Cakir, B., Schmidt, R., Reichel, H. & Huch, K. (2007a) Prognosis scores of Tokuehashi and Tomita for patients with spinal metastases of renal cancer. *Annals of Surgical Oncology*, 14(2), 998-1004.

Design: Test evaluation study, evidence level 3
Country: Germany; Setting: Department of Orthopaedics

Population N=37 consecutive patients with spinal metastases of renal cancer

Test items

Tokuehashi (1990); Tomita (2001);

Scoring

Tokuehashi (1990); Tomita (2001)

Life expectancy prognosis / Treatment consequences

Tokuehashi (1990); Tomita (2001)

Received treatment Surgery for spine fusion, reduction of pain and / or neurological deficits

Follow up 83.3 months

Results

OUTCOME	RESULT
Survival	The mean survival was 13.7 (+ - 18.9) months, range: 0-83.3, median: 6.2, 1-year survival: 13 patients, 2-year survival: 4 patients, 5-year survival: 2 patients Tokuehashi scores 0-5: mean survival: 4.7 (+ - 5.8) months, range: 0.1-2-.4, median: 2.6 Tokuehashi scores 6-8: mean survival: 9.5 (+ - 10) months, range: 0-34.9, median: 6.2. Patients with Tomita scores 2-3: mean survival: 8.7 (+ - 7.6) months, range: 2.4-19.6, median: 6.4 Tomita scores 4-5: mean survival 23.3 (+ - 30.9) months, range: 0-75.9, median: 17.2 Tomita scores 6-7: mean survival 21.6 (+ - 34.6) months, range: 1.6-83.3, median: 7.7 Tomita scores 8-10: mean survival 10.6 (+ - 11.1) months, range: 0.1-35.5, median: 5.7.
Percentage of correctly predicted survival	Tokuehashi scores 0-5: 46% of patients died within the predicted (≤ 3 months) Tokuehashi scores 6-8: 78% of patients died as predicted Tokuehashi scores 9-12: 100% of patients survived as predicted (≥ 12 months)
Kaplan-Meier life-table analysis	The prediction with the Tokuehashi system was significant ($p < 0.0010$). The prediction with the Tomita system did not predict survival significantly ($p = 0.69$)
Other	When analysing single predictors, only 'general condition (Karnofsky)' was significant ($p < 0.0001$) for the prognosticated survival

Author's conclusion The Tokuehashi system seems to be much more valuable than the Tomita score for surgical decisions in renal cancer patients with spinal metastases.

General comments The publication gave little information about the performed treatments, the Test score and received treatment may be correlated, and treatment

and outcome (survival) may not be independent

6.7 Radiotherapy

In patients with known MSCC referred for radiotherapy, what is the most effective and cost effective dose fractionation regimen?

Short Summary

Evidence from RCTs enabled some conclusions about RT (30 Gy given in 10 fractions of 3Gy) VS RT plus surgery (stabilisation) (Patchell *et al.* 2005) and split-course RT (5 Gy X 3, 4-day-rest, and then 3 Gy X 5, to a total dose of 30 Gy in 2 weeks) VS short-course RT (8 Gy, 6-day rest, and then 8 Gy, to a total dose of 16 Gy in 1 week) (Marazano *et al.* 2005). Observational studies compared the difference of effectiveness of different RT regimens which can then be considered alongside Marazano *et al.* (2005). The different RT regimens evaluated included: 1X 8 Gy in 1 day, 37.5 Gy in 15 fractions, 40 Gy in 20 fractions, 28 Gy in 7 fractions, 15 Gy in 3 fractions, 15 Gy in 5 fractions, 8 Gy twice (variations include 8 Gy, 6-day rest, and then 8 Gy, to a total dose of 16 Gy in 1 week, 5 Gy X 3, 4-day-rest, and then 3 Gy X 5, to a total dose of 30 Gy in 2 weeks, 1X 8 Gy in 1 day, 5 X 4 Gy in 1 week, 10 X 3 Gy in 2 weeks, 15 X 2.5 Gy in 3 weeks, 20 X 2 Gy in 4 weeks, 10 X 3Gy in 2 weeks, 15 X 2.5Gy in 3 weeks (Loblaw 2004, Rades 2004a, 2004b, 2005, 2006, 2007a, 2007b). However, given the low quality of case series studies conclusions are limited about the effectiveness of different RT regimens. No evidence was identified that addressed the effectiveness of radio-surgery or intensity-modulated radiotherapy in patients with MSCC.

Patchell *et al.* (2005) reported a randomised trial evaluating the effectiveness of direct decompressive surgery plus postoperative radiotherapy compared to radiotherapy alone in patients with MSCC. Significantly more patients in the surgery group than in the radiotherapy group were ambulant after treatment. Patients treated with surgery also retained the ambulation significantly longer than did those with radiotherapy alone. Significantly more patients in the surgery group regained ambulation than patients in the radiation group. The use of opioid analgesics was significantly reduced in the surgical group. Patient selection for this study may have some influence on results reported (as suggested by Loblaw A. 2004 and Maranzano and Trippa 2007) and therefore, the results of this trial cannot be used to justify surgery in all patients with MSCC and apply only to patients comparable to those included in the Patchell *et al.* (2005) study.

The evidence from the RCT by Maranzano *et al.* (2005) and from observational studies (Loblaw *et al.* 2005, Rades *et al.* 2004a, 2004b, 2005, 2006, 2007b) showed no statistical difference in outcomes such as motor function, ambulation or survival for the different RT regimens listed in above. From a multivariate analysis, which included various different patient characteristics as well long and short RT treatment regimens; long course RT was associated with improved survival compared to short dose RT, (Rades *et al.* 2007c). The RCT by Maranzano *et al.* (2005) showed that although in-field recurrences occurred only in patients treated with the short-course RT regimen, no significant difference was found in the median duration of the improvement in walking ability. From case series studies, local control or recurrence was shown to be significantly different with longer courses of RT compared to shorter courses. (Rades *et al.* 2005, 2006 and 2007a).

An abstract of an RCT by Maranzano *et al.* 2006 indicated that short course RT (8 Gy X 2) schedule indicated better response rates than single fraction RT (8Gy) in back pain control and in ability to walk maintenance. The accrual for this study is incomplete and will continue until the established sample size of 300.

Results for re-irradiation:

From case series studies that observed re-treatment of patients (Rades *et al.* 2005, 2006, 2007b), re-irradiation was reported to improve motor function in 31-39% of retreated patients. From Loblaw *et al.* 2005 the following was reported about the treatment options for recurrent MSCC in an area previously irradiated in two retrospective studies (Schiff *et al.* 1995, Wong *et al.* 1994). Schiff *et al.* (1995) retrospectively reviewed 54 patients with MSCC who had at least two RT treatments (cumulative dose: range, 36.5 to 81 Gy; median, 54 Gy) overlapping the spinal cord (range, 5 to 25 cm; median, 10 cm). There were equivalent neurological outcomes to RT-naive patients with MSCC (ambulatory rate of 90% in ambulatory patients, 43% in non-ambulatory patients) and only one episode of radiation myelopathy over an 18-year retrospective chart review. The retrospective review of Wong *et al.* (1994) reported no myelopathy when spinal cord received less than BED 100 Gy (corrected for biologically equivalent dose, $\alpha/\beta = 2$ Gy).

PICO

Population Group	Intervention	Comparison	Outcomes
Patient groups (all with a MSCC diagnosis): A. Very ill – poor prognosis B. Treatable but not fit for surgery C. As Primary tx D. Bone Pain (from spinal met.) - already addressed in topic 2 E. Post surgical gp. F. Re-treated patients	<ul style="list-style-type: none"> ▪Radiotherapy ▪LINAC ▪IMRT (usefulness) ▪radio-surgery (stereotactic) 	<ul style="list-style-type: none"> ▪different doses ▪single fractionation ▪30/10 Gys in 10 fractions ▪20/5 	<ul style="list-style-type: none"> • Improved pain and mobility/ improved QALY: • Pain second outcome • Neurology • Performance Status (Mobility (at wks); Continence) • Survival • Adverse effects • Discharge/death from hospital • Pain management

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

The findings from the RCTs are varied due to the different interventions evaluated. The study by Patchell *et al.* (2005) compares surgery plus RT with RT only and the other RCT by Maranzano *et al.* (2005), compares split with short course RT regimens.

When considering the study by Maranzano *et al.* (2005) and the observational studies included in Loblaw *et al.* (2005) and by Rades *et al.* (2007 to 2004) some positive consistencies can be observed with respect to functional outcomes, local recurrence and survival. Overall, there is limited evidence reporting no differences between different RT regimens with respect to ambulation and survival. That is, no dose-fractionation regimen is more effective than another in terms of pain improvement, or performance status. For local control some inconsistencies exist but a larger number of studies reporting better control for longer courses of RT than shorter were reported.

Surgery Plus RT compared to RT alone:

Patchell *et al.* 2005 reported a randomised trial evaluating the efficacy of direct decompressive surgery in patients with MSCC. The original study design planned for a sample size of 200 patients. However, after an interim analysis, the study was stopped

because the predetermined early stopping criterion was met. 101 patients were entered into the study. The percentage of patients able to walk after treatment was significantly ($p = 0.001$) higher in surgical patients (84%) than in the radiotherapy alone patients (57%). Patients treated with surgery also retained the ability to walk significantly longer than those with radiotherapy alone (median 122 days versus 13 days, $p = 0.003$). 32 patients (16 in each treatment group) entered the study unable to walk; patients in the surgery group regained ambulation in a significantly greater proportion than patients in the radiation alone group (62% versus 19%, $p = 0.01$). The need for corticosteroids and opioid analgesics was significantly lower in the surgical group, and muscle strength and functional status were also maintained for significantly longer in patients treated with surgery. Survival times were also significantly longer in the surgery group (median, 126 days versus 100 days, $p = 0.033$). This study suggested that patients in the surgery plus radiotherapy survive longer and continue to walk for longer proportion of the time they are alive (126 days survival with 122 days ambulation) compared to radiotherapy only patients who survived 100 days with ambulation for 13 days.

Comparison of different RT regimens:

RT regimens analysed:

From a RCT (Maranzano *et al.* 2005): Split-course RT (5 Gy X 3, 4-day-rest, and then 3 Gy X 5, to a total dose of 30 Gy in 2 weeks) versus Short-course RT (8 Gy, 6-day rest, and then 8 Gy, to a total dose of 16 Gy in 1 week)

From observational studies (Loblaw *et al.* 2005, Rades *et al.* 2004a, 2004b, 2005, 2006, 2007a, 2007b): 1X 8 Gy in 1 day, 37.5 Gy in 15 fractions, 40 Gy in 20 fractions, 28 Gy in 7 fractions, 15 Gy in 3 fractions, 15 Gy in 5 fractions, 8 Gy twice (variations include 8 Gy, 6-day rest, and then 8 Gy, to a total dose of 16 Gy in 1 week, 5 Gy X 3, 4-day-rest, and then 3 Gy X 5, to a total dose of 30 Gy in 2 weeks, 1X 8 Gy in 1 day, 5 X 4 Gy in 1 week, 10 X 3 Gy in 2 weeks, 15 X 2.5 Gy in 3 weeks, 20 X 2 Gy in 4 weeks, 10 X 3Gy in 2 weeks, 15 X 2.5Gy in 3 weeks.

- Overall, the results from low grade evidence demonstrated no statistical difference in outcomes such as motor function, ambulation or survival for the different RT regimens listed above.
- From one RCT (Maranzano *et al.* 2005), no significant difference in response, duration of response, survival, or toxicity was observed between short versus split course regimens.
- With respect to local control or recurrence, statistically significant differences were observed between shorter and longer courses of RT. That is better control was observed with longer courses of RT (Rades *et al.* 2005, 2006 and 2007a). However, when 30Gy in 10 fractions was compared with schedules using greater doses (37.5 Gy in 15 fractions and 40 Gy in 20 fractions), local control and survival in a multivariate analysis was not significantly different between the RT regimens (Rades *et al.* 2007b).
- The RCT by Maranzano *et al.* (2005) demonstrated that although in-field recurrences occurred only in patients treated with the short-course RT regimen, no significant difference was found in the median duration of walking capacity improvement, which was 3.5 months in both treatment arms.
- A retrospective case series study (Rades *et al.* 2007c), evaluated the effect of radiotherapy (RT) on motor function and of the post-RT ambulatory status on survival in MSCC patients and investigated the potential prognostic impact of the RT on these outcomes. A multivariate analyses which included various different patient characteristics as well long and short RT treatment regimens, reported that long

course RT was associated with improved survival compared to short dose RT, $p < 0.001$. Where Short course was 1x8Gy in 1 day or 5x4Gy in 1 week and Long course was 10x3Gy in 2 weeks, 15x2.5Gy in 3 weeks or 20x2Gy in 4 weeks.

- An abstract only of an RCT by Maranzano *et al.* 2006 indicates that short course RT (8 Gy X 2) schedule seems to give better response rates than single fraction RT (8Gy) in back pain control and in ability to walk maintenance. The accrual for this study is incomplete and will continue until the established sample size of 300.

Non-conventional RT (Radiosurgery and IMRT)

- Insufficient evidence was found that addressed the effectiveness of radio-surgery in patients with MSCC.
- There were 5 studies that studied the safety and to some extent, the effectiveness of radio-surgery in patients with spinal metastases (using non-randomised, small case series studies).
- 2 studies included a sample group made up of a mix of MSCC patients and patients with spinal mets. The results of each group were not reported for each patient group.
- Overall, the evidence available is limited, it is of very low quality, not comparative and does not include the patient group of interest. From the studies that report findings for patients with spinal mets, re-treatment of vertebral metastases using intensity-modulated radiotherapy can minimise further doses to the cord while delivering therapeutic doses to the disease. (Prasad 2005)
- Although there are a few reports on the safety of radiosurgery in ESCC its role is still limited and unproven in the routine management of spinal-cord compression (Prasad 2005, Klimo *et al* 2003).

Results for re-irradiation:

From case series studies that observed re-treatment of patients (Rades *et al.* 2005, 2006, 2007b), re-irradiation was reported to improve motor function in 31-39% of retreated patients. From Loblaw *et al.* 2005 the following was reported about the treatment options for recurrent MSCC in an area previously irradiated. Two retrospective studies (Schiff *et al* 1995, Wong *et al* 1994). Schiff *et al* (1995) retrospectively reviewed 54 patients with MSCC who had at least two RT treatments (cumulative dose: range, 36.5 to 81 Gy; median, 54 Gy) overlapping the spinal cord (range, 5 to 25 cm; median, 10 cm). There were equivalent neurological outcomes to RT-naive patients with MSCC (ambulatory rate of 90% in ambulatory patients, 43% in non-ambulatory patients) and only one episode of radiation myelopathy over an 18-year retrospective chart review. The retrospective review of Wong *et al.* (1994) reported no myelopathy when spinal cord received less than BED 100 Gy (corrected for biologically equivalent dose, $\alpha/\beta = 2\text{Gy}$).

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Evidence Tables
Randomised Controlled Trials

Patchell RA, Tibbs PA, Regine WF, Payne R, Saris S, Kryscio RJ, Mohiuddin M, Young B (2005) Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial.[see comment]. *Lancet* 366, 643-648.

Design: RCT, Evidence level; 1-
Country: US
setting: multi-institutional

Aim: This study compared the efficacy of direct decompressive surgery plus postoperative radiotherapy with radiotherapy alone.

Inclusion criteria

- Patients at least 18 years old with a tissue-proven diagnosis of cancer (not of CNS or spinal column origin) and MRI evidence of MESCC were eligible for the study.
- Patients also had to have at least one neurological sign or symptom (including pain) and not have been totally paraplegic for longer than 48 h before study entry.
- The MESCC had to be restricted to a single area, which could include several adjacent spinal or vertebral segments.

Exclusion criteria

- Patients with a mass that compressed only the cauda equina or spinal roots were excluded.
- Those with multiple discrete compressive lesions (unless they had one area of compression and multiple non-compressive lesions).
- Patients with certain radiosensitive tumours (lymphomas, leukaemia, multiple myeloma, and germ-cell tumours) as were patients with pre-existing or concomitant neurological problems not related directly to their MESCC (eg, brain metastases).
- Patients with previous MESCC and those who had received spinal radiation such that they were unable to receive the study dose.
- Patients also had to have a general medical status good enough to be acceptable surgical candidates and an expected survival of at least 3 months.

Population

- 101 patients, tissue-proven carcinoma and MSCC
- 50 surgery plus postoperative radiotherapy (surgery group)
- 51 RT alone (radiation group)
- Patients randomised – within strata, by permuted blocks, to surgery plus postoperative radiotherapy or RT alone

Patient Characteristics and numbers in study:

Spinal level of compression

Cervical 5 (RT group), 8 (Surgery + RT group)

T1-T6 18 20

T7-T12 28 22

Position of spinal tumour

Anterior 33 (RT group), 28 (Surgery + RT group)

Lateral 11 9

Posterior 7 13

Unstable spine 18 (RT group), and 20 (Surgery + RT group)

Interventions

Radiation group:

- RT started within 24 hours after randomization. 30Gy given in 10 fractions of 3Gy.
- Treatment was delivered to a port including one vertebral body above and below the visible lesion.

Surgery group:

- Operated on within 24 hours of randomisation.
- Study protocol did not specify operative techniques or fixation devices. The aim was to provide immediate direct circumferential decompression of the spinal cord. A variety of approaches were used according to tumour location and patient circumstances.
- Stabilisation of tumours in all locations was performed if spinal instability was present; cement (methyl methacrylate), metallic rods, bone grafting, or other fixation devices were used.

Outcomes

- **Ambulation:** A patient was deemed ambulatory if he or she could take at least two steps with each foot unassisted (4 steps total), even if a cane or walker was needed. Ambulatory status was assessed in two ways, and both methods were pre-specified. The combined ambulatory rate was the percentage of patients who maintained or regained the ability to walk immediately after completion of radiotherapy and quantified the initial success rate of treatment. Ambulatory time after treatment was a measure of long-term success.
- **Urinary continence**
- **Muscle strength and functional status:** changes in Frankel functional scale scores and American Spinal Injury Association (ASIA) motor scores
- **Need for corticosteroids and opioid analgesics:** Corticosteroid use was assessed by calculating and comparing mean daily dexamethasone equivalent doses
- **Pain:** Pain relief was assessed by calculating and comparing mean daily morphine equivalent doses.
- **Survival:** Survival time after treatment was recorded.

All time dependent endpoints were measured from the day of randomisation until death or last follow up.

Follow up

- Patients had neurological assessments before treatment, weekly during radiotherapy, and within 1 day after completion of treatment.
- Patients then had regular study follow-up assessments every 4 weeks until the end of the trial or death. Patients were also reassessed at any time they had symptoms suggestive of neurological progression.
- Median 102 days surgery grp (0-1940); 93 days RT grp. (0-1117 days)

Results (by outcome)**Overall survival:**

- Surgical treatment resulted in significant differences and an increased survival time for the surgery grp (126 days) compared to RT grp (100 days) (RR = 0.6, 95% CI = 0.38–0.96, p=0.033).
- 30 day mortality rates were 6% in the surgery group and 14 % in RT grp, (p=0.32)

Ambulation:

- Combined post-treatment ambulatory rate:
surgery group = 84%(42/50) and
RT alone grp = 57% (29/51)
Odds ratio = 6:2, 95%CI 2.0 -19.8, p=0.001, favouring surgery

- Patients in the surgery group retained the ability to walk for significantly longer than did those in the radiation group (median 122 days surgery group vs 13 days radiation group, p=0.003).

- Multivariate analysis showed surgery ($p=0.0017$) and pretreatment Frankel score ($p=0.0008$) to be associated with longer ambulatory time.
- In patients who could walk at study entry:
 - 94% (32/34) in the surgery group continued to walk after treatment
 - 74% (26/35) in the radiation group ($p=0.024$).
- Patients in the surgical group were able to walk for a median of 153 days compared with 54 days in the radiation group (odds ratio 1.82, 95% CI 1.08–3.12, $p=0.024$)
- 32 patients entered in the study were unable to walk; significantly more patients in the surgery group regained the ability to walk compared to patients in the radiotherapy group (10/16, 62% vs. 3/16, 19%, $p=0.012$).
- Non-ambulatory patients treated with surgery walked for a median of 59 days compared with a median of 0 days for patients in the radiation group ($p=0.04$).

Urinary continence, muscle strength and functional status

- Surgical treatment resulted in significant improved differences in maintenance of continence, muscle strength (ASIA scores), functional ability (Frankel scores).
 - maintenance of continence: 17 days in radiation group Vs 156 days in surgery group (RR 0.47, 95%CI 0.25-0.87, $p=0.016$)
 - maintenance of ASIA Score: 72 days in radiation group Vs 566 days in surgery group (RR 0.28, 95%CI 0.13-0.61, $p=0.001$)
 - maintenance of Frankel Score: 72 days in radiation group Vs 566 days in surgery group (RR 0.24, 95%CI 0.11-0.54, $p=0.0006$)
- At 30 days patients in the surgery grp. maintained or improved their pre-treatment ASIA score at a significantly higher rate than RT grp. patients (86% vs. 60%, $p=0.0064$). Frankel scores at or above study entry were higher in surgery grp (91% vs. 61%, $p=0.0008$) than RT group.

Other follow-up outcomes:

- Surgery did not result in prolonged hospitalisation; the median hospital stay was 10 days in both the surgery group (IQR 2–51 days) and the radiation group (0–41 days; $p=0.86$).
- Extended hospital stays (greater than 20 days) occurred in seven patients in the surgery group and 11 in the radiation group.

Rate of revision surgery/ recovery: further interventions (depending on prior surgery): not reported

QOL: not reported explicitly

Complications/safety:

- 10 patients in the radiation group (20%) had a substantial decline in motor strength during radiotherapy and crossed over to receive surgery (primary tumour histologies of crossover patients: lung (four), gastrointestinal (two), prostate (one), other genitourinary (two), sarcoma (one).)
- At the time of surgery, none of these patients could walk. 30% regained the ability to walk.
- Of the crossover patients, 40% had surgical complications consisting of three wound infections and one failure of fixation that needed additional surgery.

Pain:

- The surgical group had a substantial reduction in use of corticosteroids and opioid analgesics.

- In the surgery group, the median mean daily dexamethasone equivalent dose was 1.6 mg (IQR 0.1–44.0) compared with 4.2 mg (0.0–50.0) in the radiation group (p=0.0093).
- In the surgery group, the median mean daily morphine equivalent dose was 0.4 mg (0.0–60.0) compared with 4.8 mg (0.0–200.0) in the radiation group (p=0.002).

General comments –

Evidence level:

This RCT was well conducted, with intention to treat analysis conducted as well as randomisation and reported clearly; blinding and allocation concealment was not conducted for this trial. Although this is impractical and not feasible, blinding of the raters of patient outcomes could have been incorporated and would have gone some way to addressing bias.

A possible limitation of the study was patient selection bias. The patient population studied consisted of those patients for whom surgery would be regarded as a realistic treatment option. Patients with very radiosensitive tumours, multiple areas of spinal cord compression, or total paraplegia for longer than 48 h were excluded. Hence, the results of this trial cannot be used to justify surgery in all patients with MSCC and can only apply to patients comparable to those included in the study.

Commentary from other experts in this field:

Byrne *et al.* (2006) noted that the outcomes reported by the RT group were significantly worse than those reported elsewhere. Loblaw (2005) concluded that the ambulatory outcome of paraparetic patients treated with RT who have bony compression was worse than those without bony compression. This may explain the worse outcomes of RT reported by Patchell because 36% of patients randomised to RT had spinal instability. Many investigators use spinal instability as a criterion for surgery. It would be useful to know whether the reported benefit of surgery would be found if patients with mechanical instability were analysed separately.

[based on a comment by Loblaw, A, (2004) Journal of Supportive Oncology, 2 [5] 391-3]:
 “patients in the RT only grp. seemed to have recovered ambulation to a much lesser degree than expected from the literature, despite their receiving high dose RT and high doses of dexamethasone, while the patients in the surgery plus RT group fared the same as expected from the literature. Also, there is a significantly lower ambulatory recovery among non-ambulatory patients compared to the existing literature (retrospective case series). This may be due to the inclusion of patients with spinal instability / bony compression, which were specifically excluded from other studies”

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Design: RCT (1998 – 2002)

Level 1-

Country: Italy

setting: Multi-centre

Aim: This randomised trial was planned to assess the clinical outcome and toxicity of two different hypofractionated RT regimens in MSCC: Short course (8 Gy x 2 days) vs. split course RT (5 Gy x 3; 3 Gy x 5).

Inclusion criteria

1. MSCC had to be diagnosed by MRI or CT in patients with progressive neoplastic disease.
2. There were no criteria indicating a primary surgical approach (i.e., none of the following was present: diagnostic doubt, spinal instability, a vertebral body collapse causing bone impingement on the cord or nerve roots, or previous irradiation in the same area).
3. Patients had to have a short life expectancy (< 6 months) because of unfavourable histologies (i.e., lung, kidney, GI, head and neck carcinoma, melanoma, or sarcoma) or favourable histologies (i.e., lymphoma, seminoma, myeloma, and breast or prostate carcinoma) provided that motor or sphincter dysfunction and/or low performance status were also manifest.

All of these criteria were chosen in an attempt to enrol only MSCC patients with short life expectancy, whereas those with a longer life expectancy because of the presence of favourable histologies, good motor or sphincter function, and good performance status underwent 30 Gy in 10 fractions during 2 weeks or other more protracted RT schedules according to the choice of each centre participating in the study.

Exclusion criteria

spinal instability, vertebral body collapse causing cord or nerve root compression, previous irradiation in same area

Population

- 300 patients entered onto the trial, of which 276 (92%) are assessable and 24 (11 in the short-course and 13 in the split-course arms) were not assessable because they were lost to follow-up (seven patients) or early death (17 patients).
- The diagnosis of MSCC was established by MRI in 214 patients (76%) and by CT in the other 62 patients (24%).
- The short-course regimen = 142 patients (51%)
- The split-course regimen = 134 patients (49%)
- Patients well balanced for age, gender, performance status, ambulatory status, histology (data not reported).

99 (36%) had favourable histology:

Prostate	39/276 (14%)
Breast	28/276 (10%)
Myeloma	19/276 (7%)
Small cell lung	8/276 (3%)
Lymphoma	6/276 (2%)

- 177 (64%) had unfavourable histology:
- | | |
|---------------------|---------------|
| Non-small cell lung | 177/276 (28%) |
| Colorectal | 25/ 276 (9%) |
| Kidney | 22/276 (8%) |
| Gastric | 11/276 (4%) |
| Head and neck | 7/276 (2.5%) |
| Liver | 7/276 (2.5%) |
| Bladder | 6/276 (2%) |
| Sarcoma | 6/276 (2%) |
| Melanoma | 3/276 (1.5%) |
| Uterine | 3/276 (1.5%) |
| Other | 14/276 (5%) |

Site of MSCC

Location in spine		Location of metastases	
Cervical	8%	Spine (26%)	72/276
Thoracic	50%	Multiple bone metastases	113/276 (41%)
Lumbar	23%	Bone and visceral metastases	91/276 (33%)
Sacral	7%		
Cervicothoracic	1%		
Thoracolumbar	6%		
Lumbosacral	2%		

Interventions:

short-course RT: 8 Gy, 6-day rest, and then 8 Gy, to a total dose of 16 Gy in 1 week
split-course RT: 5 Gy X 3, 4-day-rest, and then 3 Gy X 5, to a total dose of 30 Gy in 2 weeks

Outcomes

Primary outcomes:

- symptom control (ie, back pain, and motor and sphincter function)
- duration of response
- survival

Secondary outcomes (acute and late adverse effects of the two treatment arms):

- radiation-induced acute oral or oesophageal toxicity
- diarrhoea
- emesis
- differences in outcome regarding development of radiation-induced late spinal cord morbidity.

Response to treatment was evaluated according to the patients' walking capacity, bladder function, and back pain before and after RT.

Motor performance: graded according to Tomita's groups
 group I, ability to walk without support;
 group II, ability to walk with support;
 group III, inability to walk;
 group IV, paraplegic

Categories of responders =

1. Patients who were able to walk before and after treatment
2. Patients who were unable to walk before RT who recovered walking ability after RT

Bladder function: defined by the need of a urinary catheter.

Category of responders =

Patients who maintained or recovered sphincter function

Pain: graded according to the classifications of no pain, pain controlled with minor analgesics, and pain requiring narcotics (scale derived from a questionnaire compiled by the patient and given to the physician at each follow-up).

Categories of responders =

1. Complete responders, those patients who had no pain after RT;
2. Partial responders, patients using narcotics or minor analgesics before RT who had pain requiring minor analgesics after RT;
3. Non-responders, patients with no pain before RT who developed pain or those with pain requiring minor analgesics who starting taking narcotics after RT.

For diarrhoea and oesophageal or pharyngeal toxicity: the National Cancer Institute Common Toxicity Criteria were used.

For emesis:

Nausea was graded according to a 0 to 3 scale: 0, no episodes; 1, mild (did not interfere with normal daily life); 2, moderate, (interfered with normal daily life); and 3, severe (patient bedridden because of nausea). **Vomiting** was also graded according to a 0 to 3 scale: 0, no episodes; 1, one to two episodes per day; 2, more than two but less than or equal to 10 episodes per day; 3, more than 10 episodes per day.

Recurrence was diagnosed by MRI, which was prescribed only for patients with symptomatic progression.

Follow up

- 1 month after RT, then monthly for 1 year.
- Median follow-up 33 months (range 4-61mths)

Results

RT response

- A total of 276 (92%) patients were assessable; 142 (51%) treated with the short-course and 134 (49%) treated with the split-course RT regimen.
- There was no significant difference in response, duration of response, survival, or toxicity found between the two arms. When short- versus split-course regimens were compared, after RT 56% and 59% patients had back pain relief, 68% and 71% were able to walk, and 90% and 89% had good bladder function, respectively.

Survival

- There was no significant difference in survival found between the two arms
- Median survival was 4 months and median duration of improvement was 3.5 months for both arms.
- Survival time was significantly associated with walking ability pre and post treatment and favourable histology.
- Percent probability of survival (Kaplan-Meier):

Patient group N=276	1 year	2 years	3 years	Median	P
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				survival (months)	
<i>Pre-treatment status:</i>					
Walking	n=184	15%	10%	5%	5
Non-walking	n=92	10%	6%	0%	3
<i>Post-treatment status:</i>					
Walking	n=193	18%	10%	6%	5
Non-walking	n=83	5%	0%	0%	2
<i>Histology:</i>					
Favourable	n=96	30%	30%	8%	6
Unfavourable	n=180	5%	5%	2%	3

Pain relief

- Achieved in 157 patients (56.9%; 95%CI 51.1 - 62.7)
- Complete response in 92 (33.3%; 95%CI 27.7 - 38.9)
- Partial response in 65 (23.6%; 95%CI 18.6 - 28.6)

Motor function

Responders 192 (69.6%; 95%CI 63.9 - 75.3)
Grade I 93% maintained function
Grade II 88% maintained function
Grade III 35% regained motor ability
Grade IV None of the 17 paraplegics improved

- The median duration of motor capacity improvement was independent of the patient's walking capacity. Only primary tumour type influenced the median duration of motor capacity improvement which was 6 months for favourable histologies and 3 months for unfavourable histologies (P= 0.0001).
- Median duration of improvement in motor capacity:

Patient group	Responders Number Total%	Median duration of improvement (months)	P
Post treatment walking	192/276	70	4
<i>Pre-treatment status:</i>			
Walking	167/184	91	4
Non-walking	26/92	28	3
<i>Histology:</i>			
Favourable	73/96	76	6
Non-favourable	119/180	66	3

Sphincter dysfunction

- 29 patients had sphincter dysfunction:
- Response rate 89%
- 4 (14%) regained control
- 4 (2%) of those with good bladder control worsened
- The remainder maintained bladder control

Adverse effects

- There was no significant difference in toxicity found between the two arms
- Grade 1 to 2 oral or esophageal dysphagia was observed in 39 of patients (14%).
- Grade 3 esophagitis observed in 3 patients (1%) treated in the thoracic area (2 with the split-course and 1 with the short-course regimen)
- 1 patient (0.5%) was a grade 3 pharyngeal dysphagia (in split-course RT arm) on the cervical spine.

- 20 patients (7%) had grade 1 to 2 diarrhea and 4 patients (1.5%) developed grade 3 diarrhea (2 after a short course RT on the thoracolumbar region and 2 after RT to the sacral area with the split-course regimen)

- 167 patients treated with antiemetic prophylaxis, grade 1 to 2 vomiting occurred in 22 patients (13%) and grade 3 vomiting occurred in only five patients (3%), (the same incidence in the two RT regimens).
- Nausea reported in 21 patients (12%): grade 1 to 2 in 16 patients (9%) and grade 3 in five patients (3%).
- Of patients who did not receive antiemetic prophylaxis because the treated spine was not at risk, seven (6%) had grade 1 nausea, six (5.5%) had grade 1 to 2 vomiting, and only one (1%) had grade 3 vomiting.

- No relationship was found between the RT regimen adopted and acute adverse events.

- Late spinal cord morbidity was never recorded.

Recurrence (*In-Field Recurrences*)

- 5 in-field recurrences: all identified in patients submitted to the short-course RT regimen (2% of all patients and 3.5% of the short-course RT group).

- Diagnosis of recurrence was obtained by MRI that was performed because patients had symptomatic progression (ie, presence of neurologic signs and/or symptoms that suggested myelo-radicular compression).

- The median interval between the end of the first RT and diagnosis of recurrence = 5 months (range, 3 to 7 months).

- 3 patients walking before re-treatment: 2 maintained the function, 1 became paraparetic.
- 2 patients were not walking patients before re-treatment and remained so.
- 4 out of 5 patients died, with a median survival time of 3.5 months (range, 1 to 7 months) after re-treatment.
- 1 patient is alive at 20 months.
- No spinal cord morbidity was found in this group.

- Although in-field recurrences occurred only in patients treated with the short-course RT regimen, no significant difference was found in the median duration of walking capacity improvement, which was 3.5 months in both treatment arms.

General comments –*Authors conclusions*

Both hypofractionated RT schedules adopted were effective and had acceptable toxicity. However, considering the advantages of the short-course regimen in terms of patient convenience and machine time, it could become the RT regimen of choice in the clinical practice for MSCC patients.

Study protocol:

Patients were randomly assigned (one-to-one randomization to the two arms: short-course v

split-course RT), allocation was performed by a centralized registration, and investigators were notified of assignment by telephone and fax. Treatment groups were not stratified.

Power Calculation:

To test the hypothesis for this equivalence trial that a short-course RT (8 Gy X 2) is at least as effective in producing a response as a split-course RT (5 GyX3; 3GyX5), it was calculated that 270 patients (approximately 135 in each arm) would be needed. This was intended to ensure an 80% probability (power)

that the two-sided 95% CI for the difference in response rates would be within the interval -15% to +15% if the two response rates were in fact equal and approximately 70%. When considering a dropout rate of 10% of patients, a final accrual of 300 patients was planned.

Commentary from other experts in the field:

Kwok Y. Regine WF. Patchell RA. Radiation therapy alone for spinal cord compression: time to improve upon a relatively ineffective status quo. Journal of Clinical Oncology. 23(15):3308-10, 2005 [Comment. Editorial]

These authors have raised the following criticisms of the Maranzano study:

Selection criteria:

- The inclusion of patients with favourable histology and good Karnofsky performance status allowed for longer survivals.
- Although the inclusion criteria selected for patients with a short life expectancy (≤ 6 months), this study has included groups of patients who might be anticipated to live significantly longer than 6 months. For example, one of the most significant predictors of short survival for patients with metastatic cancer is poor performance status; yet, 17% of patients in this study had Karnofsky performance status of 80 to 100. Furthermore, patients with radiosensitive tumors (such as lymphoma, seminoma, and myeloma) were included, as were those with histologies that have relatively long survivals after development of metastasis (such as breast and prostate cancer). Although patients with these favourable factors may have been equally distributed between the two treatments, the inclusion of such patients needs to be taken into account to estimate the true efficacy of radiation in the trial.

Interventions evaluated:

The most common fractionation schedule used in patients with MSCC in the United States is 30 Gy in 3-Gy daily fractions for 10 days, without a planned break. The schedules adopted for the two arms are not considered standard; therefore, this study may be interpreted by some as a randomised phase II study, rather than a true phase III study.

Furthermore, many radiation oncologists are hesitant to use the large fractions prescribed in this study in the CNS. The main determinant of late radiation injury is fraction size, and hypofractionated schedules have clearly been associated with toxicity in the brain. It is conceivable that the 13 patients who progressed to paraplegia without in-field recurrence may have suffered from late radiation-induced toxicity, even if not scored as late toxicity by the authors.

Re-considering the results:

The authors report seemingly impressive response rates, with pain, motor function, and sphincter control responses of 57%, 70%, and 89%, respectively. These numbers are undoubtedly a reflection of the inclusion of patients with favorable histology and by a definition of response that combines both stability and improvement. However, when one limits the definition of response to regaining motor function and sphincter control, the rates of success decrease to 29% and 14%, respectively.

Maranzano E, Trippa F, Rossi R, Bellavita R, Lupattelli M, Marafioti L, Pergolizzi S, Mignogna M, Cossa S, Fusco V (2006) Two hypofractionated radiotherapy (RT) schedules (8 Gy x 2 vs. 8 Gy) in metastatic spinal cord compression (MSCC). Updating of an ongoing phase III randomized multicentre trial. *Radiotherapy and Oncology* 81, 740 (ABSTRACT ONLY)

Design: RCT

Country: Italy

Purpose:

This randomised trial was planned to determine whether a single dose (8Gy) is as effective as a short-course (8 Gy X 2) RT schedule in MSCC patients with regard to symptom control, duration of response and toxicity. This is the updating of an ongoing trial.

Method:

From November 2002 to April 2006, 265 MSCC patients with a short life expectancy (<6 months) because of (a) the presence of unfavourable histologies (i.e. lung, kidney, gastrointestinal and head and neck carcinoma, melanoma, sarcoma) or (b) favourable ones (i.e. lymphoma, seminoma myeloma and breast or prostate carcinoma) provided that motor/sphincter dysfunction and/or low performance status were also manifest, underwent short-course or single dose RT without surgery. Parenteral dexamethasone (8mg bid) was given in all cases. Antiemetic therapy was prescribed in patients treated with fields covering the upper abdomen. Median follow up was 3 months (range 1-38).

Results:

219 patients with updated data are evaluable for response and toxicity. 104 patients were randomised to receive a short-course and 115 a single dose RT schedule. Male/female ratio was 142:77, median age was 67 years (range 33-88) and median Karnofsky score 60% (range 20-100%). Considering back pain relief and ability to walk maintenance, a significant difference was observed in favour of the short-course with respect to the single dose RT (78% vs. 60% and 76% vs. 57%, respectively; $p<0.01$ and $p<0.01$). No difference was found in the ability to walk recovery between RT schedules (overall response, 7%).

Median duration of response was 4 months for both groups. The incidence of acute toxicity was low in both regimens: WHO grade 2 and 3 somatitis/esophagitis was registered in 5% of and 1% of patients respectively; 9% of patients suffered from nausea that interfered with normal daily life; 2% and 1% of patients referred >2 and ≤ 10 and > 10 episodes of vomiting/d, respectively. No late toxicity was registered in patients with at least 12 months of follow up (i.e. 22% of cases).

Conclusions:

The short course RT schedule indicates better response rates than single fraction RT in back pain control and in ability to maintain ambulatory. The accrual will continue until the established sample size of 300 patients will be reached.

General comments

The abstract that was presented at a conference has been reproduced entirely above so as to indicate the nature of the study and its findings. Due to this limited evidence it has not been included in the summary of the evidence and the lead investigator (Ernesto Maranzano) has indicated that the final results of this study will be shown to us or published very soon. Hopefully this will be included in the update search of evidence early in 2008.

Systematic Review (different study designs)

Loblaw DA; Perry J; Chambers A; Laperriere NJ. Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. (2005) J Clin Oncol 23(9):2028-2037

Design: Systematic review of combined study designs, evidence level: 2- to 3
Country: international

Aim: Is there an optimal dose prescription for radiotherapy (for patients with MSCC)?

Inclusion criteria

RCTs comparing dosages of radiotherapy; phase II studies or retrospective reviews reporting dosages of radiotherapy

Exclusion criteria

Patients with intramedullary or leptomeningeal cord compression are not considered in this report.

Population

Adult patients with confirmed diagnosis of extradural malignant spinal cord compression (MSCC).

Interventions

30 Gy in 10 fractions (reference 1,2)
37.5 Gy in 15 fractions (3)
40 Gy in 20 fractions (3)
28 Gy in 7 fractions (4)
15 Gy in 3 fractions, 15 Gy in 5 fractions (5, 6-8)
8 Gy twice (6)

Outcomes

Rate of retaining or regaining ambulation; mortality rates; complication rates.

Note: For the purposes of this systematic review, ambulatory refers to patients who are able to walk with or without assistance and who may be mildly paraparetic; paretic refers to patients who are non-ambulatory and paraparetic; and paraplegic refers to those patients who have only a flicker of or no muscle movement.

Results

- 3 prospective studies: (reference 5,1,4)
- 2 case-control studies: (6, 7)
- 1 case series: (8)
- 3 retrospective reviews: (9, 2, 3) - two of which address the same patient cohort, describe optimal dosage of RT.
- The prescription of RT given to treat MSCC varies within and between studies.
- Three studies stratified the results by dosing, (3, 6, 9) and the other studies gave the same prescription to the entire cohort.
- No one regimen was more effective than any of the others for any cohort of patients in terms of rate of retaining or regaining ambulation; mortality rates; complication rates.
- See Table 6 from Loblaw (2005) showing RT Dose Fraction Prescriptions According to Pretreatment Ambulatory Status of Patients.

General comments

Evidence level:

This review is systematically conducted. It sets out clear clinical questions, systematically searches for relevant evidence, broadly outlines inclusion and exclusion criteria of included studies, grades the included evidence and summarises either descriptively or by statistically pooling the raw data where possible. The methodology of this review is of high quality but this is superseded by the evidence level of the included studies, which is low.

An important factor omitted is the detailed inclusion criteria required for case series studies. There numerous studies in the evidence body and only a select number are included. Further information would have explained inclusion further.

References of Included Studies:

1. Maranzano E, Latini P, Beneventi S, et al: Radiotherapy without steroids in selected metastatic spinal cord compression patients: A phase II trial. *Am J Clin Oncol* 19:179-183, 1996
2. Ampil FL, Chin HW: Radiotherapy alone for extradural compression by spinal myeloma. *Radiat Med* 13:129-131, 1995
3. Rades D, Karstens JH, Alberti W: Role of radiotherapy in the treatment of motor dysfunction due to metastatic spinal cord compression: Comparison of three different fractionation schedules. *Int J Radiat Oncol Biol Phys* 54:1160-1164, 2002
4. Helweg-Larsen S: Clinical outcome in metastatic spinal cord compression: A prospective study of 153 patients. *Acta Neurol Scand* 94:269-275, 1996
5. Maranzano E, Latini P: Effectiveness of radiation therapy without surgery in metastatic spinal cord compression: Final results from a prospective trial. *Int J Radiat Oncol Biol Phys* 32:959-967, 1995
6. Maranzano E, Latini P, Beneventi S, et al: Comparison of two different radiotherapy schedules for spinal cord compression in prostate cancer. *Tumori* 84:472-477, 1998
7. Greenberg HS, Kim JH, Posner JB: Epidural spinal cord compression from metastatic tumor: Results with a new treatment protocol. *Ann Neurol* 8:361-366, 1980
8. Kovner F, Spigel S, Rider I, et al: Radiation therapy of metastatic spinal cord compression: Multidisciplinary team diagnosis and treatment. *J Neurooncol* 42:85-92, 1999
9. Rades D, Karstens JH: A comparison of two different radiation schedules for metastatic spinal cord compression considering a new prognostic factor. *Strahlenther Onkol* 178:556-561, 2002

Loblaw DA; Perry J; Chambers A; Laperriere NJ. Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. (2005) J Clin Oncol 23(9):2028-2037

Design: Systematic review of combined study designs, evidence level: 3
Country: international

Aim: What are the treatment options for recurrent MSCC in an area previously irradiated?

Inclusion criteria

RCTs comparing treatments for patients with recurrent MSCC in an area previously irradiated; phase II studies or retrospective reviews reporting treatments for patients with recurrent MSCC in an area previously irradiated

Exclusion criteria

Patients with intramedullary or leptomeningeal cord compression are not considered in this report.

Population

Adult patients with confirmed diagnosis of extradural malignant spinal cord compression (MSCC).

Interventions

1. RT treatments (cumulative dose: range, 36.5 to 81 Gy; median, 54 Gy)
2. Less than 100 Gy₂ (corrected for biologically equivalent dose, $\alpha/\beta = 2$) of RT.

Outcomes

Rate of retaining or regaining ambulation; mortality rates complication rates adverse effects response rate

Note: For the purposes of this systematic review, ambulatory refers to patients who are able to walk with or without assistance and who may be mildly paraparetic; paretic refers to patients who are non-ambulatory and paraparetic; and paraplegic refers to those patients who have only a flicker of or no muscle movement.

Results

- 2 retrospective studies (Schiff *et al* 1995, Wong *et al* 1994)
- Schiff *et al* 1995 retrospectively reviewed 54 patients with MSCC who had at least two RT treatments (cumulative dose: range, 36.5 to 81 Gy; median, 54 Gy) overlapping the spinal cord (range, 5 to 25 cm; median, 10 cm). There were equivalent neurological outcomes to RT-naïve patients with MSCC (ambulatory rate of 90% in ambulatory patients, 43% in non-ambulatory patients) and only one episode of radiation myelopathy over an 18-year retrospective chart review.
- The retrospective review of Wong *et al* 1994 reported no myelopathy when spinal cord received less than 100 Gy₂ (corrected for biologically equivalent dose, $\alpha/\beta = 2$) of RT.

General comments

Evidence level:

This review is systematically conducted. It sets out clear clinical questions, systematically searches for relevant evidence, broadly outlines inclusion and exclusion criteria of included studies, grades the included evidence and summarises either descriptively or by statistically pooling the raw data where possible. The methodology of this review is of high quality but this is superseded by the evidence level of the included studies, which is low.

An important factor omitted is the detailed inclusion criteria required for case series studies. There numerous studies in the evidence body and only a select number are included. Further information would have explained inclusion further.

References of Included Studies:

Schiff D, Shaw EG, Cascino TL: Outcome after spinal re-irradiation for malignant epidural spinal cord compression. *Ann Neurol* 37:583-589, 1995

Wong CS, van Dyk J, Milosevic M, et al: Radiation myelopathy following single courses of radiotherapy and retreatment. *Int J Radiat Oncol Biol Phys* 30:575-581, 1994

Observational Studies (Prospective studies):

Rades D, Fehlauer F, Hartmann A, Wildfang I, Karstens JH, Alberti W (2004) Reducing the overall treatment time for radiotherapy of metastatic spinal cord compression (MSCC): 3-year results of a prospective observational multi-centre study. Journal of Neuro-Oncology 70, 77-82

Design: Prospective observational study (case series) Evidence level: 3

Country: Germany

Setting: multi centres

Aim: To evaluate the effectiveness of 2 standard fractionation schedules, 30 Gy/10 fractions/2 weeks and 40 Gy/20 fractions/4 weeks in terms of functional outcome and ambulatory status for MSCC patients.

Inclusion criteria

Inclusion criteria were motor dysfunction of the lower extremities, no previous surgery or RT of the spinal region concerned, and dexamethasone treatment (16–32 mg per day) during RT.

Exclusion criteria

Patients with a history of a brain tumour, brain metastasis or other severe neurological diseases, which may lead to motor dysfunction, were excluded.

Population

- 136 patients with MSCC (diagnosis based on history, clinical examination and spinal MRI or CT)

Interventions

Two different standard fractionation schedules:

30 Gy/10 fractions/2 weeks (n = 71)

40 Gy/20 fractions/4 weeks (n = 65).

The assignment of the treatment approach was related to the availability of radiotherapy dependent on capacities at the linear accelerators. In case of reduced capacities, the less time consuming schedule (30 Gy/10 fractions) was applied. The chronology of the schedules was simultaneous and not sequential.

Outcomes

Motor function

Ambulatory status

- Motor function and ambulatory status were evaluated prior to RT, at the end of RT and at 6, 12 and 24 weeks after RT.
- Motor function was graded using an eight-point scale according to the ASIA and the International Medical Society of Paraplegia (IMSOP): 0 complete paraplegia, 1 palpable or visible muscle contractions, 2 active movement of the leg without gravity, 3 active movement against gravity, 4 against mild resistance, 5 against moderate resistance, 6 against severe resistance, 7 normal strength.
- Improvement and deterioration of motor function were defined as a change of at least one point of the eight-point scale. Patients treated for new symptomatic disease during the period of follow up were excluded from further analysis, because motor function might be influenced by this additional treatment.

Follow up

For patients who survived ≥ 24 weeks, the median follow-up was 14 months (range: 6–25 months) after 30 Gy/10 fractions and 15 months (range: 6–28 months) after 40 Gy/20 fractions.

Results

Motor Function

- No significant difference of functional outcomes was observed for the two radiation schedules in terms of improvement; no change or deterioration of motor function.

Ambulation

- No significant difference with respect to pre-treatment and post-treatment ambulatory rates between the two schedules was observed.
- 19 of 67 (28%) initially non-ambulatory patients regained the ability to walk after RT, 11/36 (31%) in the 30 Gy group and 8/31 (26%) in the 40 Gy group ($P = 0.888$).
- When a multiple logistic regression analysis was performed, the time of developing motor deficits before RT (better outcome associated with a slower development of motor dysfunction, $P < 0.001$), the type of primary tumor (better outcome associated with a favorable histology, $P = 0.040$) and the pre-treatment ambulatory status (better outcome for ambulatory patients, $P = 0.045$) had a significant impact on functional outcome.
- The fractionation schedule did not have a significant impact on ambulation ($P = 0.311$).

Survival

- Thirty-five patients, 18 patients of the 30 Gy group and 17 patients of the 40 Gy group, died within 24 weeks after radiotherapy.
- 2 patients were lost to follow-up.
- From the data of patients, who died before the follow-up was complete, functional outcome was better for long-term survivors.
- Raw data about the effects of RT on motor function in patients who expired before the follow-up and in patients with complete follow-up was presented but no statistical analysis performed with respect to differences in outcomes of each group of patients.
- Complete follow-up was comparable in both groups, 73% (52/71) in the 30 Gy group and 72% (47/65) in the 40 Gy group. (Indicating a reduced effect of bias due to survival).

Adverse Events

- New symptomatic disease in the previously irradiated spinal region did not occur during the period of follow up.
- In both groups, no relevant acute or late radiation related toxicity was observed. Acute toxicity did not exceed grade 1 according to the Common Toxicity Criteria.
- In surviving patients, late toxicity such as radiation myelopathy did not occur during the period of follow-up.

General comments

Given the results indicate no difference between the 2 RT regimens, with respect to pre-treatment and post-treatment ambulatory rates and motor function it would be reasonable to consider the use of 30 Gy/10 fractions instead of 40 Gy/20 fractions because it reduces overall treatment time from 4 to 2 weeks, with flow on reduction to clinical time and patient visits to hospital.

The most rigorous way in which to evaluate these 2 RT regimens is under RCT conditions with larger patient numbers.

Rades D, Fehlaue F, Stalpers LJ, Wildfang I, Zschenker O, Schild SE, Schmoll HJ, Karstens JH, Alberti W (2004) A prospective evaluation of two radiotherapy schedules with 10 versus 20 fractions for the treatment of metastatic spinal cord compression: final results of a multicenter study. Cancer 101, 2687-2692.

Design: Prospective case series study. Evidence level: 3
Country: Germany

Aim: To evaluate two radiotherapy schedules and prognostic factors with respect to functional outcome.

Inclusion criteria

Motor dysfunction of the lower extremities, no previous surgery or RT of the spinal region concerned, no chemotherapy, and dexamethasone treatment (16–32 mg per day) during RT.

Exclusion criteria

Patients with a history of a brain tumour, brain metastasis, or other major neurological diseases, which may also cause motor dysfunction, were excluded.

Population

- 214 patients with MSCC (confirmed with MRI or CT)
- median age = 63 years (range, 24–87 years)

Interventions

The schedules:

- 30 Gy per 10 fractions over 2 weeks (n = 110)
- 40 Gy per 20 fractions over 4 weeks (n = 104)

The assignment of the treatment approach was related to the availability of RT appointments on the linear accelerators.

Outcomes

- Motor function and ambulatory status were evaluated before RT, at the end of RT, and at both 3 and 6 months after RT.
- Motor function was graded according to the American Spinal Injury Association (ASIA) and the International Medical Society of Paraplegia. Improvement and deterioration of motor function were defined as a change of at least one point on the eight-point scale.

The following potential prognostic factors were investigated: RT schedule, performance status, age, number of irradiated vertebrae, type of primary tumour, pre-treatment ambulatory status, and length of time developing motor deficits before RT. (Analysis of prognostic factors was not presented in this table as it is not the clinical question under consideration.

Follow up

6 months

Results

Motor Function

- From a univariate analysis, the comparison of the 2 RT schedules did not indicate a significant impact on motor function.

Ambulation

- Ambulatory rates before and after RT were not significantly different for the two treatment groups (see Table below from paper).
- 30% (29 of 98) of the patients, who were not ambulatory before RT, regained the ability to walk
- No significant difference between the 2 RT schedules (P = 0.999): 29% (15 of 52) after 30

Gy and 30% (14 of 46) after 40 Gy

Survival

- 63 patients died within 6 months after RT (33 patients in the 30-Gy group and 30 patients in the 40-Gy group).
- 3 patients were lost to follow up (1 patient in the 30-Gy group and 2 patients in the 40-Gy group.)
- Functional outcome was better for long-term survivors.
- The patients with complete follow-up of ≥ 6 months responded better to RT than the patients who died before 6 months after RT.
- The rate of patients with complete follow-up was 69% in both groups, (76 of 110 patients in the 30-Gy group and 72 of 104 patients in the 40-Gy group)

Adverse Events

No relevant acute or late RT related toxicity was observed (reported) for either group.

General comments

Limitations of the study:

- As a non-randomised study the internal validity of the findings is somewhat limited due to the possible effect of bias. Potential bias could be due to differences between the study populations in each intervention group. However, the authors were able to address this to some degree in that patient characteristics (described by the authors) were similar for both groups. There could be other characteristics that could alter the results that were not considered by the authors.
- The most reliable or valid evaluation is to conduct a randomised controlled trial, comparing the 2 RT regimens.

Rades D, Stalpers LJ, Veninga T, Schulte R, Hoskin PJ, Obralic N, Bajrovic A, Rudat V, Schwarz R, Hulshof MC, Poortmans P, Schild SE (2005) Evaluation of five radiation schedules and prognostic factors for metastatic spinal cord compression. Journal of Clinical Oncology 23, 3366-3375.

Design: Retrospective case series study.
Country: Germany and UK

Evidence Level: 3

Aim: To compare five different RT schedules used for MSCC with respect to resulting functional outcome and to investigate potential prognostic factors for functional outcome.

Inclusion criteria

Motor dysfunction of the lower extremities, no previous surgery or RT of the spinal region concerned, no concurrent chemotherapy, and survival of at least 1 month after RT (allowing the evaluation of motor function 1 month after RT- more appropriate than the evaluation directly after RT because no treatment effect can be expected directly after single-fraction RT such as 1 X 8 Gy)

Exclusion criteria

Patients with a history of a brain tumour, brain metastasis, or other major neurological diseases, which may result in motor dysfunction, were excluded.

Population

- 1,304 MSCC patients were included in this retrospective analysis.
- The data were obtained from patient files and from the patients' general practitioners.
- The diagnosis of MSCC was confirmed by MRI or computed CT.
- Patients received dexamethasone at a moderate to intermediate dose level (16 to 32 mg/d) during the whole RT. If 1 X 8 Gy or 5 X 4 Gy were applied, dexamethasone was administered for a week.

Interventions

- The five RT schedules that were compared were as follows:
1X 8 Gy in 1 day (n = 261),
5 X 4 Gy in 1 week (n = 279),
10 X 3 Gy in 2 weeks (n = 274),
15 X 2.5 Gy in 3 weeks (n = 233),
20 X 2 Gy in 4 weeks (n = 257)
- Potential prognostic factors were included in a multivariate analysis. The comparison of the five RT schedules with respect to functional outcome was also analysed.
- The following potential prognostic factors were investigated: age, sex, performance status, histology, number of involved vertebra, interval from cancer diagnosis to MSCC, pre-treatment ambulatory status, and time of developing motor deficits before RT. (Analysis of prognostic factors was not presented in this table as it is not the clinical question under consideration. (see Topic 6 for details))

Outcomes

The RT schedules were compared for the following three post-treatment end points: Motor function, ambulatory status, and in-field recurrences.

- Motor function and ambulatory status were evaluated before RT and at 1 month, 3 months, and 6 months after RT.
- Motor function was graded with a 5-point scale according to Tomita scales (grade 0, normal strength; grade 1, ambulatory without aid; grade 2, ambulatory with aid; grade 3,

not ambulatory; grade 4, paraplegia).

- Improvement or deterioration of motor function was defined as a change of at least 1 point.

Follow up

At least 6 months or until death.

Results

Motor Function

- No significant differences were observed between the five groups of different RT regimens at each time of follow-up.

Ambulation

- Ambulatory rates before and after RT were not significantly different for the five treatment groups ($P = 0.96$).
- Twenty-six percent of the patients (126 of 477 patients) who were not ambulatory before RT regained the ability to walk:
25% (23 of 91 patients) after 1 X 8 Gy,
26% (27 of 104 patients) after 5X4 Gy,
26% (31 of 118 patients) after 10X3 Gy,
24% (22 of 90 patients) after 15X2.5 Gy,
30% (23 of 76 patients) after 20 X 2 Gy

In-field recurrences

- The in-field recurrences (from Kaplan-Meier analysis) demonstrated significantly more recurrences occurred after 1X 8 Gy and 5X4 Gy than after 10 X 3 Gy, 15 X 2.5 Gy, and 20 X 2 Gy (see figure below).
- Between 1 X 8 Gy and 5 X 4 Gy, no significant difference was observed.
- Between 10 X 3 Gy, 15 X 2.5 Gy, and 20 X 2 Gy, there was also no significant difference observed

Re-treatment

- Surgery resulted in improvement of motor function in seven (85%) of 12 patients.
- Re-irradiation resulted in improvement of motor function in 26 (35%) of 74 patients.
- Chemotherapy resulted in improvement of motor function in none (0%) of five patients.
- Ten patients, who were irradiated with one of the three more protracted regimens, received no further treatment at the time of recurrence and deteriorated.

Adverse Events

- For the five treatment groups, no relevant acute or late RT-related toxicity was observed.
- Late toxicity, such as RT myelopathy, did not occur.

General comments

Limitations of the study:

As this study was a retrospective evaluation of cases and not an RCT, several biases must be considered. The retrospective approach did not allow for consistent, pre-determined outcomes to be reported. This includes the limitation of a more differentiated grading system for motor function than the Tomita scale. Because more detailed information about the functional status was not available data about sensory deficits or dysfunction of bowel and bladder was not evaluated in this study.

Selection bias: By definition this is when a bias is introduced by the un-controlled selection of patients that are included or excluded for a treatment. The authors explain that this bias could have been excluded because patients were not selected for specific RT regimens due to type of tumour histology or performance status. The only selection process was waiting times for specific RT.

In-field recurrence:

As reported by the authors: a bias may have been introduced as a result of the fact that more patients may have had in-field recurrences but were not referred for re-irradiation because of poor prognosis or the wrong impression that re-irradiation is not effective. The re-irradiation rate may have also been influenced by the concern about myelopathy, which becomes more of an issue after initial RT with higher doses such as 30 to 40 Gy. This question can only be properly answered in a prospective manner, where all patients who are treated with different RT schedules are assessed the same way at the same time points.
(Again highlighting the limitations of this retrospective study design)

Overall conclusions from this study:

The five RT schedules provided similar functional outcome. Study findings indicated that the three more protracted schedules resulted in fewer in-field recurrences. Authors recommend in order to minimize treatment time, the following two schedules be used: 1 X 8 Gy for patients with poor predicted survival and 10 X 3 Gy for other patients.

Rades D, Fehlaue F, Schulte R, Veninga T, Stalpers LJ, Basic H, Bajrovic A, Hoskin PJ, Tribius S, Wildfang I, Rudat V, Engenhart-Cabilic R, Karstens JH, Alberti W, Dunst J, Schild SE (2006) Prognostic factors for local control and survival after radiotherapy of metastatic spinal cord compression. *Journal of Clinical Oncology* 24, 3388-3393

Design: Retrospective consecutive cohort (1992-2005) Evidence Level 3

Country: UK, Germany, Netherlands, Bosnia, setting: Multi-centre

Aim: To evaluate potential prognostic factors for local control and survival after radiotherapy of metastatic spinal cord compression (MSCC).

Inclusion criteria

- An unselected series of consecutive patients who were treated for MSCC at the contributing centers during a certain period of time.
- RT for MSCC, motor deficits of lower extremities due to MSCC of thoracic or lumbar spine, no prior RT to index sites, confirmation of MSCC by CT or MRI, dexamethasone given from 1st day of treatment for at least one week.

Exclusion criteria

None reported

Population

number of patients = 1852, 40% female, 53% ≤ 64 years

Cohort of unselected consecutive patients treated at contributing centres during the specified time period.

Characteristics investigated as prognostic factor for local control and survival
ECOG performance 1-2 3-4
Type of primary tumour Breast ca Prostate ca Myeloma / lymphoma Lung ca Other tumours
Other bone metastases Yes No
Visceral metastases Yes No
Ambulatory status Ambulatory Non-ambulatory
Radiation schedule Short course RT Long course RT
Interval from tumour diagnosis to MSCC (months) ≤ 15 months > 15 months
Time to develop motor deficits

before RT
1-14 days
> 14 days

Interventions:

Short course vs. long course RT

Short course was the standard regime for UK, Netherlands and Bosnia, and long course the standard regime for Germany.

Short course: 1x8Gy in 1 day or 5x4Gy in 1 week

Long course: 10x3Gy in 2 weeks, 15x2.5Gy in 3 weeks or 20x2Gy in 4 weeks

Outcomes:

Motor function 5 point scale (Tomita)

Grade 0 normal strength

Grade 1 ambulatory without aid

Grade 2 ambulatory with aid

Grade 3 not ambulatory

Grade 4 paraplegia

ECOG performance status 1 to 2 vs. 3 to 4

Survival assessed at 1, 2 and 3 years.

Multivariate analyses of prognostic factors (Cox proportional hazards model) $P < 0.0045$ as significant. Significant univariate prognostic factors ($P < 0.0045$) included in multivariate analysis.

Prognostic factors: age, gender, ECOG, primary tumour, number of vertebra involved, other bone or visceral metastases, time from tumour diagnosis to MSCC, ambulatory status, time to develop motor deficits before RT.

Follow up

Motor and ambulatory status evaluated before RT and up to 24 months after. Median follow-up 7 months (0-110)

Results

Definitions:

- Local control of MSCC defined as no recurrent motor deficits as a result of progressive or recurrent MSCC in the previously irradiated spinal region.
- Recurrence of MSCC defined as recurrence of motor deficits if RT had improved motor function or progression of motor deficits if RT resulted in no change.
- Improvement in motor function defined as a change of at least one point.

Factors for local control after RT (recurrence)

- On univariate analysis, better local control was associated significantly with a favourable histology (breast cancer, prostate cancer, and myeloma/lymphoma), absence of visceral metastases, and long-course RT ($P < 0.001$).
- On multivariate analysis, absence of visceral metastases and long-course RT maintained significance.
- See Table below for values

Factor for better local control	Univariate P value	Multivariate analysis
Type of tumour		
Breast		RR 1.09 (95%CI 0.97,
Prostate		1.21)
Myeloma/lymphoma		P 0.14

v		
Other tumours	<0.001	
Visceral metastases at time of RT		
Yes		RR 2.64 (95% CI 1.76, 3.90)
No	<0.001	P <0.001
Radiation schedule		
Short course		RR 0.54 (95% CI 0.45, 0.65)
Long course	<0.001	P <0.001

- Of the 144 patients who developed a recurrence of MSCC in the pre-irradiated site, 104 patients (72%) received re-irradiation:
 - 15 patients (10%) received surgery,
 - 6 patients (4%) received chemotherapy,
 - 19 patients (13%) received no treatment.
- Re-irradiation was more frequently applied after short-course RT (91 of 98 patients; 93%) than after long-course RT (13 of 46 patients; 28%; P<.001).
- The improvement rate of all the patients who were treated for MSCC recurrence was 35% (51 of 144 patients).
- Improvement of motor function was observed in 40 of 104 patients (39%) after re-irradiation,
- Improvement of motor function was observed in 10 of 15 patients (67%) after surgery.
- Only one of six patients (17%) treated with chemotherapy and 0 of 19 patients (0%) without any treatment improved.
- Results of re-irradiation in relation to the applied fractionation schedules are summarized but statistical difference were not reported for the different fractionation schedules used.

Survival

- The median follow-up of the entire cohort was 7 months (range, 0 to 110 months) after RT.
- The median follow-up in survivors was 14 months (range, 6 to 110 months).
- On univariate analysis, better survival was not significantly associated with either course of RT.
 - For the long-course RT a significant association with survival by the log-rank test (P=.017) was demonstrated but when applying a more stringent statistical parameter (Bonferroni correction for multiple comparisons) the significance is no longer present.

Adverse events

Acute toxicity was mild or absent in all patients.

Late radiation toxicity such as myelopathy did not occur after primary irradiation or re-irradiation.

Rades D, Karstens JH, Hoskin PJ, Rudat V, Veninga T, Schild SE, Dunst J (2007) Escalation of radiation dose beyond 30 Gy in 10 fractions for metastatic spinal cord compression. *International Journal of Radiation Oncology, Biology, Physics* 67, 525-531.

Design: Evidence level 3
Country: Germany

Aim: This study investigated the potential benefit of dose escalation. It compared the effectiveness of “standard” RT (30Gy in 10 fractions) with schedules using greater doses (37.5 Gy in 15 fractions and 40 Gy in 20 fractions) with respect to functional outcome, local control and survival.

Inclusion criteria

Patients had to have motor deficits of the lower extremities due to MSCC or the thoracic or lumbar spine, no previous RT to the involved sites, confirmation of MSCC by CT or MRI and administration of dexamethasone for greater than or equal to 1 week.

Exclusion criteria

Patients with myeloma, lymphoma or melanoma were excluded (due to the different clinical course to carcinomas).
Patients with cervical spine MSCC without involvement of the thoracic spine were also excluded.

Population

- 922 patients with carcinomas causing MSCC

Interventions

- “standard” RT (30Gy in 10 fractions)
- 37.5 Gy in 15 fractions or 40 Gy in 20 fractions
- The outcome of 345 patients treated with 10 fractions of 3 Gy in 2 weeks was compared with the outcomes of 577 patients treated with 37.5 Gy in 15 fractions within 3 weeks or 40 Gy in 20 fractions within 4 weeks.
- 10 potential prognostic factors were investigated: age, gender, performance status, tumour type, interval between cancer diagnosis and MSCC, number of involved vertebrae, other bone and visceral metastases, ambulatory status, and the interval to the development of motor deficits before radiotherapy. (prognostic factors not reported for this question – see topic 6)

Outcomes

- Functional outcome: evaluated 1, 3, 6 months after RT. Using 5 point scale (0=normal, 4= paraplegia) – improvement was an change ≥ 1 point
- Local control of MSC/MSCC recurrence: no recurrent motor deficits resulting from progressive or recurrent MSCC in the previously irradiated spinal region. Diagnosis of progression was diagnosed using CT or MRI. MSCC recurrence = either recurrence of motor deficits if RT had led to an improvement in motor function or as progression of motor deficits if RT had resulted in no change of motor deficits.
- Survival: The intervals to recurrence and death were measured from RT completion. Calculated using Kaplan-Meier method.

Follow up

Patients were followed until death or for 6 to 82 months (median 14 months) for survivors.

Results

Functional outcome

- Motor function improved in 19% of patients after 30 Gy in 10 fractions and in 22% after greater doses.

- The radiation schedule had no significant impact on motor function ($p = 0.31$).
- Results at 1 month after RT ($n=922$) were similar to those observed at 3 months ($n=769$) and 6 months after RT ($n=495$)

Local Control/MSCC recurrence

- MSCC recurrence in the irradiated site developed in 39 patients after a median of 9 months (3 – 41 months).
- In a univariate analysis local control was not significantly different between the RT regimens being compared ($p=0.28$)
- In a multivariate analysis local control was not significantly different between the RT regimens being compared. ($p=0.85$)
- Better functional outcome was associated with the absence of visceral metastases, an interval between tumour diagnosis and MSCC of >12 months, ambulatory status, and an interval to the development of motor deficits of >7 days.
- Improved local control was significantly associated with no visceral metastases, improved survival with favourable histological features (breast or prostate cancer), no visceral metastases, ambulatory status, an interval between cancer diagnosis and MSCC of >12 months, and an interval to the development of motor deficits of >7 days.

Survival

- The median survival for the total cohort in this study = 7 months after RT
- In a univariate analysis the RT schedule indicated non significant difference between the 2 doses compared, however authors describe a trend in favour of doses >30 Gy) $p=0.051$.

General comments

Author conclusions: “Escalation of the radiation dose to >30 Gy in 10 fractions did not improve the outcomes in terms of motor function, local control, or survival but did increase the treatment time for these frequently debilitated patients. Therefore, doses >30 Gy in 10 fractions are not recommended”

Limitations of the study:

- The retrospective case series study design limits useful and unbiased evaluation of the different RT regimens wrt functional outcome, local control and survival.

Rades D, Hoskin PJ, Karstens JH, Rudat V, Veninga T, Stalpers LJ, Schild SE, Dunst J (2007) Radiotherapy of metastatic spinal cord compression in very elderly patients. *International Journal of Radiation Oncology, Biology, Physics* 67, 256-263

Design: Retrospective cohort (1992-2005)
setting: Multi-centre

Evidence Level 3

Aim: This study investigated the results of radiotherapy (RT) long versus short course, for metastatic spinal cord compression (MSCC) in the very elderly.

Inclusion criteria

MSCC with motor deficits of the lower extremities due to MSCC of the thoracic or lumbar spine, no previous RT to involved sites, confirmation of MSCC by CT or MRI, administration of dexamethasone for at least 1 week.

Exclusion criteria

None reported

Population

number of patients = 308 patient records aged $>$ or $=75$ years (a subset from the Rades et

2006 study)

Interventions

short course: 1 X 8 Gy or 5 X 4 Gy (treatment time 1-5 days, n=176)

long course RT: 10 X 3 Gy or 15 X 2.5 Gy or 20 X 2 Gy (treatment time 2-4 weeks, n=132)

Outcomes

- Motor function 5 point Tomita scale, improvement defined as change of at least 1 point
- Evaluated before RT and 1, 3, and 6 months after RT.
- Survival assessed at 6 months and 1 year

- Multivariate analyses of prognostic factors (Cox proportional hazards model) $P < 0.0045$ as significant. Significant univariate prognostic factors ($P < 0.0045$) included in multivariate analysis.

- Prognostic factors for functional outcome, local control of MSCC, and survival: gender, ECOG performance status (2 vs. 3-4), primary tumour, number of vertebra involved, other bone or visceral metastases, time from tumour diagnosis to MSCC (≤ 18 vs. > 18 months), ambulatory status (ambulatory vs. non-ambulatory), time to develop motor deficits before RT (1-7 vs. 8-14 vs. >14 days).

Follow up

Until death. Survivors median follow-up 13 months (6-72 months)

Results

Definitions:

Local control of MSCC defined as no recurrent motor deficits as a result of progressive or recurrent MSCC in the previously irradiated spinal region.

Motor function

- Improvement of motor deficits occurred in 25% (78/308) of patients.
- No further progression of MSCC in 59% (182/308)
- 16% (48/308) had motor function deterioration

- Of 129 non-ambulatory patients 35 (27%) regained the ability to walk after RT.

Effects of prognostic factors on functional outcomes: (further details reported in topic 6C)

- RT schedule had no impact on motor function.

Local control (recurrence)

- The local control rate for the entire cohort was 94% at 6 months and 92% at 12 months after RT.
- The radiation schedule was the only statistically significant prognostic factor associated with local control on univariate analysis, favouring long course RT ($P < 0.001$).

- Local recurrence was treated with re-irradiation in 16 out 20 patients (80%)
- After re-irradiation: 31% had improved motor function, 63% had no further progression and 6% (1 patient) deteriorated.
- Median follow-up after re-irradiation was 9 months. (ranging from 1 to 21 months)

Survival

The 1-year survival rate was 43%.

On univariate analysis, the radiation schedule had no significant impact on survival ($p=0.256$)

Conclusions:

Improved functional outcomes were associated with ambulatory status and slower

developing motor deficits. Improved local control resulted from long-course RT. Improved survival was associated with a longer interval from tumour diagnosis to MSCC, tumour type (breast/prostate cancer, myeloma/lymphoma), lack of visceral or other bone metastases, ambulatory status, and a slower development of motor deficits.

General comments

This paper is about a subset of patients from the earlier larger study of 1800 patients (Rades 2006).

Author conclusions:

“Short- and long-course RT are similarly effective in patients aged > or =75 years regarding functional outcome and survival. Long-course RT provided better local control. Patients with better expected survival should receive long-course RT and others short-course RT. The criteria for selection of an appropriate regimen for MSCC in very elderly patients should be the same as for younger individuals.”

Loblaw DA; Perry J; Chambers A; Laperriere NJ. Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. (2005) J Clin Oncol 23(9):2028-2037

Design: Systematic review of combined study designs, evidence level: 3 (observational studies)

Country: international

Aim: What are the indications for RT in the Management of MSCC?

Inclusion criteria

Studies: retrospective and prospective case series studies and one cross sectional study

Patients:

3. patients with bony compression or spinal instability
4. patients with sub-clinical cord compression (results not reported; not in PICO)

Exclusion criteria

Patients with intramedullary or leptomeningeal cord compression are not considered in this report.

Population

Adult patients with confirmed diagnosis of extradural malignant spinal cord compression (MSCC).

Interventions

Radiotherapy as primary treatment

Outcomes

Rate (and ability) of retaining or regaining ambulation

Note: For the purposes of this systematic review, ambulatory refers to patients who are able to walk with or without assistance and who may be mildly paraparetic; paretic refers to patients who are non-ambulatory and paraparetic; and paraplegic refers to those patients who have only a flicker of or no muscle movement.

Results

The results from 2 retrospective reviews and a pooled analysis of ambulatory outcomes of patients with and without bony compression (studies listed in reference list below) imply that the presence of bony compression is a negative predictive factor for achieving ambulation after RT.

Loblaw *et al* 2005 reports studies that included patients without bony compression treated with RT:

patients who are ambulatory, have ambulatory rates of 100%,
ambulatory with assistance, have ambulatory rates of 94%,
paraparetic, or have ambulatory rates of 60%,
paraplegic have ambulatory rates of 1%,

Compared to studies of patients where bony compression is not excluded, retain or regain ambulation (with or without assistance):

patients who are ambulatory, have ambulatory rates of 92%
ambulatory with assistance, have ambulatory rates of 65%
paraparetic, or have ambulatory rates of 43%
paraplegic have ambulatory rates of 14%

Patients with bony compression, particularly those who have mild to moderate paraparesis, who are treated with RT were less likely to recover ambulation compared with paretic

patients without bony compression (χ^2 7.64, $P \leq .01$).

Loblaw *et al* 2005 report that no studies were identified that specifically addressed spinal instability. Despite the lack of evidence, 3 studies reported that spinal instability to be a surgical indication.

General comments

Evidence level:

This review is systematically conducted. It sets out clear clinical questions, systematically searches for relevant evidence, broadly outlines inclusion and exclusion criteria of included studies, grades the included evidence and summarises either descriptively or by statistically pooling the raw data where possible. The methodology of this review is of high quality but this is superseded by the evidence level of the included studies, which is low.

An important factor omitted is the detailed inclusion criteria required for case series studies. There are numerous studies in the evidence body and only a select number are included. Further information would have explained inclusion further.

References of Included Studies:

Greenberg HS, Kim JH, Posner JB (1980) Epidural spinal cord compression from metastatic tumor: Results with a new treatment protocol. *Ann Neurol* 8:361-366

Helweg-Larsen S (1996) Clinical outcome in metastatic spinal cord compression: A prospective study of 153 patients. *Acta Neurol Scand* 94:269- 275

Kim RY, Spencer SA, Meredith RF, et al (1990) Extradural spinal cord compression: Analysis of factors determining functional prognosis—Prospective study. *Radiology* 176:279-282.

Kovner F, Spigel S, Rider I, et al (1999) Radiation therapy of metastatic spinal cord compression: Multidisciplinary team diagnosis and treatment. *J Neurooncol* 42:85-92

Maranzano E, Latini P: Effectiveness of radiation therapy without surgery in metastatic spinal cord compression (1995) Final results from a prospective trial. *Int J Radiat Oncol Biol Phys* 32:959-967.

Maranzano E, Latini P, Beneventi S, et al (1996) Radiotherapy without steroids in selected metastatic spinal cord compression patients: A phase II trial. *Am J Clin Oncol* 19:179-183

Maranzano E, Latini P, Checcaglini F, et al (1991) Radiation therapy in metastatic spinal cord compression:

A prospective analysis of 105 consecutive patients. *Cancer* 67:1311-1317, 1991

Maranzano E, Latini P, Beneventi S, et al (1998) Comparison of two different radiotherapy schedules for spinal cord compression in prostate cancer. *Tumori* 84:472-477

Pigott KH, Baddeley H, Maher EJ (1994) Pattern of disease in spinal cord compression on MRI scan and implications for treatment. *Clin Oncol (R Coll Radiol)* 6:7-10

Rades D, Heidenreich F, Karstens JH (2002) Final results of a prospective study of the prognostic value of the time to develop motor deficits before irradiation in metastatic spinal cord compression. *Int J Radiat Oncol Biol Phys* 53:975-979, 2002

Zelevsky MJ, Scher HI, Krol G, et al (1992) Spinal epidural tumour in patients with prostate cancer: Clinical and radiographic predictors of response to radiation therapy. *Cancer* 70:2319-2325

Rades, D., Veninga, T., Stalpers, L. J., Basic, H., Hoskin, P. J., Karstens, J. H., Schild, S. E. & Dunst, J. (2007c) Improved posttreatment functional outcome is associated with better survival in patients irradiated for metastatic spinal cord compression. *International Journal of Radiation Oncology, Biology, Physics*, 67: 1506-1509.

Design:retrospective case series, Evidence grade 3
Country: GERMANY

Aim: To evaluate effect of radiotherapy (RT) on motor function and of the post-RT ambulatory status on survival in metastatic spinal cord compression (MSCC) patients and to investigate the potential prognostic impact of the RT on these outcomes.

Inclusion criteria

Patients irradiated for MSCC at one centre.
 Patients had to have motor deficits of the lower extremities, no prior treatment with RT to the involve spine, confirmation of MSCC by CT or MRI and managed with dexamethasone (12-32mg/d)from the first day of RT for ≥ 1 week.

Exclusion criteria

Apteinets who did not fit the above criteria

Population

1852 patients were included:
 778 received short course RT (1X8 Gy/1 day or 5X4 Gy/1 week)
 1074 received long course RT (10X3Gy/2 weeks, 15X2.5 Gy/3 weeks, 20 X2 Gy/4 weeks)

Interventions

RT was delivered with a 6-10 MV linear accelerators or Cobalt-60 units

Outcomes

- Motor function: evaluated before RT and up to 24 months after RT. A 5 point scale was used with 0= normal strength and 4 = paraplegia. Improvement was a change of ≥ 1 point.
- Ambulatory status: evaluated before RT and up to 24 months after.
- Survival: analysis was conducted to evaluate the effect of motor function and ambulatory status.
- Multivariate analysis was conducted with several variables.

Median follow up for entire group was 7 months. Median follow up for surviving patients was 14 months.

Results

Survival:

Actuarial survival rate at 6 months was 56%, at 12 months it was 43%, at 24 months it was 32%

For those patients with improved motor function after RT (75%), a significantly better survival rate (at 1 year) than for those who did not have a change (40%) or deteriorated motor function (3%), $p<0.001$

Ambulation:

1 year survival rate for ambulant patients after RT was significantly better (63%) than for those who were not ambulatory(4%0, $p<0.0001$).

Multivariate Analysis:

Patient Variable	Statistical findings and association with improved survival
Effect of RT on motor function	Significant effect on survival, $p<0.001$
Post RT ambulatory status	Significant effect on survival, $p<0.001$

Interval between cancer diagnosis and MSCC >15 months	Significant effect on survival, p<0.001
Absence of other mets and visceral mets	Significant effect on survival, p<0.001
Favourable tumour types (myeloma/lymphoma, breast cancer)	Significant effect on survival, p<0.001
Time to developing motor deficits >7 days	Significant effect on survival, p<0.001
Pre-RT ambulatory status	Significant effect on survival, p<0.001
Involvement of only one or two vertebrae	Significant effect on survival, p<0.001
Long course RT	Significant effect on survival, p<0.001
Gender	No significant affect on survival , p=0.12
Performance status	No significant affect on survival, p=0.49

Conclusions: From a multivariate analyses, included various different patient characteristics as well long and short RT treatment regimens, long course RT was associated with improved survival compared to short dose RT, p<0.001.

6.8 An Economic Evaluation of Treatments for People With Suspected Metastatic Spinal Cord Compression

Introduction

Without treatment virtually all the patients with metastatic spinal cord compression (MSCC) will become paraplegic and will have limited survival (Kwok et al 2006). There is the general belief among the clinical community that surgery for MSCC patients may prevent paraplegia. Preventing paraplegia may be worth doing (despite high overall costs of the surgical procedures) if the health benefits derived from it are large enough. The decision about what treatment modality is adequate for an MSCC patient depends on the patient's clinical characteristics, such as whether there is neurological compromise, pain, or whether tumours are radiosensitive or not. In the treatment of patients threatened with paraplegia radiotherapy (RT) is relatively cheap and may be given in a single palliative dose for pain control, although more commonly it requires two or more weeks of daily treatments in an attempt to prevent disease progression to paraplegia. Around 70% of patients are able to walk after RT, and the median duration of the functional improvement is 3.5 months approximately, although there are some side effects related to treatment with RT, such as toxicity (Maranzano et al 2005). RT alone is not suitable for patients with instability pain, where the addition of vertebroplasty/kyphoplasty may provide vertebral column support by minimalist techniques. Alvarez et al. (2003) showed that the proportion of fully ambulant patients after vertebroplasty improved from 38% to 76% (although a study by Fourney et al. (2003) showed no statistically significant improvement in ambulant status). Vertebroplasty/kyphoplasty are not suitable for patients where cord compression or paraparesis already exists, and larger operations are required in order to attempt the rescue of people from deteriorating neurological states. Radical surgery for MSCC has been reported to be beneficial, especially for patients who are still ambulant before surgery (Patchell et al 2005; Sucher et al 1994).

Even if patients who are ambulant before treatment are likely to maintain their ability to walk afterwards, especially after radical surgery, some of them will become paraplegic at some point (Patchell et al 2005); therefore, it is important to assess whether the health benefits obtained from these interventions are worth the costs. In addition, there is a group of MSCC patients that are neurologically compromised and have tumours that are not very radiosensitive, for whom it is not clear what the best treatment choice is between the options of RT versus surgery followed by RT. These issues highlight the need of economic analyses to assess the cost-effectiveness of treatments for MSCC patients.

Existing economic evidence

A systematic review of the literature was conducted to identify published economic evaluations that could shed light on the cost-effectiveness of treatments for MSCC patients. In total, three studies were identified: one full economic evaluation (Thomas et al 2006) and two published abstracts (Furlan et al 2007; Klinger et al 2007). All three studies assessed the use of SRT versus RT alone in MSCC patients. None of these studies was conducted in a UK setting and, moreover, limited information was reported for the published abstracts. The clinical evidence used in all these studies was obtained from the randomised controlled trial –RCT- by Patchell and collaborators (Patchell et al 2005), which excluded MSCC patients with radiosensitive tumours. The study by Thomas et al (2006) used decision modelling based on Monte-Carlo simulation to estimate the incremental costs per life year gained with SRT compared to RT alone. This study adopted a societal perspective that included medical and non-medical costs

(e.g. out-of-pocket expenses related to home care), although indirect costs related to productivity losses were not included. QALYs were not estimated due to the lack of utility data for this group of patients; the absence of a QALY estimation limited the direct usefulness of the study for this guideline since QALY is the measure of health benefit preferred by NICE to make decisions based on cost-effectiveness. The study concluded that SRT “is cost-effective both in terms of cost per additional day of ambulation, and cost per life-year gained” (Thomas et al 2006). As the authors mentioned, the cost-effectiveness of SRT compared to RT alone depends greatly on the value that society and patients place on ambulatory function.

The abstract by Furlan et al (2007) presented a cost-utility analysis in which the health gains, in terms of QALYs, and the associated costs of SRT, compared to RT alone, were estimated. The study was conducted from the perspective of the public health care insurer and used a decision analytic model to estimate the QALY gains and the costs incurred with SRT versus RT alone. A probabilistic sensitivity analysis based on Monte-Carlo simulation was conducted to assess uncertainty. The authors concluded that adjunctive surgery is cost-effective when compared to RT alone. The other abstract (Klinger et al 2007) seemed to be a cost-effectiveness analysis using the same RCT data, and it concluded that SRT is more costly and more effective than the combination of RT and corticosteroids. However, limited information was reported for both abstracts; therefore, it is difficult to assess the reliability of these results and their applicability to the UK context.

Aims

Given the limited cost-effectiveness evidence available on treatments for MSCC patients, two economic assessments were conducted. Based on the hypothesis that surgery for the treatment of MSCC may prevent a number of patients from developing paraplegia, the objective of the first analysis was to identify under what conditions the different types of treatments (including surgery) for MSCC patients would become cost-effective. This was conducted by comparing the costs of potential treatments (i.e. radical or major surgery, vertebroplasty or RT) and the follow-up care associated with them, to the costs of caring for untreated MSCC patients who develop paraplegia. Once these costs were estimated, the specific conditions (in terms of ambulatory rates after surgery, time remaining ambulant after surgery, survival, etc.) were identified that would make these treatments cost-effective compared to no treatment.

In addition, a second analysis was conducted which assessed the cost-effectiveness of radical surgical procedures in combination with RT compared to RT alone for the treatment of MSCC patients that are neurologically compromised and have tumours that are not very radiosensitive. This analysis consisted of adapting to a UK setting the only full economic evaluation available comparing the use of surgery in combination with RT (SRT) versus RT alone for the treatment of MSCC patients (Thomas et al 2006). The economic evaluation had been conducted within a Canadian setting and was based on the only available RCT comparing surgery plus RT versus RT alone (Patchell et al 2005). A deterministic analytic decision model was used, and the incremental cost per additional day ambulant and per additional life year gained were estimated. An attempt was also made to estimate QALYs and the incremental cost per QALY gained with SRT compared to RT.

The perspective adopted in both analyses was that of the National Health Service (NHS) and Personal Social Services, which meant that all the costs and health consequences to be included were those relevant to the NHS. Costs were estimated based on 2006-2007 prices. A lifetime horizon was considered for the estimation of costs and health benefits in both assessments.

Costing paraplegia and treatment options for MSCC patients

Methods

Introduction

For the first economic analysis, the costs of treatment and follow-up care of the potential treatments for MSCC patients were compared to those of caring for untreated MSCC patients who develop paraplegia in order to identify under what conditions (mainly in terms of ambulatory rates after surgery, time remaining ambulant after surgery and survival) the potential treatments for MSCC would become cost-effective. For this, the types of patients included in the analysis and their corresponding potential appropriate treatments were identified, and the costs associated with each of the identified treatments were estimated. Additionally, it was necessary to identify baseline values for the ambulation rates, the time remaining ambulant and the mean survival after the different types of treatments so that an accurate costing of the post-hospitalisation health care cost could be conducted. Threshold analyses were then undertaken to identify the values of these parameters (i.e. ambulation rates, time remaining ambulant and average survival) that would make the potential treatments cost-effective when compared to no treatment.

Patient population and interventions

Only patients that were ambulant at the time of treatment were considered in this analysis. Three independent assessments were conducted within this study, based on the potential treatments available for the different types of patients (i.e. RT, vertebroplasty or major/complex surgery), which were chosen according to patients' characteristics and surgeon's judgement:

1. RT versus no treatment: for patients ambulant at presentation, who have multiple metastasis without immediate potential for mechanical or neurological compromise but who are at risk of developing paraplegia, or for those patients with radiosensitive tumours (such as lymphoma, myeloma and germ cell tumours) in whom surgery is not necessary.
2. Vertebroplasty in combination with RT versus no treatment: for patients ambulant at presentation, with spinal pain and/or vertebral collapse from metastasis but with no evidence of MSCC or spinal instability. The interest in vertebroplasty was based on the belief that this is a less costly option to perform than major surgery and it can prevent paraplegia if performed at an early stage.
3. Major/complex surgery in combination with RT versus no treatment for patients presenting ambulant to the hospital with a general health condition good enough as to undergo surgery and who had a good prognosis, i.e. at least 12 weeks of life expectancy.

Cost estimation

The relevant cost categories included were identified by personal communication with the collaborating GDG members and from the published literature on MSCC treatment interventions and prognosis. Some of the systematic reviews of the clinical evidence conducted within the MSCC Guideline were consulted as well, mainly those related to MSCC preventative treatments (i.e. vertebroplasty/kyphoplasty), surgical treatments and RT. The cost categories included in the analysis were: cost related to the administration of RT (including the cost of treating RT-related complications); surgery costs (including the cost of transferring the patient for surgery, the cost of pre-surgical computed tomography-guided biopsy, pre- and post-operative visits required, the use of the surgical theatre and the time of the staff involved in the surgical procedure, the cost related to the length of stay –LOS- and other consumable costs, such as implants, anaesthetics and blood transfusions); post-treatment costs, i.e. home care and care at the nursing home; and costs related to the care of the patient during the last weeks of life (either at home or at the nursing care home). Table 11 presents a detailed description of the resources used, the unit costs and the average costs per patient associated with each type of treatment and subsequent follow-up care.

The costs of RT were estimated based on the cost per fraction of complex RT as provided by the University Hospital in Birmingham. The average cost per patient related to RT administration was estimated to be £1,250 (assuming that 5 RT fractions per patient were administered). The cost of RT-related complications was based on the information provided in the economic model by Thomas et al (2006), according to which, the probability of major complications was 2.1%, while the probability of minor complications was 27.3%. Major complications included a combination of myelopathy, vertebral fracture and neurodeficit while minor complications included a combination of nausea, bone pain, diarrhoea or esophagitis. The total cost of RT per patient, including both administration of RT and treatment of major and minor complications, was £1,276.50.

The categories of costs considered in the costing of surgeries (i.e. major surgery and vertebroplasty) were as follows: transfer costs, cost of CT-guided biopsy, pre- and post-operative visits by the surgeon and the anaesthetist, theatre use and staff time during the procedure, consumables (i.e. implant costs, blood transfusions and anaesthetics) and LOS. The measurement of the resources consumed for surgical procedures was based, whenever possible, on the data from an audit conducted at the Royal Orthopaedic Hospital (ROH) in Birmingham, which included 56 MSEC patients who underwent these surgical procedures at ROH between June 2006 and October 2007. The audit provided resource consumption related to surgical costs and consumables mainly (i.e. transfer costs, cost of CT-guided biopsy, theatre time, implant costs and LOS). The number and specialisation of the surgical staff involved in the surgical procedures was identified by personal communication with the GDG members, and included: a surgeon, an assistant registrar, an anaesthetist, an anaesthetist SpR, an anaesthetist's assistant, a scrub nurse, an off-table nurse and an auxiliary. The average surgical cost per patient undergoing vertebroplasty was £9,350 while that for a patient undergoing major surgery was £13,094.

In relation to the post-treatment, follow-up care, there is not clear pattern of care for MSEC patients after treatment. It was common belief among the GDG members that patients ambulant after treatment are most likely to be discharged home, and this was confirmed by the ROH audit (with around 85% of patients ambulant post-treatment being discharged home after surgical treatment). On the other hand, patients non-ambulant after treatment are likely to be cared at home if the family can fill in the gaps in between the community care visits, otherwise it is likely that, if the patients are bed-bound, they will be institutionalised in a nursing care home (if beds are available), otherwise they may remain in hospital (often in an acute bed if non-acute facilities are scarce in the area) until they die. Based on this, it was assumed that all patients ambulant after treatment were discharged home, and the type of care received included community nurse visits, access to the GP and out-of-hours services, and rehabilitation. On the other hand, patients non-ambulant after treatment were assumed to be discharged either home or to a nursing care home (50/50 respectively, taken as an arbitrary value since no information was available to inform this proportion). The type of care received by post-treatment non-ambulant patients discharged home included community nurse visits, care from the social services, and access to the GP and out-of-hours services. The total daily cost per patient cared at home was £13 if the patient was ambulant and £193 if the patient was non-ambulant. The daily cost for being cared at a nursing home was £81.

The cost of eventual care during the last weeks of life was assumed to depend on whether the patient was cared at home, or at a nursing care home. Following previous assumptions, patients that were ambulant after treatment were assumed to be cared at home until the end of their lives, while it was assumed that half of the non-ambulant patients were cared at home, and the other half at a nursing care home during the last

weeks of their life until they died. The amount of time corresponding to end of life care was assumed to be the last two weeks of life. The average daily cost per patient for the end of life care was £274 if cared at home, and £81 if cared at the nursing care home.

Table 11. Cost estimation of MSCC treatments and subsequent follow-up care

	Resource use	Unit costs (£2006/07)	Estimated cost per patient (£2006/07)	Source
	Mean (95% CI)	Mean	Mean (range)	
RT:				
Fractions	250	5	1250	University Hospital Birmingham 2007
Major complications	0.021	605.47	13	Thomas et al 2006; OECD PPP
Minor complications	0.273	50.48	14	Thomas et al 2006; OECD PPP
Vertebroplasty:				
Transfer rates	0.5	257	129	ROH audit, PSSRU 2007
Pre- and post-operative visits: surgeon	2	77.5	155	Expert opinion, PSSRU 2008
Pre- and post-operative visits: anaesthetist	2	58.125	116	Expert opinion, PSSRU 2009
CT-guided biopsy	0	864	0	ROH audit
Theatre time per patient (hours)	2.72 (1.93, 3.50)	79.27	215	ROH audit, Rivero-Arias et al 2005
Theatre personnel*	-	-	2547	Expert opinion, ROH audit, PSSRU 2007
Anaesthetics*	-	-	25	ROH audit, Rivero-Arias et al 2005
Implants	-	-	2696	ROH audit
Blood transfusions (units of red cell)	3	127.61	383	Expert opinion; Blood & Components price list 2004/5, PSSRU 2007 to update to 2006/2007
LOS in HDU [†]	1	900	900	Expert opinion, PSSRU 2008
LOS in acute bed [†]	8.27	264	2184	Expert opinion, ROH audit, PSSRU 2007
Total cost of surgery			9350	
Major surgery:				
Transfer rate	0.5294	257	136	ROH audit, PSSRU 2007
Pre- and post-operative visits: surgeon	2	77.5	155	Expert opinion, PSSRU 2008
Pre- and post-operative visits: anaesthetist	2	58.125	116	Expert opinion, PSSRU 2009
CT-guided biopsy	0.3	864	259	ROH audit
Theatre time per patient (hours)	4.11 (3.61, 4.60)	79.27	326	ROH audit, Rivero-Arias et al 2005

Theatre personnel*	-	-	3852	Expert opinion, ROH audit, PSSRU 2007
Anaesthetics*	-	-	38	ROH audit, Rivero-Arias et al 2005
Implants	-	-	3311	ROH audit
Blood transfusions (units of red cell)	3	127.61	383	Expert opinion; Blood & Components price list 2004/5, PSSRU 2007 to update to 2006/2007
LOS in HDU†	1	900	900	Expert opinion, PSSRU 2008
LOS in acute bed†	13.71	264	3619	Expert opinion, ROH audit, PSSRU 2007
Total cost of surgery			13094	
Home care:				
Daily home care costs per ambulant patient	-	-	13	Expert opinion for quantities used; PSSRU 2007 costs for unit costs per hour
Daily home care costs per non-ambulant patient	-	-	193	Expert opinion for quantities used; PSSRU 2007 costs for unit costs per hour
Nursing care home:				
Daily care per patient	-	-	81	www.jrf.org.uk/knowledge/findings/socialcare/612.asp
Care during the last weeks of life				
Daily cost per patient cared at home			274	Expert opinion for quantities used; PSSRU 2007 costs for unit costs per hour
Daily cost per patient cared at nursing care home			81	www.jrf.org.uk/knowledge/findings/socialcare/612.asp

* Based on average time spent at the surgical theatre

† From the total LOS, it was assumed that one day was spent at the HDU and the rest in acute bed

Clinical evidence and assumptions related to the effectiveness of the alternative treatments and the resulting quality of life

In order to be able to estimate the average cost per patient incurred with each of the alternative treatments mentioned above (RT, vertebroplasty, major surgery, or no treatment) it was necessary to identify some initial clinical data in terms of the successful rates of the different options to keep patients ambulant after treatment, and in terms of the survival of patients depending on whether they were ambulant or non-ambulant after treatment. This allowed a more accurate allocation of the different health care costs according to the survival of patients and the different intensities of care required because of their functional status. An initial analysis was undertaken, which was based on what has been called here the 'ideal scenario'. This 'ideal scenario' aimed to reflect a situation where the different treatments would lead to the most favourable outcomes after treatment (in terms of ambulation rates after treatment and time retaining ability to walk). From there, the values for the clinical parameters could be changed to identify how effective the different types of treatments should be in improving ambulation, survival and quality of life by preventing paraplegia in MSCC patients in order to make those treatments cost-effective.

Based on expert opinion, it was assumed that all the patients were ambulant at presentation. In the 'ideal scenario' the success rate of treatment (RT, vertebroplasty and of major surgery), in terms of the number of patients ambulant after treatment, was assumed to be 100%. All patients ambulant after treatment were assumed to remain ambulant during their entire survival, independently of the treatment received. Patients not receiving any treatment were assumed to become paraplegic within 24 hours. This was because treatment is usually conducted on the brink of paraplegia, although the clinical belief is that if treatment could be conducted before paraplegia occurs, there would be costs avoided by preventing some patients becoming paraplegic. In this situation, the health benefits for the patients would improve because the life expectancy and the quality of life are better for ambulant patients versus those non-ambulant. In terms of the procedure-related mortality rates, under the initial, ideal scenario it was assumed that there would be no deaths due to the different treatments undergone. This is actually not a realistic assumption and was therefore tested in further analysis by substituting the assumption with published clinical evidence. The information on mean survivals reported in the study by Thomas et al (2006) was used to identify survival for patients ambulant and non-ambulant after treatment. In this study, which was based on the RCT by Patchell et al (2005), the mean survival per patient was 351.96 days (i.e. 11.57 months) for patients undergoing surgery plus RT and 216.86 days (7.13 months) for patients undergoing RT alone. According to expert opinion, all groups can be regarded for this initial analysis as surviving for a similar time, regardless of the treatment received (since survival is determined by histology rather than intervention) and whether they were ambulant or not after treatment, and it was assumed to be equal to 11.57 months (Thomas et al 2006). No studies were found that reported specific average survival for patients non-ambulant after major surgery. However, following recommendations of the GDG members, the survival of patients non-ambulant after treatment or after doing nothing can be considered as similar to that of the ambulant patients since it was highlighted that, in general terms, treatment improves ambulation rates while survival may remain the same. Mean time to paraplegia and mean survivals rather than medians were used in the analysis since "the decision about whether an intervention is cost-effective is made on the basis of the expected costs and effects at the population level" (Griffin et al 2006). The values of the clinical parameters and assumptions made for the initial, ideal scenario have been presented in Table 12.

Table 12. Values of the clinical parameters used in the analysis

Parameter	Ideal scenario	Scenario 2: Sensitivity	Sources
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analysis			
Procedure-related mortality rate			
After vertebroplasty	0	0.05	Assumption / Assumption
After major surgeries	0	0.05	Assumption / Witham 2005
After RT	0	0	Assumption / Assumption
Post-treatment ambulant status			
Proportion of ambulant patients after vertebroplasty	1	0.94	Assumption / Assumption
Proportion of ambulant patients after major surgeries	1	0.94	Assumption / Patchell 2005
Proportion of ambulant patients after RT	1	0.74	Assumption / Patchell 2005
Time to paraplegia for post-treatment ambulant patients (in months)			
After vertebroplasty	11.57	7.26	Assumption / Assumption
After major surgeries	11.57	7.26	Assumption / Patchell 2005
After RT	11.57	2.56	Assumption / Patchell 2005
After doing nothing	0.00	0.00	Assumption / Assumption
Survival for post-treatment ambulant patients (in months)			
After vertebroplasty	11.57	11.57	Assumption / Assumption
After major surgeries	11.57	11.57	Thomas 2006 / Thomas 2006
After RT	11.57	7.13	Assumption / Thomas 2006
Survival for non-ambulant patients (in months)			
After vertebroplasty	11.57	11.57	Assumption / Assumption
After major surgeries	11.57	11.57	Thomas 2006 / Thomas 2006
After RT	11.57	7.13	Assumption / Thomas 2006
After doing nothing – compared to vertebroplasty	11.57	11.57	Assumption / Assumption
After doing nothing – compared to major surgery	11.57	11.57	Assumption / Assumption
After doing nothing – compared to RT	11.57	7.13	Assumption / Assumption

Regarding the utility weights to use in the analysis in order to estimate QALYs, one study was found that assessed the health-related quality of life of patients with MSCC that underwent surgery (Falicov et al 2006). The results of this study showed that at 1 year after MSCC surgical intervention, the two most common utility values reported by patients were 0.1 and 0.7. Although there was no evidence in the paper to make any reliable interpretation about the type of patients that would be reporting such values, a possible interpretation could be that these values are representative of two big groups of patients:

1. Patients that are at the end of life after 1 year, and that are at that stage where they are not getting almost utility from being alive given the important deterioration of their quality of life; a value of 0.1 (as the one reported in the paper) could be representative of this health state.
2. The other most commonly reported utility value at 1 year was 0.7, which may be representative of a group of patients with a more or less good prognosis and who do not present many limitations in their functional status.

Based on this interpretation, the previous values were used for the analysis in the following terms: a utility of 0.7 was assigned to those patients ambulant after treatment while a utility of 0.1 was assigned to the non-ambulant patients and to patients at the end of life (i.e. 2 last weeks of life). From the Cost-Effectiveness Analysis (CEA) Registry (<https://research.tufts-nemc.org/cear/default.aspx>), which provides public electronic access to a comprehensive database of cost-effectiveness ratios in the published medical literature, some other utility weights were found in relation to MSCC patients (Hollingworth et al 2003; Hillner et al 2000; Blackmore et al 1999). The limitation with these utility weights is that they have not been reported according to the

functional status of the patients and were not specific for the type of MSCC treatments considered in this analysis.

Structure of the model

A model was developed in Excel to combine the effectiveness and cost data previously described and to conduct all the required calculations and threshold analyses.

According to the model structure followed (see

Figure 2), ambulant patients presenting to the health care centre may be potential candidates for RT, vertebroplasty or major surgery. The alternatives compared are treatment versus no treatment. If patients received appropriate MSCC treatment (i.e. vertebroplasty with RT, major surgery with RT or RT alone), there is a procedure-mortality risk associated. Patients surviving vertebroplasty, major surgery or RT may end up being either ambulant or non-ambulant after treatment and the success of the different treatments will determine how many patients avoid becoming paraplegic. Different successful rates were considered for each treatment (in terms of patients ambulant versus non-ambulant afterwards and in terms of the proportions of patients retaining their ability to walk), and different average survivals as well, depending on whether patients were ambulant or not after treatment. Each of these potential treatments was compared to the no treatment alternative, which comprised only one branch since, as it was assumed in the analysis, all patients ambulant at presentation who were not treated became paraplegic immediately. The model considered a lifetime horizon.

Cost-effectiveness comparisons

The treatments assessed in this study were not options for all types of MSCC patients since the decision about what treatment modality is adequate will depend on the patient's clinical characteristics (e.g. whether MSCC has already developed, whether there is neurological compromise, pain, or whether tumours are radiosensitive or not). Based on this, three independent cost-effectiveness assessments were conducted, each of them referring to a particular intervention appropriate for a specific sub-group of MSCC patients:

1. RT versus no treatment
2. Vertebroplasty in combination with RT versus no treatment
3. Major/complex surgery in combination with RT versus no treatment

ICERs were calculated for these three sets of comparisons for those cases in which the treatment considered was more effective and, at the same time, more costly than no treatment. Once the ICERs were calculated, threshold analyses were conducted on each of the relevant parameters or set of parameters to identify the values at which each of the treatments (i.e. RT, vertebroplasty or major surgery) would result in an incremental cost per QALY equal or lower than £20,000 versus £30,000 or higher since, following NICE's thresholds for cost-effectiveness interventions, an ICER lower than £20,000 would ensure MSCC treatments to be accepted as cost-effective while ICERs between £20,000 and £30,000 would require strong reasons to consider the interventions cost-effective (Social Value Judgements 2007; document currently under consultation). Estimated health benefits and costs were not discounted since average survival for MSCC patients is short, i.e. around 1 year, and therefore, discounting was considered to be irrelevant for this analysis.

Sensitivity analysis

Some of the assumptions made in the initial, ideal scenario may not reflect accurately the clinical reality of the treatment and prognosis for MSCC patients since such an ideal situation has not been achieved yet in clinical practice. Therefore, alternative scenarios were further considered by modifying some of the relevant assumptions in an attempt to create a more realistic scenario from which to develop further threshold analyses to identify again values of the parameters, under these new, more realistic circumstances, which would lead to the different treatments being cost-effective when compared to no treatment.

Scenario 2:

In this scenario, it was considered that procedure-related mortality could occur. A 5% mortality rate was considered for major surgery (as reported by the study by Witham et al 2006). The same mortality rate was assumed for vertebroplasty, and patients

undergoing RT were considered not to die from RT treatment. Survival for patients dying because of the surgery was assumed to be null (i.e. in the case of surgical treatment patients would die intra-operatively due to procedure-related complications). The success rate of major surgery to retain the ability to walk of initially ambulant patients was 94.12%, and the same rate was assumed for vertebroplasty; for RT, the rate of patients ambulant after treatment was assumed to be 74.3% (Patchell et al 2005). Patients ambulant after treatment were assumed to become paraplegic sometime before dying. As it was reported in the RCT by Patchell et al (2005), patients initially ambulant that underwent surgery retained their ability to walk, on median, 153 days (or 220.73 days, on average, following the adjustments proposed by Griffin et al 2006 to convert medians to means). On the other hand, patients initially ambulant that underwent RT retained their ability to walk, on median, 54 days (or 77.91 days on average). Given these circumstances, the daily cost of home care for post-treatment ambulant patients was £13 during the period they retained their ability to walk, although this cost increased to £192 once patients became paraplegic.

Survival for patients undergoing surgery remained the same as for the initial, ideal scenario (i.e. 11.57 months) although in this second, more realistic scenario, patients ambulant after RT alone were considered to survive shorter than under the ideal scenario and, on average, 7.13 months (Thomas et al 2006). Survival for non-treated patients was assumed to be 11.57 months for comparisons with patients undergoing major surgery or vertebroplasty, and 7.13 months for comparisons with patients undergoing RT. For the threshold analyses on survival times, it was necessary to modify jointly survival and time to paraplegia; to do this, the time to paraplegia was assumed to be a proportion of the total survival for ambulant patients. For example, in the case of major surgery, time to paraplegia was 7.26 months, which represented the 63% of the total survival; then, when survival for ambulant patients after major surgery was modified, the time to paraplegia was always considered to be 63% of the average survival. The rest of the parameter values remained the same as for the ideal scenario (see Table 12).

Results

RT versus no treatment

The results of the analysis based on the 'ideal scenario' showed that no treatment at all would result in higher average costs per patient (£48,673), similar survival (11.57 months) and lower number of QALYs gained (0.10 QALYs) when compared to RT alone (which would cost £9,390 per patient, and would obtain 11.57 months of survival and 0.67 QALYs per patient). Due to the assumptions made in this ideal scenario (i.e. the patient retained her ability to remain ambulant during her entire survival), on average, patients treated with RT remained ambulant 11.57 months, while those not receiving treatment became immediately paraplegic. Therefore, no treatment was a strategy dominated by RT alone under the conditions presented in the ideal scenario.

Table 13. Cost-effectiveness results for the ideal scenario and for scenario 2 when RT was compared to no treatment

	Average cost per patient	Average survival per patient	Average time ambulant per patient	Average QALYs per patient	ICER: Δ Cost per QALY
Ideal scenario					
RT alone	9390	11.57	11.57	0.67	Dominant
No treatment	48673	11.57	0.00	0.10	-
Scenario 2					

RT alone	30523	7.13	1.90	0.15	3309
No treatment	30208	7.13	0.00	0.06	-

Table 14 below reports the results of the threshold analyses conducted to identify the extreme values of some of the relevant parameters at which the ICERs would be either lower than £20,000, between £20,000 and £30,000 or higher than £30,000. Under the circumstances presented in the ideal scenario (and assuming that the rest of parameters remained unchanged), RT would result in an ICER lower than £20,000 in the following situations: when the percentage of patients ambulant after treatment was higher than 2.45%; when the average survival for all patients was at least 0.92 months (by considering that survival and time to paraplegia were varied together and the same value was allocated to both of them); and when the time to paraplegia for patients ambulant after RT (when modified independently) was, at least, 3.33 months. On the other hand, uncertainty would exist when: the percentage of patients ambulant after RT ranged between 2.20% and 2.45%; when the average survival per patient (when modified jointly with time to paraplegia for those patients ambulant after RT) was between 0.83 and 0.92 months; and when time to paraplegia for patients ambulant after RT alone (assuming the initial value for survival did not vary, i.e. it was 11.57 months) was between 3.1 months and 3.33 months. Under these circumstances, the ICER related to RT compared to no treatment would range between £20,000 and £30,000, which would mean that strong reasons should exist to recommend RT as a cost-effective option. For lower values of these parameters, the ICER would be higher than £30,000 per QALY gained, which is generally considered as not to be cost-effective.

Table 14. Threshold analysis to identify extreme values of parameters that make the ICER for RT cost-effective (i.e. < £20,000), with questionable cost-effectiveness (i.e. £20,000-£30,000), or no cost-effective (i.e. > £30,000) when compared to no treatment under the ideal scenario and under scenario 2

	ICER ≤ £20,000	ICER: £20,000- £30,000	ICER ≥ £30,000
Ideal scenario			
Proportion of ambulatory patients	≥ 0.0245	0.0220-0.0245	≤ 0.0220
Survival for post-treatment patients (in months, modifying jointly time to paraplegia)	≥ 0.92	0.83-0.92	≤ 0.83
Time to paraplegia for post-treatment ambulant patients (in months)	≥ 3.33	3.09-3.33	≤ 3.09
Survival for non-ambulant patients (in months) as a proportion of the ambulant (Scenario 3)	SNF	SNF	SNF
Scenario 2			
Proportion of ambulatory patients	≥ 0.3311	0.2485-0.3311	≤ 0.2485
Survival for post-treatment patients (in months, modifying jointly time to paraplegia)	≥ 3.69	2.86-3.69	≤ 2.86
Time to paraplegia for post-treatment ambulant patients (in months)	≥ 2.23	2.07-2.23	≤ 2.07
Survival for non-ambulant patients (in months) as a proportion of the ambulant (Scenario 3)	≥ 6.59	6.25-6.59	≤ 6.25
Daily costs of home care for non-ambulant patients (£)	≤ 284	284-338	≥ 338
Costs of treatment (£)	≤ 2864	2864-3816	≥ 3816

SNF = Solution not found

When scenario 2 was assessed (which was considered to be more realistic than the ideal scenario), RT lost its condition of dominant strategy since it became more expensive than no treatment (£30,523 per patient for RT versus £30,208 per patient for no treatment), although it would still be more effective in terms of time to paraplegia and number of QALYs gained (not in terms of survival since one of the basic assumptions was that survival would be the same, independently of whether treatment was

administered or not). Under scenario 2, patients would survive, on average, 7.13 months and they would maintain their ability to walk during only 1.9 months, on average, while the number of QALYs achieved would be 0.15 with RT compared to 0.06 with no treatment (see Table 13). Under this scenario, the incremental cost per additional QALY gained with RT, when compared to no treatment, under this scenario, was £3,309. The results of the threshold analysis showed that small variations in the modified variables had a considerable impact on the cost-effectiveness of RT (see Table 14). For example, if average patient survival was higher than 3.69 months, then the ICER for RT compared to no treatment would be lower than £20,000, making RT cost-effective according to NICE thresholds. A survival shorter than 2.86 would make the ICER increase over £30,000. When the time to paraplegia for patients ambulant after RT was longer than 2.23 months, the ICER of RT compared to no treatment was lower than £20,000; for values of the time to paraplegia between 2.07 and 2.23 months, the ICER ranged between £20,000 and £30,000; if the time to paraplegia was shorter than 2.07 months, the ICER would exceed £30,000. Therefore, very small variations in the time to paraplegia are going to have a huge impact on the resulting ICER. This may be due to the fact that caring for patients that are ambulant after RT but that become paraplegic at some point after treatment is expensive and would negatively affect the resulting ICER. Therefore, the longer the patients remain ambulant after RT, the more cost-effective RT will be when compared to no treatment. If the survival for non-ambulant patients was varied independently of that for ambulant patients (the later keeping the initial value for this analysis, i.e. 7.13 months), then non-ambulant patients would need to survive at least 6.59 months for RT to have an ICER lower than £20,000 per QALY gained when compared to no treatment; for values between 6.25 and 6.59 months, the ICER will range between £20,000 and £30,000, while if non-ambulant patients survived shorter than 6.25 months, the ICER would be higher than £30,000. Therefore, the longer the survival for non-treated patients, the more cost-effective RT will be due to the fact that caring for a non-ambulant patient is expensive and the differential cost between RT and no treatment will be reduced, reducing therefore the total value of the ICER. A threshold analysis was also conducted on the daily cost of caring at home for a non-ambulant patient: for RT to be cost-effective, the daily cost of home care per patient non-ambulant should be under £287, while any daily cost for the home care of a non-ambulant patient higher than £338 will lead to ICERs over £30,000. In addition, RT would remain cost-effective (with ICER values under £20,000) for a total cost of RT treatment under £2,864, while if this cost is £3,816, then the ICER would exceed £30,000 per QALY gained with RT when compared to no treatment.

Some further sensitivity analyses were conducted. Under the ideal scenario, if all the parameters remained constant but only the utility weights considered for ambulant patients, non-ambulant patients or patients at the end of their life were changed, no value of these utility weights individually would change the condition of dominance of RT over no treatment: individual changes in these parameters would always lead to an ICER below £20,000 when considering the ideal scenario. However, under scenario 2, if the utility value for patients ambulant after RT was 0.20 or lower, then the ICER would increase over £20,000, while if the utility values for non-ambulant patients and those for patients in the end of life were 0.60 or higher, then the ICER would again be £20,000 or higher, which does not seem to reflect a situation that could be realistically found in clinical practice.

Vertebroplasty versus no treatment

When comparisons between vertebroplasty and no treatment were conducted under the base case scenario, vertebroplasty was not only more effective (in terms of patients retaining longer their ability to walk and in terms of more QALYs gained) but it resulted to be a cheaper option when compared to no treatment (£18,622 versus £48,673, respectively). Therefore, vertebroplasty was the dominant strategy (see Table 15 below).

Table 15. Cost-effectiveness results for the ideal scenario and for scenario 2 when vertebroplasty was compared to no treatment

	Average cost per patient	Average survival per patient	Average time ambulant per patient	Average QALYs per patient	ICER: Δ Cost per QALY
Ideal scenario					
Vertebroplasty	18622	11.57	11.57	0.67	Dominant
No treatment	48673	11.57	0.00	0.10	-
Scenario 2					
Vertebroplasty	37749	10.99	6.49	0.42	Dominant
No treatment	48673	11.57	0.00	0.10	-

The results of the threshold analyses when the ideal scenario was considered (see Table 16) showed that the ICER for vertebroplasty when compared to no treatment would be under £20,000 for: ambulation rates after vertebroplasty higher than 18.36% (the higher this proportion, the lower the ICER will be and therefore the more cost-effective vertebroplasty will be when compared to no treatment); for average survivals longer than 2.85 months; for times to paraplegia among patients ambulant after vertebroplasty longer than 4.5 months; and for survivals for non ambulant patients of, at least, 1.14 months. If the proportion of patients that are ambulant after vertebroplasty falls under 16.49%, or the overall survival per patient becomes shorter than 2.58 months, or the time to paraplegia for patients ambulant after vertebroplasty decreases to less than 4.18 months, the ICER will exceed £30,000 per QALY gained. Values for this ICER between £20,000 and £30,000 will be obtained when the proportion of ambulant patients ranges between 16.49% and 18.36%, when the overall survival per patient is between 2.58 and 2.85 months, and when the time retaining the ability to walk for patients ambulant after vertebroplasty ranges between 4.18 months and 4.50 months.

Table 16. Threshold analysis to identify extreme values of parameters that make the ICER for vertebroplasty cost-effective (i.e. < £20,000), with questionable cost-effectiveness (i.e. £20,000-£30,000), or no cost-effective (i.e. > £30,000), compared to no treatment, under the ideal scenario and under scenario 2

	ICER \leq £20,000	ICER: £20,000-£30,000	ICER \geq £30,000
Ideal scenario			
Proportion of ambulatory patients	≥ 0.1836	0.1649-0.1836	≤ 0.1649
Survival for post-treatment patients (in months, modifying jointly time to paraplegia)	≥ 2.85	2.58-2.85	≤ 2.58
Time to paraplegia for post-treatment ambulant patients (in months)	≥ 4.50	4.18-4.50	≤ 4.18
Survival for non-ambulant patients (in months) as a proportion of the ambulant	≥ 1.14	≤ 1.14	SNF
Scenario 2			
Proportion of ambulatory patients	≥ 0.2715	0.2413-0.2715	≤ 0.2413
Survival for post-treatment patients (in months, modifying jointly time to paraplegia)	≥ 4.06	3.63-4.06	≤ 3.63
Time to paraplegia for post-treatment ambulant patients (in months)	≥ 4.27	3.97-4.27	≤ 3.97
Survival for non-ambulant patients (in months) as a proportion of the ambulant (Scenario 3)	≥ 6.98	6.01-6.98	≤ 6.01
Daily costs of home care for non-ambulant patients (£)	SNF	SNF	SNF
Costs of treatment (£)	≤ 26666	26666-29862	≥ 29862

SNF = Solution not found

When scenario 2 was considered, vertebroplasty still retained its condition of dominant strategy, since it was still less costly than no treatment (£37,749 per patient treated with vertebroplasty when compared to £48,673 per patient not treated), and more effective in terms of time to paraplegia and number of QALYs gained, although not in terms of survival (the average survival resulted to be longer for non-treated patients due to the mortality rate associated to the vertebroplasty procedure). Under scenario 2, patients would survive, on average, 10.99 months if treated with vertebroplasty, and 11.57 months if not treated. This result is an artefact of the assumption considered in the model about equal survival for patients treated and non-treated, while the procedure-mortality rate would reduce slightly the survival for patients treated. Patients treated with vertebroplasty would retain their ability to walk during 6.49 months, on average, and the additional number of QALYs gained with vertebroplasty when compared to no treatment would be 0.32. The results of the threshold analyses for this scenario 2 showed that vertebroplasty will be cost-effective (with ICERs under £20,000) when: the percentage of patients ambulant after treatment would exceed 27.15%; for overall survival longer than 4.06 months; when the average time that patients ambulant after vertebroplasty retained their ability to walk was longer than 4.27 months; and when the average survival for non-ambulant patients was longer than 6.98 months. For success rates between 24.13% and 27.15%, for overall survivals between 3.63 and 4.06 months, for times to paraplegia for patients ambulant after vertebroplasty ranging between 3.97 and 4.27 months, and for survivals for non-ambulant patients between 6.01 and 6.98 months, the ICER will range between £20,000 and £30,000. Therefore, the higher the success rate for vertebroplasty, the overall survival for patients, the time to paraplegia for patients ambulant after treatment and the specific survival for patients non-ambulant after treatment, the more cost-effective vertebroplasty is. When the success rates for vertebroplasty are under 24.13%, or the overall survival becomes shorter than 3.63 months, or the time to paraplegia becomes shorter than 3.97 months, or the survival for non-ambulant patients decreases to less than 6.01 months, the ICER will be higher than £30,000. Considering variations in the costs of the vertebroplasty procedure only (i.e. cost of the intervention, which was £9,350 under the ideal scenario), any cost of the procedure under £26,666 would make vertebroplasty cost-effective (if all the rest of parameters remained the same), while any cost of the procedure higher than £29,862 would lead to ICER values over £30,000.

In both scenarios, the ideal scenario and scenario 2, the utility weights considered for ambulant patients, non-ambulant patients or patients at the end of their life were changed individually and all the other parameters were left constant (i.e. according to the values chosen for each of the scenarios) to see whether different thresholds for the ICER could be achieved. Overall, no sensible value of these individual utility weights would change the condition of dominance of vertebroplasty over no treatment: individual changes in these parameters would always lead to an ICER below £20,000 per QALY gained.

Major surgery versus no treatment

When comparisons of major surgery versus no treatment were undertaken under the ideal scenario, the overall cost per patient treated with major surgery was £22,299 when compared to £48,673 per non-treated patient. Major surgery resulted in 11.57 months retaining the ability to walk per patient and higher number of QALYs when compared to no treatment (0.67 QALYs versus 0.10 QALYs, respectively; see Table 17 below). Therefore, major surgery was a dominant strategy when compared to no treatment.

Table 17. Cost-effectiveness results for the ideal scenario and for scenario 2 when major surgery was compared to no treatment

	Average cost per patient	Average survival per patient	Average time ambulant per patient	Average QALYs per patient	ICER: Δ Cost per QALY
Ideal scenario					
Major surgery	22299	11.57	11.57	0.67	Dominant
No treatment	48673	11.57	0.00	0.10	-
Scenario 2					
Major surgery	40516	10.99	6.49	0.42	Dominant
No treatment	48673	11.57	0.00	0.10	-

The results of the threshold analyses (see Table 18) showed that, as long as the percentage of patients that will be ambulant after major surgery is higher than 24.57%, the ICER for the ideal scenario will remain under the threshold of £20,000. If this proportion of patients ranged between 22.04% and 24.57%, then the ICER will be within the range of £20,000 and £30,000, and for any value under 22.04%, the ICER will exceed £30,000. As it would be expected, these results show that the higher the successful rate of major surgery in terms of maintaining ambulance status for patients after treatment, the more cost-effective the intervention will be when compared to no treatment. The ICER of major surgery compared to no treatment would be under £20,000 if the overall survival is, at least, 3.62 months; for survivals between 3.28 and 3.62 months, the ICER would be within £20,000 and £30,000, and for survivals shorter than 3.28 months, the ICER would go beyond the threshold of £30,000. Similarly, the longer the time to paraplegia for patients ambulant after major surgery, the more cost-effective this intervention will be when compared to no treatment. When the time to paraplegia for patients ambulant after major surgery is longer than 4.92 months, the ICER will be lower than £20,000; for values of the time to paraplegia between 4.56 and 4.92 months, the ICER will vary between £20,000 and £30,000; and values of time to paraplegia for patients ambulant after treatment shorter than 4.56 months will result in ICERs higher than £30,000. On the other hand, the ICER will remain under £20,000 when the survival for non-ambulant patients (i.e. patients non-ambulant after major surgery and patients no treated) is longer than 2.06 months, while for survivals between 0.38 and 2.06 months for these groups of patients, the ICER will range between £20,000 and £30,000, and for survivals lower than 0.38 months, the ICER will overpass the threshold of £30,000 per QALY gained.

Table 18. Threshold analysis to identify extreme values of parameters that make the ICER for major surgery cost-effective (i.e. < £20,000), with questionable cost-effectiveness (i.e. £20,000-£30,000), or no cost-effective (i.e. > £30,000) under the ideal scenario and under scenario 2

	ICER \leq £20,000	ICER: £20,000-£30,000	ICER \geq £30,000
Ideal scenario			
Proportion of ambulatory patients	≥ 0.2457	0.2204-0.2457	≤ 0.2204
Survival for post-treatment patients (in months, modifying jointly time to paraplegia)	≥ 3.62	3.28-3.62	≤ 3.28
Time to paraplegia for post-treatment ambulant patients (in months)	≥ 4.92	4.56-4.92	≤ 4.56
Survival for non-ambulant patients (in months) as a proportion of the ambulant (Scenario 3)	≥ 2.06	0.38-2.06	≤ 0.38

Scenario 2

Proportion of ambulatory patients	≥ 0.3848	0.3416-0.3848	≤ 0.3416
Survival for post-treatment patients (in months, modifying jointly time to paraplegia)	≥ 5.26	4.70-5.26	≤ 4.70
Time to paraplegia for post-treatment ambulant patients (in months)	≥ 4.75	4.41-4.75	≤ 4.41
Survival for non-ambulant patients (in months) as a proportion of the ambulant	≥ 7.71	6.76-7.71	≤ 6.76
Daily costs of home care for non-ambulant patients (£)	SNF	SNF	SNF
Costs of treatment (£)	≤ 27644	27644-30840	30840

SNF = Solution not found

When scenario 2 was considered, the average cost per patient treated with major surgery was still lower than that incurred by a patient not treated (£40,516 versus £48,673, respectively), while major surgery would still be more effective in terms of time to paraplegia and number of QALYs gained (not in terms of survival due to the assumption of similar survivals for all patients and the procedure-related mortality associated with major surgery). Under scenario 2, patients treated with major surgery would retain their ability to walk during 6.49 months, on average, and the additional number of QALYs gained with major surgery when compared to no treatment would be 0.32. Therefore, major surgery will still maintain its condition of dominance in terms of time ambulant and number of QALYs gained (see Table 17).

The results of the threshold analyses for scenario 2 showed that major surgery would result in an ICER lower than £20,000 if the success rate for major surgery was over 38.48, if the overall patient survival was longer than 5.26 months; if the time to paraplegia for patients ambulant after major surgery was longer than 4.75 months, or if the survival for non-ambulant and non-treated patients was over 7.71 months. On the other hand, an ICER between £20,000 and £30,000 per QALY would be obtained if the success rates for major surgery were between 34.16% and 38.48%; if the overall patient survival was between 4.70 and 5.26 months; if the time to paraplegia for patients ambulant after major surgery was between 4.41 and 4.75 months; or if the specific survival for non-ambulant and non-treated patients was between 6.76 and 7.71 months. When the success rate of major surgery was lower than 34.16%, or the overall patient survival was shorter than 4.70 months, or the time to paraplegia for patients ambulant after major surgery was shorter than 4.41, or the survival for non-ambulant and non-treated patients was shorter than 6.76, then the ICERs for major surgery compared to no treatment surpassed the threshold of £30,000. In addition, the cost of the procedure (i.e. major surgery alone) could be as high as £27,644 to make major surgery cost-effective (i.e. with an ICER under £20,000 per QALY), while if this cost was over £30,840, the ICER per QALY would exceed £30,000. When only the utility weights considered for ambulant patients, non-ambulant patients or patients at the end of their life were changed individually (and all the other parameters remained constant), no value of these utility weights individually was found that would change the ICER across the different thresholds set by NICE (i.e. lower than £20,000; between £20,000 and £30,000; and higher than £30,000).

Cost-effectiveness analysis of surgery in combination with radiotherapy (SRT) versus radiotherapy alone (RT): update to the Canadian model to the UK setting

Methods

Introduction

There is a group of MSSC patients that are neurologically compromised and have tumours that are not very radiosensitive, for whom it is not clear what the best treatment choice is between the options of RT versus surgery followed by RT. A second analysis was undertaken to assess the cost-effectiveness of radical surgical procedures in combination with RT (SRT) compared to RT alone (RT) for the treatment of this specific

group of MSSC patients. This analysis consisted of adapting to a UK setting the only economic evaluation available comparing these two interventions for the treatment of MSCC patients (Thomas et al 2006). This economic evaluation had been conducted within a Canadian setting and was based on the only available RCT comparing SRT versus RT (Patchell et al 2005). The aim of our study was to update this Canadian model to reflect the costs that would be incurred if the interventions were conducted in the UK context. For this, the perspective of the National Health Service and the Personal Social Services was adopted.

Patient population and interventions

The patient population considered for this economic evaluation comprises a highly selective group of MSSC patients that are neurologically compromised and have moderately or poorly radiosensitive tumours. Patients with very radiosensitive tumours such as lymphoma, myeloma and germ cell tumours have been excluded from the analysis as surgery in these instances is usually not necessary. The interventions compared in the economic evaluation were: radical surgical decompression in combination with RT (SRT) versus RT alone. As reported in the Canadian paper, 'surgery was performed within 24 h of study entry with the intent to remove as much [tumour] as possible, provide immediate decompression, and stabilise the spine'. A total dose of 30 Gy was administered at 3 Gy per fraction per day. Patients undergoing SRT received RT 2 weeks after surgery (Thomas et al 2006).

Clinical evidence

The clinical evidence in terms of effectiveness of SRT versus RT alone used in the economic evaluation by Thomas et al (2006) was obtained from the RCT published by Patchell et al (2005). The same clinical evidence was considered in the update of the model for the UK setting. The primary endpoint for this RCT was the number of days patients retained their ability to walk after treatment, although survival was assessed as well as a secondary endpoint. For the purpose of our economic evaluation, both time retaining ability to walk and survival were considered as the endpoints for the cost-effectiveness assessment.

In the study by Thomas et al (2006), Weibull curves were estimated from the results of the RCT (Patchell et al 2005) for both endpoints of the analysis: time retaining the ability to walk and survival, and for each of the treatments assessed (SRT versus RT), the resulting expected days of ambulation and survival have been presented in Table 19 below. These values were used as input parameters and endpoints for the model estimating the cost-effectiveness of SRT versus RT in the UK context. Additionally, an attempt was made to estimate the number of QALYs gained with each intervention by using the same utility scores as those used in the previous model (i.e. 0.7 for ambulant patients, and 0.1 for non-ambulant patients).

Table 19. Estimated clinical outcomes from Weibull curves

Clinical outcomes	RT alone	SRT
Expected days of survival (mean)	221.11	377.06
Expected days of ambulation (mean)	92.36	312.47

Source: Thomas et al (2006)

Cost analysis

The perspective adopted for the analysis was that of the NHS and Personal Social Services. The price year was 2006-2007. The aggregated categories of costs included in the analysis were: the costs of treatment with SRT, the cost of treatment with RT and the post-treatment costs of caring for patients until they die. These costs were directly derived from the cost analysis conducted in the previous economic analysis. Based on

that cost analysis, the average cost per patient undergoing surgery was £13,094 and the average total cost per treatment with RT was £1,276.50. Although the model by Thomas et al (2006) included the costs of diagnosing MSCC patients, this cost was excluded from the UK update since it was considered to be the same across both groups of patients (SRT versus RT alone). For the purposes of this analysis, the LOS was obtained from the ROH data rather than from the RCT by Patchell et al (2005) to reflect clinical practice in the UK context (see Table 11). Similar assumptions to those formulated in the previous economic analysis were considered for this economic evaluation. For example, it was assumed that patients ambulant would be cared at home, at a cost of £13 per day, while patients non-ambulant would be either cared at home or at a nursing care home (50/50 arbitrarily assumed), depending on whether the family could care for the patient in between community visits. The daily cost for being cared at home when non-ambulant was £193 (ROH audit; NHS Reference Costs 2006/07) and £81 if cared at the nursing home (Joseph Rowntree Foundation). Additionally, the period of end of life corresponded to the last 2 weeks lived by the patient. For the last weeks of life it was arbitrary assumed (as it had been done in the previous analysis) that 50% of patients could be cared at home, at a daily cost of £274, otherwise they had to be cared at the nursing care home (again at a cost of £81 per day).

Cost-effectiveness comparisons

The results of the economic evaluation are presented as average costs, average time retaining the ability to walk and average survival per patient, following what had been done in the Canadian model (Thomas et al 2006). When applicable (i.e. when one of the treatment strategies was more effective and at the same time more costly than the other), ICERs were estimated. In addition, based on the estimation of the number of QALYs gained following what had been done in the previous model, the incremental cost per QALY gained was also estimated when applicable. It is important to highlight that this was just an attempt to capture QALY gains with SRT and RT, given the limitations presented by the utility scores used. Discounting of health benefits and costs was not necessary given the short survival of these MSCC patients.

Sensitivity analysis

Deterministic one-way and two-way sensitivity analyses were conducted to assess the robustness of the results, which means the values of one or two variables were modified at a time to see if the conclusions of the cost-effectiveness assessment would change when different values of the relevant parameters were considered at analysis. An approximate 95% confidence interval for the average cost of surgery (95% CI: 12,143, 14,048) was obtained from the ROH audit data and this interval was used as the range of plausible values to consider in the sensitivity analysis. In addition, the cost of MSCC surgery obtained from the Payment by Results (PbR) National Tariffs was also taken into account to see how the results obtained for the base-case analysis changed. Two-way sensitivity analyses were conducted on the average survival and the average time ambulant by considering the 25th and 75th percentiles of the means (Thomas et al 2006). The percentage of patients discharged to a rehabilitation care unit after SRT was considered to be 12.5% in a one-way sensitivity analysis. The 95% CI for the LOS was used to assess the impact that modifications on the values of this variable had on the results. In addition, the daily cost of caring at home for a patient non-ambulant after treatment with RT or with SRT was modified upwards and downwards by 25% to see the impact of this change on the final results. Finally, the daily post-hospitalisation care cost for patients treated with either SRT or RT were varied by 25%. Additionally, a threshold analysis was conducted to identify the values of the utility scores that would make SRT either cost-effective (i.e. with an ICER of £20,000 or lower per QALY gained), with questionable cost-effectiveness (with an ICER between £20,000 and

£30,000 per QALY gained) or very unlikely to be considered cost-effective at all (i.e. when the ICER was over £30,000 per QALY gained) when compared to RT alone.

Results

The results of the base-case analysis showed that patients treated with SRT would retain their ability to walk for 220 days more when compared to those treated only with RT, while the difference in survival in favour of the SRT group would be of 156 days. The average cost per patient treated with SRT was £27,536, compared to £20,611 in the case of patients treated with RT alone (the costs per category have been presented in Table 20). This small difference in costs is believed to be due to the fact that, although the administration of RT by itself is less expensive than the specific cost of surgery, patients treated with RT will become paraplegic earlier and the costs of caring for a non-ambulant patient are more than twice higher than those of caring for an ambulant patient, which is finally reflected in the total cost for the RT alone strategy. Each additional day of ambulation obtained by SRT would cost an extra £31.46 when compared to RT alone, while each additional life year gained with SRT would cost £16,207 extra.

Table 20. Baseline results

Baseline results*	SRT	RT
Surgery costs/hospitalisation costs	13,096	0
RT costs	1,276	1,276
Post-hospitalisation costs	13,164	19,335
Total cost	27,536	20,611
Days ambulant	312.47	92.36
Survival	377.06	221.11
QALYs	0.62	0.21
Δ Cost	6,925	-
Δ Effectiveness - Days ambulant	220.11	-
Δ Effectiveness - Survival	155.95	-
Δ Effectiveness – QALYs	0.41	-
ICER - Days ambulant	31.46	-
ICER - Survival (per day)	44.40	-
ICER - Survival (per year)	16,207	-
ICER – QALYs	17,117	-

*Comparisons between SRT and RT
Costs in UK£ 2006/07

A summary table with the resulting ICERs obtained from the one-way and two-way sensitivity analyses undertaken has been presented (see Table 21). The results for the incremental cost per life year gained with SRT compared to RT were under £10,000 when: the cost of surgery was that of the PbRs National Tariffs; non-ambulant patients that could not be cared at home were assumed to remain in the hospital rather than to be cared at a nursing care home; the daily cost of care for a patient after being treated with RT alone increased by 25%; and when the daily cost of care for a patient after being treated with SRT decreased by 25%. On the other hand, ICERs per life year gained over £20,000 were observed for the following scenarios: when the daily cost of care for a patient after being treated with SRT increased by 25%, when the survival and the ambulation time for patients treated with SRT was considered to be equal to the 25th lower percentile; and when the daily cost of care for a patient after being treated with RT alone decreased by 25% (this latter case presented the highest ICER observed in the analysis: £27,520 per additional life year gained with SRT when compared to RT alone).

Table 21. Incremental cost per life year gained: results from the baseline and the sensitivity analyses

Parameters modified	ICER
Baseline Results	16207

One-way sensitivity analysis: surgery -- 95% CI upper	18437
One-way sensitivity analysis: surgery -- 95% CI lower	13977
One-way sensitivity analysis: surgery -- PbR National Tariff for non-elective intervention	1903
One-way sensitivity analysis: patients cared at hospital rather than at nursing care unit	2434
One-way sensitivity analysis: 12.5% of patients cared at rehab care unit included for surgery	18054
One-way sensitivity analysis: LOS--upper 95% CI	17819
One-way sensitivity analysis: LOS--lower 95% CI	14595
One-way sensitivity analysis: daily cost for non-ambulant at home + 25%	12588
One-way sensitivity analysis: daily cost for non-ambulant at home - 25%	19826
Two-way sensitivity analysis: RT:surv/amb lower/p25	13570
Two-way sensitivity analysis: RT: surv/amb upper/p75	18645
Two-way sensitivity analysis: SRT:surv/amb lower/p25	25354
Two-way sensitivity analysis: SRT: surv/amb upper/p75	12925
PH Daily costs for SRT: +25%	23910
PH Daily costs for SRT: -25%	8505
PH Daily costs for RT: +25%	4894
PH Daily costs for RT: -25%	27520

However, the cost per life year gained is difficult to interpret since there is not a threshold identified as cost-effective, as it is the case with the incremental cost per life year gained. Therefore, an attempt was made to estimate the number of QALYs gained with SRT compared to RT alone. When the number of QALYs were estimated based on the utility scores used for the previous model (i.e. 0.7 for ambulant patients and 0.1 for non-ambulant patients) the number of QALYs obtained per patient undergoing SRT were 0.62 compared to 0.21 QALYs obtained by patients with RT alone; therefore, the incremental QALY gained with SRT, compared to RT alone, was 0.41 and the incremental cost per each additional QALY gained with SRT compared to RT alone was £17,117, which was under the threshold identified by NICE for cost-effective interventions (i.e. £20,000 per QALY gained).

Threshold analysis were carried out to identify the values of the utility scores that would make SRT either cost-effective (i.e. with an ICER of £20,000 or lower per QALY gained), with questionable cost-effectiveness (with an ICER between £20,000 and £30,000 per QALY gained) or very unlikely to be cost-effective at all (i.e. when the ICER was over £30,000 per QALY gained) when compared to RT alone (see Table 22). When the utility score for ambulant patients was left fixed to a value equal to 0.7, the utility for non-ambulant patients had to be 0.43 or lower so that SRT remained cost-effective, i.e. the ICER obtained per QALY gained remained lower than £20,000. There was not value found for the utility score of non-ambulant patients that would lead to an ICER higher than £30,000 if the utility score for ambulant patients was 0.7. On the other hand, when the utility score for non-ambulant patients was left fixed to a value equal to 0.1, the utility score for ambulant patients had to be at least 0.60 or higher so that SRT remained cost-effective, i.e. the ICER obtained per QALY gained remained lower than £20,000 when the utility score for ambulant patients was 0.60 or more, or lower than £30,000 if this utility was 0.41 or higher.

Table 22. Threshold analysis to identify the extreme values of the utility scores that would make the ICER for SRT cost-effective (i.e. < £20,000), with questionable cost-effectiveness (i.e. £20,000-£30,000), or no cost-effective (i.e. > £30,000) when compared to RT alone

Utility values		ICER: Δ cost / Δ QALYs
Ambulant	Non-ambulant	
Base-case:		
0.7	0.1	17,117
Threshold analyses:		
0.7	≥ 0.4317	≥ 20000
≤ 0.6033	0.1	≥ 20000
0.7	SNF	≥ 30000
≤ 0.4119	0.1	≥ 30000

SNF = Solution not found

Discussion

Two economic analyses were undertaken in an attempt to shed light about what type of treatments are cost-effective for MSCC patients when compared to either no treatment (which was the aim of the first analysis and focused on comparing RT versus no treatment, vertebroplasty versus no treatment and major surgery versus no treatment), or when two alternative treatments were compared (which was the purpose of the second analysis and compared SRT with RT).

The first analysis identified under what conditions (in terms of rates of success of surgery, time of ambulation, survival and quality of life) vertebroplasty, major surgery or RT would become cost-effective when compared to no treatment. The aim of the analysis was to assess at what point these different interventions would be cost-effective at keeping patients ambulant when compared to no treatment at all: if MSCC patients are left without treatment, they will become paraplegic; then the purpose of the analysis was to identify how long patients would have to survive and to remain ambulant in order to make the treatments worthwhile. Treatment selection was taken out of the economic evaluation by considering that the surgeons would follow the Tokuhashi scores (Tokuhashi et al 2005) for the selection of the appropriate treatment according to the patient's clinical status. This meant that, for this first analysis, not all the treatments were alternative options for all the MSCC patients and the decision about what treatment modality was adequate for an MSCC patient was assumed to depend on the patient's clinical characteristics (e.g. whether there is neurological compromise, pain, or whether tumours are radiosensitive or not). Therefore, each assessed treatment was a stand alone intervention in the sense that a specific type of patient could get either a specific type of treatment (lets say RT alone) or no treatment at all, but there was not the option to compare different types of treatments for the same patient. The costs of each treatment and the corresponding follow-up care were compared to the costs of caring for untreated MSCC patients who develop paraplegia, and threshold analysis were conducted to identify extreme values for the ICERs.

It was observed that under the base-case scenario, all three treatments (each for a particular type of MSCC patient) resulted to be dominant interventions (they resulted in higher number of QALYs at a lower cost) when compared to no treatment. Under scenario 2, which was thought to be more realistic (since it included procedure-related mortality and the surgical and RT success rates for patients remaining ambulant after treatment), RT lost its condition of dominant strategy and presented an incremental cost per additional QALY gained equal to £3,309 when compared to no treatment; this is identified as being cost-effective following NICE's thresholds. For all the comparisons between treatments and no treatment, it was observed that any of these treatments would be more cost-effective in the following situations: the higher the success rate in

terms of the percentage of ambulant patients after treatment, the longer the overall survival for patients, the longer the patients remained ambulant after treatment, and the longer the specific survival was for patients non-ambulant after treatment and for those patients non-treated. In some cases very small variations in the values considered for some of the variables modified in the threshold analysis made a considerable impact on the cost-effectiveness of the treatments, passing from thresholds of £20,000 to thresholds of £30,000 per QALY gained without too much variation in the value of the parameter, for example, for small changes in the overall survival post-treatment, and for small changes in the time to paraplegia for patients ambulant after treatment. Based on the assumptions presented under scenario 2 (the scenario considered to be more realistic), patients undergoing major surgery had to survive at least 5.26 months for the ICER to be under the £20,000 per QALY. This seems to be achievable in a UK context. A recently published prospective study conducted in UK (Mannion et al 2008) assessed patients with actual or imminent MSCC that were carefully selected to undergo surgical decompression with fixation, when required, followed by RT, according to the severity of paraparesis, pain, primary tumour and the extent of the disease. According to the results observed, the median survival was 13 months and the percentage of patients ambulant after surgery was 80% (compared to 68% before surgery). Additionally, 50% of the patients initially non-ambulant recovered the ability to walk after surgery (i.e. 10 patients out of 20). The authors of this study concluded that careful patient selection can result in successful outcomes after surgery among this patient population.

An additional finding from the threshold analyses was that the higher the survival for non-ambulant patients (including those patients that did not receive treatment), the more cost-effective MSCC treatments will be, since non-ambulant patients surviving longer would incur in high care costs during their survival, increasing the cost of caring for patients not treated. Therefore, it is important to clearly identify what the most likely value for the survival of non-ambulant patients is in reality to get a more accurate idea of the cost-effectiveness of the MSCC treatments when compared to no treatment.

According to the published evidence, the survival of patients is proportional to diagnosis, general health, and neurological ability (e.g., lung cancer has a worse prognosis compared to that of breast or prostate cancer). The analysis here presented did not consider what happens with the cost-effectiveness of the individual treatments assessed when different types of patients, according to their type of tumour, are the basis for the analysis. Moreover, the analyses are based on a series of assumptions; some of them may reflect the reality better than others. The threshold analyses undertaken were conducted to shed light about the uncertainty surrounding assumptions and data.

Some relevant costs were excluded from the analysis, mainly due to the difficulties to obtain some minimally reliable data to incorporate them:

- Intra-operative and post-operative complications, such as wound breakdown, stabilisation failure, wound infections and excessive haemorrhage, which may occur with major MSCC surgery, while leak seems to be a common complication of vertebroplasty.
- Additional costs associated with procedure-related mortality: it is likely that mortality due to MSCC surgery will incur in high costs before the patient dies. However, the analysis did not consider any additional cost in this kind of situation, but only the normal cost of the procedure.
- Rehabilitation costs for non-ambulant patients have not been included since only very few of them would receive any kind of rehabilitation at home (only those showing clear prospects of regaining control in their lower limbs while in hospital).
- Home adaptation: MSCC patients who become paraplegic are likely to require some home adaptation. For that, community occupational therapists (OTs) may

arrange equipment or modifications to the patient's home in order to increase their independence, safety and quality of life. Between 2 and 3 visits from the OTs will be required, apart from the costs incurred in the equipment and/or modifications (which will differ across patients).

- Reoperation rates: some patients may require secondary surgery after undergoing a major procedure (Schoeggel et al 2002; Sucher et al 1994), and this has not been considered in the cost estimation.

It is important to highlight that the threshold analyses were conducted by modifying one or several variables at a time so that the modifications undertaken were as realistic as possible. For example, for the base-case analysis, which assumed that ambulant patients would remain ambulant their entire survival, modifications of survival for ambulant patients were accompanied for similar modifications in the time to paraplegia in order to keep the assumption stable. In addition, scenario 2 considered that time to paraplegia could vary as a proportion of the overall survival, and the survival for non-ambulant patients could vary as a proportion of that for ambulant patients. Therefore, these variables were modified jointly to identify the values leading to the alternative ICER thresholds (i.e. £20,000 versus £30,000 per QALY gained). The ROH audit provided relevant data on resource quantities used during surgery (both major surgery and vertebroplasty), and it was the basis for the cost estimation. Data from 54 patients were available. It is not clear what role selection bias and information bias may have played in the cost results obtained. However, it is the belief of the GDG members that the costs obtained are not too different from those observed during clinical practice.

Data on RT-related complications were obtained from the study by Thomas et al (2006), which used a questionnaire sent to the surgeons at different places in Canada to ask for the most common types of complications experienced by MSSC patients undergoing RT. Therefore, the estimation of these costs reflected the Canadian clinical experience and was not evidence-based. As a consequence, the applicability of this information to the UK context may be limited if the type of complications experienced by patients and the patterns of treatment for those complications differ across contexts. For the purposes of these analyses, the average cost per patient for RT-related complications was rather small (£27), therefore it is very unlikely that this may have influenced the results.

The second economic analysis undertaken assessed the cost-effectiveness of radical surgical procedures in combination with RT compared to RT alone for the treatment of MSSC patients that are neurologically compromised and have tumours that are not very radiosensitive. For these patients it is not clear what the best treatment choice is. This analysis consisted of adapting the only economic evaluation available comparing the use of surgery in combination with radiotherapy (RT) versus RT alone for the treatment of MSSC patients (Thomas et al 2006) to reflect the costs incurred if the interventions were conducted in a UK setting. The ICERs in terms of the incremental cost per life year gained obtained in the UK setting appear to be higher than those obtained in the study by Thomas et al (2006) for the Canadian setting: the incremental cost per additional life year gained with SRT when compared to RT alone in UK was £16,207, while that for the Canadian setting (once adjusted to £2006-2007 prices; OECD Purchase Power Parities, PSSRU 2006/07) was around £7,840. Additionally, an economic evaluation on the same topic (SRT versus RT alone) has been recently published in the form of an abstract (Furlan et al 2007). For this economic evaluation, a cost-utility assessment was conducted (i.e. it estimated QALYs as the measure of health benefit of the analysis) based on the same clinical data (i.e. the RCT published by Patchell et al 2005), and deriving utilities from the Harvard University Catalogue and the Health Outcomes Data Repository Data Health Utility list. Using an analytic decision model to combine clinical effectiveness and costs, the results of this study showed that the ICER for SRT, when compared to RT alone, was Can\$43,796 (or £22,017 in 2006 prices); therefore, SRT

seemed to be a strategy with borderline cost-effectiveness compared to RT alone. However, given the limited data reported in the abstract, the methodological quality of the study could not be assessed and therefore there is uncertainty regarding the reliability and applicability of these results to the UK setting. What it seems clear from the abstract is that hospice palliative care was a relevant component of the care received by MSCC patients, which is not applicable to the UK context, where hospice care is not a common way of managing MSCC patients.

One of the limitations of this second analysis was in the estimation of the number of QALYs gained. The information on quality of life for patients with MSCC is very limited, which seems to be the reason why in the Canadian economic evaluation the incremental cost per QALY was not estimated. NICE has established that its preferred measure of health benefit is the QALY because it takes into account not only the increased life expectancy from an intervention, but also the quality of the increased life. According to NICE, interventions presenting an ICER lower than £20,000 per QALY gained are presumed to be cost-effective, while there should be strong reasons for recommending health care interventions with ICERs higher than £20,000, and even stronger reasons if the ICER exceeds £30,000 (Social Value Judgements 2007). Therefore, an attempt was made to estimate the number of QALYs gained with SRT when compared to RT alone by using the utility scores considered for the first analysis. Besides, some further threshold analyses were undertaken and, according to the obtained results, SRT seemed to be a cost-effective strategy in most of the cases.

Conclusion

Based on the results obtained, it seems that each of the independently assessed MSCC treatments (i.e. RT, vertebroplasty and major surgery) seemed cost-effective when compared to no treatment. The conditions that have resulted from the threshold analyses and that need to be met in order to consider RT, vertebroplasty and major surgery cost-effective interventions when compared to no treatment seem to be attainable. Additionally, SRT seemed to be cost-effective as well, when compared to RT alone, for patients neurologically compromised and that have moderately or poorly radiosensitive tumours

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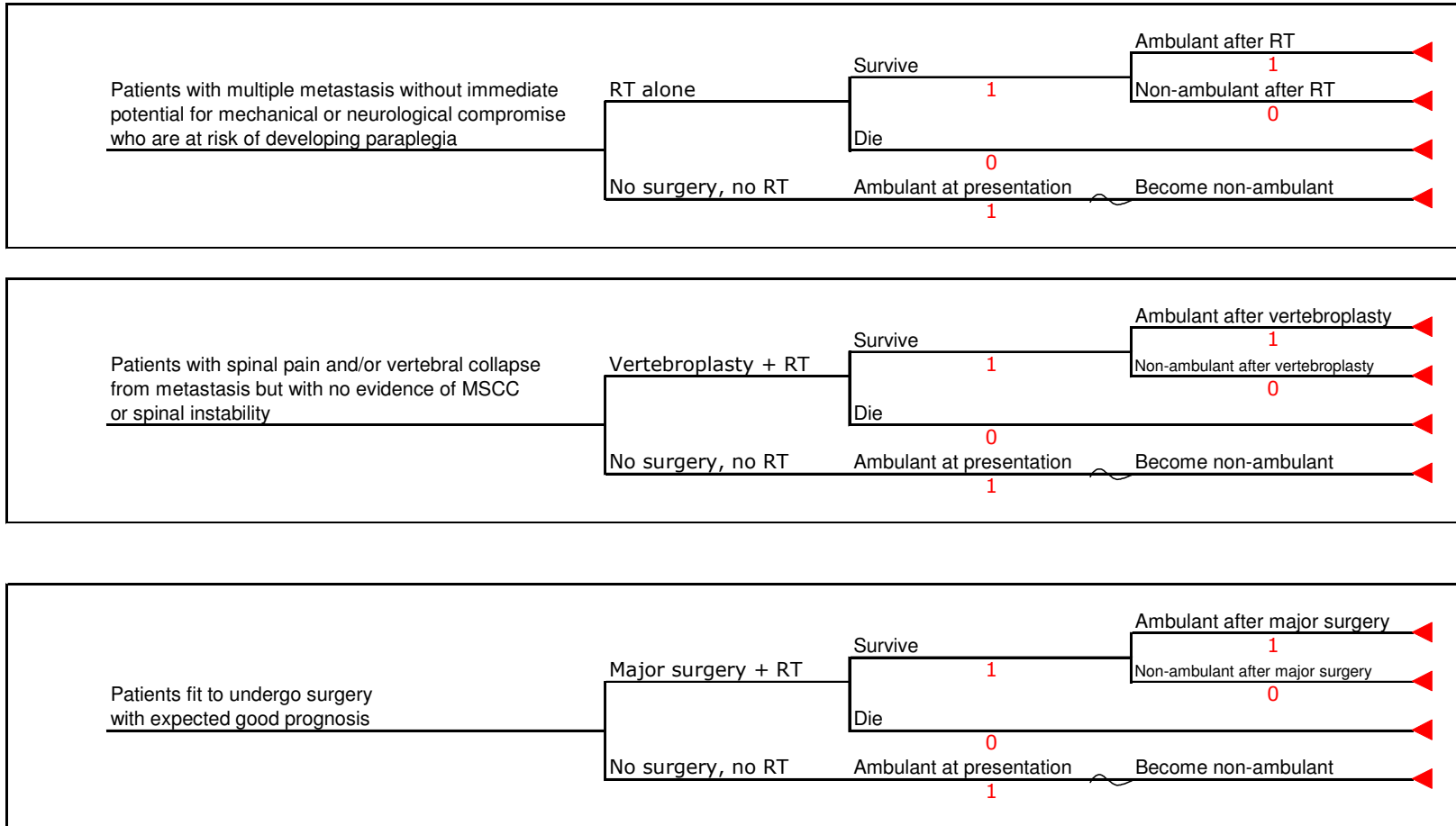
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Figure 2. Model structure used for the threshold analyses which independently compared potential treatments for MSCC patients with no treatment (parameters shown correspond to the ideal scenario)



Chapter 7 – Supportive Care

7.2 Interventions for thrombo-prophylaxis

The following evidence based guidelines were identified and addressed thrombo-prophylaxis. These include:

1. NICE Clinical Guideline (April 2007): Venous Thromboembolism: Reducing the Risk in Surgical Inpatients.

<http://guidance.nice.org.uk/CG46/niceguidance/pdf/English>

(Full list of recommendations pp 29 to 32.)

2. Report Of The Independent Expert Working Group On The Prevention Of Venous thromboembolism in hospitalised patients. Department of Health/ Chief Medical Officer March 2007.

3. Scottish Intercollegiate Guidelines Network (SIGN). Prophylaxis of venous thromboembolism. Edinburgh: SIGN; 2002. (SIGN publication no. 62).

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Report Of The Independent Expert Working Group On The Prevention Of Venous thromboembolism in hospitalised patients. Department of Health/ Chief Medical Officer March 2007.

The Government established an independent expert working group (EWG) to report to the Chief Medical Officer on how current best practice and guidance on managing VTE could be promoted and implemented, and on what resources might be needed to support delivery of any strategy through existing structures. This is the EWG's report.

3 main tasks of the EWG were:

1. Guideline Review (overall level of evidence : 4)

The subgroup identified its aims as:

- 1) identify current guidelines for VTE prevention
- 2) document areas of agreement/disagreement between guidelines
- 3) give summary recommendations for VTE prophylaxis for hospitalised patients

2. Analysis of existing evidence on interventions (overall level of evidence : 4)

3. Report on the resources that might be needed to support delivery of any strategy through existing structures. *Core elements of a VTE education strategy were described in the final report*

Inclusion criteria

Guideline Review

The following clinical areas where guidelines were relevant included

- ⌞ general surgery
- ⌞ gynaecological surgery
- ⌞ orthopaedic surgery
- ⌞ medical inpatients

The subgroup Chair and his assistant evaluated independently papers for possible inclusion, and any disagreements were resolved by discussion. The complete search was made available to the rest of the subgroup members for their review.

Analysis of existing evidence

Published evidence-based reviews, meta-analyses and literature summaries (published as part of clinical guidelines for VTE prevention)

Results

Task 1. Guideline Review

To identify relevant guidelines a systematic search (of Medline) was conducted as well as hand searching:

The six guidelines for review were:

Identified by electronic database search:

1. 'Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy', Chest 2004; 126 (3 Suppl): 338S–400S.
2. 'Prevention of venous thromboembolism. International Consensus Statement. Guidelines compiled in accordance with the scientific evidence', International Angiology, 2001; 20: 1–37.

Identified by hand search:

3. Guidelines on the use and monitoring of heparin. BCSH Haemostasis and Thrombosis Task Force. (2006).1
4. Prophylaxis of venous thromboembolism. SIGN guideline No. 62. ISBN 1899893 03 2. 2002.
5. Total Hip Replacement: A Guide to Best Practice. British Orthopaedic Association (BOA). 1999.
6. Total Knee Replacement – a guide to good practice. BOA. Undated.

Taken from the report:

Summary

A preliminary consensus was reached, resulting in this Guideline Assessment Document.

The main findings are:

- only four sets of guidelines were produced by systematic review with formal evidence-based graded recommendations
 - general and gynaecological surgery: all four sets of guidelines provide similar levels of recommendation for heparin, both UFH and LMWH
 - orthopaedic surgery: all four sets of guidelines provide similar levels of recommendation for heparin, both UFH and LMWH. The notable discrepancy is the recommendation for aspirin in the SIGN guideline with a Grade A recommendation, versus the ACCP Grade 1A against the use of aspirin
 - medical inpatients: all four sets of guidelines provide Grade A recommendations for LMWH
 - there were significant differences between the guidelines with regard to levels of risk and interventions, the main difference being the use of heparin or aspirin in high-risk orthopaedic surgery
- risk assignment and interventions for medical patients are even less well defined than for surgical patients

Task 2. Analysis of existing evidence

Please see report for all findings from the evidence presented.

[DoH guideline prevention of VTE in hospitalised patients.pdf](#)

General comments

To read the full report please use this link:

[DoH guideline prevention of VTE in hospitalised patients.pdf](#)

1. Guideline Review (overall level of evidence : 4)

Although this work was conducted using a very systematic approach wrt identifying and including the relevant evidence (guidelines), assessment was not formal and therefore lacked comment about the keys areas of appraisal (outlined in the AGREE tool) that are important to the development of an EBM guideline.

Assessment of guideline quality: No formal assessment of the quality of the guidelines was conducted, that is, using an appraisal tool such as AGREE

- A description of the included guidelines is included in the full report and it is not reproduced in this table.

- Areas of agreement/disagreement between guidelines is also fully described
- A summary of recommendations for VTE prophylaxis for hospitalised patients is also fully described in the full report.

2. Analysis of existing evidence on interventions (overall level of evidence : 4)

No formal literature search was conducted. There was a description about inclusion/exclusion criteria included (wrt study designs and study content).

7.3 Management of pressure ulcers

The following NICE guidelines were identified and addressed pressure ulcer management. NICE Clinical Guideline (2003): Pressure ulcer prevention: Pressure ulcer risk assessment and prevention, including the use of pressure-relieving devices (beds, mattresses and overlays) for the prevention of pressure ulcers in primary and secondary care and NICE Clinical Guideline (2005): The management of pressure ulcers in primary and secondary care.

References

NICE Clinical guideline CG7 (2003) Pressure relieving devices: the use of pressure relieving devices for the prevention of pressure ulcers in primary and secondary care.

<http://www.nice.org.uk/guidance/index.jsp?action=byID&o=10928>

NICE Clinical guideline CG29 (2005) Pressure ulcers: The management of pressure ulcers in primary and secondary care.

<http://www.nice.org.uk/guidance/index.jsp?action=byID&o=10972>

7.4 Bladder and bowel continence management

What are the most effectiveness bladder management interventions for patients with spinal cord injury?

Short Summary

The following NICE Guideline has addressed the issue of bowel management and cross reference to the following guideline is required: NICE Clinical Guideline (June 2007): Faecal Incontinence: The Management of Faecal Incontinence in Adults.

No studies were retrieved that included patients with MSCC specifically. However, several Cochrane systematic reviews provided relevant evidence about bladder management that can be extrapolated to MSCC patients. Jahn *et al.* (2007) evaluated which type of in-dwelling urinary catheter is best to use for long-term bladder drainage in adults. Overall, the included studies provided insufficient evidence to indicate which types of catheters are best to use in which patients. One study did suggest, that the use of a hydrogel coated latex catheter rather than a silicone catheter may be better tolerated. Jamison *et al.* (2004) assessed the effects of using different types of urinary catheters and external (sheath) catheters in managing the neurogenic bladder, compared to alternative management strategies or interventions. Out of 400 studies considered there were no studies found that met the inclusion criteria. Niël-Weise *et al.* (2005a) reviewed catheter policies in order to determine if any were better than others in terms of effectiveness, complications, quality of life and cost-effectiveness in long-term catheterised adults and children. Limited evidence indicated that when antibiotic prophylaxis was compared with antibiotics when clinically indicated, for patients using intermittent catheterisation, there were inconsistent findings about the effect of antibiotic prophylaxis on symptomatic urinary tract infection. For patients using indwelling urethral catheterisation, one study reported fewer events of symptomatic UTI in the prophylaxis group. When antibiotic prophylaxis was compared with giving antibiotics when microbiologically indicated, for patients using intermittent catheterisation, there was limited evidence that receiving antibiotics reduced the rate of bacteriuria (asymptomatic and symptomatic). There was also limited evidence that prophylactic antibiotics reduced symptomatic bacteriuria. Niël-Weise *et al.* (2005b) investigated the outcomes of alternative approaches to catheterisation for short-term bladder drainage in adults. Patients managed with an indwelling catheter had more cases of bacteriuria, more frequent recatheterisation and more suffered discomfort than patients managed with suprapubic catheterisation. There was no evidence of complications during insertion, although not all trials reported this outcome explicitly. Findings from three studies suggested that when indwelling urethral catheterisation was compared to intermittent catheterisation there were fewer cases of bacteriuria in patients with the intermittent catheterisation. Only a proportion of the participants in the studies included in these reviews had spinal cord injury.

PICO

Patients	Interventions	Comparisons	Outcomes
Patients with MSCC requiring bladder management. <ul style="list-style-type: none">• Urinary retention / incomplete bladder emptying• Detrusor over-activity	<ul style="list-style-type: none">• Anti-muscarinic drug treatment.• Treatment options for facilitating voiding include: (catheterization - intermittent / indwelling / suprapubic	No management Different interventions (listed in Interventions list)	<ul style="list-style-type: none">• UTI management• Quality of life• Incontinence• Pressure sores

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

Cochrane systematic reviews provided evidence on several issues, these included:

1. Jahn *et al.*(2007), evaluated which type of in-dwelling urinary catheter is best to use for long-term bladder drainage in adults. Overall, the included trials provided insufficient evidence to indicate which types of catheters are best to use in which patients. One trial did suggest, that the use of a hydrogel coated latex catheter rather than a silicone catheter may be better tolerated.

2. Jamison *et al.*(2004) assessed the effects of using different types of urinary catheters and external (sheath) catheters in managing the neurogenic bladder, compared to alternative management strategies or interventions. Out of 400 studies considered there were no trials found that met the inclusion criteria.

3. Niël-Weise *et al* (2005a) reviewed catheter policies in order to determine if any were better than others in terms of effectiveness, complications, quality of life and cost-effectiveness in long-term catheterised adults and children. Limited evidence showed that when antibiotic prophylaxis was compared with antibiotics when clinically indicated, for patients using intermittent catheterisation, there were inconsistent findings about the effect of antibiotic prophylaxis on symptomatic urinary tract infection. For patients using indwelling urethral catheterisation, one study reported fewer events of symptomatic UTI in the prophylaxis group. When antibiotic prophylaxis was compared with giving antibiotics when microbiologically indicated, for patients using intermittent catheterisation, there was limited evidence that receiving antibiotics reduced the rate of bacteriuria (asymptomatic and symptomatic). There was also limited evidence that prophylactic antibiotics reduced symptomatic bacteriuria.

4. Niël-Weise *et al.* (2005b) investigated the outcomes of alternative approaches to catheterisation for short-term bladder drainage in adults.

Patients managed with an indwelling catheter had more cases of bacteriuria, more frequent recatheterisation and more suffered discomfort than patients managed with suprapubic catheterisation. There was no evidence of complications during insertion, although not all trials reported this outcome explicitly. Findings from 3 studies indicated that when indwelling urethral catheterisation was compared to intermittent catheterisation there were fewer cases of bacteriuria in patients with the intermittent catheterisation.

Only a proportion of the participants in the studies included in these reviews had spinal cord injury. No studies were retrieved that included patients with MSCC specifically.

One good quality RCT (Lee *et al.* 2007) evaluated whether Methenamine Hippurate (MH) or cranberry tablets can prevent urinary tract infections (UTI) in patients with neuropathic bladder following spinal cord injury (SCI). This study reported that from multivariate analysis patients randomised to MH did not have a significantly longer UTI-free period compared to placebo and patients randomised to cranberry did not have significantly longer UTI-free period compared to placebo. There is no benefit in the prevention of UTI from the addition of MH or cranberry tablets to the usual management of patients with neuropathic bladder from SCI.

References

Jahn P, Preuss M, Kernig A, Seifert-Hühmer A, Langer G. Types of indwelling urinary catheters for long-term bladder drainage in adults. *Cochrane Database of Systematic Reviews* 2007, Issue 3. Art. No.: CD004997. DOI: 10.1002/14651858.CD004997.pub2.

Jamison J, Maguire S, McCann J (2004) Catheter policies for management of long term voiding problems in adults with neurogenic bladder disorders. *Cochrane Database of Systematic Reviews* CD004375.

Lee, B. B., Haran, M. J., Hunt, L. M., Simpson, J. M., Marial, O., Rutkowski, S. B., Middleton, J. W., Kotsiou, G., Tudehope, M. & Cameron, I. D. (2007) Spinal-injured neuropathic bladder antisepsis (SINBA) trial. *Spinal Cord*, 45: 542-550.

NICE Clinical Guideline CG49 (June 2007): Faecal Incontinence: The Management of Faecal Incontinence in Adults.
<http://guidance.nice.org.uk/CG49/guidance/pdf/English>

Niël-Weise BS, van den Broek PJ. Urinary catheter policies for short-term bladder drainage in adults. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.: CD004203. DOI: 10.1002/14651858.CD004203.pub2.

Niël-Weise BS, van den Broek PJ. Urinary catheter policies for long-term bladder drainage. *Cochrane Database of Systematic Reviews* 2005, Issue 1. Art. No.: CD004201. DOI: 10.1002/14651858.CD004201.pub2.

Evidence Tables

<p>Jahn P, Preuss M, Kernig A, Seifert-Hühmer A, Langer G (2007) Types of indwelling urinary catheters for long-term bladder drainage in adults. Cochrane Database of Systematic Reviews: Reviews. In 'Cochrane Database of Systematic Reviews 2007 Issue 3'. (John Wiley & Sons, Ltd: Chichester (UK))</p>
<p>Design: Systematic review of RCTS, Evidence level 1++</p>
<p>Inclusion criteria</p> <p>For studies: Randomised controlled studies (RCTs) of parallel or crossover design comparing alternative types of indwelling urinary catheters in adults having long-term bladder drainage (more than thirty days).</p> <p>For participants: Adults with indwelling urethral or suprapubic catheters for more than thirty days, irrespective of primary disease and care setting.</p>
<p>Exclusion criteria</p>
<p>Population</p>
<p>Interventions</p> <p>To determine which is the best type of indwelling urinary catheter to use in adults having long-term bladder drainage.</p> <p>The review investigated the following comparisons:</p> <ol style="list-style-type: none">1. Antiseptic impregnated urethral catheters versus standard urethral catheters.2. Antibiotic impregnated urethral catheters versus standard urethral catheters.3. Antibiotic impregnated urethral catheters versus antiseptic impregnated urethral catheters.4. One type of standard urethral catheter versus another.5. One type of antiseptic impregnated urethral catheter versus another.6. One type of antibiotic impregnated urethral catheter versus another. <p>Specific interventions included: Indwelling urinary catheters used for long-term bladder drainage. These may be:</p> <ul style="list-style-type: none">• indwelling urethral catheters (standard or antiseptic coated or antibiotic coated);• suprapubic catheters (standard or antiseptic coated or antibiotic coated).
<p>Outcomes</p> <p><i>Primary interventions:</i> catheter-associated urinary tract infection (as defined in the specific trial reports).</p> <p><i>Secondary outcomes:</i></p>

Complications/adverse effects:

- asymptomatic bacteriuria;
- symptomatic urinary tract infection;
- other adverse effects of the intervention (e.g. encrustation, blockage, stone formation, retention).

Co-interventions:

- use of prophylactic antibiotics;
- use of antibiotics to treat infection.

Patient reported:

- patient satisfaction;
- patient comfort.

Clinician reported:

- practitioners' satisfaction;
- length of time catheters used.

Quality of life:

- generic health status or quality of life-measures (e.g. SF 36, Ware 1992);
- psychological outcome measures (e.g. HADS, Zigmond 1983).

Interventions and outcomes

Each trial involved different catheters and different populations, and so a meta-analysis was not conducted.

Nakada 1996 compared a silver impregnated catheter (Silver Lubricath Foley) with a silicone-coated catheter. This study used a cross over design, with participants changing to the alternative catheter every two weeks. Data were reported for UTI rate, leakage of urine, urethral pain, residual urine sensation, pain on removing catheter and degree of urinary turbidity.

Bergqvist 1979 randomised participants to a PVC catheter group, latex catheter group and silicone catheter group. The outcomes of interest were the numbers of bacteriuria, complications and encrustation of the catheter surface and frequency of catheter changes.

Bull 1991 randomised participants to a hydrophilic polymer (hydrogel) coated latex catheter and silicone (silicone elastomer) coated urethral catheter. The outcomes of interest were the time the catheters remained in situ without encrustation, incidence of encrustation and comfort of catheter.

Results

Of the 11457 studies retrieved only 3 studies were eligible for inclusion (Bergqvist 1979; Bull 1991; Nakada 1996).

Two were parallel-group RCTs (Bergqvist 1979; Bull 1991) and one was a randomised cross-over trial (Nakada 1996) which used alternation to allocate participants to the first arm of the trial.

The studies were conducted in Europe (Bergqvist 1979; Bull 1991) and Japan (Nakada 1996). One parallel-group RCTs (Bull 1991) included 69 community

based adults. Two studies (Bergqvist 1979; Nakada 1996) included 21 and 12 long-term catheterised patients from unknown settings.

Results on the comparisons:

1. Antiseptic impregnated urethral catheters versus standard urethral catheters

The Nakada study (12 participants) compared a type of silver alloyed (silver and hydrogel coated) Foley catheter with a standard silicone coated catheter.

- No significant differences between the different types of catheters in terms of urinary tract infections because all the participants had UTIs.
- No significant differences in adverse effects such as: events of leakage of urine (4 out of 10 versus 7 out of 10 patients);
- urethral pain and discomfort (1 out of 10 versus 4 out of 10 patients)
- residual urine sensation (2 out of 10 versus 5 out of 10 patients)
- turbid urine (1 out of 10 versus 4 out of 10 patients)

2. Antibiotic impregnated urethral catheters versus standard urethral catheters.

The review reported that no studies were found that addressed this comparison.

3. Antibiotic impregnated urethral catheters versus antiseptic impregnated urethral catheters.

The review reported that no studies were found that addressed this comparison.

4. One type of standard urethral catheter versus another.

Two studies using different outcome measurements compared four different types of standard catheters to investigate UTI:

- Hydrogel coated latex catheter (Bull 1991);
 - Latex catheter (Bergqvist 1979);
 - PVC catheter (Bergqvist 1979);
 - Silicone catheter (Bergqvist 1979; Bull 1991)
-
- Data from the two studies could not be combined because there were significant clinical differences between the studies regarding the types of standard catheters and outcome measurements.
 - No significant differences between the different types of catheters in terms of urinary tract infections because all the participants had UTIs.
 - In the Bergqvist trial, fewer patients were unable to retain the hydrogel coated latex catheter (9 out of 36) for 16 weeks compared with the silicone catheter (20 out of 33) (RR 0.41, 95% CI 0.22 to 0.77, and they also preferred the latex catheter (RR for dissatisfaction 0.68, 95% CI 0.49 to 0.95)
 - The numbers were too few to detect plausible differences in other outcomes such as pain or purulent discharge, stricture, local irritation or concrement on the catheter surface.

- The significant difference in the length of time the catheter remained in situ suggests that the hydrogel coated latex catheter (90 days) might be more cost-effective than the silicone coated catheter (57 days) (MD 33 days, 95% CI 15 to 50, Bull 1991).

5. One type of antiseptic impregnated urethral catheter versus another.

The review reported that no studies were found that addressed this comparison.

6. One type of antibiotic impregnated urethral catheter versus another.

The review reported that no studies were found that addressed this comparison.

General comments –

Given the large numbers of studies retrieved not many relevant studies have been conducted, as evidence by this review. What this dearth of evidence points to is the need for further research.

The research recommendations taken from the review are listed below (this maybe used to inform NICE guideline recommendations) research:

References of included studies:

Bergqvist D, Hedelin H, Stenstrom G, Stahl A. [Clinical evaluation of Foley catheters]. *Lakartidningen* 1979;76(15):1416–8.

Bull E, Chilton CP, Gould CA, Sutton, TM. Single-blind, randomised, parallel group study of the Bard Biocath catheter and a silicone elastomer coated catheter. *British Journal of Urology* 1991;68(4):394–9.

Nakada J, Kawahara M, Onodera S, Oishi Y. Clinical Study of Silver Lubricath Foley Catheter. *Acta Urologica Japan* 1996;42:311–8.

Jamison J, Maguire S, McCann J (2004) Catheter policies for management of long term voiding problems in adults with neurogenic bladder disorders. [Review] [17 refs]. *Cochrane Database of Systematic Reviews* CD004375.

Design: Systematic review of RCTs, Evidence level 1++

Review Objectives:

To assess the effects of using different types of urinary catheters and external (sheath) catheters in managing the neurogenic bladder, compared to alternative management strategies or interventions.

Review Inclusions/Exclusions:

All randomised and quasi-randomised controlled trials comparing methods of using catheters to manage urinary voiding in people with neurogenic bladder.

Main results:

Approximately 400 studies were examined. No trials were found that met the inclusion criteria, and 5 studies were excluded from the review.

Authors' conclusions

“Despite a comprehensive search no evidence from randomised or quasi-randomised controlled trials was found. It was not possible to draw any conclusions regarding the use of different types of catheter in managing the neurogenic”

General comments

Niël-Weise BS, van den Broek PJ (2005) Urinary catheter policies for long-term bladder drainage. Cochrane Database of Systematic Reviews: Reviews. In 'Cochrane Database of Systematic Reviews 2005 Issue 1'. (John Wiley & Sons, Ltd: Chichester (UK))

Design: Systematic review of RCTs, Evidence Level 1++

Inclusion criteria

For studies:

All randomised and quasi-randomised studies comparing catheter policies (route of insertion and use of antibiotics) for long-term catheterisation of the bladder in adults and children.

Exclusion criteria

Studies were excluded for a variety of reasons – all of which were described for individual studies in the review. In general these reasons were:

- Studies that did not evaluate interventions using randomised and quasi-randomised studies.
- Studies that did not compare interventions as outlined in the interventions section.
- Studies that did not provide enough detail to allow for the judgement of the study methods used.

The following interventions were not considered in the present review:

- catheterisation insertion techniques (eg clean, sterile, with or without antiseptic or antibiotic cream);
- meatal care management techniques (eg routine hygiene, antiseptic or antibiotic cream)

management of drainage systems (eg use of sterile or clean drainage bags, use of antiseptic solutions, washout/irrigation of drainage bags).

Population

- All patients requiring long-term catheterisation for urinary incontinence or retention that cannot be managed by another method.
- This included people suffering from stress, urge and mixed incontinence, dementia, prostatic hypertrophy unsuitable for other management, stroke, neurological problems, spinal cord injury and spina bifida. They may receive this care at home, in residential homes or in hospital. In this review, long term is defined as more than 14 days.

Interventions

This review aimed to determine if certain catheter policies are better than others in terms of effectiveness, complications, quality of life and cost-effectiveness in long-term catheterised adults and children.

The authors evaluated the following comparisons:

1. indwelling urethral catheterisation compared with suprapubic catheterisation;
2. indwelling urethral catheterisation compared with intermittent catheterisation;

3. suprapubic catheterisation compared with intermittent catheterisation;
4. antibiotic prophylaxis compared with giving antibiotics when clinically indicated;
5. antibiotic prophylaxis compared with giving antibiotics when microbiologically indicated; and
6. giving antibiotics, if microbiologically indicated, compared with giving antibiotics if clinically indicated.

The interventions considered were:

1. continuous indwelling urethral, intermittent urethral, and suprapubic use of catheters;
2. antibiotic prophylaxis (continuous use), use of antibiotics if clinically indicated (eg pain, fever) and use of antibiotics if microbiologically indicated (growth of bacteria from a specimen of urine in the absence of clinical symptoms).

Antibiotics were divided into two categories:

- broad spectrum (active against a wide range of bacteria); and
- narrow spectrum (active against certain types of bacteria only, usually prescribed when a culture of a urine sample has identified a particular bacterium shown to be sensitive to the antibiotic, or when only a limited range of bacteria of known sensitivity are likely to be present).
- the routes of administration (oral or intravenous, but not local or topical) were considered.

Incidence Density Rate (IDR) = the proportion of people who become infected during a specified period of time as the proportion of the total time at which individuals in a population are at risk. Incidence density accounts for the varying time periods of follow up. Incidence density offers a precise estimate of the rate of occurrence of a particular disease.

Incident Density Difference (IDD) = The difference between incidence density rates. Where a negative value indicates a reduction in IDR.

Outcomes

- | | |
|---|--|
| <ul style="list-style-type: none"> • patient comfort ; • patient satisfaction ; • ease of use for patient; • sexual function; • incontinence/bypass leakage; • need to use supplementary pads/bed pads; • ease of use for practitioner; • need to change catheters; • number of catheters used; • length of time catheters used. • Complications/adverse effects | <ul style="list-style-type: none"> • asymptomatic bacteriuria; • symptomatic urinary tract infections; • use of prophylactic antibiotics; • use of rescue antibiotics; • urethral strictures; • bladder stones; • urgency/bladder spasms/detrusor over-activity; • other adverse effects of intervention (other than urinary tract infection). • Quality of life • Economic outcomes: NOT reported as they were not listed |
|---|--|

Follow up**Results*****Studies included:***

- 7 studies were included in the review (Anderson 1980; Duffy 1982; Gribble 1993; Johnson 1994; Mohler 1987; Rutschmann 1995; Schlager 1998).
- 4 were crossover studies (Duffy 1982, Johnson 1994, Rutschmann 1995, Schlager 1998)
- 3 were parallel-group randomised controlled studies (Anderson 1980; Gribble 1993, Mohler 1987).

Types of study participants:

- 6 of the studies involved patients with neurogenic bladder of differing types, all of whom had been using intermittent catheterisation.
- 2 studies included hospitalised adults with acute neurogenic bladder following recent spinal cord injury who were using intermittent self-catheterisation (Anderson 1980, Gribble 1993).
 - Only male patients were included (Anderson 1980)
 - Almost seven times more males were included, but the distribution of men and women was equal between the trial groups (Gribble 1993).
- 1 trial also involved adult hospitalised patients who were using intermittent catheterisation for neurogenic bladder, but it was not clear whether the neurogenic bladder was an acute problem or longstanding (Mohler 1987). In this trial, three times more males were included, but the trial groups were comparable with regard to sex.
- 1 crossover trial included mainly male volunteers with neurogenic bladder using intermittent self-catheterisation at home (Duffy 1982); the reasons why patients suffered from neurogenic bladder were not reported.
- 1 trial included elderly nursing home inpatients with long-term urethral catheters (Rutschmann 1995). In this trial, indications for catheterisation were various.
- The studies by Schlager 1998 and Johnson 1994 included children and the results of these studies are not included in this report.
- In the 4 crossover studies, all patients were catheterised for longer than 14 days.
- In 3 studies, patients were catheterised for 12 weeks (Duffy 1982; Rutschmann 1995).
- In the included parallel-group RCTs, the duration of catheterisation was not the same for all patients.
- In 1 trial, patients were catheterised for a mean of nine weeks, ranging from one to 16 weeks (Gribble 1993). In the other 2 studies, the longest patients were catheterised until hospital discharge (Anderson 1980; Mohler 1987); the mean duration was not reported for either of these studies.

Comparisons:

Comparison 1: Indwelling urethral catheterisation compared with suprapubic catheterisation

The review reported that no studies were found that addressed this comparison.

Comparison 2: Indwelling urethral catheterisation compared with intermittent catheterisation

The review reported that no studies were found that addressed this comparison.

Comparison 3: Suprapubic catheterisation compared with intermittent catheterisation

The review reported that no studies were found that addressed this comparison.

Comparison 4: Antibiotic prophylaxis compared with giving antibiotics when clinically indicated.

- 3 eligible studies addressed this comparison (Johnson 1994; Rutschmann 1995; Schlager 1998). All three were crossover studies.
- Two studies tested nitrofurantoin against placebo in children using intermittent catheterisation (Johnson 1994; Schlager 1998); one trial tested noroxacin against placebo in elderly patients using indwelling urethral catheterisation (Rutschmann 1995).

Bacteriuria (asymptomatic and symptomatic):

Bacteriuria was not considered as an outcome measure in the review because of asymptomatic bacteriuria were not treated and therefore, it was not a useful measure in this setting.

Symptomatic urinary tract infection (UTI):

a) Participants with intermittent catheterisation – data from studies including children and not reported here.

b) Participants with indwelling urethral catheterisation - In the open trial of prophylaxis amongst patients with indwelling catheter (Rutschmann 1995), there were fewer symptomatic UTIs during prophylaxis than during control periods (one in 276 catheterisation weeks versus 12 in 259 weeks)

Other outcome measures:

a) Participants with intermittent catheterisation - No data on other outcomes were reported.

b) Participants with indwelling urethral catheterisation

1 study (Rutschmann 1995), reported that the antibiotic group were better in terms of rate of visual encrustation per catheterisation week rate of catheter-obstructions, rate of adverse events, number of patients with improved general condition and number of gram-negative isolates.

For the outcome 'percentage of resistant strains', the results were in favour of the control group.

Comparison 5: Antibiotic prophylaxis compared with giving antibiotics when microbiologically indicated.

- For all studies the trial populations were adult patients using intermittent catheterisation.
- Anderson 1980 tested nitrofurantoin against no nitrofurantoin;
- Duffy 1982 tested nitrofurantoin against placebo
- Gribble 1993 and Mohler 1987 tested TMP-SMX against placebo.

Bacteriuria (asymptomatic and symptomatic)

a) Participants with intermittent catheterisation

- The rate of bacteriuria per catheterisation week was calculated – when the Anderson and Mohler studies were pooled the patients in the prophylactic antibiotic group had fewer episodes of bacteriuria than patients not receiving prophylactic antibiotics, (IDR of the pooled analysis 0.61, 95% CI 0.44 to 0.87, IDD -0.14, 95% CI -0.23 to -0.05)
- The results of the Duffy 1982 trial also indicated in favour of the prophylaxis group.
- Anderson 1980 analysed the effect according to the frequency of catheterisation and found some evidence that the effect of prophylaxis was greater in the subgroup who used intermittent catheterisation every four hours rather than every eight hours (every four hours: IDR 0.15, 95% CI 0.05 to 0.42, every eight hours: IDR 0.49, 95% CI 0.21 to 1.12).
- Gribble 1993 found that although there were fewer patients having at least one episode of bacteriuria in the antibiotic group, it was not statistically significant (RR 0.86, 95% CI 0.72 to 1.02)

b) Participants with indwelling urethral catheterisation

No eligible studies were found.

Symptomatic bacteriuria

a) Participants with intermittent catheterisation

- For the Mohler 1987 study the rate of symptomatic bacteriuria per catheterisation week was calculated
- Results showed that patients in the prophylactic antibiotic group had a lower rate than patients not receiving prophylactic antibiotics but this was not statistically significant (IDR 0.56, 95% CI 0.27 to 1.15)
- In the Gribble trial, fewer patients in the prophylactic antibiotic group had at least one episode of symptomatic bacteriuria, and this was statistically significant (RR 0.19, 95% CI 0.07 to 0.53, risk difference (RD) -0.26, 95% CI -0.39 to -0.13)

b) Participants with indwelling urethral catheterisation

No eligible studies were found.

Other outcome measures

a) Participants with intermittent catheterisation

- The rate of adverse events per catheterisation week were reported in the review. The results were better in the antibiotic group but were not statistically significant (IDR 0.74, 95% CI 0.53 to 1.02, (Gribble 1993).
- No significant difference in the number of patients having at least one episode of adverse events (RR 0.86, 95% CI 0.64 to 1.14, (Gribble 1993).

- Fewer patients in the prophylaxis group were prescribed antibiotics for at least one episode of urinary

b) Participants with indwelling urethral catheterisation

No eligible studies were found.

Comparison 6: Giving antibiotics, if microbiologically indicated, compared with giving antibiotics if clinically indicated

No eligible studies were found.

General comments

This review presents a very limited body of evidence, with some comparisons revealing no eligible studies to provide results. When evidence was available the studies were of poor quality and insufficient to provide any comment for clinical practice.

References of studies included in the review

Anderson RU. Prophylaxis of bacteriuria during intermittent catheterization of the acute neurogenic bladder. *Journal of Urology* 1980;123(3):364-6.

Duffy L, Smith AD. Nitrofurantoin macrocrystals prevent bacteriuria in intermittent self-catheterization. *Urology* 1982;20(1):47

Gribble MJ, Puterman ML. Prophylaxis of urinary tract infection in persons with recent spinal cord injury: a prospective, randomized, double-blind, placebo-controlled study of trimethoprim-sulfamethoxazole. *American Journal of Medicine* 1993;95(2):141

Johnson HW, Anderson JD, Chambers GK, Arnold WJ, Irwin BJ, Brinton JR. A short-term study of nitrofurantoin prophylaxis in children managed with clean intermittent catheterization. *Pediatrics* 1994;93(5):752

Mohler JL, Cowen DL, Flanigan RC. Suppression and treatment of urinary tract infection in patients with an intermittently catheterized neurogenic bladder. *Journal of Urology* 1987;138(2):336

Rutschmann OT, Zwahlen A. Use of noroxacin for prevention of symptomatic urinary tract infection in chronically catheterized patients. *Journal of Clinical Microbiology and Infectious Diseases* 1995; 14:44

Schlager TA, Anderson S, Trudell J, Hendley JO. Nitrofurantoin prophylaxis for bacteriuria and urinary tract infection in children with neurogenic bladder on intermittent catheterization. *Journal of Pediatrics* 1998;132:704

Niël-Weise BS, van den Broek PJ. Urinary catheter policies for short-term bladder drainage in adults. Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD004203. DOI: 10.1002/14651858.CD004203.pub2.

Design: Systematic review of RCTs, Evidence level 1++

Review Objectives:

To determine the advantages and disadvantages of alternative approaches to catheterisation for short-term bladder drainage in adults.

Review Inclusions/Exclusions:

All randomised and quasi-randomised trials comparing catheter route of insertion for adults catheterised for up to 14 days.

Main results:

Seventeen parallel-group randomised controlled trials met the inclusion criteria.

Fourteen trials compared indwelling urethral catheterisation with suprapubic catheterisation. Groups managed with an indwelling catheter had more cases of bacteriuria (RR 2.60; 95%CI 2.12 to 3.18), more frequent recatheterisation (RR 4.12; 95%CI 2.94 to 7.56), and more people with discomfort (RR 2.98; 95%CI 2.31 to 3.85). There were no reports of complications during insertion, although not all trials stated this explicitly.

Three trials compared indwelling urethral catheterisation with intermittent catheterisation. In the two trials with data, there were fewer cases of bacteriuria in the intermittent catheterisation group (RR 2.90; 95%CI 1.44 to 5.84). Costs analyses reported in two trials favoured the indwelling group.

Lee, B. B., Haran, M. J., Hunt, L. M., Simpson, J. M., Marial, O., Rutkowski, S. B., Middleton, J. W., Kotsiou, G., Tudehope, M. & Cameron, I. D. (2007) Spinal-injured neuropathic bladder antiseptis (SINBA) trial. Spinal Cord, 45: 542-550.

Design: RCT , evidence grade 1+
Country: Australia

Aim: To determine whether Methenamine Hippurate (MH) or cranberry tablets can prevent urinary tract infections (UTI) in patients with neuropathic bladder following spinal cord injury (SCI).

Inclusion criteria

Patients with SCI with neurogenic bladder: stable bladder management with either indwelling urethral or suprapubic catheter, intermittent catheter or reflex voiding with or without a condom drainage device, absence of complex urological or serious renal pathology, not currently prescribed antibiotics and absence of symptoms of a UTI at the time of enrolment.

Exclusion criteria

Patients with a precious allergy to the tested interventions. And those not meeting the above criteria.

Population

543 patients were included with only 305 actually participating in the study.

- Patients were randomised adequately.
- Power calculations and Intention to treat analysis were conducted.
- No stat. sig differences between the treatment groups

Interventions

Patients were allocated into the following groups:

1. MH 2g (1 g twice-daily) with cranberry (1600mg - 800 mg twice-daily); n= 150
2. MH 2g with cranberry placebo; n= 155
3. Cranberry (1600mg) with MH placebo; n= 153
4. Cranberry placebo; n= 152

Total sample population of 305 patients spilt into 4 groups in factorial analysis and recombined to allow comparison of the entire population in 2 groups: MH versus MH placebo and cranberry versus cranberry placebo.

Outcomes

Primary outcome: First Symptomatic UTI event (patients recorded bi-weekly symptoms) from randomization or 6 months if this did not occur.

Symptomatic UTI event = increase in body temperature; new or increasing symptoms or autonomic dysreflexia.

Follow up: 6 months

Results

- The Kaplan-Meier curves reported no UTI-free survival benefit for either intervention

was detected. The unadjusted analysis confirms this findings: For MH treatment: Hazard Ratio (HR) = 0.94 95%CI 0.86-1.32, p=0.73) and for cranberry treatment: HR =0.93, 95% CI 0.66-1.29, p=0.65)

- Multivariate analysis (Cox proportional hazards) indicated:
 - i) no significant effects of MH compared to placebo after adjusting for the number of general practitioner visits for UTI in the previous 6 months; duration of SCI; bladder management type; completeness of injury and baseline urinary organisms (HR=0.96, 95% CI: 0.68-1.35, p=0.75)
 - ii) no significant effects of cranberry compared to placebo after adjusting for the number of general practitioner visits for UTI in the previous 6 months; duration of SCI; bladder management type; completeness of injury and baseline urinary organisms (HR=0.93, 95% CI: 0.67-1.31, p=0.70)
- When the multivariable analysis was conducted for combined treatment versus placebo (subgroup) this indicated no significant effect of combined therapy with MH and cranberry compared to placebo with adjustment for covariates described above.
- No difference in adverse events between the intervention groups was reported. There is no benefit in the prevention of UTI from the addition of MH or cranberry tablets to the usual management of patients with neuropathic bladder from SCI.

General comments

While there are some minor issues with respect to patient numbers and patient characteristics no major limitations exist.

7.5 Maintaining circulatory and respiratory functioning

Circulatory Management and Respiratory Management in MSCC (and spinal cord injury) patients.

Short Summary

Respiratory Management

Referral to the evidence-based guideline from the Paralyzed Veterans of America publication (2005) provided some of the evidence for respiratory management for MSCC patients. The Respiratory Management in patients with spinal cord injury: A Clinical Practice Guideline for Health-Care Providers (Consortium for Spinal Cord Medicine: Respiratory Management Following Spinal Cord Injury (Paralyzed Veterans of America publication 2005) was appraised using the AGREE Instrument (2003), it was rated as being of moderate quality.

Maintaining circulatory functioning:

Two expert reviews reported outcomes from using fludrocortisone (Bloomfield *et al.* 2002 and Claydon *et al.* 2006), although used widely, fludrocortisone has no high level evidence of effect on hypotension. Clinical consensus as described in these studies recommended that fludrocortisone be used as treatment of vasovagal syncope and orthostatic hypotension. For compression bandages, two studies (one small non-randomised, comparative study (Rimaud *et al.* 2007) and one expert review (Claydon *et al.* 2006) reported outcomes. This very limited evidence suggested the use of compression bandages or support stockings to restrict venous pooling in the visceral area and dependent limbs to manage hypotension. For electrically induced and voluntary activation of physiologic muscle pump, one comparative, non-randomised study evaluated this intervention (Faghri *et al.* 2002). Limited evidence indicated effectiveness of functional electrical stimulation (FES) during standing and tilting in spinal cord-injured individuals and may prevent orthostatic hypotension and circulatory hypokinesia and improve tolerance to tilting and standing.

The evidence from two very small non-randomised comparative studies (Svensson *et al.* 1995, Ter *et al.* 2006) evaluated passive leg movements and suggest that passive leg movements do not prevent thrombosis in acute spinal cord injury (SCI) patients or alter the arterial peripheral circulation in patients with SCI or control participants.

PICO

Patients	Interventions	Comparisons	Outcomes
Patients with MSCC and postural hypotension	<ul style="list-style-type: none">• TED stockings• (Anti embolism stockings and medical support stockings)• Abdominal binders	<ul style="list-style-type: none">• no treatment	<ul style="list-style-type: none">• postural hypotension symptoms

	<ul style="list-style-type: none"> • ephedrine • fludrocortisone 		
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Patients	INTERVENTIONS	COMPARISONS (for each intervention listed)	OUTCOMES (as they relate to the different interventions listed)
Patients with MSCC	lower limb passive movements		<ul style="list-style-type: none"> • maintenance of circulation • prevent DVT • maintain joint mobility • muscle length

These PICO tables were used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

Circulatory Management in MSCC

With respect to applicability, the patient group described in the PICO included patients with MSCC and postural hypotension. No studies were found that included this patient group; therefore the patient group was expanded to include patients with Spinal cord injury (SCI).

The body of evidence: Management of Hypotension:

- Fludrocortisone: 2 expert reviews reported outcomes from using this treatment (Bloomfield *et al.* 2002 and Claydon *et al.* 2006)
- Compression bandages: 2 studies reported outcomes (1 small non-randomised, comparative study and 1 expert review) (Claydon *et al.* 2006, Rimaud *et al.* 2007).
- Electrically induced and voluntary activation of physiologic muscle pump: 1 Comparative, non-randomised study evaluated this intervention. (Faghri *et al.* 2002).

With respect to consistency of reporting; the evidence of different interventions for the management of hypotension is very low grade. The studies included covered varied interventions and therefore provide varied results: Fludrocortisone, although used widely, has no high level evidence of effect on hypotension. Compression stockings; very limited evidence to support the use for managing hypotension. Exercise (Electrically induced and voluntary activation of physiologic muscle pump) was shown to have an affect on circulation and orthostatic hypotension but given the findings come from one study.

The evidence of effectiveness of different interventions involving Passive leg movements: Exercise: 1 before and after study, evaluating 2 different series of exercises. Passive leg movements: 1 very small non-randomised comparative study. The evidence for passive leg movements is limited and of low grade, from the 2 studies included the results indicate that passive leg movements

does not prevent thrombosis in acute SCI patients or alter the arterial peripheral circulation in patients with SCI or control subjects.

Evidence Summary:

Management Of Hypotension:

Fludrocortisone

The results reported in a review (Bloomfield *et al.* 2002) about the effectiveness of Fludrocortisone were presented in a narrative format. Essentially there is limited evidence (as reported by this review), one RCT comparing Fludrocortisone with atenolol and consensus support for the use of this drug.

- There is only very limited data supporting the value of fludrocortisone for the treatment of vasovagal syncope, although fludrocortisone is widely used and often considered one of the first lines of therapy for this condition.
- There is no randomised placebo controlled studies that have assessed the efficacy of fludrocortisone in preventing recurrences of vasovagal syncope.
- Only two small studies have evaluated fludrocortisone in paediatric patients (Scott 1995, Grubb 1992).
- Evidence suggests that fludrocortisone may not be well tolerated in elderly patients

•References of Included Studies

Scott WA, Pongiglione G, Bromberg BI, *et al.* Randomized comparison of atenolol and fludrocortisone acetate in the treatment of pediatric neurally mediated syncope. *Am J Cardiol* 1995; 76: 400-2

Grubb BP, Temesy-Armos P, Moore J, *et al.* The use of head upright tilt table testing in the evaluation and management of syncope in children and adolescents. *PACE* 1992; 15: 742-8

- Another unsystematic review (Claydon *et al.* 2006) reported that the mechanism of action of fludrocortisone and listed as a strategy for the management of hypotension in Spinal Cord Injured (SCI) patients.
- 2 other references were also cited but on further inspection of these citations, one was a single case study and the other a low grade comparative study with 6 patients with hypoadrenergic orthostatic hypotension.

Salt and Water Intake:

Frisbie *et al.* (2004) examined whether salt and water intake correlated with the severity of postural hypotension (PH). Findings included:

The ephedrine requirements, in order of decreasing severity of PH, were 100 mg/d, 25 mg/d, 12.5 mg/d, and no ephedrine needed.

- The 24-hour sodium excretions in that order were 50, 92, 180, and 164 mEq.
- The urine volumes were 1.4, 3, 2.6, and 5.4 L, respectively.
- In the same order of decreasing PH severity, the sitting position relative to the recumbent position was characterised by increasing rates of creatinine secretion (ratios of 0.69, 0.74, 0.95, and 0.80), increasing rates of water excretion (ratios of 0.49, 0.28, 0.69, and 0.99), decreasing urine osmolality (ratios of 1.2, 1.8, 1.3, and 0.8), and increasing sodium concentrations (ratios of 0.9, 1.3, 1.2, and 2.6).

- Conclusion: In this study individuals with tetraplegia, severe PH was accompanied by avid conservation of water and impaired retention of sodium in the sitting position, as well as limited salt and water intake

Compression Stockings

- An unsystematic review (Claydon *et al.* 2006) reported that “the use of compression bandages or support stockings to restrict venous pooling in the visceral area and dependent limbs should be encouraged”

[this review did cite 3 other studies that also presented evidence but these citations were other unsystematic review articles]

- Rimaud *et al.* 2007, examined the effects of graduated compression stockings on cardiovascular and metabolic responses to exercise and exercise recovery in patients with spinal cord injury. The study found that post-exercise venous lactate concentration was reduced in SCI participants with lesion levels below T6 while wearing graduated elastic stockings during both exercise and recovery (10.9+/-3.9 mmol/L vs 12.5+/-4.6 mmol/L, P<.05). There were no significant differences in submaximal and maximal values (heart rate, Vo₂, power output) between subjects tested with and without graduated elastic stockings.

- The authors concluded that wearing elastic stockings affects post exercise responses by decreasing lactate concentration in well-trained, low-level paraplegic patients after a maximal exercise. The relatively low pressure generated by the stockings may not, however, influence the venous system enough to produce improved performance and cardiovascular responses

Exercise: Electrically induced and voluntary activation of physiologic muscle pump:

Faghri *et al.* (2002) compared the haemodynamic responses of stroke volume, cardiac output, blood pressure, total peripheral resistance and heart rate to changes in position from sitting to standing and during 30 min of stationary standing between able-bodied and spinal cord-injured participants. The findings were:

- FES-induced activation of the physiologic muscle pump during change in position from sitting to standing prevented orthostatic hypotension in spinal cord-injured subjects.

- During standing it had equal or even greater effect on improving blood circulation when compared with voluntary activation in able-bodied subjects.

- The use of FES during standing and tilting in spinal cord-injured individuals may prevent orthostatic hypotension and circulatory hypokinesia and improve tolerance to tilting and standing.

Passive Leg Movements:

Svensson *et al.* (1995) examined the effects of passive leg movements on lower limb blood flow in acute SCI patients, post injury

- The increase in blood flow was slight or absent after treatment and there was no difference between the 5- and 30-movement series.

- The parameters studied did not indicate any useful effects of passive leg movements in the prevention of thrombosis in acute SCI patients.

Ter *et al.* (2006) assessed peripheral circulatory responses during and after passive leg movements and passive cycling in participants with SCI and compared them to healthy controls. The outcomes of 2 forms of passive exercise : passive cycling, were compared between the groups. The outcomes of arterial blood flow, skin blood flow and skin temperature were registered using venous occlusion plethysmography, laser-Doppler technique and a skin thermometer, respectively, before and after a series of 5 and 30 repetitions of passive leg flexion-extension movements.

- This small non randomised, comparative study found that in both groups, no changes in leg blood flow, vascular resistance, or blood pressure were observed during or after the 2 interventions.

- The results of the study demonstrated that passive leg movements and passive cycling do not alter the arterial peripheral circulation in participants with SCI or control participants.

Respiratory Management

The following evidence based guideline was identified and addressed Respiratory Management in patients with spinal cord injury: A Clinical Practice Guideline for Health-Care Providers (Consortium for Spinal Cord Medicine: Respiratory Management Following Spinal Cord Injury: (Paralysed Veterans of America publication 2005)). This guideline presents a comprehensive evidence-based review of the literature. With respect to appraisal of this guideline, using the AGREE Instrument, 14 out of 23 appraisal issues were rated high. 9 issues were rated weak. It was published in 2006, the search strategy was only conducted up till 2001 (with one 2004 article included). The reason for this time discrepancy is not described.

References

Bloomfield DM (2002) Strategy for the management of vasovagal syncope. *Drugs & Aging* 19, 179-202.

Claydon VE (2006) Orthostatic hypotension following spinal cord injury: Understanding clinical pathophysiology. *Spinal Cord* 341-351.

A Clinical Practice Guideline for Health-Care Providers (2005) Consortium for Spinal Cord Medicine: Respiratory Management Following Spinal Cord Injury: (Paralysed Veterans of America publication)
<http://www.pva.org/site/DocServer/resmgmt.pdf?docID=703>

Faghri PD (2002) Electrically induced and voluntary activation of physiologic muscle pump: A comparison between spinal cord-injured and able-bodied individuals. *Clinical Rehabilitation* 878-885.

Frisbie JH (2004) Postural hypotension, hyponatremia, and salt and water intake: Case reports. *Journal of Spinal Cord Medicine* 133-137

Rimaud D, Calmels P, Roche F, Mongold JJ, Trudeau F, Devillard X (2007) Effects of graduated compression stockings on cardiovascular and metabolic responses to exercise and exercise recovery in persons with spinal cord injury. *Archives of Physical Medicine & Rehabilitation* 88, 703-709.

Svensson M, Siosteen A, Wetterqvist H, Sullivan L (1995) Influence of physiotherapy on leg blood flow in patients with complete spinal cord injury lesions. *Physiotherapy Theory and Practice* 11, 97-107.

Ter WW, De Groot PC, van Kuppevelt DH, Hopman MT (2006) Passive leg movements and passive cycling do not alter arterial leg blood flow in participants with spinal cord injury. *Physical Therapy* 86, 636-645.

EVIDENCE TABLES

Bloomfield DM (2002) Strategy for the management of vasovagal syncope. *Drugs & Aging* 19, 179-202.

Design: Expert Review, Evidence level 4

Aim: This review described the diagnosis and treatment of vasovagal syncope. It included specific areas such as;

- Pathophysiology of Vasovagal Syncope and Related Disorders of Orthostatic Intolerance
- Evaluation of the Patient with Suspected Vasovagal Syncope and the Role of Tilt Table Testing
- Who Needs Treatment?
- Initial Approaches to Treatment
- Pharmacological Treatments (β -Blockers, Fludrocortisone, α -Adrenergic Agonists, Selective Serotonin Reuptake Inhibitors, ACE Inhibitors, Disopyramide, Anticholinergic Agents, Theophylline, Clonidine, Pacing and Tilt Training)
- Tailoring Treatment: An Algorithm
- Empirical Treatment of Vasovagal Syncope
- Tilt-Guided Therapy
- Vasovagal Response During Tilt Table Testing
- The Dysautonomic Response to Tilt Table Testing
- Assessing the Response to Treatment

Inclusion criteria

- Any study types that are relevant to this topic.
- There was no systematic search of the literature
- There was not systematic grading of included evidence, although comments were made that reported the overall evidence body

Population

Individuals who suffer from disorders of autonomic control associated with orthostatic intolerance (which are a diverse group of syndromes) that can result in syncope and near-syncope.

Interventions

- Fludrocortisone was the only intervention from the list of interventions in the PICO, therefore it is the only one I have reported.
- If there are other interventions that are relevant please indicate to AM.

Outcomes

Results

The results reported in this review about the effectiveness of Fludrocortisone were presented in a narrative format. Essentially there is limited evidence (as reported by this review), one RCT comparing Fludrocortisone with atenolol and consensus support for the use of this drug.

- Data supporting the value of fludrocortisone for the treatment of vasovagal syncope are extremely limited, although fludrocortisone is widely used and often considered one of the first lines of therapy for this condition.
- No randomised placebo controlled studies have assessed the efficacy of fludrocortisone in preventing recurrences of vasovagal syncope.

- Two small studies have evaluated fludrocortisone in paediatric patients (Scott 1995, Grubb 1992).
- Fludrocortisone may not be well tolerated in elderly patients

References of Included Studies

Scott WA, Pongiglione G, Bromberg BI, et al. Randomized comparison of atenolol and fludrocortisone acetate in the treatment of pediatric neurally mediated syncope. *Am J Cardiol* 1995; 76: 400-2

Grubb BP, Temesy-Armos P, Moore J, et al. The use of head upright tilt table testing in the evaluation and management of syncope in children and adolescents. *PACE* 1992; 15: 742-8

Bloomfield DM, Sheldon R, Grubb BP, et al. Putting it together: a new treatment algorithm for vasovagal syncope and related disorders. *Am J Cardiol* 1999; 84 (8A): 33Q-9Q

Claydon VE (2006) Orthostatic hypotension following spinal cord injury: Understanding clinical pathophysiology. *Spinal Cord* 341-351.

Design: Expert, Unsystematic review, evidence level 4

Aim: The aim of this review is to outline the incidence and patho-physiological mechanisms underlying the orthostatic hypotension that commonly occurs following SCI. The aetiology of this condition is described. The management of orthostatic hypotension is also examined.

Inclusion criteria

Not described

Exclusion criteria

Not described

Population

Patients who have SCIs

Interventions

- Abdominal Compression Bandages and /or support stockings
- Fludrocortisone

Outcomes

Results

Compression bandages:

As quoted from the review:

“The use of compression bandages or support stockings to restrict venous pooling in the visceral area and dependent limbs should be encouraged”

[this review did cite 3 other studies that also presented evidence but these citations were other unsystematic review articles]

Fludrocortisone

- Reference was made to the mechanism of action of this drug and listed as a strategy for the management of hypotension in SCI patients.
- 2 other refs were also cited but on further inspection of these citations, one was a single case study and the other a low grade comparative study with 6 patients with hypoadrenergic orthostatic hypotension.

General comments

The evidence about the management of orthostatic hypotension is presented in a narrative format. All the evidence included in this review was of low grade with no RCTs cited.

Faghri PD (2002) Electrically induced and voluntary activation of physiologic muscle pump: A comparison between spinal cord-injured and able-bodied individuals. *Clinical Rehabilitation* 878-885.

Design: Comparative, non-randomised, evidence level 2-
Country: USA

Aim: The purpose of the present study was to compare the haemodynamic responses of stroke volume, cardiac output, blood pressure, total peripheral resistance and heart rate to changes in position from sitting to standing and during 30 min of stationary standing between able-bodied and spinal cord-injured participants.

Inclusion criteria

spinal cord-injured individuals

Exclusion criteria

- Individuals with cardiac problem, pacemaker, recent fracture, incompetence uncontrolled spasticity and venous thrombosis within the last four weeks were excluded from the study.
- Individuals were excluded from the study if the Doppler ultrasound examination revealed evidence of a venous insufficiency or deep venous thrombosis.

Population

- 14 healthy spinal cord-injured individuals (C3–T12, ASIA criteria) were recruited
- Mean age 29 ± 6 years, weight 70 ± 15 kg and height 170 ± 8 cm

Interventions

- Participants were used as their own control.
- All participants participated in two testing conditions on two separate days:
(1) stationary standing, defined as standing without any intervention for 30 min and
(2) dynamic standing, defined as standing utilizing FES during 30 min of standing for spinal cord-injured participants and performing voluntary tiptoe contractions during 30 min for able-bodied participants.
- The two testing conditions were at least 24 hours apart for each participant, and the order of testing was random (by tossing a coin)

Outcomes

- stroke volume, cardiac output, heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and total peripheral resistance during change in position from sitting to standing
- systolic blood pressure, diastolic blood pressure, mean arterial pressure will be reported in full

Results

- During stationary standings, when participants moved from sitting to standing, spinal cord-injured participants showed significant reductions in systolic blood pressure,

diastolic blood pressure and mean arterial pressure, while these values were maintained in able bodied participants ($p < 0.05$).

- During dynamic standing in which FES-induced contractions of the muscles started in spinal cord-injured participants while they were sitting and continued until standing, all of the blood pressure values were maintained to pre-standing values. There were no changes in any of these variables in able-bodied participants during change in position from sitting to standing.

Percentage changes in the haemodynamic values from standing at time zero were compared with 5 and 30 min of standing during all the standing sessions (stationary and dynamic).

- During stationary standing in spinal cord-injured subjects, there were significant reductions in all of the haemodynamic values except for significant increases in total peripheral resistance at 5 and 30 min of standing.
- During dynamic standing in spinal cord-injured subjects, at 5 min, there were no changes in any of the haemodynamic variables.
- Following 30 min of this standing, while subjects maintained all the blood pressure values to pre-standing values, there were significant increase in heart rate and reduction in stroke volume ($p < 0.05$).

Cardiac output was maintained and no changes were observed in total peripheral resistance.

- During stationary standing by able-bodied subjects there were significant reductions in stroke volume, cardiac output and an increase in total peripheral resistance following 30 min.
- During dynamic standing able-bodied subjects maintained all of their haemodynamic values at 5 min, however, following 30 min, cardiac output decreased while heart rate and total peripheral resistance increased.

General comments

Frisbie JH (2004) Postural hypotension, hyponatremia, and salt and water intake: Case reports. Journal of Spinal Cord Medicine 133-137

Design: Case series , Evidence level 3
Country: US

Aim: This study examined whether salt and water intake correlated with the severity of postural hypotension (PH)

Inclusion criteria

Exclusion criteria

Population

Participants were 4 patients with tetraplegia, motor and sensory complete, aged 68 to 83 years, who were paralyzed for 9 to 54 years, who had PH. These patients were ranked by the amount of ephedrine prescribed on a daily basis to treat PH over the preceding 2-year period.

Interventions

salt and water intake

Outcomes

The total urinary output of sodium and water and the effect of orthostasis on urine output rate, osmolality, sodium concentration, and creatinine secretion were determined over a 48-hour period of collection and compared with severity of PH.

Results

- The ephedrine requirements, in order of decreasing severity of PH: 100 mg/d, 25 mg/d, 12.5 mg/d, and no ephedrine needed.
- The 24-hour sodium excretions in order of decreasing severity of PH: 50, 92, 180, and 164 mEq.
- The urine volumes were 1.4, 3, 2.6, and 5.4 L, respectively.
- In the same order of decreasing PH severity, the sitting position relative to the recumbent position was characterized by increasing rates of creatinine secretion (ratios of 0.69, 0.74, 0.95, and 0.80), increasing rates of water excretion (ratios of 0.49, 0.28, 0.69, and 0.99), decreasing urine osmolality (ratios of 1.2, 1.8, 1.3, and 0.8), and increasing sodium concentrations (ratios of 0.9, 1.3, 1.2, and 2.6).

General comments

In individuals with tetraplegia, severe PH was accompanied by avid conservation of water and impaired retention of sodium in the sitting position, as well as limited salt and water intake.

This is a very small observational study presenting very limited evidence about whether salt and water intake correlated with the severity of postural hypotension. In order to understand this process the study would need to have included several more participants and conducted a controlled study.

Rimaud D, Calmels P, Roche F, Mongold JJ, Trudeau F, Devillard X (2007) Effects of graduated compression stockings on cardiovascular and metabolic responses to exercise and exercise recovery in persons with spinal cord injury. *Archives of Physical Medicine & Rehabilitation* 88, 703-709.

Design: Comparative, non randomised study, evidence level 2-

Country: Physical medicine and rehabilitation department in France

Aim: To investigate whether reporting blood redistribution by means of graduated elastic stockings affects exercise and post exercise responses in people with spinal cord injury (SCI).

Inclusion criteria

men with traumatic SCI

Exclusion criteria

Population

Fourteen men with traumatic SCI, grouped according to their level of injury.

Interventions

Participants performed 2 maximal wheelchair exercise tests 1 week apart, in random order and under a counter-balanced design. One test was done with and the other without graduated elastic stockings (21 mmHg).

Outcomes

- Blood lactate, blood pressure, heart rate, maximal power output, and oxygen consumption (Vo₂).
- BP was reported in detail as it was the relevant outcome measure listed in the PICO.

Results

Different systolic blood pressure (SBP) were recorded according to conditions, injury level and exercise.

- For low-level group; a significantly higher SBP at rest with the stockings on than without them (139±24mmHg vs 126±16mmHg, P<0.05)
- For high-level group: lower SBP at rest was recorded with stockings than without (132±20mmHg vs 141±12 mmHg, no significant difference)
- SBP was significantly lower at rest without stockings in the low-level group than in the high-level group (P<0.05)
- Under both conditions, SBP increased at the end of the test in the low-level group (126±16mmHg at rest 141±38mmHg at peak exercise without stockings: 139± 24mmHg to 144± 40mmHg with, not significantly different).
- Compared to; post exercise, SBP dropped in the high level group even with stockings (141±12mmHg at rest to 127±21mmHg at peak exercise without the stockings: 132±20mmHg to 119±37mmHg with the stockings, no significant difference)
- Post exercise venous lactate concentration was reduced in SCI participants with lesion levels below T6 while wearing graduated elastic stockings during both exercise and recovery (10.9±/-3.9 mmol/L vs 12.5±/-4.6 mmol/L, P<0.05).
- There were no significant differences in sub-maximal and maximal values (heart rate,

Vo₂, power output) between participants tested with and without graduated elastic stockings

General comments

Wearing elastic stockings affects post exercise responses by decreasing lactate concentration in well-trained, low-level paraplegic patients after a maximal exercise. The relatively low pressure generated by the stockings may not, however, influence the venous system enough to produce improved performance and cardiovascular responses.

Applicability of this study is limited due to the lack of comparability of the participant group with MSCC patients.

Svensson M, Siosteen A, Wetterqvist H, Sullivan L (1995) Influence of physiotherapy on leg blood flow in patients with complete spinal cord injury lesions. *Physiotherapy Theory and Practice* 11, 97-107.

Design: Before and After study (observational), evidence level 2-
Country: Sweden

Aim: To examine the effects of passive leg movements on lower limb blood flow in acute SCI patients, post injury.

Inclusion criteria
Patients with traumatic SCI

Exclusion criteria
Patients with cardiovascular disease or any other condition that would affect the study outcomes.

Population

- 6 patients with traumatic SCI
- Aged b/n 18-71 (median 24) years
- Level of injury varied from C5 to T8
- 3 were tetraplegic, 3 paraplegics

Interventions
5 and 30 movement series of exercises over 4 weeks – maximal passive flexion-extension in all joints of the leg with hip flexion limited to 70 ° in order to avoid movements of the pelvis and spine.

- Resting blood flow was taken prior to tx.
- One leg of each patient, always the same, was treated with the 5 movement and then 30 movement series. The contralateral leg remained untreated and not moved at all.
- Measurements were taken after 5 movement series and the after the 30 movement series.

Outcomes

- Arterial blood flow (recorded by venous occlusion plethysmography)
- Skin blood flow (recorded by laser-Doppler)
- Skin Temperature

Results
Arterial blood flow

- Comparison of the treatments involving 5 and 30 repetitions showed approx. the same relative increase in blood flow.

In the treated leg:

- 5 passive leg movements resulted in a mean increase of 0.37 ± 0.26 ml/100g/min
- 30 movements resulted in a mean increase of 0.19 ± 0.25 ml/100g/min

In the untreated leg:

- 5 passive leg movements resulted in a mean increase of 0.29 ± 0.31 ml/100g/min
- 30 movements resulted in a mean increase of 0.21 ± 0.22 ml/100g/min

➔ The increase in blood flow was lower after treatment with 30 movements compared to 5 movements.

- In the first week of measurement: blood flow increased significantly after 5 movements in both treated and untreated leg ($P < 0.05$).
- No other significant differences were reported when pre- and post treatment blood flow were compared.

Skin Blood Flow

In the treated leg:

- 5 passive leg movements resulted in a mean increase in skin blood flow of $2.6 \pm 1.68\%$
- 30 movements resulted in a mean increase in skin blood flow of $1.3 \pm 1.1\%$

In the untreated leg:

- 5 passive leg movements resulted in a mean increase in skin blood flow of $2.2 \pm 2.36\%$
- 30 movements resulted in a mean increase in skin blood flow of $0.6 \pm 0.52\%$

➔ The increase was lower after the 30 movement series than after the 5 movement series.

The increase in skin blood flow was significant in the treated leg after 5 passive leg movements during the first week of measurements, other differences recorded were not statistically significant.

Skin Temperature

In the treated leg:

- 5 passive leg movements resulted in a mean increase in temp of $0.9 \pm 1.0^\circ\text{C}$
- 30 movements resulted in a mean increase in temp of $0.03 \pm 0.3^\circ\text{C}$

In the untreated leg:

- 5 passive leg movements resulted in a mean increase in temp of $1.07 \pm 1.2^\circ\text{C}$
- 30 movements resulted in a mean increase in temp of $0.5 \pm 0.3^\circ\text{C}$

➔ Out of 74 temperature measurements recorded, 48 indicated an increase.

General comments

This low quality evidence indicated that an increase in blood flow was slight or absent after treatment and there was no difference between the 5- and 30-movement series. The parameters studied did not indicate any useful effects of passive leg movements in the prevention of thrombosis in acute SCI patients.

Ter WW, De Groot PC, van Kuppevelt DH, Hopman MT (2006) Passive leg movements and passive cycling do not alter arterial leg blood flow in participants with spinal cord injury. *Physical Therapy* 86, 636-645

Design: Comparative, non-randomised study. Evidence level 2-

Aim: The purpose of this study was to assess peripheral circulatory responses during and after passive leg movements and passive cycling in participants with SCI (and control participants who were healthy by using protocols like those used in the clinical setting in rehabilitation centres.)

Inclusion criteria

All of the participants with SCI had motor complete lesions (American Spinal Injury Association class A or B) with injury levels between T2 and L1, and time since injury varied from 1 to 17.5 years

All participants were between 20 and 49 years of age and had no history of diabetes, cardiac diseases, recent DVT, or recent pressure ulcers.

Exclusion criteria

Population

- 8 men with SCI and 8 male participants who were healthy (control participants)

Interventions

- Passive leg movements carried out by a physical therapist and passive cycling (2 forms of passive exercise)
- The tests were performed between 8:30 am and 1:00 pm.
- The same investigator performed the test procedures, and passive leg movements were applied by 1 physical therapist in exactly the same sequence and manner for all participants.
- Successively, each participant underwent 2 interventions, which consisted of passive leg movements and passive cycling.

Outcomes

- Leg blood flow (LBF) at rest, during and after 10 minutes of standardized passive leg movements, and during and after 20 minutes of passive leg cycling (Echo Doppler measurements)
- Blood pressure was measured continuously
- Total peripheral resistance (TPR)
- Leg vascular resistance (LVR)
- Mean arterial pressure (MAP)
- Cardiac output (CO)

For the variables LBF, LVR, TPR, MAP, and CO, 2-factor repeated-measures analyses were applied with time (rest, intervention, and recovery values) as the within-participant factor and group (SCI and control) as the between participant factor. The level of statistical significance for all tests was set at $P < 0.05$.

Results

Resting Properties:

- At supine rest, the arterial diameter and blood flow of the common femoral artery were decreased significantly in participants with SCI compared with control participants.
- The LVR in participants with SCI was significantly higher than that in control participants.
- No differences between the groups were seen in any other variable at rest.

Passive Leg Movements:

- Repeated-measures analyses were applied to the data, and no significant main effect was found for blood flow
- (P=0.68), LVR (P=0.71), TPR (P=0.59), MAP (P=0.46), or CO (P=0.65), indicating that the variables did not change over the time period examined.
- No significant effect of an interaction of group and time was found for blood flow (P=0.35), LVR (P=0.22), TPR (P=0.68), or MAP (P=0.57).

Passive Leg Cycling:

- Repeated-measures analyses revealed no changes over time for blood flow (P=0.14), LVR (P=0.34), TPR (P=0.59), MAP (P=0.37), or CO (P=0.84).
- No significant effect of an interaction of group and time was found for blood flow (P=0.68), LVR (P=0.35), TPR (P=0.35), MAP (P=0.57), or CO (P=0.83).

RESPIRATORY MANAGEMENT

<p>Respiratory Management Following Spinal Cord Injury. A Clinical Practice Guideline for Health-Care Providers (2005) Consortium for Spinal Cord Medicine (Paralysed Veterans of America publication) http://www.pva.org/site/DocServer/resmgmt.pdf?docID=703</p>
<p>Design: Clinical Practice Guideline Country: US Setting: National Health Care System</p>
<p>Inclusion criteria <i>Study participants:</i> Patients with acute traumatic cervical SCI, regardless of the degree of completeness of injury. With a focus on the period of days to months following acute injury as well as on the long-term follow-up over years.</p> <p><i>Study designs:</i> The study design is controlled trial, prospective trial with historical controls, prospective or retrospective cohort study, or case series with 10 or more subjects.</p>
<p>Exclusion criteria <i>Study participants:</i> Excluded from consideration were non-pulmonary complications of SCI and venous thromboembolism/pulmonary embolus.</p> <p>The evidence does not cover patients with SCI occurring below the cervical level or respiratory muscle weakness caused by neuromuscular or other spinal cord diseases, such as Guillain-Barré syndrome and polio.</p> <p><i>Study designs:</i> Articles were excluded when the study population was children (all subjects or mean age < 18 years) or when the study design a case series with fewer than 10 subjects or a case report. Each article was independently reviewed by at least two investigators</p>
<p>Population Patients with acute traumatic cervical SCI, regardless of the degree of completeness of injury. With a focus on the period of days to months following acute injury as well as on the long-term follow-up over years.</p>
<p>Interventions</p> <ul style="list-style-type: none">• Initial assessment of acute sci• prevention and treatment of atelectasis and pneumonia• medications• mechanical ventilation (indications for mechanical ventilation, respiratory failure, intractable atelectasis, large versus small tidal volumes)• surfactant, positive-end expiratory pressure (peep), and atelectasis• complications of short-term and long-term ventilation (atelectasis, pneumonia, pulmonary embolism and pleural effusion, long-term ventilation, cuff deflations)• weaning from the ventilator (progressive ventilator-free breathing versus

<p>synchronized - intermittent mandatory ventilation, partial weaning)</p> <ul style="list-style-type: none"> • electrophrenic respiration • sleep-disordered breathing • dysphagia and aspiration • psychosocial assessment and treatment (adjustment to ventilator-dependent tetraplegia, enhancement of coping skills and wellness, affective status, substance abuse, pain, secondary mild brain injury, decision-making capacity, advance directives, family care-giving, intimacy and sexuality, establishment of an effective communication system) • education program development <p>discharge planning (home modifications, Caregivers, durable medical equipment, transportation, finances, leisure, vocational pursuits, transition resources)</p>
<p>Outcomes health outcomes, health services utilization, economic outcomes, or physiological measures related to respiratory status.</p>
<p>General comments – Over all this guideline presents a comprehensive evidence-based review of the literature. Although published in 2005, the search strategy was only conducted up till 2001. The reason for this discrepancy is not described. I can only assume it is due to the lengthy process of legal and peer review processes.</p> <p>The strengths and weakness of the guideline are described below using the AGREE tool to appraise the guideline.</p> <p><i>The AGREE tool identified the following areas that were strong for this guideline:</i></p> <ol style="list-style-type: none"> 1. The patients to whom the guideline is meant to apply are specifically described. 2. The guideline development group includes individuals from all the relevant professional groups. 3. The patients' views and preferences have been sought. 4. The target users of the guideline are clearly defined. 5. Systematic methods are used to search for evidence. 6. The criteria for selecting the evidence is clearly described. 7. The methods used for formulating the recommendations are clearly described. 8. The health benefits, side effects and risks are considered in formulating the recommendations. 9. The guideline is externally reviewed by experts prior to publication. 10. The recommendations are specific and unambiguous. 11. The different options for diagnosis and/or treatment of the condition are clearly presented. 12. Key recommendations are easily identifiable. 13. The guideline is editorially independent from the funding body. <p><i>The AGREE tool identified the following areas that were weak for this guideline:</i></p> <ol style="list-style-type: none"> 1. The overall objectives of the guideline are specifically described 2. The clinical questions covered by the guideline were not specifically described. 3. The guideline was not piloted among target users.

4. There is not an explicit link between the recommendations and the supporting evidence.
5. A procedure for updating the guideline was not provided.
6. The guideline was not supported with tools for application.
7. The potential organisational barriers in applying the recommendations were not discussed.
8. The potential cost implications of applying the recommendations were not considered.
9. The guideline does not present key review criteria for monitoring and/or audit purposes.
10. Conflicts of interest of guideline development members was not recorded.

7.6 Access to specialist rehabilitation and transition to care at home

A. Can MSCC patients benefit from specialised rehabilitation centres dedicated to patients with spinal injuries (neuro-patients)?

B. Which MSCC patient factors predict for beneficial outcomes from rehabilitation specialised services?

Short Summary

There is insufficient evidence of effectiveness of specialised rehabilitation for patients with MSCC. There were no randomised, controlled comparisons available between specialised rehabilitation and no rehabilitation or any other form of rehabilitation. The available evidence comes from case series studies and includes populations of which a very small proportion were MSCC patients. (Eriks 2003; Hacking 1993; McKinley *et al.* 1999, McKinley *et al.* 2000 and McKinley *et al.* 2001 ; New 2005). In general, patients with traumatic spinal cord injury had greater improvement in their functional independence than non traumatic spinal cord injury patients (this group contained a subset of MSCC patients). Spinal epidural metastasis (SEM) treatment plus intensive rehabilitation programme was compared to receiving only SEM treatment in a biased observational study (Ruff *et al.* 2007). Patients who received intensive rehabilitation survived longer. Median survival for rehabilitation group was significantly longer compared to the no rehabilitation group. Patients in the rehabilitation group were statistically more likely to be discharged home than the no rehabilitation group. Patients in the no rehabilitation group were statistically more likely to be diagnosed with clinical depression compared to rehabilitation patients. After completing rehabilitation, the rehabilitation group had significantly higher satisfaction with life score than that of the no rehabilitation group patients. After completion of rehabilitation intervention, rehabilitation group had lower pain levels than no rehabilitation group patients.

From the case series studies (which included populations with a very small proportion of MSCC patients) the following patient characteristics (age, tumour type and functional abilities) were identified as prognostic factors that predicted longer survival of patients after specialised rehabilitation programmes. The results varied across all studies and specific measures also varied. In general, patients with less aggressive tumours, the more independent, mobile, and younger the patient the better the prognosis wrt to longer survival (>1 year).(Murray *et al.* 1985, Hacking *et al.* 1993, Guo *et al.* 2003, Parsch *et al.* 2003, Eriks *et al.* 2004, Tang *et al.* 2007)

A. PICO

Population Group	Intervention	Comparison	Outcomes
Patients with known MSCC who have had surgery/ RT	being seen in a neurology or spinal injuries rehabilitation centre	no referral / not seen	Improvement in: <ul style="list-style-type: none">▪mobility,▪pain,▪continence,▪pressure sore incidence

			<ul style="list-style-type: none"> ▪independent living ▪length of hospital stay ▪quality of life on return home emergency readmission rate
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This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

B. PICO

Population Group	Factors	Outcomes
Patients with known MSCC who have had surgery/ RT, following referral to a spinal injuries rehabilitation centre.	<ul style="list-style-type: none"> • Performance status (Bartel index and Kanofsky) • Neurological level (pre-op, post-op) • Frankel • Neurological impairment post op (ASIA /Frankel Score) • Neurological level post op • Life expectancy • Extent of bony-metastatic disease • Patient preference • Overall prognosis 	Prediction successful outcomes: <ul style="list-style-type: none"> ▪mobility, ▪pain, ▪continence, ▪pressure sore incidence ▪independent living ▪length of hospital stay ▪quality of life on return home ▪emergency readmission rate

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

Results from comparative studies.

- In studies that compared specialised rehabilitation for traumatic SCI with specialised rehabilitation non-traumatic SCI patients, the length of stay in a rehabilitation unit was shorter for non-traumatic SCI patients (McKinley *et al.* 2001, McKinley *et al.* 2000 and McKinley *et al.* 1999). Ranging from 22 -25 days (non-traumatic SCI patients) Vs 38 – 57 days (traumatic SCI)
- The FIM (functional independence measurement) on admission for the different groups evaluated in the above studies indicated no statistical difference.
- FIM scores after rehabilitation (on discharge) was significantly higher for the traumatic SCI compared to the non-traumatic SCI patients.
- FIM change (measured as the difference between discharge and admission FIM scores) for SCI patients who were traumatically injured showed greater improvement in FIM change scores than their non traumatically injured counterparts.
- Spinal epidural metastasis (SEM) treatment plus an intensive rehabilitation programme (training in transfers, skin care, nutrition, and pulmonary exercise with incentive spirometry – rehab group) was compared to a group

of patients who only received spinal epidural metastasis (SEM) treatment (no rehab group). Patients in the rehab group survived longer. Median survival for rehab group = 26 weeks (95%CI 23.9-28.1 weeks). Median survival for no rehab group = 6 weeks (95%CI 5.9- 6.1), $p < 0.001$. The relative risk of being discharged home for the rehab group compared with the no rehab group = 3.75, 95% CI 2.31-6.09. The relative risk of being diagnosed with clinical depression among no rehab group patients compared to rehab patients = 10.4, 95% CI 5.81-18.6. After completing rehabilitation, the rehab group had higher Satisfaction with life score (SWLS) than that of the no rehab group patients, $p < 0.001$. the rehab group SWLS indicated satisfaction with life. After completion of rehab intervention, rehab group had lower pain levels than no rehab group patients, $p < 0.001$. (Ruff *et al.* 2007)

Results from other studies:

- A significant difference was observed for the FIM motor gain (Difference between admission and discharge scores) for the tumour aetiology group. (New 2005)
- Length of stay varied across different studies 55.8 days to 112 days. (New 2005, Hacking 1993, Eriks 2003)
- Functional outcomes were measured with various methods including, Frankel score and Barthel Index. Associations between these scores and survival or improved functional outcomes were reported. (see below for further details)

Patient characteristics that predict for beneficial outcomes from specialised rehabilitation

- Associations between functional outcome scores and survival were reported.
- Patient characteristics (age, tumour type and functional abilities) were identified as prognostic factors that predicted longer survival of patients after specialised rehabilitation programmes. The results varied across all studies and specific measures also varied. In general, patients with less aggressive tumours, the more independent, mobile, and younger the patient the better the prognosis wrt to longer survival (>1 year). (Murray *et al.* 1985, Hacking *et al.* 1993, Guo *et al.* 2003, Parsch *et al.* 2003, Eriks *et al.* 2004, Tang *et al.* 2007)

Care in the home

Effectiveness of home based supportive care for patients with incurable cancer was evaluated in a systematic review (Smeenk *et al.* 1998). The studies included reported diverse programmes and therefore results varied across studies. In general, home based care did not have a negative outcome on quality of life. Positive outcomes were reported for patient satisfaction, psychological impact and re-admission rates.

References

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Ruff, R. L., Adamson, V. W., Ruff, S. S. & Wang, X. (2007) Directed rehabilitation reduces pain and depression while increasing independence and satisfaction with life for patients with paraplegia due to epidural metastatic

spinal cord compression. *Journal of Rehabilitation Research & Development*, 44: 1-10.

Smeenk F W, van Haastregt J C, de Witte L P, Crebolder H F. (1998) Effectiveness of home care programmes for patients with incurable cancer on their quality of life and time spent in hospital: systematic review. *BMJ* 316. 1939-1944.

Evidence Tables

McKinley WO, Seel RT, Gadi RK, Tewksbury MA: Nontraumatic vs. traumatic spinal cord injury: a rehabilitation outcome comparison. Am J Phys Med Rehabilitation 2001;80:693–699.

Design: Longitudinal study (using a matched block design), 2+
Country: US
Setting: tertiary care

Inclusion criteria

Patients were selected from rehabilitation inpatients with SCI admitted to level I trauma centres between 1992 and 1999.

Patients were designated as eligible for inclusion in this study based on the following criteria:

- (1) admittance to the acute care hospital within 60 days of injury
- (2) complete data available for age, injury level, completeness of injury, inpatient rehabilitation lengths of stay and charges, and FIM motor scores
- (3) having received at least 5 days of inpatient rehabilitation care.

Exclusion criteria

Population

- 93% of all patients were admitted to a model systems facility within 21 days of injury.
- Nearly 68% of the injuries were paraplegic.
- The majority of all injuries were incomplete.
- 36% of patients had ASIA “C” ratings
- 41% had ASIA “D” ratings
- Approximately 60% of the matched patients were aged 30–59 yr

86 patients with non traumatic SCI admitted to a SCI rehabilitation unit and 86 patients with traumatic SCI admitted to regional model SCI centres.

NOTE: patients with metastatic disease were only a subset of the non traumatic SCI patient group, exact number was not reported.

Interventions

The objective of this study was to study the functional outcome of inpatient rehabilitation in individuals with non traumatic spinal cord injury (NT/SCI). A comparison between NT/SCI and traumatic SCI (T/SCI) controlling for age, level of injury, and American Spinal Injury association (ASIA) classification was used to assist in more clearly contrasting outcomes between these groups.

A comprehensive program of inpatient rehabilitation was provided to patients and tailored to meet their needs and abilities. Within each centre, the following services were provided:

nursing, occupational therapy, psychiatry and related medical services, physical therapy, psychological and neurologic assessment, recreational therapy, and social services.

Outcomes

- **Length of Stay**: The duration of stay in acute medical care and inpatient rehabilitation was calculated separately.
- **Charges**: This was actual hospital charges for each patient.

- **FIM Motor Score:** FIM motor scores ranging from 13 to 91 were assigned with higher scores denoting greater levels of independence. Scores were derived at the time of rehabilitation admission and discharge.
- **FIM Motor Change Scores:** scores were calculated based on the difference between rehabilitation discharge and rehabilitation admission scores.
- **FIM Motor efficiency Scores:** scores were calculated based on dividing patients' change scores by corresponding rehabilitation lengths of stay.

Results

Length of Stay:

Patients with T/SCI had significantly greater rehabilitation stays (M = 41.49 days) than patients with NT/SCI (M = 22.46 days), $P < 0.001$

Charges:

Traumatic spinal cord injury patients had significantly higher charges (M = \$66,117) than NT/SCI patients (M = \$25,165), $P < 0.003$

Mean rehabilitation daily charges for T/SCI patients (\$1,629) were significantly greater than charges for NT/SCI patients (\$1,148), $P = 0.019$. Daily charges differed by almost \$500/day between the two etiology groups.

No significant interaction effects (etiology X injury characteristics; etiology X age category) were found for length of stay or rehabilitation charges.

FIM Motor Score:

Analysis of FIM motor scores at rehabilitation admission revealed no significant difference b/n the patient groups.

Patients with SCI through traumatic means were discharged with significantly higher FIM motor ratings (M=68.01) than their non traumatically injured counterparts (M=55.84), ($P = 0.001$).

FIM Motor Change Scores:

The SCI patients who were traumatically injured showed greater improvement in FIM scores (M= 31.37) than their non traumatically injured counterparts (M= 18.81) $P < 0.001$.

No statistical differences were found in acute care length of stay, admission FIM scores, FIM efficiency, and community discharge rates.

General comments –

The intervention of intensive rehabilitation evaluated in this study provides some useful results indicating the positive effect however, in order to fully evaluate the effectiveness of this intervention a controlled trial needs to be conducted.

What it indicates is how effective intensive rehabilitation programmes are for NT/SCI patients when compared to T/SCI patients who are placed in the same intensive rehabilitation programme.

Because the number of patients with metastatic disease was only a subset of the non traumatic SCI patient group, it is very difficult to evaluate the effectiveness of this programme for these patients. This limits the value of this study for the MSCC guideline.

Observational Studies

McKinley, Huang & Tewksbury . Neoplastic vs. traumatic spinal cord injury: an inpatient rehabilitation comparison. American Journal of Physical Medicine & Rehabilitation 79[2], 138-144. 2000.

Design: Prospective cohort study (therapy), evidence level 2-
Country: United States,
setting: Tertiary care

Inclusion criteria

Patients met our facility's SCI rehabilitation admission criteria, including ability to tolerate 3 or more hours per day of interdisciplinary rehabilitation and had a prognosis of no less than 3 mo survival.

Exclusion criteria

Patients who did not meet the inclusion criteria.

Population

Prospective data were collected on 34 patients with a diagnosis of neoplastic involvement of the spinal cord who were consecutively admitted to a level I tertiary care center rehabilitation medicine unit during a 5-yr period. Of these 34 patients, 85% had a metastatic tumour, n=29

159 patients with SCI of traumatic origin (motor vehicle accident, 44%; gunshot wound, 28%; falls, 24%; other, 4%) consecutively admitted during the same time period

Interventions

The purpose of this study was to compare the demographics, injury characteristics, and functional outcome after inpatient rehabilitation of patients with neoplastic SCC and traumatic SCI.

Outcomes

- acute and rehabilitation hospital length of stay,
- Functional Independence Measure (FIM) scores
- FIM change (measured as the difference between discharge and admission FIM scores),
- FIM efficiency (FIM change per week)
- discharge to home

Patients were evaluated with the FIM instrument at admission to rehabilitation (within 72 hr) and again within 24 hr of discharge. To ensure interrater reliability, all FIM ratings were obtained by Uniform Data System-certified rehabilitation professionals.

FIM motor scores include self-care, sphincter control, mobility, and locomotion areas, and cognitive scores include communication and social cognition areas. Within each area, two or more specific activities/items are evaluated, with a total of 18 items. Each of the 18 items is evaluated in terms of dependence of functioning, using a seven-point scale, with a higher number indicating increasing independence.

Follow up 5 years

Results

Demographics:

Patients with neoplastic SCC were significantly ($P < 0.05$) older than those with traumatic SCI (58 vs. 39 yr) and were less often male (50% vs. 82%) and employed (27% vs. 60%)

Injury Characteristics:

Significant differences ($P < 0.05$) were noted between the two comparison groups in terms of their injury characteristics.

1. Patients with neoplastic SCC more often presented with paraplegia (88% vs. 52%).
2. The thoracic level was more commonly involved in the neoplastic group (76% vs. 38%), whereas cervical level involvement was seen in the traumatic SCI group (48% vs. 12%). Lumbosacral involvement was similar in the two groups.
3. Patients with neoplastic SCC more commonly presented with incomplete SCI (88% vs. 60%).

Length of Stay and Discharge to Home Rate

1. Patients with neoplastic SCC had a significantly shorter rehabilitation length of stay than those with traumatic SCI (23 vs. 38 days), ($P < 0.05$).
2. No significant differences between the two groups in acute care length of stay.
3. No significant differences between the two groups in terms of discharge living status. Both groups had a predominance of individuals discharged to home.

Functional Independence Measure Comparisons

No significant differences were observed in admission or discharge FIM scores or in FIM efficiency between the two groups; however, individuals with neoplastic SCC had significantly ($P < 0.05$) lower FIM change scores (19.7 vs. 27.3) compared with those with traumatic SCI.

No significant differences in admission or discharge FIM motor scores were found between neoplastic SCC and traumatic SCI individuals; however, individuals with neoplastic SCC had significantly lower FIM motor changes (15.1 vs. 24.7), $P < 0.05$.

General comments

Limits requiring attention:

1. Sample sizes of each group included in the study were not equivalent.
2. Possible confounders were not identified or controlled for.
3. Authors importantly point out: Examination of patients with neoplastic SCC **not** admitted to rehabilitation may reveal more information about outcomes in these populations

Conclusions:

During inpatient rehabilitation, patients with neoplastic SCC can achieve comparable rates of functional gains, have a shorter rehabilitation length of stay, and can achieve similar discharge-to-community rates to traumatic SCI patients.

McKinley, Huang & Brunsvold . Neoplastic versus traumatic spinal cord injury: an outcome comparison after inpatient rehabilitation. Archives.of Physical.Medicine & Rehabilitation 80[10], 1253-1257. 1999.

Design: Prospectice Case series, evidence level 3

Country: US

Setting: Tertiary Care

Inclusion criteria

- Prospective data were collected on consecutive patients (n = 34) with a diagnosis of neoplastic involvement of the spinal cord who were admitted to a level I tertiary care centre rehabilitation medicine unit over a 5-year period. (86.2% had metastatic tumor)
- The facility SCI rehabilitation admission criteria was used to include patients.
- This included: ability to tolerate 3 or more hours daily of interdisciplinary rehabilitation, and had a prognosis of at least 3 months' survival.

Exclusion criteria

- Five patients with neoplastic SCI were unmatched and were excluded from analyses

Population

- Patients (n = 34) with a diagnosis of neoplastic involvement of the spinal cord.
- A comparison data group (n = 4,001) included consecutive patients with SCI of traumatic etiology (motor vehicle accident, gunshot wound, falls, etc) admitted to the regional Model Spinal Cord Injury Centres and compiled at the National SCI database during the same time period.
- Neoplastic spinal cord patients were matched with traumatic SCI patients wrt age, level of injury, and ASIA Impairment Classification.
- 29 patients with neoplastic SCI were successfully mached with 29 counterparts with traumatic SCI.
- 86.2% of patients in the neoplastic SCI group had metastatic disease.

Interventions

This study aimed to compare outcomes of patients with neoplastic and traumatic SCI when admitted to an inpatient rehabilitation unit, controlling for age, LOI (level of injury), and American Spinal Injury Association (ASIA).

Authors hypothesized that patients with neoplastic SCC would:

- (1) make functional gains comparable to those of age- and LOI/ASIA-matched traumatic SCI patients,
- (2) have a shorter rehabilitation length of stay given their potential for limited life expectancy, and
- (3) have comparable success with discharge to the community.

Outcomes

- Acute and rehabilitation hospital length of stay
 - Functional Independence Measure (FIM) scores,
 - FIM change (measured as a difference between discharge and admission FIM),
 - FIM efficiency (FIM change/per week), and discharge to home.
- Patients were evaluated with the FIM at admission to rehabilitation (within 72 hours) and again within 24 hours of discharge.
- The FIM focuses on six areas of functioning: self-care, sphincter control, mobility, locomotion, communication, and social cognition. Within each area, two or more specific activities/items are evaluated, with a total of 18 items. Each of the 18 items is evaluated in terms of dependence of functioning, using a 7-point scale, with a higher number indicating increasing independence. FIM motor scores (including self-care, sphincter control, mobility, and locomotion) and cognitive scores (communication and social cognition) were analysed.

Follow up

5 Years

Results**Length of stay and discharge to home.**

- Patients with neoplastic SCI had a significantly ($p < 0.01$) shorter rehabilitation length of stay than those with traumatic SCI (25.17 vs 57.46 days).
- There were no significant differences between the two groups in acute care length of stay.
- There were no significant differences between the two groups in discharge living status.
- Both groups had a predominance (72% and 83%) of individuals discharged to home.

FIM comparisons.

- No significant differences between the two groups in admission FIM scores.
- Patients with neoplastic SCI had significantly lower discharge FIM scores (84.04 vs 95.00, $p < .05$) and FIM change scores (18.72 vs 37.07, $p < 0.01$) than those with traumatic SCI.
- There was no significant difference in FIM efficiency between the two groups.

FIM motor and cognitive score comparisons.

- Significant differences in FIM motor scores were found between the two SCI groups within the admission (37.68 vs 30.55), $p < 0.05$.
 - Significant differences in FIM discharge (53.15 vs 63.17), $p < 0.05$
 - Significant differences in FIM motor change (15.47 vs 32.62) $p < 0.05$.
- No significant FIM cognitive score differences between groups were noted.

Guo Y, Young B, Palmer JL, Mun Y, Bruera E: Prognostic factors for survival in metastatic spinal cord compression: A retrospective study in a rehabilitation setting. Am J Phys Med Rehabilitation;82:665–668. 2003

Design: Retrospective case series, evidence level 3

Country: US

setting: Tertiary care cancer centre - inpatient rehabilitation unit.

<p>Inclusion criteria</p> <p>Patients admitted to the unit between January 1996 and December 1998 with a diagnosis of MSCC.</p> <p>[The admission criteria included: inability to function independently in activities of daily living or mobility, with conditions such as neurogenic bowel or bladder, incoordination, dysarthria, and spasticity; and requiring at least two of the following services: physical therapy, occupational therapy, speech pathology, and rehabilitation nursing]</p> <p>Inclusion into the study:</p> <ol style="list-style-type: none"> 1) diagnosis of spinal cord compression secondary to metastatic tumor and 2) admission to the cancer centre's inpatient rehabilitation service, all with neurologic and functional deficits.
<p>Exclusion criteria</p> <p>Patients with a history of spinal cord compression or spinal cord compression secondary to a local tumor were excluded.</p>
<p>Population</p> <p>A total of 60 patients met these inclusion criteria</p>
<p>Interventions</p> <p>The rehabilitation programme evaluated in this study was aimed at the following aspects:</p> <ol style="list-style-type: none"> 1) to train the family to assist the patient with transferring to and from different surfaces (i.e., bed, wheelchair, toilet) and activities of daily living, 2) assess the patient's equipment need, 3) manage the patient's neurogenic bowel and bladder, 4) manage pain, 5) assist the patient and family in coping with the psychological distress, 6) teach the patient and family about skin care, 7) to evaluate and treat nutritional deficit.
<p>Outcomes</p> <p>Demographic and clinical variables were collected for all patients.</p> <p>Clinical variables included primary tumor site, number of organ systems with metastasis, major comorbidity, hemoglobin and albumin levels within a month before rehabilitation admission, treatment rendered for MSCC, opioids used for pain control, psychological symptoms during rehabilitation, diagnosis date, date of admission to inpatient rehabilitation, and date of death.</p> <p>Survival data were collected from the institutional database in 2000.</p> <p>Descriptive statistics were used to examine the different demographic and clinical variables.</p> <p>Kaplan-Meier method was used for survival analysis and was conducted for all patients and for subsets of patients corresponding to each prognostic factor.</p>
<p>Follow up</p>

2 years

Results

- 35 of 60 patients (58%) were <60 yr old
- 49 patients (82%) were discharged to home.
- The average length of stay in our inpatient rehabilitation unit is 16.7 days.
- The median survival time for all 60 patients combined was 4.1 months when calculated from the date of rehabilitation admission to the date of death.
- The median survival time was 5.2 months when it was measured from the date of MSCC diagnosis to the date of death.

- The only prognostic factor that was statistically significant by Kaplan-Meier survival analysis was primary tumor site ($P < 0.0001$)
- Other factors also analysed but found to not have a significant influence on survival included: specific treatment for MSCC, the use of opioids for pain control, psychological symptoms, the number of organs with metastases.

General comments –

The limited numbers included in the analyses limited the power of the study.

McKinley, Conti-Wyneken, Vokac & Cifu . Rehabilitationilitative functional outcome of patients with neoplastic spinal cord compressions. Archives.of Physical.Medicine & Rehabilitation 77[9], 892-895. 1996.

Design:, Retrospective Case series, evidence level 3
Country: United States,
Setting: Tertiary care

Inclusion criteria

Patients were admitted who met standard SCI rehabilitation criteria, were able to tolerate 3 or more hours of intensive rehabilitation, and had a prognosis of no less than 3 months' survival.

Exclusion criteria

Population

32 patients (18 men and 14 women) were included

Interventions

This study presents descriptive data on the functional outcome of individuals with SCI secondary to neoplastic compression admitted to spinal cord injury rehabilitation unit. The inpatient Rehabilitation Unit offered an interdisciplinary team approach for treatment, rehabilitation, and education for patients, family, and/or caretakers.

A 5-year review was conducted of all patients with neoplastic involvement of the spinal cord admitted to a spinal cord injury unit in a major medical centre.

Outcomes

- Demographic data
- Clinical data included tumour type, tumour treatment (surgery, radiation therapy, chemotherapy, or steroids), medical complications, neurological level, and American Spinal Injury Association (ASIA) classification of SCI.
- Functional data included length of stay, functional outcomes (utilising Functional Independent Measurement scores in mobility and self-care areas), bladder management and disposition.

Follow up

Prospective follow-up telephone and mail survey completed between 3 and 15 months after discharge was used to assess post discharge morbidity and functional ability.

Patients and/or their families were asked for a description of ambulation and dressing ability, medical complications, and a subjective evaluation of the effectiveness of their stay on the rehabilitation unit.

Results

Demographics:

32 patients (18 men and 14 women) were included
Mean age = 61 years

8 patients < 50 years

4 patients = 50 to 59

12 = 60 to 69

5 = 70 to 79

3 patients > 80 years

Clinical data:

9 patients (28%) had metastatic lung tumour,

6 (17%) had metastatic prostate tumour

3 (9%) had metastatic breast tumour.

Other tumors represented both primary and secondary spinal cord tumors.

Treatment options included radiation therapy in 22 patients, corticosteroids in 19 patients, surgery in 18 patients, and chemotherapy in 8 patients.

Neurological:

The spinal cord level of involvement ranged from the upper cervical to the lumbosacral level, with the thoracic segments most commonly involved (25 patients, 78%).

The patients were classified in correlation with the American Spinal Injury Association (ASIA) standards. On admission to the Rehabilitation Unit,

3 patients were classified as ASIA A,

5 were ASIA B,

21 were ASIA C

3 were ASIA D.

11 patients improved their ASIA classification by the time of discharge, with all 11 progressing from a ASIA C to D.

Functional:

- The average length of stay on the Rehabilitation Unit was 27 days (range 7 to 54).
- The average length of stay in the acute hospital setting (pre-rehabilitation) was 17 days (range 7 to 42).

- 6 of the 32 patients (19%) were bladder-continent on rehabilitation admission.

Of the 26 incontinent patients, 5 became continent of bladder function during rehabilitation, 16 were discharged

on an intermittent catheterization program, and 5 were discharged with an indwelling catheter.

- The functional independence measure (FIM) admission was compared to FIM discharge function in 10 different categories (see table below taken from paper).
- Functional improvements were shown in all areas assessed, with statistically significant improvements observed in the areas of upper and lower extremity dressing, grooming, toilet and tub transfers, wheelchair use and transfers, ambulation, and stair climbing (paired t test, $p < 0.005$).

At discharge from inpatient rehabilitation, 27 patients (84%) returned home with assistance of family, 4 patients were transferred from the Rehabilitation Unit for medical

issues and did not return, and 1 patient died before discharge from the Rehabilitation Unit. The 4 patients transferred from rehabilitation died within 2 months.

Follow-up:

- 20 patients provided follow up responses. 12 (60%) of patients had died and 8 were still living.
- The patients who died had survived an average of 101 days after discharge from the Rehabilitation Unit (range 22 to 285 days).
- Maintenance of ambulation and ability to dress was assessed at 3 months after discharge for 16 patients and at 1 month for 4 patients who died within 3 months of discharge.
- Sixteen (80%) of the 20 patients maintained mobility function at either the same or an improved level compared with their discharge function.
- 15 (75%) of the 20 patients maintained the same or an improved level of function for dressing compared with their discharge function.

Author's conclude that this study found that functional improvements occur during comprehensive inpatient rehabilitation for patients with spinal cord compression secondary to neoplasm. Furthermore, these improvements can be maintained for at least 3 months after discharge.

These results indicate that if a patient starts with a reasonable level of mobility and the ability to dress oneself then after rehabilitation, these abilities will be maintained or possible improved.

General comments

Generally a young sample and small sample will limit the generalisability to a wider population. The number of MSCC patients was just over 50%, this will affect the results reported. It is unclear what the influence would be because the clinical and neurological factors for the MSCC patients was not reported.

The retrospective design of this study limits the accuracy of the data collected.

A multivariate analysis would have provided valuable information about which characteristics (eg. ASIA scores or FIM scores) are predictive of positive outcomes.

New. PW. Functional Outcomes and Disability After Nontraumatic Spinal Cord Injury Rehabilitation: Results From a Retrospective Study. Arch Phys Med Rehabil Vol 86 (2) 250-261. 2005.

Design:, Retrospective Case series, evidence level 3

Country: Australia

Setting: Tertiary care: Spinal Rehabilitation Unit

Inclusion criteria

- Patients were referred from either public or private hospitals after acute medical or surgical treatments of their non traumatic SCI and any associated conditions.
- Patients were admitted into the program once they are medically stable. Admission decisions were based on the patients' perceived ability to benefit from and participate in the program.
- Discharge decisions were made with the involvement of the patient and family.
- No third-party payment source has influence over LOS or discharge destination.

The study sample initially consisted of 70 patients.

8 patients died before discharge home. The discharge outcomes exclude these patients who died.

Exclusion criteria

- Patients were excluded from the study if they did not have a non traumatic SCI or if they had a peripheral nerve injury not associated with myelopathy or cauda equina involvement.
- Patients not admitted for their initial rehabilitation after the onset of a non traumatic SCI and those with an LOS (length of stay) of less than 7 days were also excluded.

Population

This study described the demographic characteristics, clinical features, and outcomes, with a focus on the functional status and disability, in a group of patients undergoing initial inpatient rehabilitation after non traumatic spinal cord injury (SCI).

Non traumatic SCI included any cause of damage to the spinal cord, cauda equina, or the conus that was not due to trauma. Aetiology of the SCI was classified further into groups as follows: Tumor; Degeneration; Vascular aetiology group.

The medical records for all patients admitted to the Spinal Rehabilitation Unit between January 1, 1995, and December 31, 1997

Tumour group = 23 patients (out of 70 total), 32.9% of total patient group.

Degenerative SCI: 25.7% 18 patients

Vascular SCI: 14.3% 10 patients

Transverse myelitis SCI: 10.0% 7 patients

Infection SCI: 4.3% 3 patients

Multiple sclerosis SCI: 2.9% 2 patients

Other SCI: 10.0% 7 patients

Neurological category was not assigned for any aetiology group only for the group as a whole.

Interventions

Spinal Rehabilitation Unit (at a general medical centre).

The unit provides specialist interdisciplinary rehabilitation, principally for adult non traumatic SCI patients. It also provides ongoing follow-up post discharge for all patients and offers comprehensive outpatient and domiciliary rehabilitation programs where appropriate.

Outcomes

FIM subscales scores, key demographic characteristics (gender, age), and key clinical features (LOS, mortality, discharge home) with patients grouped according to their level of injury and ASIA classification status.

The above variables with patients grouped into the most common etiology groups (tumor, degenerative, vascular, other) was also analysed.

Follow up

Not reported

Results

For all non traumatic SCI patients:

Forty-one patients (58.6%) were paraplegic incomplete, 23 (32.9%) were tetraplegic incomplete, and 6 (8.6%) were paraplegic complete.

- Eight patients (11.4%) died before hospital discharge. Of those who survived, 47 (75.8%) were discharged home, 11 (17.7%) were transferred to a nursing home, and 4 (6.4%) went elsewhere in the community.
- The geometric mean LOS was 55.8 days.
- 9 patients (14.5%) were discharged walking unaided,
- 27 (43.5%) were walking at least 10m with a gait aid
- 26 (41.9%) were wheelchair dependent for mobility.
- 30 patients (48.4%) were voiding on sensation,
- 7 (11.1%) used intermittent catheterization, 23 (37.2%) had an indwelling catheter,
- 2 (2.8%) used reflex voiding.
- 11 patients (17.7%) were bowel continent on sensation
- 47 (75.8%) were bowel continent with a bowel program,
- 1 patient (1.6%) had a colostomy
- 3 patients (4.8%) were discharged with bowel incontinent.
- The mean FIM motor score was 39.6 on admission and 58.7 at discharge (paired t test, $t = -11.2$; $P < 0.000$).
- The different aetiology groups had significant differences between them for age, the proportion of patients from each group who died, the mean discharge FIM motor score, and the mean FIM motor gain.

- All aetiology groups had a statistically significant increase in their mean FIM motor score between admission and discharge, but no significant differences existed between their mean motor FIM efficiency ratings.

For the tumour aetiology group only: a significant difference was observed for the FIM motor gain (Difference between admission and discharge scores.) $p < 0.001$

General comments

This study provides limited understanding about MSCC patients outcomes after specialised rehabilitation where outcomes include: ASIA scores, mobility, bladder and bowel management interventions required, use of supports (formal or informal), accommodation settings, or FIM cognitive scores. The results presented include all patients with non traumatic SCI and MSCC patients make up a small proportion of this group.

The only section that provides direct measures wrt to MSCC patients is the analysis that reports tumour specific outcomes and demographic and FIM motor scores. (as reported in the results section in **bold**).

In general the authors conclude that most non traumatic SCI patients returned home with a good level of functioning regarding mobility, bladder, and bowel status, in comparison to other studies of patients with SCI. Patients' disability was usually significantly reduced during rehabilitation.

If the GDG require further results of all non traumatic SCI patients please contact AM.

Murray P. Functional Outcome and Survival in Spinal Cord Injury Secondary to Neoplasia. Cancer 55:197-201, 1985.

Design: Retrospective Case series, Evidence Level 3
Country: US
Setting: Tertiary unit.

Inclusion criteria

A 12-year retrospective review was conducted of all patients with malignant neoplasms and spinal cord injury admitted to the rehabilitation unit at Strong Memorial Hospital in Rochester, New York.

The patients are admitted to the rehabilitation unit following screening for rehabilitation potential by the staff physiatrist.

Exclusion criteria

Population

27 patients were identified who met the study criteria. (12 female and 15 male patients.)
Age range was 16 to 74 years (mean = 55.0 ± 14.9 years.)

Interventions

This study evaluated the long-term functional outcome of patients with spinal cord injury secondary to neoplastic disease (SCI) at a specialised rehabilitation unit located within a general hospital.

The study specifically addresses the question of whether there is a population of patients with neoplasia-related SCI with good long-term outcome.

Outcomes

Medical records were reviewed and the following extracted and evaluated: demographic data regarding level of injury, type of injury, type of tumour, pre morbid chronic medications, type of antitumour therapy, length of stay on rehabilitation, time from SCI to rehabilitation admission, and number of complications specifically related to SCI (deep venous thrombophlebitis, sepsis, pain requiring narcotics, spasticity requiring antispastic medications and decubitus).

A Frankel score was determined for each patient based on the initial clinical examination.

Functional outcomes were determined at discharge from occupational and physical therapy summaries and at 3 and 12 months by telephone follow-up with patient or family. Independence in activities of daily living (ADL) was defined as the ability of patients to care for personal hygiene, feeding, and dressing by themselves if provided with the proper equipment for each task.

Independence in ambulation was defined as the ability to walk unassisted or propel a wheelchair unassisted and the ability to transfer from bed, chair, and commode to a standing position or to a wheelchair.

Follow up

Functional outcomes were determined at 3 and 12 months by telephone follow-up with patient or family.

Results

Characteristics of Patients by Degree of Neurologic Injury/LOS/Discharge data:

Neither age nor length of stay on rehabilitation was statistically different in the three groups (age: $F = 2.03$, $df = 2, 24$, NS; length of stay: $F = 2.43$, $df = 2, 24$, NS).

Discharge to institutional settings was more frequent in the group with Frankel scores of 2 or 3 ($\chi^2 = 8.93$; $df = 2$; $P < 0.025$).

Survival

The 1-year survival in the three Frankel groups was not statistically different ($\chi^2 = 2.84$; $df = 2$; $P > 0.05$).

Independent function:

- The independence in these activities (independent in either ambulation, activities of daily living, or both at discharge and follow-up) obtained during the rehabilitation stay was well-maintained in all patients with incomplete injuries (Frankel 2, 3, and 4).
- One patient was independent at 12-month follow-up in the group with complete injuries (Frankel 1). This difference was significant. (Fisher's exact test, $S = -62$; $P = 0.05$).
- The patients with incomplete injuries (Frankel 2, 3, and 4) were examined in more detail to attempt to discover possible predictors of independence at 1 year.
- None of these possible predictors (*age, length of stay on rehabilitation, presence of family supports, number of medical complications after SCI, prescription chronic medications, and length of time from injury to patient admission to rehabilitation with respect to independence at 1 year after discharge from rehabilitation*) were related to outcome at one year.

The sample was divided into 4 categories-(1) solid tumor, (2) primary central nervous system (CNS) tumor, (3) lymphoproliferative tumor, and (4) radiation myelitis. The study examined the effects on independent functioning at discharge at 1 year and on 1-year survival itself.

- The uniformly good outcome of the patients with primary CNS tumors or radiation myelitis is significantly better than that of the patients with lymphoma or solid tumors. (Fisher's exact test, independent function $S = -48$; $P = 0.05$; 1-year survival, $S = -42$; $P = 0.05$)

Authors note that the group of patients they have studied differs from previous study groups in being younger, less likely to have lumbosacral injuries, and having a much better overall 1-year survival.

One-year survival and independent function at 1 year were significantly related to severity of the neurologic injury. In patients with incomplete injuries, those with lymphoma or solid tumor had lower survival and independent function rates at 1 year than those with

primary CNS tumors or injuries secondary to radiation myelitis.

General comments

Author's overall conclusions: SCI secondary to neoplasia does not invariably imply poor 1-year survival, however patients with more severe neurologic injury seem to have worse survival and functional outcomes.

Issues to consider:

- Sample was small, and relatively young.
- Selection bias: Patients with lymphoma and primary CNS tumor were overrepresented in the sample (possibly b/c the expected long-term survival is better than in patients with solid tumours)
- Retrospective study design limits the collection of relevant and accurate data. A prospective study design allows for prepared outcomes to be collected more consistently and accurately.

Hacking, Van As & Lankhorst . Factors related to the outcome of inpatient rehabilitation in patients with neoplastic epidural spinal cord compression. Paraplegia 31[6], 367-374. 1993.

Design: Retrospective case series, evidence level 3

Country: The Netherlands

Setting: tertiary, specialised spinal cord unit

Inclusion criteria

Clinical records of all patients with neoplastic epidural spinal cord compression, admitted to any Dutch spinal cord unit (SCU) between 1-1-1985 and 1-1-1990.

Exclusion criteria

Population

74 patients with MSCC included: 48 men, 26 women.

Interventions

This study aimed to develop a method to predict the survival and the functional outcome following neoplastic spinal cord injury (SCI), in order to select patients for an intensive inpatient rehabilitation programme.

Outcomes

Clinical records

Progression rate of neurological symptoms

Functional performance

Mobility

In order to evaluate indicators related to life expectancy patients were divided into 2 groups by their length of survival after discharge from spinal unit (with one year being the division).

The likelihood and Odds ratio were determined for all variables.

Follow up

Results

- The average stay at the SCU was 112 days,
- The average survival after discharge was 423 days
- The average survival after SCI was 611 days

- Analysis indicated that 6 indicators were associated with prolonged survival after discharge (> one year) and improved functional level. These included
 - tumour biology (lymphoma, myeloma, breast and kidney tumours);
 - SCI as the presenting symptom of the malignancy;
 - slow (> 1 week) progression rate of neurological symptoms;
 - tumours treated with a combination of surgery and radiotherapy;
 - (partial) bowel control at admission;
 - (partial) independence regarding transfer activities at admission

A scoring system consisting of the above indicators and likelihood ratios was used. A sum score (range 0-6) predicted the survival of a patient after discharge. A patient with a

sum score of 0-1 has zero probability of living longer than one year after discharge and 0.19 of functional improvement during stay at the SCU. A score of 5-6 yields probabilities of 0.77 and 0.92 respectively.

The authors conclude that the sum score can be helpful when selecting patients for an intensive inpatient rehabilitation programme or modifying such a programme.

General comments

This scoring system did provide a useful method for selecting patients who will benefit from specialised rehabilitation care, however, in order for this system to be used more extensively, it needs to be validated with a larger population and in different settings. Neither of these points have been addressed and therefore limits the use of it.

Eriks, Angenot & Lankhorst . Epidural metastatic spinal cord compression: functional outcome and survival after inpatient rehabilitation. Spinal Cord. 42[4], 235-239. 2004.

Design: Retrospective case series, evidence level 3

Country: The Netherlands

Setting: tertiary, specialised rehabilitation centre.

Inclusion criteria

Exclusion criteria

Population

Patients with SCC due to epidural metastases and who were admitted into a spinal cord units, Spinal Rehabilitation Center Amsterdam.

Interventions

This study aimed to:

1. describe patients with epidural metastatic spinal cord compression (SCC) admitted to nine Dutch spinal cord units (SCUs) between 01-01-1990 and 01-01-2000.
2. identify factors that predict survival >1 year after in-patient rehabilitation of patients with epidural metastatic SCC.

Outcomes

1. Clinical records were reviewed and demographic, clinical and functional data were collected according to a protocol. The date of admittance to the SCU, rehabilitation goals, length of stay, ASIA classification and Barthel Index (functional ability scored on a 20 point index on admittance and on discharge), date of discharge and date of death were recorded.
2. The odds ratio (OR) was calculated for all determinants on admittance to the SCU in order to find indicators that predict survival >1 year after discharge from the SCU. An OR ≥ 2 was considered to be clinically significant.

Follow up

Results

- 131 patients with epidural metastatic SCC were admitted.
- 117 clinical records were retrieved and 97 clinical records provided complete data.
- The average age on admittance was 58 years (53% male).
- The average Barthel score on admittance was 7.2/20 points.
- The average length of stay in the SCU was 104 days (3 - 336).
- Overall, 66% of the patients were discharged.
 - The average Barthel score on discharge was 12.0 points.
 - The average survival after discharge was 808 (0 - 3669) days.
- During their stay on the SCU: 7 patients died.

- At 1 year after discharge, 52% of the patients were still alive.
 - These patients suffered less complications, had been admitted less often to a hospital during rehabilitation, had made better functional progress and had been discharged home more often.

A survival >1 year after discharge is related to;

- ASIA D (OR 4.3),
- MRC 4 and 5 (OR 5.4) [MRC scale scores for muscular strength and level of lesion],
- tumour in remission (OR 3.8)
- independence or partial independence on the Barthel items: dressing independently or with minor assistance (OR 4.3)
- making transfers independently or with assistance (OR 5.0)

General comments

Selection bias of patients included in the study will affect the results. The selection of patients admitted into the specialists centre for this study include:

- Prognosis of survival > 1 year
- Patient physically able to receive rehabilitation treatment
- Patient has the possibility to go home after discharge from the unit.

Parsch D.Mikut R.Abel R. Postacute management of patients with spinal cord injury due to metastatic tumour disease: survival and efficacy of rehabilitation. Spinal Cord. 41 (4) 205-210 2003.

Design: Retrospective case series

Country: Germany

Setting: Spinal Cord Injury Unit, University Hospital, Heidelberg

Inclusion criteria

All patients had to have received primary treatment. And have been admitted to the unit between 1979 and 1995.

Exclusion criteria

Population

- 68 patients (30 males and 38 females) with SCI due to tumour mets of the spine.
- 17 patients did not complete the rehabilitation programme (11 due to change illness and 6 patients died)
- 68 was used as the denominator in all calculations which would have balanced any possibly inflated effect size.

Interventions

This study was performed to analyse the clinical presentation and survival rate of individuals with spinal cord injury (SCI) due to spinal metastasis after primary treatment, and to evaluate the efficacy of rehabilitation efforts.

The rehabilitation programme offered was within a SCI unit taking 4 to 6 weeks to complete. It focused on:

- effective pain control
- voiding and bowel management
- treatment of pressure sore
- mobilization with a physical therapist
- adaptation of aids (wheelchair, mattress) with an OT
- social services supported post –rehabilitation placement of patients
- psychological counseling was also offered.

Outcomes

- Patient records were searched for DOB, gender, type of tumour, type of onset of symptoms, a description of the neurological deficit (level of lesion, Frankel score) and dates of admission and discharge.
- Functional status : using patient records the FIM scoring was retrospectively determined at admission and discharge.
- Patient’s mobility was categorised into bedridden, wheel-chair user or minimum walking ability preserved.
- Presence of pressure sores was also noted.
- Survival (Kaplan-Meier methods to estimate survival)
- Cox regression and “fuzzy logic” were used to determine prognostic factors for survival (after rehabilitation).

Follow up

5 years

Results

- Of the 68 patients, 66 patients died at 11 months (median, inter-quartile range (IQR) 4-29 months) after the onset of neurological symptoms at an average age of 58 years.
- The most common primary tumour types were breast, lung, kidney and prostate with 3 patients with an unknown primary tumour.
- 59 thoracic and 2 lumbar lesions were observed.
- Frankel Scores included: Frankel A (21 patients), Frankel B (11), Frankel C (24) and Frankel D (12)
- 55 patients were bedridden and 13 were mobile (10 with a wheelchair and 3 having walking ability).
- The median length of stay was 50 days.
- For those patients that did complete the programme, the FIM score improved from 62 at admission to 84 at discharge. With rehabilitation efficiency (FIM difference/length of stay) of 0.33

From the multivariate analysis:

- The FIM score proved to be the most reliable prognostic factor of survival.
- With the higher the FIM score being associated with longer survival.
- Frankel B, C, D provided better prognosis compared to Frankel A.
- Younger age at the time of SCI and being female increased the chance of longer survival.

Fuzzy logic recommendations:

- A good or very good FIM score at admission (approx > 65) indicates longer survival
- A poor or very poor FIM score at admission (≤ 65) indicates short term survival
- Low Frankel score (B,C, D) and not very aggressive tumours (thyroid carcinoma and lymphoma) are indicators of longer survival.
- Wheelchair mobility or walking ability also indicate longer term survival.

[Longer survival >10 months (n=35) and shorter survival <10 months (n=33)]

Author's conclusion:

"Since institutionalised rehabilitation efforts are effective, this group of patients should be accepted into such a program"

General comments

Retrospective determination of FIM scores was done, highlighting the inherent flaw with retrospective study design, i.e. the level of inaccuracy or data collected and possible bias in designating Frankel or FIM scores).

Tang, V., Harvey, D., Park, D. J., Jiang, S. & Rathbone, M. P. (2007) Prognostic indicators in metastatic spinal cord compression: using functional independence measure and Tokuhashi scale to optimize rehabilitation planning. *Spinal Cord* 45: 671-677.

Design: Retrospective case series, evidence grade 3
Country: Canada

Aim: To determine if patients with MSCC make significant functional gains through rehabilitation. To study survival and predictors of survival in MSCC. To explore predictive factors for high or low functional gains in MSCC

Inclusion criteria

Patients with MSCC admitted to In-patient oncology, rehabilitation ward.

Exclusion criteria

Population

69 consecutive inpatient records: 6 patients excluded for incomplete patient records. Total = 63 patients (3 patients died while on the ward and FIM score = 18)

Interventions

Patient records were scanned for data about mobility, personal and clinical details about primary and spinal disease, estimated Tokuhashi Score, survival.

Outcomes

- FIM scores – made up of 6 areas of care, 2 of sphincter control, 3 areas of transfer ability, 2 associated with mobility, 2 associated with communication and 3 associated with social cognition. Total 18 items, scores range 1-7 (1= complete independence, 7 = assistance required)
- Survival – calculated as survival in months after rehabilitation.
- Kaplan Meier survival analyses used to estimate survival associated with Tokuhashi score, FIM scores (admission, change), length of rehab, age, gender, ASIA score, neurological level, treatment of MSCC (surgery VS no surgery).
- Multivariate analysis (Cox regression) conducted to determine prognostic factors with the the above factors.
- Exploratory log regression used to identify factors associated with low and high FIM change (≤ 13 VS >13). Independent variables = Tokuhashi score, admission FIM score, length of rehab, age, gender, ASIA score, neurological level, treatment of MSCC.

Results

FIM scores

Significant improvement in FIM scores from admission to discharge (P= 0.00004)

Survival

- 63 patients: 46 recorded date of death, 15 patients were alive at follow up, 2 lost to follow-up.
- Estimated median survival after rehab = 10 months

Univariate analyses of prognostic factors for survival

- A significant difference in survival between patients with a high Tokuhashi score (9-15)

compared to a low score (0-8), P=0.003

- A significant difference in survival between patients with a low FIM change (≤ 13) compared to high FIM change (> 13), P=0.012
- No significant differences in survival for admission FIM score, length of rehab, ASIA score, gender, surgical treatment.

Multivariate analysis of prognostic factors for survival

High FIM change and high Tokuhashi score were positive prognostic factors for survival.

$\chi^2 = 13.412$, df=2, P=0.001

Predictors of functional gain

Tokuhashi Score; OR= 1.3, 95%CI 1.04-1.62, P=0.022 and length of rehab; OR= 1.04, 95%CI 1.01-1.07, P=0.021 were significantly associated with high FIM gain.

General comments

The retrospective nature of this study limits the confidence of the predictions that are reported. A prospective study is required to affirm these calculations.

It would be beneficial to know more about the rehabilitation that patients received and the effects of different patient and clinical characteristics with different rehab interventions may have had.

The authors describe the limits of short follow-up time. While the numbers in the study also limited the reported findings, extended follow-up time would have provided valuable data.

Smeenk F W, van Haastregt J C, de Witte L P, Crebolder H F. Effectiveness of home care programmes for patients with incurable cancer on their quality of life and time spent in hospital: systematic review. BMJ 316. 1939-1944, 1998

This review was been appraised and listed on the Centre for Reviews and Dissemination, University of York (Database of Abstracts of Reviews of Effects) DARE.

Refer to : Effectiveness of home care programmes for patients with incurable cancer on their quality of life and time spent in hospital [Abstract Number 11998008745] Database of Abstracts of Reviews of Effects, available <http://www.crd.york.ac.uk/crdweb/> Abstract of: Effectiveness of home care programmes for patients with incurable cancer on their quality of life and time spent in hospital. Smeenk F W, van Haastregt J C, de Witte L P, Crebolder H F. 1998 BMJ 316. 1939-1944

Evidence level 2++ (added by NICE reviewer)

Ruff, R. L., Adamson, V. W., Ruff, S. S. & Wang, X. (2007) Directed rehabilitation reduces pain and depression while increasing independence and satisfaction with life for patients with paraplegia due to epidural metastatic spinal cord compression. *Journal of Rehabilitation Research & Development*, 44: 1-10.

Design: Prospective Study, Evidence level 2-
Country: US

Aim: To evaluate if directed rehabilitation affected survival, pain, depression, independence, and satisfaction with life for veterans who were non ambulatory after spinal epidural metastasis (SEM) treatment.

Inclusion criteria

male veterans with SEM and who were unable to walk after completion of SEM treatment.

Exclusion criteria

- Refusal of SEM treatment,
- Cauda equina disease with myelopathy
- prior SEM that had produced myelopathy
- surgical treatment of SEM
- patients were excluded with a poor prognosis

Population

12 consecutive male veterans with SEM and who were unable to walk after completion of SEM treatment.

30 non-ambulatory patients (as a historical comparative group – no rehab group)

Interventions

- SEM treatment prior to 2 week rehabilitation programme which focussed on training in transfers, skin care, nutrition, and pulmonary exercise with incentive spirometry. (rehab group)
- The included patients were compared to 30 non-ambulatory patients from a previous descriptive study. This historical comparative group received SEM treatment but not the 2 week rehabilitation programme. (no rehab group)

Outcomes

Patient survival, pain control, depression, mobility independence, frequency of returning home, and self reported satisfaction with life.

Results

Survival

- Patients in the rehab group survived longer. Median survival for rehab group = 26 weeks (95%CI 23.9-28.1 weeks). Median survival for no rehab group = 6 weeks (95%CI 5.9-6.1), $p < 0.001$
- No patients in the rehab group died of complications of myelopathy, 47% in the no rehab group died of complications of myelopathy, $p < 0.001$.
- 92% of patients in the rehab group died from systemic cancer and 53% in the no rehab group

Mobility Independence

- For rehab group: 67% learned to independently transfer from bed to wheelchair and wheel chair to commode
- For no rehab group: no patients learned this activity: the difference was stat. significantly different, $p < 0.001$
- On completion of the intervention (Rehab group) or 2 weeks after completion of SEM treatment (no rehab group): 75% of patients (rehab group) compared to 20% of patients in (no rehab group) were discharged to home, $p < 0.01$.
- The risk ratio of being discharged home for the rehab group compared with the no rehab group = 3.75, 95% CI 2.31-6.09

Depression

8.3% of patients in the rehab group were clinically depressed 2 weeks after completion of the intervention

86.7% of patients in the no rehab group were clinically depressed and treated with anti-depressant 2 weeks after completing SEM treatment.

The risk ratio for being diagnosed with clinical depression among no rehab group patients compared to rehab patients = 10.4, 95% CI 5.81-18.6

Satisfaction with life

- For no rehab group Satisfaction with life score (SWLS) did not improve from the start of SEM treatment until 2 weeks after completion of treatment.
- Rehab group had higher SWLS after completing the intervention, than at the start of rehabilitation, $p < 0.001$.
- After completing rehabilitation, the rehab group had higher SWLS than that of the no rehab group patients, $p < 0.001$. the rehab group SWLS indicated satisfaction with life.
- Note: a high SWLS indicates satisfaction with life.

Pain

- Before starting SEM treatment both groups reported high levels of pain
- In association with SEM treatment both groups reported a decrease pain level.
- The difference between before and after SEM treatment was significantly different, $p > 0.001$
- 2 weeks after completion of SEM treatment, pain levels differed significantly between the 2 groups. Rehab group pain levels were lower after rehab intervention compared to after completion of SEM treatment, $p < 0.001$.
- After completion of rehab, rehab group had lower pain levels than no rehab group patients, $p < 0.001$.

General comments

At best this is a pilot study and in order to evaluate this intensive rehabilitation intervention without bias, a RCT is required. This study was influenced by patient selection bias, and

bias associated with the researchers involved (i.e. no blinding at any point in study protocol). – possible RESEARCH REC

Appendix A - Literature Searches

NATIONAL COLLABORATING CENTRE FOR CANCER				
Clinical Guideline Metastatic Spinal Cord Compression		Literature search summary		
Question title: What is the most effective way of delivering care and co-ordinating services for patients with MSCC or suspected MSCC?				
Question no: 11a				
Literature search details				
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1950 – 2007	210	38	16/03/07
<i>Premedline</i>	1950 - 2007	0	0	16/03/07
<i>Embase</i>	1980 – 2007	1247	35	16/03/07
<i>Cochrane Library</i>	1800 – 2007	35	0	16/03/07
<i>Cinahl</i>	1982 – 2007	61	10	16/03/07
<i>BNI</i>	1994 – 2007	0	0	16/03/07
<i>Psychinfo</i>	1967- 2007	1	0	16/03/07
<i>SIGLE</i>	1980 - 2005	0	0	19/03/07
<i>Web of Science (SCI & SSCI)</i>	1970 – 2007	220	18	19/03/07
<i>ISI Proceedings</i>	1990 – 2007	30	2	19/03/07
<i>Biomed Central</i>	1997 - 2007	384	0	19/03/07
UPDATE SEARCH				
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2007 – 04/2008	21	0	18/04/08
<i>Premedline</i>	2007 – 04/2008	2	0	18/04/08
<i>Embase</i>	2007 – 04/2008	4	1	18/04/08
<i>Cochrane Library</i>	2007 – 04/2008	15	0	18/04/08
<i>Cinahl</i>	2007 – 04/2008	11	0	18/04/08
<i>BNI</i>	2007 – 04/2008	0	0	18/04/08
<i>Psychinfo</i>	2007 – 04/2008	3	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	2007 – 04/2008	34	1	18/04/08
<i>ISI Proceedings</i>	2007 – 04/2008	3	0	18/04/08
<i>Biomed Central</i>	2007 – 04/2008	160	0	18/04/08
Total References retrieved (after de-duplication): 80 (update search: 2)				
Medline search strategy (<i>This search strategy is adapted to each database.</i>)				
<i>Spinal Cord Compression AND multidisciplinary teams</i>				
<ol style="list-style-type: none"> 1. exp Spinal Neoplasms/ 2. (spin\$ adj metasta\$).tw. 3. (spin\$ adj (cancer\$ or carcinoma\$ or malignan\$ or tumo?r\$ or neoplas\$ or intraepithelial\$ or adeno\$)).tw. 				

4. exp Spinal Cord Compression/
5. (skelet\$ adj3 event\$).tw.
6. or/1-5
7. exp Patient Care Planning/
8. exp Patient Care Team/
9. multidisciplin\$ team\$.tw.
10. (health adj1 team\$).tw.
11. interdisciplin\$ team\$.tw.
12. exp "Delivery of Health Care"/
13. (cooperat\$ or co-operat\$).tw.
14. multiprofession\$.tw.
15. exp "Referral and Consultation"/
16. exp Physician's Practice Patterns/
17. exp "Practice Guideline [Publication Type]"/
18. or/7-17
19. 6 and 18

Health Economics Literature search details

A Health Economics Literature search was not required.

Any further comments:

The update search was performed to include the years 2007 – 18 April 2008 only.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline

Literature search summary

Metastatic Spinal Cord Compression

Question title: In patients with MSCC, what effect does delay from presentation to definitive treatment have on clinical outcomes (mobility, urinary continence, lack of pain, survival independent living)?

Question no: 5a

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1950 – 2006	568	66	30/10/06
<i>Premedline</i>	1950 – 2006	1	0	31/10/06
<i>Embase</i>	1980 – 2006	650	37	31/10/06
<i>Cochrane Library</i>	1800 – 2006	2	0	31/10/06
<i>Cinahl</i>	1982 – 2006	12	0	31/10/06
<i>BNI</i>	1994 – 2006	13	0	31/10/06
<i>Psychinfo</i>	1967 – 2006	10	0	31/10/06
<i>SIGLE</i>	1980 – 2005	0	0	31/10/06
<i>Web of Science (SCI & SSCI)</i>	1970 – 2006	99	9	31/10/06
<i>ISI Proceedings</i>	1990 – 2006	5	3	31/10/06
<i>Biomed Central</i>	1997 - 2006	166	0	31/10/06

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2006 – 04/2008	10	2	18/04/08
<i>Premedline</i>	2006 – 04/2008	2	0	18/04/08
<i>Embase</i>	2006 – 04/2008	24	8	18/04/08
<i>Cochrane Library</i>	2006 – 04/2008	3	0	18/04/08
<i>Cinahl</i>	2006 – 04/2008	10	1	18/04/08
<i>BNI</i>	2006 – 04/2008	0	0	18/04/08
<i>Psychinfo</i>	2006 – 04/2008	4	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	2006 – 04/2008	25	1	18/04/08
<i>ISI Proceedings</i>	2006 – 04/2008	5	0	18/04/08
<i>Biomed Central</i>	2006 – 04/2008	4	0	18/04/08

Total References retrieved (after de-duplication): 96 (update search: 11)

Medline search strategy (*This search strategy is adapted to each database.*)

Spinal Cord Compression AND Metastasis AND (Time Factors OR Delay) AND (Mobility OR Continence OR Pain)

- 1 Spinal Cord Compression/
- 2 (spin\$ adj2 compress\$).tw.
- 3 (compress\$ adj1 myelopath\$).tw.
- 4 (MSCC or MESCC or SCC).tw.
- 5 or/1-4
- 6 exp Neoplasm Metastasis/
- 7 exp Spinal Cord Neoplasms/
- 8 (metasta\$ adj spin\$).tw.
- 9 or/6-8
- 10 5 and 9
- 11 exp Time Factors/
- 12 (delay\$ adj treatment\$).tw.
- 13 (delay\$ adj presentation\$).tw.
- 14 exp Follow-Up Studies/
- 15 exp Risk Assessment/
- 16 exp Treatment Outcome/
- 17 exp Prognosis/
- 18 or/11-17
- 19 10 and 18
- 20 exp Urinary Incontinence/
- 21 exp Pain/
- 22 (lack adj2 pain\$).tw.
- 23 exp Survival/px, sn, ph [Psychology, Statistics & Numerical Data, Physiology]
- 24 mobil\$tw.
- 25 exp Movement/
- 26 exp Motor Activity/
- 27 exp Kinesis/
- 28 exp "Activities of Daily Living"/
- 29 independent liv\$.tw.
- 30 or/20-29

Health Economics Literature search details

SIGN Health Economics and SCHARR Quality of Life filter added to search.

Database name	No of references found	Finish date of search
<i>Medline</i>	4	30/04/07
<i>Premedline</i>	0	30/04/07
<i>Embase</i>	0	30/04/07
<i>Cochrane Library (except NHSEED)</i>	0	30/04/07
<i>NHSEED</i>	0	30/04/07
<i>Cinahl</i>	0	30/04/07
<i>Psycinfo</i>	0	30/04/07
<i>BNI</i>	0	30/04/07
<i>EconLit</i>	0	30/04/07
<i>Web of Science (SCI & SSCI)</i>	0	30/04/07
<i>ISI Proceedings</i>	0	30/04/07
<i>SIGLE</i>	0	30/04/07

UPDATE SEARCH		
Database name	No of references found	Finish date of search
<i>Medline</i>	0	18/04/08
<i>Premedline</i>	0	18/04/08
<i>Embase</i>	0	18/04/08
<i>Cochrane Library (except NHSEED)</i>	0	18/04/08
<i>NHSEED</i>	0	18/04/08
<i>Cinahl</i>	0	18/04/08
<i>Psycinfo</i>	0	18/04/08
<i>BNI</i>	0	18/04/08
<i>EconLit</i>	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	0	18/04/08
<i>ISI Proceedings</i>	0	18/04/08

Any further comments:

The update search was performed to include the years 2006 – 18 April 2008 only.

The Health Economics update search was performed to include the years 2007 – 18 April 2008 only.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline

Metastatic Spinal Cord Compression

Literature search summary

Question title: : In patients with MSCC, what effect does performance status at the time of treatment have on clinical outcomes (mobility, urinary continence, lack of pain, survival independent living)?

Question no: 5b

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1950 – 2006	137	23	01/11/06
<i>Premedline</i>	1950 – 2006	0	0	01/11/06
<i>Embase</i>	1980 – 2006	210	24	02/11/06
<i>Cochrane Library</i>	1800 – 2006	20	0	01/11/06
<i>Cinahl</i>	1982 – 2006	9	1	01/11/06
<i>BNI</i>	1994 – 2006	0	0	01/11/06
<i>Psychinfo</i>	1967 – 2006	2	0	01/11/06
<i>SIGLE</i>	1980 – 2005	0	0	02/11/06
<i>Web of Science (SCI & SSCI)</i>	1970 – 2006	217	14	06/11/06
<i>ISI Proceedings</i>	1990 – 2006	18	0	06/11/06
<i>Biomed Central</i>	1997 - 2006	119	0	06/11/06

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2006 – 04/2008	32	11	18/04/08
<i>Premedline</i>	2006 – 04/2008	2	1	18/04/08
<i>Embase</i>	2006 – 04/2008	73	12	18/04/08
<i>Cochrane Library</i>	2006 – 04/2008	11	1	18/04/08
<i>Cinahl</i>	2006 – 04/2008	7	1	18/04/08
<i>BNI</i>	2006 – 04/2008	0	0	18/04/08
<i>Psychinfo</i>	2006 – 04/2008	2	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	2006 – 04/2008	60	5	18/04/08
<i>ISI Proceedings</i>	2006 – 04/2008	5	0	18/04/08
<i>Biomed Central</i>	2006 – 04/2008	36	0	18/04/08

Total References retrieved (after de-duplication): 46 (update search: 16)

Medline search strategy (*This search strategy is adapted to each database.*)

Spinal Cord Compression AND Metastasis AND Performance Status

1. Spinal Cord Compression/
2. (spin\$ adj2 compress\$).tw.
3. (compress\$ adj1 myelopath\$).tw.
4. (MSCC or MESCC).tw.
5. or/1-4
6. exp Spinal Cord Neoplasms/
7. (metasta\$ adj2 spin\$ cord\$).tw.
8. exp Neoplasm Metastasis/
9. or/6-8
10. 5 and 9
11. performance\$ status\$.tw.
12. (Eastern Cooperative Oncology Group or ECOG).tw.
13. exp Karnofsky Performance Status/
14. performance measur\$.tw.
15. exp "Outcome and Process Assessment (Health Care)"/
16. (grad\$ or scor\$).tw.
17. or/11-16

18. 10 and 17

Health Economics Literature search details

A Health Economics Literature search was not required

Any further comments:

The update search as performed to include the years 2006 – 18 April 2008 only.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline

Metastatic Spinal Cord Compression

Literature search summary

Question title: What is the most effective way to communicate the symptoms of MSCC to patients with primary carcinoma [to your patient]?

Question no: 18

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1950 – 2007	9	1	01/08/07
<i>Premedline</i>	1950 – 2007	0	0	01/08/07
<i>Embase</i>	1980 – 2007	10	1	01/08/07
<i>Cochrane Library</i>	1800 – 2007	18	0	01/08/07
<i>Cinahl</i>	1982 – 2007	0	0	01/08/07
<i>BNI</i>	1994 – 2007	0	0	01/08/07
<i>Psychinfo</i>	1967 – 2007	0	0	01/08/07
<i>SIGLE</i>	1980 – 2005	0	0	01/08/07
<i>Web of Science (SCI & SSCI)</i>	1970 – 2007	22	2	01/08/07
<i>ISI Proceedings</i>	1990 – 2007	27	0	06/08/07
<i>Biomed Central</i>	1997 - 2007	0	0	06/08/07

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2007 – 04/2008	2	0	18/04/08
<i>Premedline</i>	2007 – 04/2008	2	1	18/04/08
<i>Embase</i>	2007 – 04/2008	3	0	18/04/08
<i>Cochrane Library</i>	2007 – 04/2008	2	0	18/04/08
<i>Cinahl</i>	2007 – 04/2008	1	0	18/04/08
<i>BNI</i>	2007 – 04/2008	0	0	18/04/08
<i>Psychinfo</i>	2007 – 04/2008	0	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	2007 – 04/2008	4	1	18/04/08
<i>ISI Proceedings</i>	2007 – 04/2008	1	0	18/04/08
<i>Biomed Central</i>	2007 – 04/2008	0	0	18/04/08

Total References retrieved (after de-duplication): 4 (update search:) 1

Medline search strategy (This search strategy is adapted to each database.)

Spinal Cord Compression AND Risk AND Communication

- 1 exp Spinal Cord Compression/
- 2 (spin\$ adj2 compress\$).tw.
- 3 (compress\$ adj1 myelopath\$).tw.
- 4 (MSCC or MESCC).tw.
- 5 (nerv\$ root\$ adj compress\$).tw.
- 6 vertebra\$ collaps\$.tw.
- 7 spin\$ collaps\$.tw.
- 8 or/1-7
- 9 exp risk/
- 10 risk\$.tw.
- 11 exp disease susceptibility/
- 12 susceptib\$.tw.
- 13 or/9-12
- 14 communication/
- 15 persuasive communication/
- 16 counseling/
- 17 health promotion/
- 18 consumer participation/
- 19 patient education/
- 20 decision making/
- 21 informed consent/
- 22 ((patient\$ or consumer\$) adj3 (communicat\$ or counsel\$ or inform\$ or discuss\$ or decision\$ or decid\$ or participat\$)).tw.
- 23 "Patient Acceptance of Health Care"/
- 24 choice behavior/
- 25 or/14-24
- 26 13 and 25
- 27 8 and 26

Health Economics Literature search details

A Health Economics Literature search was not required.

Any further comments:

Poor evidence.

The update search was performed to include the years 2007 – 18 April 2008 only.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline

Metastatic Spinal Cord Compression

Literature search summary

Question title: In patients with cancer at risk of developing spinal cord compression, what symptoms and signs give early indications that malignant SCC is developing?

Question no: 3

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1950 – 2006	975	181	16/10/06
<i>Premedline</i>	1950 – 2006	7	3	16/10/06
<i>Embase</i>	1980 – 2006	938	198	17/10/06
<i>Cochrane Library</i>	1800 – 2006	57	1	16/10/06
<i>Cinahl</i>	1982 – 2006	63	26	16/10/06
<i>BNI</i>	1994 – 2006	4	1	16/10/06
<i>Psychinfo</i>	1967 - 2006	4	1	16/10/06
<i>SIGLE</i>	1980 - 2005	1	0	17/10/06
<i>Web of Science (SCI & SSCI)</i>	1970 – 2006	305	56	17/10/06
<i>ISI Proceedings</i>	1990 – 2006	14	1	17/10/06
<i>Biomed Central</i>	1997 - 2006	30	0	17/10/06

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2006 – 04/2008	135	20	18/04/08
<i>Premedline</i>	2006 – 04/2008	4	3	18/04/08
<i>Embase</i>	2006 – 04/2008	234	8	18/04/08
<i>Cochrane Library</i>	2006 – 04/2008	2	0	18/04/08
<i>Cinahl</i>	2006 – 04/2008	32	5	18/04/08
<i>BNI</i>	2006 – 04/2008	2	1	18/04/08
<i>Psychinfo</i>	2006 – 04/2008	0	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	2006 – 04/2008	72	6	18/04/08
<i>ISI Proceedings</i>	2006 – 04/2008	4	0	18/04/08
<i>Biomed Central</i>	2006 – 04/2008	12	0	18/04/08

Total References retrieved (after de-duplication): 355 (update search: 33)

Medline search strategy (*This search strategy is adapted to each database.*)

Spinal Cord Compression AND Cancer AND Diagnosis AND Symptoms

- 1 Spinal Cord Compression/
- 2 (spin\$ adj2 compress\$).tw.
- 3 (compress\$ adj1 myelopath\$).tw.
- 4 (MSCC or MESCC).mp.
- 5 *Spinal Cord Compression/mo, pa, pp, di, pc, ra, ri, rt, ep, rh, su, et, th, us, hi [Mortality, Pathology, Physiopathology, Diagnosis, Prevention & Control, Radiography, Radionuclide Imaging, Radiotherapy, Epidemiology, Rehabilitation, Surgery, Etiology, Therapy, Ultrasonography, History]
- 6 *Spinal Cord Neoplasms/mo, pa, pp, pc, ra, di, ri, rt, rh, ep, su, th, et, us, hi [Mortality, Pathology, Physiopathology, Prevention & Control, Radiography, Diagnosis, Radionuclide Imaging, Radiotherapy, Rehabilitation, Epidemiology, Surgery, Therapy, Etiology, Ultrasonography, History]
- 7 or/1-6
- 8 exp Pain/
- 9 spin\$ pain.tw.
- 10 referred pain\$.tw.
- 11 radicular pain\$.tw.
- 12 exp Back Pain/
- 13 exp Paraplegia/

- 14 exp Paralysis/
- 15 Paresthesia/
- 16 exp Paraparesis/
- 17 exp Movement Disorders/
- 18 exp Fecal Incontinence/ or exp Urinary Incontinence/
- 19 exp Valsalva Maneuver/
- 20 Lhermitte sign.mp.
- 21 symptom\$.tw.
- 22 or/8-21
- 23 (cancer\$ or carcinoma\$ or malignan\$ or tumo?r\$ or adeno\$ or neoplas\$ or intraepithelial\$.tw.
- 24 Neoplasms/
- 25 or/23-24
- 26 exp Early Diagnosis/ or exp Diagnosis/
- 27 exp "Diagnostic Techniques and Procedures"/
- 28 exp "Sensitivity and Specificity"/
- 29 diagnos\$.tw.
- 30 exp Medical History Taking/
- 31 exp Risk Factors/
- 32 exp Prognosis/
- 33 (clinical adj predict\$.tw.
- 34 (prognos\$ adj factor\$.tw.
- 35 (predict\$ adj factor\$.tw.
- 36 (prognos\$ adj risk\$.tw.
- 37 (predict\$ adj risk\$.tw.
- 38 (risk\$ adj factor\$.tw.
- 39 or/26-38
- 40 7 and 22
- 41 40 and 25
- 42 41 and 39

Health Economics Literature search details

SIGN Health Economics and SCHARR Quality of Life filter added to search.

Database name	No of references found	Finish date of search
<i>Medline</i>	10	13/02/07
<i>Premedline</i>	9	13/02/07
<i>Embase</i>	17	13/02/07
<i>Cochrane Library (except NHSEED)</i>	1	13/02/07
<i>NHSEED</i>	0	13/02/07
<i>Cinahl</i>	5	13/02/07
<i>Psycinfo</i>	4	13/02/07
<i>BNI</i>	4	13/02/07
<i>EconLit</i>	0	13/02/07
<i>Web of Science (SCI & SSCI)</i>	36	13/02/07
<i>ISI Proceedings</i>	5	13/02/07
<i>SIGLE</i>	0	13/02/07
UPDATE SEARCH		
Database name	No of references found	Finish date of search
<i>Medline</i>	0	18/04/08
<i>Premedline</i>	0	18/04/08
<i>Embase</i>	0	18/04/08
<i>Cochrane Library (except NHSEED)</i>	0	18/04/08
<i>NHSEED</i>	0	18/04/08

Cinahl	0	18/04/08
Psycinfo	0	18/04/08
BNI	0	18/04/08
EconLit	0	18/04/08
Web of Science (SCI & SSCI)	0	18/04/08
ISI Proceedings	0	18/04/08

Any further comments:
The update search was performed to include the years 2006 – 18 April 2008 only.
The Health Economics update search was performed to include the years 2007 – 18 April 2008 only.

NATIONAL COLLABORATING CENTRE FOR CANCER				
Clinical Guideline		Literature search summary		
Metastatic Spinal Cord Compression				
Question title: In patients with suspected bone metastases in the spine, does MRI (or CT?) scanning (compared to not scanning) identify patients at risk of developing MSCC and improve outcomes (prevention of established MSCC, mobility, cost)				
Question no: 1a				
Literature search details				
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1950 – 2007	2079	145	26/03/07
<i>Premedline</i>	1950 – 2007	50	4	27/03/07
<i>Embase</i>	1980 – 2007	1272	50	27/03/07
<i>Cochrane Library</i>	1800 – 2007	7	6	27/03/07
<i>Cinahl</i>	1982 – 2007	67	4	27/03/07
<i>BNI</i>	1994 – 2007	8	1	27/03/07
<i>Psychinfo</i>	1967 – 2007	254	0	27/03/07
<i>SIGLE</i>	1980 – 2005	0	0	27/03/07
<i>Web of Science (SCI & SSCI)</i>	1970 – 2007	208	64	27/03/07
<i>ISI Proceedings</i>	1990 - 2007	14	2	27/03/07
<i>Biomed Central</i>	1997 - 2007	16	0	27/03/07
UPDATE SEARCH				
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2007 – 04/2008	5	2	18/04/08
<i>Premedline</i>	2007 – 04/2008	59	9	18/04/08
<i>Embase</i>	2007 – 04/2008	8	1	18/04/08
<i>Cochrane Library</i>	2007 – 04/2008	6	0	18/04/08
<i>Cinahl</i>	2007 – 04/2008	1	0	18/04/08
<i>BNI</i>	2007 – 04/2008	0	0	18/04/08
<i>Psychinfo</i>	2007 – 04/2008	1	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	2007 – 04/2008	23	5	18/04/08
<i>ISI Proceedings</i>	2007 – 04/2008	1	1	18/04/08

Total References retrieved (after de-duplication): 215 (update search: 17)

Medline search strategy (*This search strategy is adapted to each database.*)

Spinal Cord Compression AND Bone metastases AND Imaging
RCT filter applied

1. Spinal Cord Compression/
2. (spin\$ adj2 compress\$).tw.
3. 1 or 2
4. exp "Bone and Bones"/
5. exp Bone Neoplasms/
6. (bon\$ adj metastas\$).tw.
7. exp Spinal Cord Neoplasms/
8. exp Spinal Neoplasms/
9. (spin\$ adj metastas\$).tw.
10. or/4-9
11. 3 and 10
12. exp magnetic resonance imaging/
13. Magnetic Resonance Spectroscopy/
14. magnetic resonance.tw.
15. MRI\$1.tw.
16. NMR\$1.tw.
17. MRS\$1.tw.
18. MRT.tw.
19. MR imaging.tw.
20. MR scan\$.tw.
21. MR spectroscop\$.tw.
22. (magnet\$ adj3 (scan\$ or imaging)).tw.
23. (diffusion adj2 (scan\$ or imaging)).tw.
24. (functional adj2 (scan\$ or imaging)).tw.
25. exp Tomography, X-Ray Computed/
26. (comput\$ adj1 tomograph\$).tw.
27. ((ct or cat) adj (scan\$ or imaging)).tw.
28. electron beam computed tomography\$.tw.
29. 3-dimensional computerized tomography\$.tw.
30. (spiral adj CT).tw.
31. CT myelography.tw.
32. ((multi\$ slice or multi\$ detector) adj CT).tw.
33. ((positron emission tomography or PET) adj1 CT).tw.
34. Bone\$ scintigraph\$.tw.
35. skelet\$ survey\$.tw.
36. plain film\$.tw.
37. radioisotop\$ bon\$ scan\$.tw.
38. or/12-37
39. 11 and 38

Health Economics Literature search details

SIGN Health Economics filter and SCHARR Quality of Life filter added to search.

Database name	No of references	Finish date of search
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	found	
<i>Medline</i>	11	25/04/07
<i>Premedline</i>	0	25/04/07
<i>Embase</i>	14	25/04/07
<i>Cochrane Library (except NHSEED)</i>	2	02/05/07
<i>NHSEED</i>	0	02/05/07
<i>Cinahl</i>	1	25/04/07
<i>Psycinfo</i>	11	25/04/07
<i>BNI</i>	0	25/04/07
<i>EconLit</i>	0	25/04/07
<i>Web of Science (SCI & SSCI)</i>	9	25/04/07
<i>ISI Proceedings</i>	1	25/04/07
<i>SIGLE</i>	0	25/04/07
UPDATE SEARCH		
Database name	No of references found	Finish date of search
<i>Medline</i>	1	18/04/08
<i>Premedline</i>	0	18/04/08
<i>Embase</i>	0	18/04/08
<i>Cochrane Library (except NHSEED)</i>	0	18/04/08
<i>NHSEED</i>	0	18/04/08
<i>Cinahl</i>	0	18/04/08
<i>Psycinfo</i>	0	18/04/08
<i>BNI</i>	0	18/04/08
<i>EconLit</i>	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	0	18/04/08
<i>ISI Proceedings</i>	0	18/04/08

Any further comments:
The update search was performed to include the years 2007 – 18 April 2008 only.
The Health Economics update search was performed to include the years 2007 – 18 April 2008 only.

NATIONAL COLLABORATING CENTRE FOR CANCER	
Clinical Guideline Metastatic Spinal Cord Compression	Literature search summary
Question title: In patients with suspected bone metastases in the spine, does serial imaging identify patients at risk of developing MSCC and improve outcomes (prevention of established MSCC, mobility, cost)?	
Question no: 1b	

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1950 – 2007	63	6	02/04/07
<i>Premedline</i>	1950 – 2007	2	1	02/04/07
<i>Embase</i>	1980 – 2007	50	9	02/04/07
<i>Cochrane Library</i>	1800 – 2007	86	0	02/04/07
<i>Cinahl</i>	1982 – 2007	0	0	02/04/07
<i>BNI</i>	1994 – 2007	8	1	02/04/07
<i>Psychinfo</i>	1967 – 2007	0	0	02/04/07
<i>SIGLE</i>	1980 – 2005	0	0	03/04/07
<i>Web of Science (SCI & SSCI)</i>	1970 – 2007	785	18	03/04/07
<i>ISI Proceedings</i>	1990 – 2007	70	5	03/04/07
<i>Biomed Central</i>	1997 - 2007	7	0	03/04/07

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2007 – 04/2008	5	0	18/04/08
<i>Premedline</i>	2007 – 04/2008	3	1	18/04/08
<i>Embase</i>	2007 – 04/2008	10	0	18/04/08
<i>Cochrane Library</i>	2007 – 04/2008	0	0	18/04/08
<i>Cinahl</i>	2007 – 04/2008	2	0	18/04/08
<i>BNI</i>	2007 – 04/2008	0	0	18/04/08
<i>Psychinfo</i>	2007 – 04/2008	0	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	2007 – 04/2008	66	1	18/04/08
<i>ISI Proceedings</i>	2007 – 04/2008	8	1	18/04/08
<i>Biomed Central</i>	2007 – 04/2008	5	0	18/04/08

Total References retrieved (after de-duplication): 18 (update search: 2)

Medline search strategy (*This search strategy is adapted to each database.*)

Imaging AND Spinal Cord Compression

1. exp magnetic resonance imaging/
2. Magnetic Resonance Spectroscopy/
3. magnetic resonance.tw.
4. MRI\$1.tw.
5. NMR\$1.tw.
6. MRS\$1.tw.
7. MRT.tw.
8. MR imaging.tw.
9. MR scan\$.tw.
10. MR spectroscop\$.tw.
11. (magnet\$ adj3 (scan\$ or imaging)).tw.
12. (diffusion adj2 (scan\$ or imaging)).tw.
13. (functional adj2 (scan\$ or imaging)).tw.
14. exp Tomography, X-Ray Computed/
15. (comput\$ adj1 tomograph\$).tw.
16. ((ct or cat) adj (scan\$ or imaging)).tw.

17. electron beam computed tomography\$.tw.
18. 3-dimensional computerized tomography\$.tw.
19. (spiral adj CT).tw.
20. CT myelography.tw.
21. ((multi\$ slice or multi\$ detector) adj CT).tw.
22. ((positron emission tomography or PET) adj1 CT).tw.
23. Bone\$ scintigraph\$.tw.
24. skelet\$ survey\$.tw.
25. plain film\$.tw.
26. radioisotop\$ bon\$ scan\$.tw.
27. or/12-37
28. serial imag\$.tw.
29. (frequenc\$ adj1 imag\$).tw.
30. (frequenc\$ adj1 scan\$).tw.
31. exp Sequence Analysis/
32. or/28-31
33. exp "Bone and Bones"/
34. exp Bone Neoplasms/
35. (bon\$ adj metastas\$).tw.
36. exp Spinal Cord Neoplasms/
37. exp Spinal Neoplasms/
38. (spin\$ adj metastas\$).tw.
39. or/33-38
40. 27 and 32
41. 40 and 39

Health Economics Literature search details

SIGN Health Economics and SCHARR Quality of Life filter added to search.

Database name	No of references found	Finish date of search
<i>Medline</i>	1	26/04/07
<i>Premedline</i>	0	26/04/07
<i>Embase</i>	0	26/04/07
<i>Cochrane Library (except NHSEED)</i>	0	02/05/07
<i>NHSEED</i>	0	02/05/07
<i>Cinahl</i>	0	26/04/07
<i>Psycinfo</i>	0	26/04/07
<i>BNI</i>	0	26/04/07
<i>EconLit</i>	0	26/04/07
<i>Web of Science (SCI & SSCI)</i>	9	26/04/07
<i>ISI Proceedings</i>	1	26/04/07
<i>SIGLE</i>	0	26/04/07

UPDATE SEARCH

Database name	No of references found	Finish date of search
<i>Medline</i>	0	18/04/08
<i>Premedline</i>	0	18/04/08
<i>Embase</i>	0	18/04/08
<i>Cochrane Library (except NHSEED)</i>	0	18/04/08
<i>NHSEED</i>	0	18/04/08
<i>Cinahl</i>	0	18/04/08
<i>Psycinfo</i>	0	18/04/08
<i>BNI</i>	0	18/04/08

<i>EconLit</i>	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	0	18/04/08
<i>ISI Proceedings</i>	0	18/04/08

Any further comments:
The update search was performed to include the years 2007 – 18 April 2008 only.
The Health Economics update search was performed to include the years 2007 – 18 April 2008 only.

NATIONAL COLLABORATING CENTRE FOR CANCER				
Clinical Guideline		Literature search summary		
Metastatic Spinal Cord Compression				
Question title: What is the best imaging modality for diagnosis of spinal cord compression?				
Question no: 4				
Literature search details				
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1950 – 2006	265	66	23/10/06
<i>Premedline</i>	1950 – 2006	2	0	25/10/06
<i>Embase</i>	1980 – 2006	315	40	24/10/06
<i>Cochrane Library</i>	1800 – 2006	14	3	25/10/06
<i>Cinahl</i>	1982 – 2006	2	0	25/10/06
<i>BNI</i>	1994 – 2006	0	0	25/10/06
<i>Psychinfo</i>	1967 – 2006	10	0	25/10/06
<i>SIGLE</i>	1980 – 2005	0	0	25/10/06
<i>Web of Science (SCI & SSCI)</i>	1970 – 2006	56	7	25/10/06
<i>ISI Proceedings</i>	1990 – 2006	13	3	25/10/06
<i>Biomed Central</i>	1997 - 2006	129	0	25/10/06
UPDATE SEARCH				
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2006 – 04/2008	21	3	18/04/08
<i>Premedline</i>	2006 – 04/2008	0	0	18/04/08
<i>Embase</i>	2006 – 04/2008	114	9	18/04/08
<i>Cochrane Library</i>	2006 – 04/2008	5	1	18/04/08
<i>Cinahl</i>	2006 – 04/2008	3	0	18/04/08
<i>BNI</i>	2006 – 04/2008	0	0	18/04/08
<i>Psychinfo</i>	2006 – 04/2008	5	0	18/04/08
<i>Web of Science (SCI & SSCI) and ISI Proceedings</i>	2006 – 04/2008	29	3	18/04/08
<i>Biomed Central</i>	2006 – 04/2008	129	0	18/04/08
Total References retrieved (after de-duplication): 99 (update search: 14)				

Medline search strategy (This search strategy is adapted to each database.)

Spinal Cord Compression OR Paraparesis AND Diagnosis AND Metastasis AND (MRI OR CT Diagnostic Imaging)

- 1 Spinal Cord Compression/
- 2 (spin\$ adj2 compress\$).tw.
- 3 (compress\$ adj1 myelopath\$).tw.
- 4 (MSCC or MESCC).mp.
- 5 or/1-4
- 6 exp Paraplegia/
- 7 exp Paralysis/
- 8 Paresthesia/
- 9 exp Paraparesis/
- 10 or/6-9
- 11 exp Neoplasm Metastasis/
- 12 metastas\$.tw.
- 13 (viscera\$ adj metastas\$).tw.
- 14 (spin\$ adj metastas\$).tw.
- 15 *Spinal Cord Neoplasms/mo, pa, pp, pc, ra, di, ri, rt, rh, ep, su, th, et, us, hi [Mortality, Pathology, Physiopathology, Prevention & Control, Radiography, Diagnosis, Radionuclide Imaging, Radiotherapy, Rehabilitation, Epidemiology, Surgery, Therapy, Etiology, Ultrasonography, History]
- 16 or/11-15

- 17 exp Diagnostic Imaging/
- 18 (diagnos\$ adj3 imag\$).tw.
- 19 exp magnetic resonance imaging/
- 20 Magnetic Resonance Spectroscopy/
- 21 magnetic resonance.tw.
- 22 MRI\$1.tw.
- 23 NMR\$1.tw.
- 24 MRS\$1.tw.
- 25 MRT.tw.
- 26 MR imaging.tw.
- 27 MR scan\$.tw.
- 28 MR spectroscop\$.tw.
- 29 MR elastograph\$.tw.
- 30 (magnet\$ adj3 (scan\$ or imaging)).tw.
- 31 (diffusion adj2 (scan\$ or imaging)).tw.
- 32 (planar adj (scan\$ or imaging\$)).tw.
- 33 (planar adj tomogra\$).tw.
- 34 (echoplanar adj (scan\$ or imaging)).tw.
- 35 zeugmatogra\$.tw.
- 36 MRE.tw.
- 37 SPECT\$1.tw.
- 38 FMRI\$.tw.
- 39 (functional adj2 (scan\$ or imaging)).tw.
- 40 or/17-39
- 41 exp Tomography, X-Ray Computed/
- 42 (comput\$ adj1 tomograph\$).tw.
- 43 ((ct or cat) adj (scan\$ or imaging)).tw.
- 44 cine-ct.tw.
- 45 electron beam computed tomography\$.tw.
- 46 tomodensitometry\$.tw.
- 47 3-dimensional computerized tomography\$.tw.
- 48 (spiral adj CT).tw.
- 49 CT myelography.tw.
- 50 ((multi\$ slice or multi\$ detector) adj CT).tw.
- 51 ((positron emission tomography or PET) adj1 CT).tw.

52 Bone\$ scintigraph\$.tw.
 53 or/41-52
 54 exp Diagnosis/
 55 exp Diagnosis, Computer-Assisted/
 56 exp "Diagnostic Techniques and Procedures"/
 57 exp "Sensitivity and Specificity"/
 58 diagnos\$.tw.
 59 or/54-58
 60 (5 or 10) and 59
 61 60 and 16
 62 40 and 53
 63 61 and 62

Health Economics Literature search details

SIGN Health Economics and SCHARR Quality of Life filter added to search.

Database name	No of references found	Finish date of search
<i>Medline</i>	12	25/04/07
<i>Premedline</i>	0	25/04/07
<i>Embase</i>	41	25/04/07
<i>Cochrane Library (except NHSEED)</i>	0	02/05/07
<i>NHSEED</i>	1	02/05/07
<i>Cinahl</i>	0	25/04/07
<i>Psycinfo</i>	0	25/04/07
<i>BNI</i>	0	25/04/07
<i>EconLit</i>	0	25/04/07
<i>Web of Science (SCI & SSCI)</i>	7	25/04/07
<i>ISI Proceedings</i>	0	25/04/07
<i>SIGLE</i>	0	25/04/07

UPDATE SEARCH

Database name	No of references found	Finish date of search
<i>Medline</i>	0	18/04/08
<i>Premedline</i>	0	18/04/08
<i>Embase</i>	1	18/04/08
<i>Cochrane Library (except NHSEED)</i>	0	18/04/08
<i>NHSEED</i>	0	18/04/08
<i>Cinahl</i>	0	18/04/08
<i>Psycinfo</i>	0	18/04/08
<i>BNI</i>	0	18/04/08
<i>EconLit</i>	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	0	18/04/08
<i>ISI Proceedings</i>	0	18/04/08

Any further comments:

The update search was performed to include the years 2006- 18 April 2008 only.

The Health Economics Literature update search was performed to include the years 2007- 18 April 2008 only.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline

Literature search summary

Metastatic Spinal Cord Compression

Question title: What is the effectiveness of Bisphosphonates at treating spinal pain and/or preventing spinal collapse and/or spinal cord compression?

Question no: 2a

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1950 – 2006	154	81	11/12/06
<i>Premedline</i>	1950 – 2006	74	20	11/12/06
<i>Embase</i>	1980 – 2006	56	20	11/12/06
<i>Cochrane Library</i>	1800 – 2006	109	16	11/12/06
<i>Cinahl</i>	1982 – 2006	8	6	11/12/06
<i>BNI</i>	1994 – 2006	17	10	11/12/06
<i>Psychinfo</i>	1967 – 2006	5	5	11/12/06
<i>SIGLE</i>	1980 – 2005	0	0	12/12/06
<i>Web of Science (SCI & SSCI)</i>	1970 – 2006	472	154	12/12/06
<i>ISI Proceedings</i>	1990 – 2006	75	24	12/12/06
<i>Biomed Central</i>	1997 - 2006	87	6	12/12/06

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2006 – 04/2008	77	5	18/04/08
<i>Premedline</i>	2006 – 04/2008	52	1	18/04/08
<i>Embase</i>	2006 – 04/2008	20	1	18/04/08
<i>Cochrane Library</i>	2006 – 04/2008	11	0	18/04/08
<i>Cinahl</i>	2006 – 04/2008	0	0	18/04/08
<i>BNI</i>	2006 – 04/2008	9	0	18/04/08
<i>Psychinfo</i>	2006 – 04/2008	5	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	2006 – 04/2008	107	3	18/04/08
<i>ISI Proceedings</i>	2006 – 04/2008	18	7	18/04/08
<i>Biomed Central</i>	2006 – 04/2008	6	0	18/04/08

Total References retrieved (after de-duplication): 267 (update search: 17)

Medline search strategy (*This search strategy is adapted to each database.*)

Vertebral Metastases AND Bisphosphonate
SR Filter added

1. exp Spine/
2. exp Lumbar Vertebrae/
3. exp Thoracic Vertebrae/
4. exp Spinal Neoplasms/
5. exp Neoplasm Metastasis/
6. (spin\$ adj3 metasta\$).tw.
7. (vertebra\$ adj3 (cancer\$ or carcinoma\$ or malignan\$ or tumo?r\$ or neoplas\$ or intraepithelial\$ or adeno\$)).tw.
8. vertebra\$ metastas\$.tw.

9. vertebra\$ collaps\$.tw.
10. spin\$ collaps\$.tw.
11. exp Spinal Cord Compression/
12. (skelet\$ adj3 event\$).tw.
13. or/1-12

14. exp Clodronic Acid/
15. clodronat\$.tw.
16. exp Diphosphonates/
17. Diphosphonat\$.tw.
18. bisphosphonate\$.tw.
19. zoledronat\$.tw.
20. pamidronat\$.tw.
21. exp Alendronate/
22. Alendronat\$.tw.
23. risedronat\$.tw.
24. exp Etidronic Acid/
25. etidronat\$.tw.
26. tiludronat\$.tw.
27. or/14-26
28. 13 and 27

Health Economics Literature search details

SIGN Health Economics and SCHARR Quality of Life filter added to search.

Database name	No of references found	Finish date of search
<i>Medline</i>	39	26/04/07
<i>Premedline</i>	2	26/04/07
<i>Embase</i>	78	26/04/07
<i>Cochrane Library (except NHSEED)</i>	2	02/05/07
<i>NHSEED</i>	0	02/05/07
<i>Cinahl</i>	27	26/04/07
<i>Psycinfo</i>	5	26/04/07
<i>BNI</i>	0	26/04/07
<i>EconLit</i>	0	26/04/07
<i>Web of Science (SCI & SSCI)</i>	107	26/04/07
<i>ISI Proceedings</i>	20	26/04/07
UPDATE SEARCH		
Database name	No of references found	Finish date of search
<i>Medline</i>	6	18/04/08
<i>Premedline</i>	2	18/04/08
<i>Embase</i>	1	18/04/08
<i>Cochrane Library (except NHSEED)</i>	0	18/04/08
<i>NHSEED</i>	0	18/04/08
<i>Cinahl</i>	0	18/04/08
<i>Psycinfo</i>	0	18/04/08
<i>BNI</i>	0	18/04/08
<i>EconLit</i>	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	11	18/04/08
<i>ISI Proceedings</i>	1	18/04/08

Any further comments:

The update search was performed to include the years 2006 – 18 April 2008 only.

The Health Economics update search was performed to include the years 2007 – 18 April 2008 only.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline**Literature search summary**

Metastatic Spinal Cord Compression

Question title: What is the effectiveness of Radiotherapy at treating spinal pain and/or preventing spinal collapse and/or spinal cord compression?

Question no: 2c

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1950 – 2006	2165	182	24/01/07
<i>Premedline</i>	1950 – 2006	43	11	29/01/07
<i>Embase</i>	1980 – 2006	4132	100	25/01/07
<i>Cochrane Library</i>	1800 – 2006	866	33	24/01/07
<i>Cinahl</i>	1982 – 2006	81	4	29/01/07
<i>BNI</i>	1994 – 2006	1	1	29/01/07
<i>Psychinfo</i>	1967- 2006	0	0	29/01/07
<i>SIGLE</i>	1980 - 2005	0	0	29/01/07
<i>Web of Science (SCI & SSCI)</i>	1970 – 2006	1939	115	29/01/07
<i>ISI Proceedings</i>	1990 – 2006	218	11	29/01/07
<i>Biomed Central</i>	1997 - 2006	18	0	29/01/07

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2006 – 04/2008	505	34	18/04/08
<i>Premedline</i>	2006 – 04/2008	36	7	18/04/08
<i>Embase</i>	2006 – 04/2008	574	12	18/04/08
<i>Cochrane Library</i>	2006 – 04/2008	44	2	18/04/08
<i>Cinahl</i>	2006 – 04/2008	28	0	18/04/08
<i>BNI</i>	2006 – 04/2008	0	0	18/04/08
<i>Psychinfo</i>	2006 – 04/2008	0	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	2006 – 04/2008	273	32	18/04/08
<i>ISI Proceedings</i>	2006 – 04/2008	35	7	18/04/08
<i>Biomed Central</i>	2006 – 04/2008	15	0	18/04/08

Total References retrieved (after de-duplication): 332 (update search: 59)

Medline search strategy (*This search strategy is adapted to each database.*)

Spinal Cord Compression AND Radiotherapy

(RCT, SR and OS filter applied)

1. exp Spine/
2. exp Spinal Neoplasms/
3. exp Neoplasm Metastasis/
4. exp Bone Neoplasms/
5. osseous metasta\$.tw.
6. (spin\$ adj3 metasta\$).tw.
7. (vertebra\$ adj3 (cancer\$ or carcinoma\$ or malignan\$ or tumo?r\$ or neoplas\$ or intraepithelial\$ or adeno\$)).tw.
8. vertebra\$ metastas\$.tw.
9. spin\$ collaps\$.tw.
10. spin\$ instabil\$.tw.
11. exp Spinal Cord Compression/
12. spin\$ pain.tw.
13. or/1-12
14. exp Radiotherapy/
15. radiotherap\$.tw.
16. (radiat\$ adj2 therap\$).tw.
17. irradiat\$.tw.
18. (interstitial adj (irradiation or radiation)).tw.
19. (radiat\$ adj2 treatment\$).tw.
20. (three dimensional adj2 radiotherap\$).tw.
21. 3D radiotherap\$.tw.
22. 3DCRT.tw.
23. external beam radiotherap\$.tw.
24. systemic radiotherap\$.tw.
25. or/14-24

Health Economics Literature search details

SIGN Health Economics and SCHARR Quality of Life filter added to search.

Database name	No of references found	Finish date of search
<i>Medline</i>	150	26/04/07
<i>Premedline</i>	1	26/04/07
<i>Embase</i>	482	26/04/07
<i>Cochrane Library (except NHSEED)</i>	5	02/05/07
<i>NHSEED</i>	6	02/05/07
<i>Cinahl</i>	38	26/04/07
<i>Psycinfo</i>	0	26/04/07
<i>BNI</i>	0	26/04/07
<i>EconLit</i>	0	26/04/07
<i>Web of Science (SCI & SSCI)</i>	124	26/04/07
<i>ISI Proceedings</i>	11	26/04/07
<i>SIGLE</i>	0	26/04/07
UPDATE SEARCH		
Database name	No of references found	Finish date of search
<i>Medline</i>	1	18/04/08
<i>Premedline</i>	0	18/04/08
<i>Embase</i>	2	18/04/08

<i>Cochrane Library (except NHSEED)</i>	0	18/04/08
<i>NHSEED</i>	2	18/04/08
<i>Cinahl</i>	1	18/04/08
<i>Psycinfo</i>	0	18/04/08
<i>BNI</i>	0	18/04/08
<i>EconLit</i>	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	2	18/04/08
<i>ISI Proceedings</i>	0	18/04/08

Any further comments:
The update search was performed to include the years 2007 – 18 April 2008 only.
The Health Economics update search was performed to include the years 2007 – 18 April 2008 only.

NATIONAL COLLABORATING CENTRE FOR CANCER				
Clinical Guideline		Literature search summary		
Metastatic Spinal Cord Compression				
Question title: What is the effectiveness of vertebroplasty / kyphoplasty at treating spinal pain and/or preventing spinal collapse and/or spinal cord compression?				
Question no: 2d				
Literature search details				
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1950 – 2007	843	133	08/02/2007
<i>Premedline</i>	1950 – 2007	106	24	08/02/2007
<i>Embase</i>	1980 – 2007	701	56	08/02/2007
<i>Cochrane Library</i>	1800 – 2007	312	25	08/02/2007
<i>Cinahl</i>	1982 – 2007	41	2	08/02/2007
<i>BNI</i>	1994 – 2007	3	0	08/02/2007
<i>Psychinfo</i>	1967- 2007	9	2	08/02/2007
<i>SIGLE</i>	1980 - 2005	0	0	09/02/2007
<i>Web of Science (SCI & SSCI)</i>	1970 – 2007	739	123	09/02/2007
<i>ISI Proceedings</i>	1990 – 2007	96	10	09/02/2007
<i>Biomed Central</i>	1997 - 2007	2	1	09/02/2007
UPDATE SEARCH				
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2007 – 04/2008	141	13	18/04/08
<i>Premedline</i>	2007 – 04/2008	121	2	18/04/08
<i>Embase</i>	2007 – 04/2008	133	7	18/04/08
<i>Cochrane Library</i>	2007 – 04/2008	48	2	18/04/08
<i>Cinahl</i>	2007 – 04/2008	15	0	18/04/08
<i>BNI</i>	2007 – 04/2008	1	0	18/04/08
<i>Psychinfo</i>	2007 – 04/2008	2	1	18/04/08

Web of Science (SCI & SSCI)	2007 – 04/2008	208	7	18/04/08
ISI Proceedings	2007 – 04/2008	45	0	18/04/08
Biomed Central	2007 – 04/2008	0	0	18/04/08

Total References retrieved (after de-duplication): 273 (update search: 28)

Medline search strategy (This search strategy is adapted to each database.)

Vertebral Metastasis AND (Vertebroplasty OR Kyphoplasty)
(RCT and SR filter applied)

1. exp Spine/
2. exp Lumbar Vertebrae/
3. exp Thoracic Vertebrae/
4. exp Spinal Neoplasms/
5. exp Neoplasm Metastasis/
6. (spin\$ adj3 metasta\$.tw.
7. (vertebra\$ adj3 (cancer\$ or carcinoma\$ or malignan\$ or tumo?r\$ or neoplas\$ or intraepithelial\$ or adeno\$)).tw.
8. vertebra\$ metastas\$.tw.
9. vertebra\$ collaps\$.tw.
10. spin\$ collaps\$.tw.
11. exp Spinal Cord Compression/
12. (skelet\$ adj3 event\$.tw.
13. exp Multiple Myeloma/
14. spin\$ tumo?r\$.tw.
15. exp Back Pain/
16. or/1-15
17. vertebroplast\$.tw.
18. kyphoplast\$.tw.
19. exp Surgical Procedures, Minimally Invasive/mt [Methods]
20. spin\$ stabili?\$.tw.
21. (vertebra\$ adj3 augment\$.tw.
22. image\$ guid\$ therap\$.tw.
23. nonsurgic\$.tw.
24. exp Spinal Fractures/
25. exp Fractures, Compression/
26. exp Polymethyl Methacrylate/
27. PMMA.tw.
28. or/17-27

Health Economics Literature search details

SIGN Health Economics and SCHARR Quality of Life filter added to search.

Database name	No of references found	Finish date of search
Medline	128	26/04/07
Premedline	5	26/04/07
Embase	182	26/04/07
Cochrane Library (except NHSEED)	2	02/05/07
NHSEED	0	02/05/07
Cinahl	42	26/04/07

<i>Psycinfo</i>	0	26/04/07
<i>BNI</i>	0	26/04/07
<i>EconLit</i>	0	26/04/07
<i>Web of Science (SCI & SSCI)</i>	74	26/04/07
<i>ISI Proceedings</i>	6	26/04/07
<i>SIGLE</i>	0	26/04/07
UPDATE SEARCH		
Database name	No of references found	Finish date of search
<i>Medline</i>	0	18/04/08
<i>Premedline</i>	0	18/04/08
<i>Embase</i>	2	18/04/08
<i>Cochrane Library (except NHSEED)</i>	2	18/04/08
<i>NHSEED</i>	0	18/04/08
<i>Cinahl</i>	0	18/04/08
<i>Psycinfo</i>	0	18/04/08
<i>BNI</i>	0	18/04/08
<i>EconLit</i>	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	0	18/04/08
<i>ISI Proceedings</i>	0	18/04/08

Any further comments:
The update search was performed to include the years 2007 – 18 April 2008 only.
The Health Economics update search was performed to include the years 2007 –18 April 2008 only.

NATIONAL COLLABORATING CENTRE FOR CANCER				
Clinical Guideline		Literature search summary		
Metastatic Spinal Cord Compression				
Question no: 2f				
Question title: What is the effectiveness of stabilisation surgery to prevent vertebral collapse, (where stabilisation surgery is +/-)				
Literature search details				
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1950 – 2007	749	59	14/02/07
<i>Premedline</i>	1950 – 2007	39	0	14/02/07
<i>Embase</i>	1980 – 2007	218	18	14/02/07
<i>Cochrane Library</i>	1800 – 2007	743	4	14/02/07
<i>Cinahl</i>	1982 – 2007	16	3	14/02/07
<i>BNI</i>	1994 – 2007	0	0	14/02/07
<i>Psycinfo</i>	1967 – 2007	1	0	14/02/07
<i>SIGLE</i>	1980 – 2005	0	0	14/02/07
<i>Web of Science (SCI & SSCI)</i>	1970 – 2007	1846	101	15/02/07
<i>ISI Proceedings</i>	1990 – 2007	118	9	15/02/07
<i>Biomed Central</i>	1997 - 2007	159	0	14/02/07

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2007 – 04/2008	124	8	18/04/08
<i>Premedline</i>	2007 – 04/2008	53	6	18/04/08
<i>Embase</i>	2007 – 04/2008	43	4	18/04/08
<i>Cochrane Library</i>	2007 – 04/2008	98	1	18/04/08
<i>Cinahl</i>	2007 – 04/2008	11	0	18/04/08
<i>BNI</i>	2007 – 04/2008	0	0	18/04/08
<i>Psychinfo</i>	2007 – 04/2008	0	0	18/04/08
<i>SIGLE</i>	-			
<i>Web of Science (SCI & SSCI)</i>	2007 – 04/2008	270	14	18/04/08
<i>ISI Proceedings</i>	2007 – 04/2008	20	1	18/04/08
<i>Biomed Central</i>	2007 – 04/2008	152	0	18/04/08

Total References retrieved (after de-duplication): 164 (update search: 28)

Medline search strategy (*This search strategy is adapted to each database.*)

Spinal Cord Compression OR Vertebral metastasis AND Stabilisation surgery
RCT and SR filters applied

1. exp Spine/
2. exp Spinal Neoplasms/
3. exp Neoplasm Metastasis/
4. (spin\$ adj3 metasta\$.tw.
5. (vertebra\$ adj3 (cancer\$ or carcinoma\$ or malignan\$ or tumo?r\$ or neoplas\$ or intraepithelial\$ or adeno\$)).tw.
6. vertebra\$ metastas\$.tw.
7. vertebra\$ collaps\$.tw.
8. spin\$ collaps\$.tw.
9. exp Spinal Cord Compression/
10. spin\$ tumo?r\$.tw.
11. or/1-10
12. surg\$ debulk\$.tw.
13. intralesion\$.tw.
14. debulk\$.tw.
15. ((total or en bloc or radical) and (resection or removal)).tw.
16. surg\$ excision\$.tw.
17. spin\$ reconstruct\$.tw.
18. posterior tumo?r remov\$.tw.
19. stabili\$ surg\$.tw.
20. exp Decompression, Surgical/
21. surg\$ decompress\$.tw.
22. prevent\$ surg\$.tw.
23. or/12-22

Health Economics Literature search details

SIGN Health Economics filter and SCHARR Quality of Life added to search.

Database name	No of references found	Finish date of search
<i>Medline</i>	65	26/04/07

Premedline	2	26/04/07
Embase	43	26/04/07
Cochrane Library (except NHSEED)	2	02/05/07
NHSEED	4	02/05/07
Cinahl	20	26/04/07
Psycinfo	0	26/04/07
BNI	0	26/04/07
EconLit	0	26/04/07
Web of Science (SCI & SSCI)	73	26/04/07
ISI Proceedings	6	26/04/07
SIGLE	0	26/04/07
UPDATE SEARCH		
Database name	No of references found	Finish date of search
Medline	0	18/04/08
Premedline	0	18/04/08
Embase	0	18/04/08
Cochrane Library (except NHSEED)	0	18/04/08
NHSEED	0	18/04/08
Cinahl	1	18/04/08
Psycinfo	0	18/04/08
BNI	0	18/04/08
EconLit	0	18/04/08
Web of Science (SCI & SSCI)	5	18/04/08
ISI Proceedings	0	18/04/08
Any further comments:		
The update search was performed to include the years 2007 – 18 April 2008 only.		
The Health Economics update search was performed to include the years 2007 – 18 April 2008 only.		

NATIONAL COLLABORATING CENTRE FOR CANCER				
Clinical Guideline		Literature search summary		
Metastatic Spinal Cord Compression				
Question title: For patients with known MSCC who have had surgery/radiotherapy/no treatment does 'early' mobilisation give better outcomes (mobility, pain) than 'delayed'?				
Question no: 14				
Literature search details				
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1950 – 2007	349	27	13/03/07
Premedline	1950 – 2007	3	0	13/03/07
Embase	1980 – 2007	336	9	14/03/07
Cochrane Library	1800 – 2007	2	1	13/03/07
Cinahl	1982 – 2007	37	1	13/03/07
BNI	1994 – 2007	0	0	13/03/07
Psycinfo	1967 – 2007	1	0	13/03/07

SIGLE	1980 – 2005	0	0	14/03/07
Web of Science (SCI & SSCI)	1970 – 2007	552	2	14/03/07
ISI Proceedings	1990 – 2007	28	0	14/03/07
Biomed Central	1997 - 2007	65	0	14/03/07

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2007 – 04/2008	7	0	18/04/08
Premedline	2007 – 04/2008	0	0	18/04/08
Embase	2007 – 04/2008	0	0	18/04/08
Cochrane Library	2007 – 04/2008	0	0	18/04/08
Cinahl	2007 – 04/2008	0	0	18/04/08
BNI	2007 – 04/2008	0	0	18/04/08
Psychinfo	2007 – 04/2008	0	0	18/04/08
Web of Science (SCI & SSCI)	2007 – 04/2008	131	3	18/04/08
ISI Proceedings	2007 – 04/2008	5	0	18/04/08
Biomed Central	2007 – 04/2008	58	0	18/04/08

Total References retrieved (after de-duplication): 38 (update search: 3)

Medline search strategy (*This search strategy is adapted to each database.*)

Spinal Cord Compression AND Early OR Late Mobilisation

1. Spinal Cord Compression/
2. (spin\$ adj2 compress\$).tw.
3. or/1-2
4. neurol\$ funct\$.tw.
5. neurol\$ impair\$.tw.
6. exp Movement/
7. sitting\$.tw.
8. exp Walking/
9. spin\$ blood\$ flow\$.tw.
10. cord perfusion\$.tw.
11. flat\$ rest\$.tw.
12. (early adj mobili\$).tw.
13. (late adj mobili\$).tw.
14. log roll\$.tw.
15. exp Postoperative Complications
16. or/4-15

Health Economics Literature search details

A Health Economics Literature search was not required.

Any further comments:

The update search was performed to include the years 2007 – 18 April 2008 only.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline

Literature search summary

Metastatic Spinal Cord Compression

Question title: For patients with suspected/confirmed MSCC, what is the most effective steroid regime wrt preserving or improving mobility; neurology; duration of effect and toxicity?

Question no: 13

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1950 – 2007	594	72	22/03/07
<i>Premedline</i>	1950 – 2007	3	0	22/03/07
<i>Embase</i>	1980 – 2007	576	46	22/03/07
<i>Cochrane Library</i>	1800 – 2007	45	3	22/03/07
<i>Cinahl</i>	1982 – 2007	21	5	22/03/07
<i>BNI</i>	1994 – 2007	396	0	22/03/07
<i>Psychinfo</i>	1967- 2007	4	0	22/03/07
<i>SIGLE</i>	1980 - 2005	0	0	23/03/07
<i>Web of Science (SCI & SSCI)</i>	1970 – 2007	398	58	23/03/07
<i>ISI Proceedings</i>	1990 – 2007	25	2	23/03/07
<i>Biomed Central</i>	1997 - 2007	441	1	23/03/07

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2007 – 04/2008	25	4	18/04/08
<i>Premedline</i>	2007 – 04/2008	3	2	18/04/08
<i>Embase</i>	2007 – 04/2008	144	11	18/04/08
<i>Cochrane Library</i>	2007 – 04/2008	19	1	18/04/08
<i>Cinahl</i>	2007 – 04/2008	5	2	18/04/08
<i>BNI</i>	2007 – 04/2008	69	0	18/04/08
<i>Psychinfo</i>	2007 – 04/2008	0	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	2007 – 04/2008	48	4	18/04/08
<i>ISI Proceedings</i>	2007 – 04/2008	4	2	18/04/08
<i>Biomed Central</i>	2007 – 04/2008	8	0	18/04/08

Total References retrieved (after de-duplication): 130 (update search: 14)

Medline search strategy (*This search strategy is adapted to each database.*)

Spinal Cord Compression AND Steroids

1. Spinal Cord Compression/
2. (spin\$ adj2 compress\$).tw.
3. (spin\$ adj metastas\$).tw.
4. exp Spinal Cord Neoplasms/
5. exp Spinal Neoplasms/
6. ((vertebra\$ or spin\$) adj3 (cancer\$ or carcinoma\$ or malignan\$ or tumo?r\$ or neoplas\$ or intraepithelial\$ or adeno\$)).tw.
7. or/1-6
8. exp Steroids/
9. steroid\$.tw.

10. exp Anti-Inflammatory Agents/
11. (anti adj inflammatory agent\$.tw.
12. exp Dexamethasone/
13. Dexamethason\$.tw.
14. exp Prednisolone/
15. Prednisolon\$.tw.
16. exp Methylprednisolone/
17. (methyl adj prednisolon\$.tw.
18. or/8-17
19. 7 and 18

Health Economics Literature search details

A Health Economics Literature search was not required.

Any further comments:

The update search was performed to include the years 2007 – 18 April 2008 only.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline

Metastatic Spinal Cord Compression

Literature search summary

Question title: Case selection for treatment – what is the validity of Tomita and Tokuhashi scoring systems?

Question no: 6a

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1950 – 2007	2611	148	07/03/07
<i>Premedline</i>	1950 – 2007	17	0	07/03/07
<i>Embase</i>	1980 – 2007	1973	31	08/03/07
<i>Cochrane Library</i>	1800 – 2007	67	0	08/03/07
<i>Cinahl</i>	1982 - 2007	72	14	07/03/07
<i>BNI</i>	1994 – 2007	0	0	07/03/07
<i>Psychinfo</i>	1967 – 2007	0	0	07/03/07
<i>SIGLE</i>	1980 – 2005	0	0	08/03/07
<i>Web of Science (SCI & SSCI)</i>	1970 – 2007	1031	6	08/03/07
<i>ISI Proceedings</i>	1990 – 2007	75	0	08/03/07
<i>Biomed Central</i>	1997 - 2007	1353	0	06/03/07

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2007 – 04/2008	32	3	18/04/08
<i>Premedline</i>	2007 – 04/2008	23	2	18/04/08
<i>Embase</i>	2007 – 04/2008	1	0	18/04/08
<i>Cochrane Library</i>	2007 – 04/2008	50	1	18/04/08
<i>Cinahl</i>	2007 – 04/2008	12	7	18/04/08
<i>BNI</i>	2007 – 04/2008	0	0	18/04/08
<i>Psychinfo</i>	2007 – 04/2008	0	0	18/04/08

Web of Science (SCI & SSCI)	2007 – 04/2008	152	12	18/04/08
ISI Proceedings	2007 – 04/2008	11	2	18/04/08
Biomed Central	2007 – 04/2008	10	0	18/04/08

Total References retrieved (after de-duplication): 118 (update search: 18)

Medline search strategy (*This search strategy is adapted to each database.*)

Scoring systems AND Spinal Cord Compression

1. scor\$ system\$.tw.
2. clinic\$ parameter\$.tw.
3. exp Models, Statistical/
4. evaluation\$.tw.
5. scor\$ method\$.tw.
6. diagnos\$ tool\$.tw.
7. exp Patient Care Planning/
8. exp "Outcome and Process Assessment (Health Care)"/
9. exp "Severity of Illness Index"/
10. exp Physical Examination/
11. exp Neurologic Examination/
12. exp Questionnaires/
13. exp Algorithms/
14. symptom\$ control\$.tw.
15. or/71-84
16. exp Spinal Neoplasms/
17. (spin\$ adj (cancer\$ or carcinoma\$ or malignan\$ or tumo?r\$ or neoplas\$ or intraepithelial\$ or adeno\$)).tw.
18. exp Spinal Cord Compression/
19. (skelet\$ adj3 event\$).tw.
20. or/86-89
21. 85 and 90

Health Economics Literature search details

A Health Economics Literature search was not required

Any further comments:

The update search was performed to include the years 2007 – 18 April 2008 only.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline

Metastatic Spinal Cord Compression

Literature search summary

Question title: Case selection for surgery – for patients with an established diagnosis of MSCC, what factors predict for successful outcomes (mobility, continence, lack of pain, survival) following surgery?

Question no: 6b

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1950 – 2007	177	95	27/02/07
<i>Premedline</i>	1950 – 2007	1	0	27/02/07
<i>Embase</i>	1980 – 2007	243	43	27/02/07
<i>Cochrane Library</i>	1800 – 2007	25	2	27/02/07
<i>Cinahl</i>	1982 – 2007	22	15	27/02/07
<i>BNI</i>	1994 – 2007	0	0	27/02/07
<i>Psychinfo</i>	1967 – 2007	0	0	27/02/07
<i>SIGLE</i>	1980 – 2005	0	0	27/02/07
<i>Web of Science (SCI & SSCI)</i>	1970 – 2007	604	55	01/03/07
<i>ISI Proceedings</i>	1990 – 2007	36	1	01/03/07
<i>Biomed Central</i>	1997 - 2007	65	0	01/03/07

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2007 – 04/2008	43	1	18/04/08
<i>Premedline</i>	2007 – 04/2008	3	1	18/04/08
<i>Embase</i>	2007 – 04/2008	71	9	18/04/08
<i>Cochrane Library</i>	2007 – 04/2008	14	1	18/04/08
<i>Cinahl</i>	2007 – 04/2008	14	4	18/04/08
<i>BNI</i>	2007 – 04/2008	0	0	18/04/08
<i>Psychinfo</i>	2007 – 04/2008	0	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	2007 – 04/2008	96	10	18/04/08
<i>ISI Proceedings</i>	2007 – 04/2008	6	0	18/04/08
<i>Biomed Central</i>	2007 – 04/2008	45	0	18/04/08

Total References retrieved (after de-duplication): 154 ; (update search: 25)

Medline search strategy (*This search strategy is adapted to each database.*)

MSCC AND Surgery AND Outcome (mobility, continence, lack of pain, survival)

1. Spinal Cord Compression/
2. (spin\$ adj2 compress\$).tw.
3. (compress\$ adj1 myelopath\$).tw.
4. (MSCC or MESCC).tw.
5. (nerv\$ root\$ adj compress\$).tw.
6. vertebra\$ collaps\$.tw.
7. spin\$ collaps\$.tw.
8. or/1-7
9. surg\$ debulk\$.tw.
10. intralesion\$.tw.
11. debulk\$.tw.
12. ((total or en bloc or radical) and (resection or removal)).tw.
13. surg\$ excision\$.tw.
14. spin\$ reconstruct\$.tw.
15. posterior tumo?r remov\$.tw.
16. stabili\$ surg\$.tw.
17. exp Decompression, Surgical/

18. surg\$ decompress\$.tw.
19. or/9-18
20. 8 and 19
21. exp Fecal Incontinence/ or exp Urinary Incontinence/
22. exp Back Pain/ or exp Low Back Pain/
23. Karnofsky performance index\$.tw.
24. surviv\$.tw.
25. exp Morbidity/
26. exp Motor Skills/
27. mobili\$.tw.
28. exp Prognosis/hi, sn, is, mt [History, Statistics & Numerical Data, Instrumentation, Methods]
29. prognos\$.tw.
30. or/21-29
31. 20 and 30

Health Economics Literature search details

A Health Economics Literature search was not required

Any further comments:

The update search was performed to include the years 2007 – 18 April 2008 only.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline

Metastatic Spinal Cord Compression

Literature search summary

Question title: Case selection for radiotherapy - for patients with an established diagnosis of MSCC, what factors predict for successful outcomes (mobility, continence, lack of pain, survival) following radiotherapy?

Question no: 6c

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1950 – 2007	271	67	05/03/07
<i>Premedline</i>	1950 – 2007	5	1	05/03/07
<i>Embase</i>	1980 – 2007	313	55	06/03/07
<i>Cochrane Library</i>	1800 – 2007	5	2	05/03/07
<i>Cinahl</i>	1982 – 2007	17	0	05/03/07
<i>BNI</i>	1994 – 2007	0	0	05/03/07
<i>Psychinfo</i>	1967 – 2007	1	0	05/03/07
<i>SIGLE</i>	1980 – 2005	0	0	06/03/07
<i>Web of Science (SCI & SSCI)</i>	1970 – 2007	354	38	06/03/07
<i>ISI Proceedings</i>	1990 – 2007	21	0	06/03/07
<i>Biomed Central</i>	1997 - 2007	155	0	06/03/07

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2007 – 04/2008	39	5	18/04/08

Premedline	2007 – 04/2008	4	2	18/04/08
Embase	2007 – 04/2008	74	12	18/04/08
Cochrane Library	2007 – 04/2008	2	0	18/04/08
Cinahl	2007 – 04/2008	10	0	18/04/08
BNI	2007 – 04/2008	0	0	18/04/08
Psychinfo	2007 – 04/2008	0	0	18/04/08
Web of Science (SCI & SSC)	2007 – 04/2008	76	2	18/04/08
ISI Proceedings	2007 – 04/2008	6	0	18/04/08
Biomed Central	2007 – 04/2008	43	0	18/04/08

Total References retrieved (after de-duplication): 117 (update search: 16)

Medline search strategy (*This search strategy is adapted to each database.*)

MSCC AND Radiotherapy AND Incontinence (or motor skills or prognosis)

1. Spinal Cord Compression/
2. (spin\$ adj2 compress\$).tw.
3. (compress\$ adj1 myelopath\$).tw.
4. (MSCC or MESCC).tw.
5. (nerv\$ root\$ adj compress\$).tw.
6. vertebra\$ collaps\$.tw.
7. spin\$ collaps\$.tw.
8. or/1-7
9. exp Fecal Incontinence/ or exp Urinary Incontinence/
10. exp Back Pain/ or exp Low Back Pain/
11. Karnofsky performance index\$.tw.
12. surviv\$.tw.
13. exp Morbidity/
14. exp Motor Skills/
15. mobili\$.tw.
16. exp Prognosis/hi, sn, is, mt [History, Statistics & Numerical Data, Instrumentation, Methods]
17. prognos\$.tw.
18. or/9-17
19. exp Radiotherapy/
20. radiotherap\$.tw.
21. (radiat\$ adj2 therap\$).tw.
22. irradiat\$.tw.
23. (interstitial adj (irradiation or radiation)).tw.
24. (radiat\$ adj2 treatment\$).tw.
25. (three dimensional adj2 radiotherap\$).tw.
26. 3D radiotherap\$.tw.
27. 3DCRT.tw.
28. external beam radiotherap\$.tw.
29. systemic radiotherap\$.tw.
30. or/19-29
31. 8 and 30
32. 31 and 18

Health Economics Literature search details

A Health Economics Literature search was not required.

Any further comments:

The update search was performed to include the years 2007- 18 April 2008 only.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline

Literature search summary

Metastatic Spinal Cord Compression

Question title: What surgical technique is the most effective in treating patients with known MSCC in terms of outcomes outlined in PICO?

Question no: 8

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1950 – 2007	182	71	04/04/07
<i>Premedline</i>	1950 – 2007	16	4	04/04/07
<i>Embase</i>	1980 – 2007	99	24	04/04/07
<i>Cochrane Library</i>	1800 – 2007	77	1	04/04/07
<i>Cinahl</i>	1982 – 2007	4	4	04/04/07
<i>BNI</i>	1994 – 2007	0	0	04/04/07
<i>Psychinfo</i>	1967 – 2007	1	0	04/04/07
<i>SIGLE</i>	1980 – 2005	0	0	16/04/07
<i>Web of Science (SCI & SSCI)</i>	1970 – 2007	935	60	16/04/07
<i>ISI Proceedings</i>	1990 – 2007	30	3	04/04/07
<i>Biomed Central</i>	1997 - 2007	48	0	04/04/07

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2007 – 04/2008	19	3	18/04/08
<i>Premedline</i>	2007 – 04/2008	12	2	18/04/08
<i>Embase</i>	2007 – 04/2008	11	4	18/04/08
<i>Cochrane Library</i>	2007 – 04/2008	21	2	18/04/08
<i>Cinahl</i>	2007 – 04/2008	3	3	18/04/08
<i>BNI</i>	2007 – 04/2008	0	0	18/04/08
<i>Psychinfo</i>	2007 – 04/2008	0	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	2007 – 04/2008	106	6	18/04/08
<i>ISI Proceedings</i>	2007 – 04/2008	4	0	18/04/08
<i>Biomed Central</i>	2007 – 04/2008	24	0	18/04/08

Total References retrieved (after de-duplication): 173 (update search: 15)

Medline search strategy (*This search strategy is adapted to each database.*)

Spinal Cord compression AND Laminectomy And (RCT AND SR filters)

1. exp Spinal Cord Compression/su [Surgery]
2. (spin\$ adj2 compress\$).tw.
3. (compress\$ adj1 myelopath\$).tw.
4. (MSCC or MESCC).tw.
5. (nerv\$ root\$ adj compress\$).tw.
6. vertebra\$ collaps\$.tw.
7. spin\$ collaps\$.tw.

8. or/1-7
9. surg\$ debulk\$.tw.
10. intralesion\$.tw.
11. debulk\$.tw.
12. ((total or en bloc or radical) and (resection or removal)).tw.
13. surg\$ excision\$.tw.
14. spin\$ reconstruct\$.tw.
15. posterior tumor removal\$.tw.
16. stabiliz\$ surg\$.tw.
17. exp Decompression, Surgical/
18. surg\$ decompress\$.tw.
19. exp Laminectomy/
20. lamin\$.tw.
21. exp Spinal Fusion/
22. anterior\$ surger\$.tw.
23. corporectom\$.tw.
24. exp Endoscopy/
25. endoscop\$ surgical\$ procedure\$.tw.
26. vertebroplast\$.tw.
27. or/9-26
28. 8 and 27

Health Economics Literature search details

SIGN Health Economics filter and SCHARR Quality of Life filter added to search.

Database name	No of references found	Finish date of search
<i>Medline</i>	28	25/04/07
<i>Premedline</i>	0	25/04/07
<i>Embase</i>	16	25/04/07
<i>Cochrane Library (except NHSEED)</i>	0	25/04/07
<i>NHSEED</i>	0	25/04/07
<i>Cinahl</i>	10	25/04/07
<i>Psycinfo</i>	0	25/04/07
<i>BNI</i>	0	25/04/07
<i>EconLit</i>	0	25/04/07
<i>Web of Science (SCI & SSCI)</i>	29	25/04/07
<i>ISI Proceedings</i>	1	25/04/07
<i>SIGLE</i>	0	25/04/07
UPDATE SEARCH		
Database name	No of references found	Finish date of search
<i>Medline</i>	0	18/04/08
<i>Premedline</i>	0	18/04/08
<i>Embase</i>	0	18/04/08
<i>Cochrane Library (except NHSEED)</i>	0	18/04/08
<i>NHSEED</i>	0	18/04/08
<i>Cinahl</i>	0	18/04/08
<i>Psycinfo</i>	0	18/04/08
<i>BNI</i>	0	18/04/08
<i>EconLit</i>	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	2	18/04/08
<i>ISI Proceedings</i>	0	18/04/08

Any further comments:

The update search was performed to include the years 2007 – 18 April 2008 only.
The Health Economics update search was performed to include the years 2007 – 18 April 2008 only.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline

Literature search summary

Metastatic Spinal Cord Compression

Question title: In patients with known MSCC referred for radiotherapy, what is the most effective and cost effective dose fractionation regimen?

Question no: 9

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1950 – 2007	842	129	18/04/07
<i>Premedline</i>	1950 – 2007	16	4	18/04/07
<i>Embase</i>	1980 – 2007	916	92	18/04/07
<i>Cochrane Library</i>	1800 – 2007	38	5	18/04/07
<i>Cinahl</i>	1982 – 2007	46	4	18/04/07
<i>BNI</i>	1994 – 2007	1	0	18/04/07
<i>Psychinfo</i>	1967 – 2007	10	2	18/04/07
<i>SIGLE</i>	1980 – 2005	0	0	19/04/07
<i>Web of Science (SCI & SSCI)</i>	1970 – 2007	773	59	19/04/07
<i>ISI Proceedings</i>	1990 – 2007	63	18	18/04/07
<i>Biomed Central</i>	1997 - 2007	46	1	18/04/07

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2007 – 04/2008	18	2	18/04/08
<i>Premedline</i>	2007 – 04/2008	15	2	18/04/08
<i>Embase</i>	2007 – 04/2008	21	5	18/04/08
<i>Cochrane Library</i>	2007 – 04/2008	13	2	18/04/08
<i>Cinahl</i>	2007 – 04/2008	14	2	18/04/08
<i>BNI</i>	2007 – 04/2008	0	0	18/04/08
<i>Psychinfo</i>	2007 – 04/2008	0	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	2007 – 04/2008	102	19	18/04/08
<i>ISI Proceedings</i>	2007 – 04/2008	13	5	18/04/08
<i>Biomed Central</i>	2007 – 04/2008	21	0	18/04/08

Total References retrieved (after de-duplication): 191 (update search: 26)

Medline search strategy (*This search strategy is adapted to each database.*)

Radiotherapy/Dose fractionation AND MSCC
RCT and SR filters applied

1. exp Radiotherapy/
2. radiotherap\$.tw.
3. (radiat\$ adj2 therap\$).tw.
4. irradiat\$.tw.
5. (interstitial adj (irradiation or radiation)).tw.
6. (radiat\$ adj2 treatment\$).tw.
7. (three dimensional adj2 radiotherap\$).tw.
8. 3D radiotherap\$.tw.
9. 3DCRT.tw.
10. external beam radiotherap\$.tw.
11. systemic radiotherap\$.tw.
12. exp Radiosurgery/
13. LINAC\$.tw.
14. IMRT\$.tw.
15. exp Radiotherapy Planning, Computer-Assisted/
16. exp Radiotherapy Dosage/
17. intensity-modulated radiation therap\$.tw.
18. exp Dose Fractionation/
19. (dose\$ or dosage\$).tw.
20. or/1-19
21. Spinal Cord Compression/
22. (spin\$ adj2 compress\$).tw.
23. (compress\$ adj1 myelopath\$).tw.
24. (MSCC or MESCC).tw.
25. or/21-24
26. 20 and 25

Health Economics Literature search details

A Health Economics Literature search was not required.

Any further comments:

The update search was performed to include the years 2007 – 18 April 2008 only.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline

Metastatic Spinal Cord Compression

Literature search summary

Question title: What is the most effective bladder and bowel management for patients with spinal cord injury (MSCC)?

Question no: 11b

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1950 – 2007	289	81	19/07/07
<i>Premedline</i>	1950 – 2007	64	31	20/07/07
<i>Embase</i>	1980 – 2007	159	45	20/07/07
<i>Cochrane Library</i>	1800 – 2007	217	45	20/07/07
<i>Cinahl</i>	1982 – 2007	19	10	20/07/07
<i>BNI</i>	1994 – 2007	28	12	20/07/07

Psychinfo	1967 – 2007	8	1	20/07/07
SIGLE	1980 – 2005	3	2	24/07/07
Web of Science (+ ISI Proc.)	1970 – 2007	113	58	24/07/07
Biomed Central	1990 - 2007	21	2	24/07/07

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2007 – 04/2008	12	10	18/04/08
Premedline	2007 – 04/2008	27	6	18/04/08
Embase	2007 – 04/2008	18	10	18/04/08
Cochrane Library	2007 – 04/2008	39	1	18/04/08
Cinahl	2007 – 04/2008	1	0	18/04/08
BNI	2007 – 04/2008	7	2	18/04/08
Psychinfo	2007 – 04/2008	0	0	18/04/08
Web of Science (SCI & SSCI) and ISI Proceedings	2007 – 04/2008	15	4	18/04/08
Biomed Central	2007 – 04/2008	4	0	18/04/08

Total References retrieved (after de-duplication): 222 (update search: 23)

Medline search strategy (*This search strategy is adapted to each database.*)

(Bladder management OR Incontinence) AND (Spinal Cord Compression OR Spinal Injury)

1. bladder management\$.tw.
2. exp Urinary Bladder, Neurogenic/
3. exp Urinary Retention/
4. exp Urination Disorders/
5. urin\$ retention\$.tw.
6. incomplete bladder empty\$.tw.
7. exp Urinary Incontinence/
8. detrusor\$.tw.
9. overactive bladder\$.tw.
10. detrusor\$ overactiv\$.tw.
11. exp Urinary Catheterization/
12. or/1-11
13. Spinal Cord Compression/
14. (spin\$ adj2 compress\$.tw.
15. exp Spinal Cord Injuries/co, pp, di, rh, th [Complications, Physiopathology, Diagnosis, Rehabilitation, Therapy]
16. Cord injur\$.tw.
17. exp Cauda Equina/ab, pp, in [Abnormalities, Physiopathology, Injuries]
18. Spin\$ Injur\$.tw.
19. upper motor neuron.mp.
20. or/13-19
21. 12 and 20
22. exp Muscarinic Antagonists/ad, ae, ct, tu, to, ur [Administration & Dosage, Adverse Effects, Contraindications, Therapeutic Use, Toxicity, Urine]
23. 21 and 22
24. anticholinergic\$.tw.
25. 24 and 21
26. reflex voiding\$.tw.
27. 26 and 21
28. 21 or 23 or 25 or 27

Health Economics Literature search details

A Health Economics Literature search was not required.

Any further comments:

The update search was performed to include the years 2007- 18 April 2008 only.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline

Metastatic Spinal Cord Compression

Literature search summary

Question title: What is the most effective pressure ulcer management for patients with spinal cord injury (MSCC)?

Question no: 11b

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1950 – 2007	474	38	20/03/07
<i>Premedline</i>	1950 – 2007	19	0	21/03/07
<i>Embase</i>	1980 – 2007	254	24	20/03/07
<i>Cochrane Library</i>	1800 – 2007	96	6	21/03/07
<i>Cinahl</i>	1982 – 2007	65	14	21/03/07
<i>BNI</i>	1994 – 2007	338	35	20/03/07
<i>Psychinfo</i>	1967 – 2007	8	2	21/03/07
<i>SIGLE</i>	1980 – 2005	1	1	21/03/07
<i>Web of Science (SCI & SSCI)</i>	1970 – 2007	393	18	21/03/07
<i>ISI Proceedings</i>	1990 – 2007	33	2	21/03/07
<i>Biomed Central</i>	1997 - 2007	94	0	21/03/07

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2007 – 04/2008	30	3	18/04/08
<i>Premedline</i>	2007 – 04/2008	14	3	18/04/08
<i>Embase</i>	2007 – 04/2008	40	5	18/04/08
<i>Cochrane Library</i>	2007 – 04/2008	8	1	18/04/08
<i>Cinahl</i>	2007 – 04/2008	3	0	18/04/08
<i>BNI</i>	2007 – 04/2008	52	2	18/04/08
<i>Psychinfo</i>	2007 – 04/2008	1	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	2007 – 04/2008	9	1	18/04/08
<i>ISI Proceedings</i>	2007 – 04/2008	3	2	18/04/08
<i>Biomed Central</i>	2007 – 04/2008	0	0	18/04/08

Total References retrieved (after de-duplication): 98 (update search: 11)

Medline search strategy (*This search strategy is adapted to each database.*)

Pressure Sore AND Spinal Cord Compression

1. exp Skin/
2. exp Skin Care/
3. exp Tissues/
4. exp Pressure Ulcer/co, di, pc, th [Complications, Diagnosis, Prevention & Control, Therapy]
5. (bed adj1 sore\$.tw.
6. pressure\$ sore\$.tw.
7. exp Tissue Survival/
8. tissue\$ viabilit\$ assessment\$.tw.
9. or/1-8
10. exp Technology Assessment, Biomedical/
11. exp Equipment Design/
12. exp Therapeutics/
13. exp Treatment Outcome/
14. or/10-13
15. Spinal Cord Compression/
16. (spin\$ adj2 compress\$.tw.
17. or/15-16
18. 9 and 14 and 17
19. from 18 keep 29
20. 9 and 17
21. bladder management\$.tw.
22. bowel management\$.tw.
23. exp Urinary Bladder, Neurogenic/
24. exp Rehabilitation/
25. exp Patient Education/
26. or/21-25
30. 26 and 17
31. thromboprophylax\$.tw.
32. exp Thrombosis/pc [Prevention & Control]
33. 31 or 32
34. 33 and 17
35. emotion\$ support\$.tw.
36. psychol\$ support\$.tw.
37. exp Family/
38. exp Counseling/
39. or/35-38
40. 39 and 17
41. exp Hospitals, Special/
42. 41 and 17
43. exp Hospitals, General/
44. 43 and 17
45. exp Hospices/
46. 45 and 17
47. exp Primary Health Care/
48. 46 and 17
49. exp Residential Facilities/ or exp Home Care Services/ or exp Nursing Homes/ or exp Homes for the Aged/
or exp Health Services for the Aged/
50. 49 and 17
51. mobilitt\$.tw.
52. 61 and 17
53. circulatory function\$.tw.
54. 53 and 17
55. respiratory function\$.tw.
56. 55 and 17

Health Economics Literature search details

A Health Economics Literature Search was not required.

Any further comments:

The update search was performed to include the years 2007 – 18 April 2008 only.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline

Metastatic Spinal Cord Compression

Literature search summary

Question title: What is the most effective respiratory and circulatory management for patients with spinal cord injury (MSCC)?

Question no: 11b

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1950 – 2007	201	33	23/10/07
<i>Premedline</i>	1950 – 2007	97	4	23/10/07
<i>Embase</i>	1980 – 2007	300	25	23/10/07
<i>Cochrane Library</i>	1800 – 2007	7	0	24/10/07
<i>Cinahl</i>	1982 – 2007	182	14	23/10/07
<i>BNI</i>	1994 – 2007	0	0	23/10/07
<i>Psychinfo</i>	1967 – 2007	1	0	23/10/07
<i>SIGLE</i>	1980 – 2005	0	0	24/10/07
<i>Web of Science (SCI & SSCI) and ISI Proceedings</i>	1970 – 2007 1990- 2007	52	7	24/10/07
<i>Biomed Central</i>	1997 - 2007	8	0	24/10/07

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2007 – 04/2008	40	5	18/04/08
<i>Premedline</i>	2007 – 04/2008	6	0	18/04/08
<i>Embase</i>	2007 – 04/2008	59	5	18/04/08
<i>Cochrane Library</i>	2007 – 04/2008	3	0	18/04/08
<i>Cinahl</i>	2007 – 04/2008	5	1	18/04/08
<i>BNI</i>	2007 – 04/2008	0	0	18/04/08
<i>Psychinfo</i>	2007 – 04/2008	1	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	2007 – 04/2008	8	0	18/04/08
<i>ISI Proceedings</i>	2007 – 04/2008	3	0	18/04/08
<i>Biomed Central</i>	2007 – 04/2008	0	0	18/04/08

Total References retrieved (after de-duplication): 69 (update search: 10)

Medline search strategy (*This search strategy is adapted to each database.*)

Spinal Cord Compression (or Spinal Injury) OR Hypotension AND Bandages or Stockings OR Blood Circulation
RCT and SR filters applied

1. Spinal Cord Compression/

2. (spin\$ adj2 compress\$).tw.
3. (compress\$ adj1 myelopath\$).tw.
4. (MSCC or MESCC).tw.
5. or/1-4
6. exp Hypotension, Orthostatic/
7. postur\$ hypotens\$.tw.
8. exp Autonomic Nervous System Diseases/
9. exp Blood Pressure/
10. exp Blood Flow Velocity/
11. exp Lower Body Negative Pressure/
12. hypertention.mp.
13. or/6-12
14. exp Bandages/
15. TED stocking\$.tw.
16. Abdominal binder\$.tw.
17. exp Ephedrine/
18. exp Fludrocortisone/
19. lower limb compression bandaging\$.tw.
20. exp Leg/
21. or/14-20
22. 13 or 21
23. 5 and 22

82. exp Spinal Cord Injuries/
83. 82 and 13
84. 83 and 21

88. exp "Range of Motion, Articular"/
89. exp Lower Extremity/
90. exp Leg/
91. exp Movement/ and exp Muscles/
92. exp Mobility Limitation/
93. mobilit\$.tw.
94. or/88-93
95. exp Blood Circulation/
96. exp Venous Thrombosis/pc [Prevention & Control]
97. deep vein thrombosi\$.tw.
98. muscle length.mp.
99. or/95-98
100. 94 or 99
101. 5 and 100

Health Economics Literature search details

A Health Economics Literature search was not required.

Any further comments:

The search was performed to include the years 2007 – 18 April 2008 only.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline

Metastatic Spinal Cord Compression

Literature search summary

Question title: Given that specialised centres for patients with spinal injuries (or specialised wards for neuro-patients) exist and provide services that benefit patients; can MSCC patients also benefit from

these kinds of services (wards/centres)?

Question no: 16a

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1950 - 2007	170	35	23/04/07
<i>Premedline</i>	1950 – 2007	12	0	24/04/07
<i>Embase</i>	1980 – 2007	233	13	24/04/07
<i>Cochrane Library</i>	1800 – 2007	114	0	24/04/07
<i>Cinahl</i>	1982 – 2007	62	7	24/04/07
<i>BNI</i>	1994 – 2007	1	0	24/04/07
<i>Psychinfo</i>	1967 – 2007	5	0	24/04/07
<i>SIGLE</i>	1980 – 2005	0	0	24/04/07
<i>Web of Science (SCI & SSCI)</i>	1970 – 2007	41	63	24/04/07
<i>ISI Proceedings</i>	1990 – 2007	3	0	24/04/07
<i>Biomed Central</i>	1997 - 2007	71	0	24/04/07

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2007 – 04/2008	12	2	18/04/08
<i>Premedline</i>	2007 – 04/2008	9	2	18/04/08
<i>Embase</i>	2007 – 04/2008	38	6	18/04/08
<i>Cochrane Library</i>	2007 – 04/2008	24	0	18/04/08
<i>Cinahl</i>	2007 – 04/2008	4	2	18/04/08
<i>BNI</i>	2007 – 04/2008	0	0	18/04/08
<i>Psychinfo</i>	2007 – 04/2008	7	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	2007 – 04/2008	14	5	18/04/08
<i>ISI Proceedings</i>	2007 – 04/2008	2	1	18/04/08
<i>Biomed Central</i>	2007 – 04/2008	31	0	18/04/08

Total References retrieved (after de-duplication): 44 (update search: 12)

Medline search strategy (*This search strategy is adapted to each database.*)

Spinal Cord Compression AND Rehabilitation Centres or Spinal Injury or Referral

1. Spinal Cord Compression/
2. (spin\$ adj2 compress\$).tw.
3. (compress\$ adj1 myelopath\$).tw.
4. (MSCC or MESCC).tw.
5. or/1-4
6. exp Spinal Cord Injuries/rh [Rehabilitation]
7. exp Spinal Injuries/rh [Rehabilitation]
8. exp Rehabilitation/
9. exp Rehabilitation Centers/
10. rehab\$.tw.
11. (neuro adj rehab\$).tw.
12. special\$ ward\$.tw.
13. exp "Referral and Consultation"/

14. spin\$ injur\$ rehab\$ centre\$.tw.
 15. or/6-14
 16. 5 and 15

Health Economics Literature search details

A Health Economics Literature search was not required.

Any further comments:

The update search was performed to include the years 2007 – 18 April 2008 only.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline

Literature search summary

Metastatic Spinal Cord Compression

Question title: Which MSCC patient factors will predict for beneficial outcomes from specialised services?

Question no: 16b

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1950 – 2007	59	11	24/04/07
<i>Premedline</i>	1950 – 2007	11	0	25/04/07
<i>Embase</i>	1980 – 2007	124	8	25/04/07
<i>Cochrane Library</i>	1800 – 2007	0	0	25/04/07
<i>Cinahl</i>	1982 – 2007	22	2	25/04/07
<i>BNI</i>	1994 – 2007	0	0	25/04/07
<i>Psychinfo</i>	1967 – 2007	3	0	25/04/07
<i>SIGLE</i>	1980 – 2005	0	0	25/04/07
<i>Web of Science (SCI & SSCI)</i>	1970 – 2007	40	3	25/04/07
<i>ISI Proceedings</i>	1990 – 2007	3	0	25/04/07
<i>Biomed Central</i>	1997 - 2007	21	0	25/04/07

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2007 – 43/2008	3	1	18/04/08
<i>Premedline</i>	2007 – 04/2008	6	0	18/04/08
<i>Embase</i>	2007 – 04/2008	18	4	18/04/08
<i>Cochrane Library</i>	2007 – 04/2008	0	0	18/04/08
<i>Cinahl</i>	2007 – 04/2008	2	1	18/04/08
<i>BNI</i>	2007 – 04/2008	0	0	18/04/08
<i>Psychinfo</i>	2007 – 04/2008	2	0	18/04/08
<i>Web of Science (SCI & SSCI)</i>	2007 – 04/2008	6	3	18/04/08
<i>ISI Proceedings</i>	2007 – 04/2008	1	1	18/04/08
<i>Biomed Central</i>	2007 – 04/2008	11	0	18/04/08

Total References retrieved (after de-duplication): 3 (update search: 1)

Medline search strategy (*This search strategy is adapted to each database.*)

Spinal Cord compression AND Spinal Injuries rehabilitation centres OR referral

1. Spinal Cord Compression/
2. (spin\$ adj2 compress\$).tw.
3. (compress\$ adj1 myelopath\$).tw.
4. (MSCC or MESCC).tw.
5. or/1-4
6. exp Spinal Cord Injuries/rh [Rehabilitation]
7. exp Spinal Injuries/rh [Rehabilitation]
8. special\$ ward\$.tw.
9. exp "Referral and Consultation"/
10. spin\$ injur\$ rehab\$ centre\$.tw.
11. or/6-10
12. 5 and 11

Health Economics Literature search details

A Health Economics Literature search was not required.

Any further comments:

The update search was performed to include the years 2007 – 18 April 2008 only.

Appendix B - Position Paper. Interventional Pain management in metastatic spinal cord compression

*Dr Manohar Sharma
Consultant in Pain Medicine
Walton Centre for Neurology and Neurosurgery*

This paper will specifically look in to the role of pain interventions in patients who have malignant spinal cord compression. I understand the evidence base for these interventions is not strong.

Causes of pain

Malignant spinal metastasis usually presents with either back pain or radicular pain even before onset of neurological deficit or bowel/bladder sphincter compromise. Pain is caused by tumour infiltration of vertebral body, inter-vertebral foramen or compression of meninges, nerve roots or spinal cord. In extreme cases there may be no pain, but only dense neurological deficit.

Pharmacologic / non-pharmacologic Interventions

Pharmacotherapy, radiotherapy, hormone therapy, chemotherapy and surgical procedures (including orthopaedic and palliative surgery) to deal with primary cancer or metastatic disease can be very effective to control pain in most of the patients. Cognitive behaviour therapy and immobilisation has a place in some patients. In remaining patients who are refractory to these therapies and the one suffering from incident type movement related pain, some of the interventional pain procedures can be very effective¹.

Neuro-Surgical interventions

Spinal decompression may be effective in the early stages of the disease process, although if patient has developed paraplegia, then it may not be as effective and may not be well tolerated^{2,3}.

Pain procedures

Before contemplating spinal pain interventions, one needs tissue diagnosis to confirm the malignant nature of disease. Interventional analgesia is needed when pain is severe, uncontrolled and has associated intractable side effects from medications.

Epidural / intrathecal analgesia

Epidural or Intrathecal analgesia can be effective in patients with malignant spinal cord compression pain, when pain cannot be controlled by above mentioned means. This mode of analgesic delivery has to be carefully planned so as to avoid using the epidural or spinal interspace involved with malignancy. Generally epidural catheter is inserted one or two space higher than the known level of malignancy. In very rare circumstances, one may have to consider another epidural below the level of spinal compression (Manuscript being prepared). The decision to initiate epidural analgesia below the level of spinal compression may be difficult as there is risk of paraplegia or sudden neurological deterioration^{4,5}. Spinal analgesia can be technically more

difficult if patient is not able to position themselves because of neurological deficit.

In a retrospective review Applegren et al. reviewed their case series of intrathecal analgesia and concluded that in presence of spinal epidural metastasis and partial or complete spinal cord compression, intrathecal analgesia may not be as effective⁶. During the period of intrathecal treatment, patients with confirmed epidural metastasis and total spinal canal stenosis needed significantly higher daily doses of morphine (means, 77 ± 103 versus 22 ± 29 mg) and bupivacaine (means, 65 ± 44 versus 33 ± 20 mg) and had poor analgesia ($p < .05$). This means the drug delivered in intrathecal or epidural space may not spread/diffuse as evenly as expected. Incidence of post dural puncture headache was reduced by spinal cord compression, but there was increased incidence of neurological deterioration by either medullary coning or sudden unexpected paraplegia.

Significant inter-patient variation in daily dosages of analgesics has been reported for both epidural and intrathecal analgesia in patients with epidural metastasis. Epidural morphine dose may vary from 6 to 120 mg per day at the start of treatment⁷, 16 to 600 mg per day at steady state and 28 to 600 mg per day at the final stage of treatment have been reported⁸.

Rathmell et al. presented a case of spinal cord compression at L1 level managed by epidural analgesia⁹. They inserted epidural catheter at T11/12 interspace. This case highlights the need for MR imaging to look for the extent of metastatic spread so as to plan placement of epidural catheter at unaffected spinal level.

Two to three fold increases in intrathecal morphine dose has also been reported by Sallerin-Caute and colleagues for refractory cancer pain and may reflect the effect of tumour progression¹⁰. Yaksh and Onofrio reported a marked time-dependent increase from 4.8 mg/day at one week to 16 mg/day at 24 weeks and 21 mg/day at 52 weeks¹¹. Similar results have been reported by Penn and Paice, with the view that this tolerance can be managed without many problems¹².

Epidural / Intrathecal neurolysis

Intrathecal neurolysis can be very effective method for nociceptive pain relief in cancer patients with limited life expectancy and who have pain covering 2-3 dermatomes (especially sacral and thoracic dermatomes). It may have a role in patients who have impaired bowel/bladder control or are severely compromised. Intrathecal phenol or alcohol administration requires careful positioning of the patient so as to allow neurolytic agent to stay close to affected sensory nerve roots. Randomised prospective studies are lacking. Based on the published studies 74% of patients can achieve good to moderate pain relief¹³. Papo and Visca reported their series of subarachnoid neurolysis in 290 cancer pain patients and reported good to fair results in 75% of the patients¹⁴. Best results were obtained in pain localised to sacral dermatomes.

In some patients with spinal cord compression, it may become very difficult to keep or maintain epidural catheter in place safely. There is also risk of infection, disconnection or rarely break/snapping of epidural catheter. In these circumstances we have found epidural phenol to be very effective (manuscript being prepared).

Percutaneous / open cordotomy

Percutaneous cervical cordotomy has largely replaced open cordotomy¹⁵. It is very effective for unilateral incident or neuropathic pain below C4 dermatome¹⁶. Many patients in the initial stages of spinal cord compression present with unilateral radicular pain. Very rarely if pain later appears on the other side then either percutaneous or open cordotomy may be performed on the other side. This procedure is normally carried out on the side opposite to pain, as pain fibres cross to other side as antero-lateral spinothalamic tract. This procedure needs more expertise and patient co-operation to achieve best results¹⁷. CT guided percutaneous cordotomy may have a place in future to make this procedure technically easier¹⁸. This procedure is relatively underused at the moment in cancer pain, although I am aware that there are attempts being made to develop a "Pain in Palliative care" special interest group in British Pain Society. Need to develop this kind of group is highlighted by recent paper which demonstrates poor links (under referral of complex cancer pain patients for joint Pain-Palliative care assessment) between pain specialists and palliative care¹⁹.

Intraventricular / cisternal administration of opioids

This route of opioid administration is not much used in England, but may be very useful in patients with spinal cord compression. Spinal analgesia although easy to accomplish may have higher risks, in patients with malignant spinal cord compression. Many case series²⁰ and a Cochrane review²¹ have demonstrated reasonable degree of efficacy and safety for this particular way of delivering opioids in cancer pain. Spinal opioid delivery is often effective for treating cancer pain that has not been adequately controlled by systemic treatment. However, long-term use of neuraxial therapy can be complicated by problems associated with the catheters. The data from uncontrolled studies suggests that Intra-cerebro-ventricular route is at least as effective against pain as other neuraxial treatments and may be a successful treatment for patients whose cancer pain is resistant to other treatments.

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Appendix C MSCC Guideline Economic Plan

This document identifies the priorities for economic analysis and the proposed methods for addressing these questions as described in section 8.1.3.1 of the Guidelines Manual (2006).

Process for agreement

The economic plan was prepared by the guideline economist in consultation with the rest of the NCC technical team and GDG. It was discussed and agreed on 01/08/07 by the following people^f:

For the NCC and GDG:

NCC economist:	Raquel Aguiar-Ibáñez
NCC representative(s) ^g :	Andrew Champion Katrina Asquith-Coe Angela Bennett
GDG representative(s) ^h :	Mr Barrie White (Chair) Mr Alistair Stirling (Lead Clinician)

For NICE:

CCP lead ⁱ :	Tim Stokes
Commissioning manager:	Nicole Elliott
Economic lead ^j :	Francis Ruiz
Costing lead:	Christopher Evans

Proposals for any substantive changes will be circulated by email to this group. If revisions are agreed, they will be listed as addenda to this document (section 5 below).

^f This may be done by face-to-face meeting, teleconference, or email as convenient.

^g May be the project manager, a systematic reviewer or research fellow and/or the centre director or manager, as appropriate for the NCC and guideline.

^h May be GDG chair, clinical lead and/or other members as appropriate.

ⁱ CCP Director or Associate Director who is taking the lead for the guideline.

^j One of the CCP health economic Technical Advisors.

Proposed economic plan

Complete one row for each clinical question in the guideline:

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis?^k</i>	<i>Comment and explanation</i>
<p>TOPIC 1:</p> <p>A) In patients with suspected bone metastases in the spine, does MRI (or CT) scanning (compared to not scanning) identify patients at risk of developing MSCC and improve clinical outcomes (prevention of established MSCC, mobility, cost)? Is this policy cost-effective?</p> <p>B) In patients with known bone metastases in the spine, does serial imaging identify patients at risk of developing MSCC improve clinical outcomes (prevention of established MSCC, improve mobility, cost)? Is this policy cost-effective?</p>	<p>3. High priority for anal</p>	<p>This topic has been designated as a high priority topic for economic evaluation. There is potential for a relatively large population to be affected by a positive recommendation and for increased investment in imaging capital. There are potentially significant health benefits to be had if a positive recommendation leads to the avoidance of serious neurological complications of MSCC.</p> <p>The literature searches for this topic have identified two economic evaluations of MRI scanning in the diagnosis of cancer related lower back pain and, or spinal cord compression: Hollingworth (2003); and Jordan (1995). Although these articles may be more directly relevant for topic 4 (see topic 4 for further details), they are also of interest for topic 1. Both evaluations are set in the context of the USA, and so will not be directly applicable to the UK healthcare setting. Any remodelling will need to take account of NHS and PSS treatment patterns for resource use estimation and valuation.</p> <p>No imaging modalities other than MRI have been identified by the economic literature search for this topic, and so the GDG will need to take a view on the need for de novo modelling of these other imaging modalities.</p>

^k

- 1 **'Not relevant'**: questions where economic analysis is not appropriate (e.g. about definitions, prognosis or information needs for patient);
- 2 **'In literature'**: questions where high-quality, recent and relevant economic evaluations are already available;
- 3 **'High priority for analysis'**: questions where an economic analysis is planned (important implications and analysis is thought to be feasible);
- 4 **'Medium priority for analysis'**: questions where an economic analysis may be done (less important implications or questions over feasibility);
- 5 **'Low priority for analysis'**: questions where economic analysis could be done, but the expected impact on outcomes and NHS resources is low.

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^k</i>	<i>Comment and explanation</i>
<p>2</p> <p>TOPIC 2:</p> <p>What therapies are effective at treating spinal pain and/or preventing spinal collapse and/or spinal cord compression?</p> <p>A) What is the effectiveness of Bisphosphonates at treating spinal pain and/or preventing spinal collapse and/or spinal cord compression?</p> <p>C) What is the effectiveness of RT at treating spinal pain and/or preventing spinal collapse and/or spinal cord compression?</p> <p>D) What is the effectiveness of Vertebroplasty/ Kyphoplasty at treating spinal pain and/or preventing spinal collapse and/or spinal cord compression?</p> <p>E) What is the effectiveness of Chemotherapy/immunotherapy at treating spinal pain and/or preventing spinal collapse and/or spinal cord compression?</p> <p>F) What is the effectiveness of Stabilisation surgery to prevent vertebral collapse, (where Stabilisation surgery is +/- Intra-lesional debulking to prevent cord compromise)?</p>	<p>3. High priority for anal</p>	<p>Sub-topics for this PICO question include bisphosphonates, vertebroplasty, radiotherapy, and stabilisation surgery. This topic and its sub topics have been designated as a high priority topic for economic evaluation because potentially high numbers of patients will be affected and there are potentially large resource and health implications of positive/negative recommendations.</p>
<p>3</p> <p>TOPIC 3:</p> <p>In patients with cancer at risk of developing spinal cord compression, what symptoms and signs give early indications that malignant SCC is developing?</p>	<p>1. Not relevant</p>	<p>As it stands this PICO question does not lend itself easily to economic evaluation. There are issues that cannot be clearly defined from an economic evaluation point of view, such as: what are the comparators? what is the margin to be measured? Additionally, the financial implications are likely to be relatively low compared to other topics in this guideline. Consequently, it has been designated as low priority for economic evaluation.</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis?*</i>	<i>Comment and explanation</i>
<p>TOPIC 4:</p> <p>What is the best imaging modality for diagnosis of spinal cord compression?</p> <p>4</p>	<p>3. High priority for anal</p>	<p>This topic has been designated as a high priority topic for economic evaluation. There is potential for a relatively large population to be affected by a positive recommendation and for increased investment in imaging capital. There are potentially significant health benefits to be had if a positive recommendation leads to the avoidance of serious neurological complications of MSCC.</p> <p>The literature searches for this topic have identified two economic evaluations of MRI scanning in the diagnosis of cancer related lower back pain and, or spinal cord compression: Hollingworth et al (2003); and Jordan et al (1995). Both evaluations are set in the context of the USA, and so will not be directly applicable to the UK healthcare setting. Hollingworth et al (2003) compare MRI with lumbar x-ray whilst Jordan et al (1995) compare MRI with no MRI including myelography. The GDG needs to clarify whether or not these are relevant comparators for the current UK healthcare setting or whether other imaging modalities should also be considered. Initial feedback highlights that in UK the only relevant imaging technique seems to be MRI, except for a small group of patients in whom MRI is contraindicated because of pacemakers, etc. (although this group is too small numerically to be relevant).</p> <p>Any remodelling will need to take account of NHS and PSS treatment patterns for resource use estimation and valuation.</p> <p>No imaging modalities other than MRI have been identified by the economic literature search for this topic, and so the</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^k</i>	<i>Comment and explanation</i>
		GDG will need to take a view on the need for de novo modelling of non-MRI imaging modalities.
<p>TOPIC 5:</p> <p>5a. The impact of delays on outcome</p> <ul style="list-style-type: none"> o The Effect Delay in Diagnosis on outcome o The Effect Delay in Treatment on outcome <p>5b. The impact of delays on outcome</p> <ul style="list-style-type: none"> o The effect of performance status at the time of treatment <p>5c. The impact of delays in treatment on outcome –</p> <ul style="list-style-type: none"> o How soon should definitive treatment be undertaken to prevent permanent neurological deficit? o Access to imaging services – especially out of hours (including MRI and CT) o Access to urgent and specialist surgical and oncological opinion o Access to spinal surgery 24/7 o Access to RT 24/7 	4. Medium priority for a	<p>Overall, this topic has been designated as medium priority for economic evaluation. Having said this, there is a lot of interest from GDG members in the looking at the economics of out of hours services and in particular for imaging services.</p> <p>There is clinical evidence to suggest that shortening delays in treatment does improve clinical outcomes. The difficulty from an economics perspective lies in defining the delay. i.e. what is an acceptable/unacceptable delay and what are the resource implications of removing the delay. In this respect, questions covered by 5c are more readily amenable to economic evaluation than is question 5a. It should be also be noted that no clinical evidence has been found for the effects of delay in diagnosis on the outcomes 'survival', 'pain', and 'independent living'.</p> <p>The relevant timescale is from onset of symptoms/signs (and what these are, because acceptable threshold varies with degree of neurological compromise) to definitive intervention. This is a composite including time to imaging, time to opinion and time to intervention as broken down by factors in question 5c. The relevant consideration should focus therefore on the total time, rather than on individual times as expressed by the individual questions. Realistically, surgery or radiotherapy are not going to be commenced after 21:00 hours unless there was a radical reorganisation of services. This suggest that considering 12</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^k</i>	<i>Comment and explanation</i>
		hours or less as an acceptable delay from onset to intervention may be a realistic target. It should be considered that this delay is not ideal in some circumstances but may be achievable in most.
<p>TOPIC 6:</p> <p>6.a. Case selection for treatment: role of scoring systems</p> <p>6.b. Case selection for surgery.</p> <p>6.c. Case selection for Rt</p> <p>6</p>	5. Low priority for analysis	<p>An appropriate case selection and modality of treatment is required to avoid wasting resources in inappropriate interventions and to avoid as well potential situations in which patients who may benefit are not treated. However the available literature will not readily yield either comparators or economic evidence.</p> <p>Given that this PICO question, as it stands now, does not lend itself easily to economic evaluation due to lack of data on comparators and on economic evidence, the topic has consequently been designated as low priority for economic evaluation.</p>
<p>TOPIC 8:</p> <p>7</p> <p>What surgical technique (among: laminectomy, either alone or in combination with fusion or with mechanical support; anterior surgery; 360 front and back; bone graft; cages; endoscopic surgery; vertebroplasty in combination with laminectomy) is the most effective in treating patients with known MSCC (in terms of the following outcomes: long term deformities, overall survival, symptom control: pain control, continence, ambulation, sphincter function, rate of revision surgery or further interventions -depending on prior surgery-, QoL, economics, complication/safety?)</p>	3. High priority for analysis	<p>This topic has been designated as a high priority topic for economic evaluation because it affects a large proportion of MSCC patients and there are potentially large financial and health benefits to the NHS and the patients.</p> <p>Having said this, some of the surgical interventions identified by the PICO are unlikely to be deemed as high priority individually because they are rarely used for MSCC patients. These include laminectomy alone, anterior surgery, 360 front and back, and endoscopic surgery.</p> <p>Bone grafts and cages are not used in isolation and so the GDG needs to clarify how and when these interventions</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^k</i>	<i>Comment and explanation</i>
		<p>are used and what the comparators are before a final determination can be made on the appropriateness of economic evaluation.</p> <p>There is one Canadian economic evaluation available, developed by Thomas et al (2006), which is highly relevant and has been given a preliminary review and presented to the GDG. At the moment we are in correspondence with the modeller involved in this work with a view to working with him to adapt the model for the UK costs and the inclusion of QALYs.</p> <p>Anterior surgery in isolation should be included as this is used quite frequently.</p> <p>There is an ongoing prospective study of UK patients (from a centre in Birmingham and, potentially, Reading and Nottingham) which will be available as well. This would allow to include in the analysis the only real current UK data as to surgical costs and costs of the subsequent care (including as well the costs of paralysis and consequent dependency, i.e. costs related to failure to prevent avoidable paralysis).</p> <p>Autograft has minimal cost except slightly increased surgical time (15 minutes). The cost of a femoral head allograft seem to be relevant for this topic. On the other hand, BMPs and other commercial products are currently used infrequently in UK for this indication and it may be inappropriate to include these in the economic analysis.</p>
8 TOPIC 9:	4. Medium priority for a	This topic has been designated as a medium level priority

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^k</i>	<i>Comment and explanation</i>
Radiotherapy for treatment of MSEC - what is the most cost-effective dose fractionation regimen?		for economic evaluation. As it only considers differences in the fractionation regimen, then the likely cost and health implications will be small relative to other topics in this Guideline.
<p>TOPICS 11, 12, 14, 15, 16 and 21: Supportive care & rehabilitation</p> <p>TOPIC 11: Supportive care (physio, OT, nurse)</p> <p>TOPIC 12: Specialist palliative care</p> <p>TOPIC 14: Mobilisation - how? when? and how quickly?</p> <p>TOPIC 15: Bladder and bowel continence management</p> <p>TOPIC 16: Access to specialist rehabilitation</p> <p>9 a) Can patients benefit? b) What are the predictors?</p> <p>TOPIC 21: Transition to care at home</p>	5. Low priority for analysis	<p>These topics have been grouped together under a general topic called: Supportive care and rehabilitation. The overall topic has been designated as low to medium priority for economic evaluation. A search of the CRD NHS EED database found no relevant economic evaluations for the topics. Although it has been highlighted that some of the costs related to these topics (e.g. paralysis, incontinence, etc. in topic 11) are high, there is a lot of uncertainty around the definition of the PICO topics. As such, it is uncertain at this stage what the implications are for numbers of patients affected and the financial and health implications of any likely GDG recommendations.</p> <p>Topic 14 has been designated as low priority for economic analysis due to the lack of clinical and economic evidence available for this topic and the relatively low resource implications compared with other topics in this Guideline.</p> <p>Topic 16 has been designated as medium priority for economic analysis. Topic b is not relevant for economic appraisal. For topic a, the number of patients which could be affected and the cost implications of good access to specialist rehabilitation could be high, however, it is unclear how much clinical evidence is likely to be available to support a full economic evaluation.</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis?*</i>	<i>Comment and explanation</i>
10 TOPIC 13: Corticosteroids - indications, dose, duration, withdrawal, when?	5. Low priority for analysis	Although corticosteroids are a common treatment for MSCC patients, their costs are relatively low and so the financial implications are not as great as for other topics in this guideline.
11 TOPIC 18: Communicating treatment options and risks to patients diagnosed with spinal cord compression	5. Low priority for analysis	<p>Patients need to be adequately informed about the treatment options available to them. Moreover, a good communication of their risks is required if appropriate decisions are to be made (Edwards 2004). In addition, it has been suggested that the rate of early diagnosis can be improved and some potential paralysis can be prevented by informing patients at high risk of developing MSCC about their risk of developing the condition, and about the signs and symptoms of MSCC (West of Scotland Cancer Network 2007).</p> <p>Clinical evidence on the impact on patients' health derived from using different interventions to communicate the risks of developing MSCC is likely to be very limited (if available at all). As a consequence, conducting an economic evaluation of this topic may not be feasible. Moreover, there are no relevant financial implications associated with this topic when compared to those of the topics identified as high economic priorities within this guideline. Therefore, this topic has been identified as a low priority for economic analysis.</p>
12 TOPIC 20: Overall coordination of services for MSCC (local, cancer network, regional, supra-regional)	5. Low priority for analysis	The efficient coordination of services for MSCC could minimise hospital costs and enable smooth transition between locus of care, and it could optimise the standard of care. The costs of employing a coordinating Nurse consultant to facilitate this are expected to be small by

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^k</i>	<i>Comment and explanation</i>
		<p>comparison with current situation (although this would need to be proved).</p> <p>This topic has therefore been designated low priority for economic assessment. However, if time permits, it may be possible to undertake some scenario analyses to cost out the various options for service delivery. This would be a relatively time consuming task in the context of the guideline and undertaking it would be at the opportunity cost of doing some other higher priority economic evaluation for this guideline. This topic will have implications for the costing team at NICE which should be communicated as early as possible in the development of the Guideline.</p>
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<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis?^k</i>	<i>Comment and explanation</i>
28	Select from list:	
29	Select from list:	
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For each question where economic analysis is proposed:

<i>Question number(s) ^l</i>	<i>Outline proposed method of analysis ^m</i>
Topics 1, 2, 4, 5 and 8	<p>The approach proposed to conduct the economic analyses for the high priority topics selected within this guideline (i.e. topics 1, 2, 4, 5 and 8) is by developing one or, as maximum, two general models:</p> <ul style="list-style-type: none"> <p>Model 1: Diagnosis and treatment of MSCC patients (covering <u>topic 4</u> for diagnosis and <u>topic 8</u>-surgery, as one of the possible treatments for MSCC patients).</p> <p>The idea of linking topics 4 and 8 together rests on the fact that issues such as the sensitivity and the specificity of diagnostic tests should translate into an improvement, in the long term, of either survival and/or quality of life for patients.</p> <p><u>In relation to topic 4 (diagnosis):</u></p> <p>The cost-effectiveness of the intervention is likely to hinge on the sensitivity and specificity of any proposed imaging technique for the chosen population. Costs of increased imaging will be offset to some degree by avoidance of other diagnostic interventions for patients with a negative imaging test. Early positive diagnosis may lead to earlier, more appropriate treatment for patients and have beneficial health and quality of life outcomes; additionally, it may lead to opportunity savings in terms of emergency and other procedures avoided.</p> <p><u>In relation to topic 5 (Delays):</u></p> <p>This will be a challenging area for economic analysis as clinical practice is likely to vary across the NHS, and also evidence of clinical benefit is likely to be limited. There will also be externalities for both costs and benefits if non MSCC patients benefit from new investment. The GDG will need to be clear in its specification of what out of hours service will be considered, compared to current practice, so that the incremental costs can be estimated. Estimates will need to be made about the numbers of patients (MSCC and others) likely to benefit from the proposed new service in order that costs can be apportioned appropriately, as well as enabling the estimation of incremental health gain. As a fallback, the estimation of incremental costs could be combined with a threshold cost-effectiveness estimate in order to indicate the threshold benefit required from any new investment.</p> <ul style="list-style-type: none"> <p>In relation to the assessment of access to out of hour imaging (5c), there is a need to clarify the comparators. It has been suggested that possible comparators are a current 9-to-5 imaging service versus the addition of an early evening service and/or limited weekend service. It is unclear whether there is any clinical evidence to inform an economic evaluation of these comparators, although a costing exercise could be undertaken to estimate the</p>

^l Two or more questions may be addressed by a single analysis if appropriate.

^m Give a brief description of the type of analysis that is proposed, as far as is known at this stage. Consider the type of economic evaluation (CEA, CUA, CCA,...); how outcomes will be measured (QALYs, LYS,...); the type of modelling (decision tree, Markov, simulation...); proposed comparators and population subgroups to be considered; potential sources of information and assumptions; and whether analysis could be based on an existing model. Follow methods advised in the Guidelines Manual whenever possible. Note that this is not expected to be a full project protocol, and that the methods of analysis may change.

incremental costs of a weekend service with a view to indicating how many QALYs would need to be generated by such an investment. Complicating factors would include accounting for external health benefits for non-MSCC patients who would benefit from provision of the new services.

- Regarding access to urgent and specialist oncological opinion (5c), the type of service envisaged would need to be clarified so that costs could be estimated. Again, the availability of clinical evidence to support any economic evaluation is likely to be limited (no RCTs seem to be available), although a threshold QALY analysis could be undertaken.
- The proposed services for the access to 24/7 spinal surgery and the access to 24/7 radiotherapy, (5c), need to be defined according to current provision so that incremental costs could be defined. Again, the availability of clinical evidence to support any economic evaluation is likely to be limited. (e.g. no availability of RCTs), although a threshold QALY analysis could be undertaken.

An NCC literature search found no economic evaluations addressing the economics of out of hours services or delays in the treatment or diagnosis of MSCC patients. Four UK based papers may provide useful background information and, or resource use information for any de novo modelling, (see Baines 2002, Husband 1998, McLinton 2006, and Poortmans 2001.).

It is initially expected that the analysis for topic 5 could be approached in this initial model by conducting sensitivity analyses that would take into account how patients' outcomes would be affected by delaying diagnosis and/or treatment.

In relation to topic 8 (surgery):

The Canadian model presented by Thomas et al (2006) provides a useful platform on which to build a similar model for the UK. The key adaptations for the UK would be a re-estimation of resource use and costs for the UK setting and enhancing it to include QALYs. At the moment we are in correspondence with the modeller (Bohdan Nosyk, bnosyk@sm.hivnet.ubc.ca) for further consideration of how to work collaboratively with the GDG to revise the model. The adapted model should prove useful as a platform for modelling the cost-effectiveness of the sub-topic surgical interventions and is likely to form a sub-model for any de novo models for the prevention (topic 2) and imaging (topics 1 and 4) cost-effectiveness models.

The ideal economic model should capture costs and health effects over the patient's lifetime and from an NHS perspective:

- In terms of costs, those to be included will be the costs borne by the NHS, including personal social services (PSS) if applicable.
- In terms of health benefits, the ideal outcome to consider will be the number of quality adjusted life years (QALYs) gained. Some additional outcomes that could be considered in the model are: life years gained; the improvement in mobility (i.e. increase in the number of ambulant patients) by avoiding delays in diagnosis and/or treatment; etc.

This would involve including relevant cost and effectiveness data from other non-high priority topics (such as data about the rehabilitation

strategy recommended by the GDG in relation to topics 14 to 16). However, it is important to highlight that by including non-high priority topics in the model we will not be providing any cost-effectiveness assessment for such topics. The only cost-effectiveness assessment will be based on the topics identified as high priority for economic analysis.

There is an observational study which is being carried out currently at one UK hospital by the lead clinician (Mr Alistair Stirling). Although there may be limitations in terms of how representative the study population and the unit cost data are compared to the overall UK, this study may prove to be of great usefulness in providing UK health care resource utilisation and unit cost data to populate the model developed for topics 4, 5 and 8.

- **Model 2:** Identification of patients at high risk of MSCC and preventative treatments (covering topic 1 for the identification of patients at high risk of developing MSCC, and topic 2 for the inclusion of the treatments that could be used to prevent MSCC among those patients identified as high risk).

In relation to topic 1 (i.e. identification of patients at high risk of developing MSCC), the cost-effectiveness of the intervention is likely to hinge on the sensitivity and specificity of any proposed imaging technique to identify patients at risk of developing MSCC. Costs of increased imaging will be offset to some degree by avoidance of other diagnostic interventions for patients with a negative imaging test. Early positive diagnosis may lead to earlier, more appropriate preventative treatment for patients at risk and have beneficial health and quality of life outcomes and may lead to opportunity savings in terms of emergency and other procedures avoided.

Currently it is not clear whether both models 1 and 2 (including all the high priority topics) could be combined into a one more general/broader model which would include the whole clinical pathway for MSCC (i.e. from the identification of patients at high risk of developing MSCC to the management of MSCC patients).

As previously mentioned, costs and health effects over the patient's lifetime and from an NHS perspective should be ideally captured:

- In terms of costs, those to be included will be the costs borne by the NHS, including personal social services (PSS) if applicable.
- In terms of health benefits, the ideal outcome to consider will be the number of quality adjusted life years (QALYs) gained. Some additional outcomes that could be considered in the model are: life years gained; number of MSCC cases avoided by identifying high risk patients and/or administering preventative treatment.

Following the methodological recommendations presented in the Guide to the Methods of Technology Appraisal (www.nice.org.uk; reference N0515), for both models (model 1 and model 2) discounting will be conducted using a discount rate of 3.5% for both health outcomes and costs.

	<p>An incremental cost-effectiveness analysis will be conducted after ranking the alternative strategies from the most to the least cost-effective and excluding, if necessary, the dominated strategies (i.e. those strategies achieving lower effectiveness and incurring higher costs when compared to any other). The results of the incremental analysis will be reported as the incremental cost per additional unit of benefit obtained with the most effective and most expensive strategy when compared to the next most effective and most expensive one.</p> <p>Whenever possible, probability distributions will be assigned to different clinical and cost parameters so that a probabilistic sensitivity analysis can be carried out to assess the overall uncertainty of the models and the robustness of the results. In addition, one-way and multi-way deterministic sensitivity analyses will be conducted to identify those variables contributing the more to uncertainty.</p>
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Addenda to economic plan

The following substantive revisions to the plans set out in section 3 above have been agreed.

<i>Date</i>	<i>Question number(s)</i>	<i>Agreed change to number or type of analyses</i>
Dec 2007	Topic 1	No clinical evidence was found that assessed the use of MRI scanning with the aim of preventing MSCC. No de novo modelling was attempted because there was no clinical evidence to suggest that available treatments prevent the development of MSCC. Thus, scanning people with suspected bone metastases using MRI to prevent MSCC can not be considered cost-effective given current clinical evidence.
Dec 2007	Topic 2	No evidence was found that specifically examined the cost-effectiveness of treatments to prevent spinal collapse / MSCC in people with known vertebral metastases. No de novo modelling was undertaken because there was judged to be insufficient clinical evidence establishing a link between treatment and the prevention of spinal collapse / MSCC.
Dec 2007	Topic 4	During the compilation of the guideline, the GDG recommended that MRI was to be the imaging modality of choice for detecting MSCC. Therefore this topic was no longer considered to be a priority for health economic assessment.