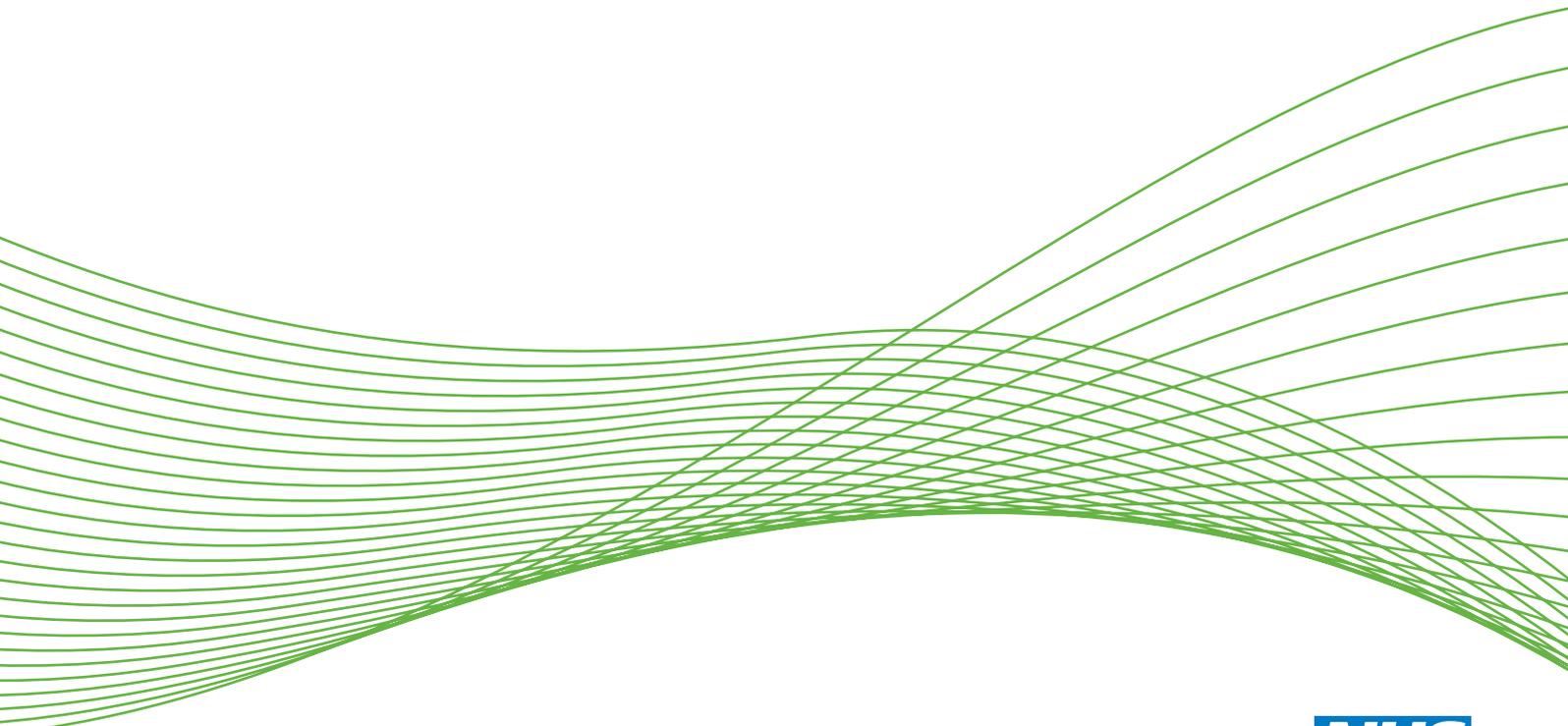


## A systematic review of evidence on malignant spinal metastases: natural history and technologies for identifying patients at high risk of vertebral fracture and spinal cord compression

*P Sutcliffe, M Connock, D Shyangdan, R Court, N-B Kandala and A Clarke*



***National Institute for  
Health Research***



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# Abstract

## A systematic review of evidence on malignant spinal metastases: natural history and technologies for identifying patients at high risk of vertebral fracture and spinal cord compression

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**Background:** Spinal metastases can lead to significant morbidity and reduction in quality of life due to spinal cord compression (SCC). Between 5% and 20% of patients with spinal metastases develop metastatic spinal cord compression during the course of their disease. An early study estimated average survival for patients with SCC to be between 3 and 7 months, with a 36% probability of survival to 12 months. An understanding of the natural history and early diagnosis of spinal metastases and prediction of collapse of the metastatic vertebrae are important.

**Objectives:** To undertake a systematic review to examine the natural history of metastatic spinal lesions and to identify patients at high risk of vertebral fracture and SCC.

**Data sources:** The search strategy covered the concepts of metastasis, the spine and adults. Searches were undertaken from inception to June 2011 in 13 electronic databases [MEDLINE; MEDLINE In-Process & Other Non-Indexed Citations; EMBASE; Cochrane Database of Systematic Reviews; Cochrane Central Register of Controlled Trials (CENTRAL); Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), HTA databases (NHS Centre for Reviews and Dissemination); Science Citation Index and Conference Proceedings (Web of Science); UK Clinical Research Network (UKCRN) Portfolio Database; Current Controlled Trials; ClinicalTrials.gov].

**Review methods:** Titles and abstracts of retrieved studies were assessed by two reviewers independently. Disagreement was resolved by consensus agreement. Full data were extracted independently by one reviewer. All included studies were reviewed by a second researcher with disagreements resolved by discussion. A quality assessment instrument was used to assess bias in six domains: study population, attrition, prognostic factor measurement, outcome measurement, confounding measurement and account, and analysis. Data were tabulated and discussed in a narrative review. Each tumour type was looked at separately.

**Results:** In all, 2425 potentially relevant articles were identified, of which 31 met the inclusion criteria. No study examined natural history alone. Seventeen studies reported retrospective data, 10 were prospective studies, and three were other study designs. There was one systematic review. There were no randomised controlled trials (RCTs). Approximately 5782 participants were included. Sample sizes ranged from 41 to 859. The age of participants ranged between 7 and 92 years. Types of cancers reported on were lung alone ( $n = 3$ ), prostate alone ( $n = 6$ ), breast alone ( $n = 7$ ), mixed cancers ( $n = 13$ ) and unclear ( $n = 1$ ). A

total of 93 prognostic factors were identified as potentially significant in predicting risk of SCC or collapse. Overall findings indicated that the more spinal metastases present and the longer a patient was at risk, the greater the reported likelihood of development of SCC and collapse. There was an increased risk of developing SCC if a cancer had already spread to the bones. In the prostate cancer studies, tumour grade, metastatic load and time on hormone therapy were associated with increased risk of SCC. In one study, risk of SCC before death was 24%, and 2.37 times greater with a Gleason score  $\geq 7$  than with a score of  $< 7$  ( $p = 0.003$ ). Other research found that patients with six or more bone lesions were at greater risk of SCC than those with fewer than six lesions [odds ratio (OR) 2.9, 95% confidence interval (CI) 1.012 to 8.35,  $p = 0.047$ ]. For breast cancer patients who received a computerised tomography (CT) scan for suspected SCC, multiple logistic regression in one study identified four independent variables predictive of a positive test: bone metastases  $\geq 2$  years (OR 3.0 95% CI 1.2 to 7.6;  $p = 0.02$ ); metastatic disease at initial diagnosis (OR 3.4, 95% CI 1.0 to 11.4;  $p = 0.05$ ); objective weakness (OR 3.8, 95% CI 1.5 to 9.5;  $p = 0.005$ ); and vertebral compression fracture on spine radiograph (OR 2.6, 95% CI 1.0 to 6.5;  $p = 0.05$ ). A further study on mixed cancers, among patients who received surgery for SCC, reported that vertebral body compression fractures were associated with presurgery chemotherapy (OR 2.283, 95% CI 1.064 to 4.898;  $p = 0.03$ ), cancer type [primary breast cancer (OR 4.179, 95% CI 1.457 to 11.983;  $p = 0.008$ )], thoracic involvement (OR 3.505, 95% CI 1.343 to 9.143;  $p = 0.01$ ) and anterior cord compression (OR 3.213, 95% CI 1.416 to 7.293;  $p = 0.005$ ).

**Limitations:** Many of the included studies provided limited information about patient populations and selection criteria and they varied in methodological quality, rigour and transparency. Several studies identified type of cancer (e.g. breast, lung or prostate cancer) as a significant factor in predicting SCC, but it remains difficult to determine the risk differential partly because of residual bias. Consideration of quantitative results from the studies does not easily allow generation of a coherent numerical summary, studies were heterogeneous especially with regard to population, results were not consistent between studies, and study results almost universally lacked corroboration from other independent studies.

**Conclusion:** No studies were found which examined natural history. Overall burden of metastatic disease, confirmed metastatic bone involvement and immediate symptomatology suggestive of spinal column involvement are already well known as factors for metastatic SCC, vertebral collapse or progression of vertebral collapse. Although we identified a large number of additional possible prognostic factors, those which currently offer the most potential are unclear. Current clinical consensus favours magnetic resonance imaging and CT imaging modalities for the investigation of SCC and vertebral fracture. Future research should concentrate on: (1) prospective randomised designs to establish clinical and quality-of-life outcomes and cost-effectiveness of identification and treatment of patients at high risk of vertebral collapse and SCC; (2) Service Delivery and Organisation research on magnetic resonance imaging (MRI) scans and scanning (in tandem with research studies on use of MRI to monitor progression) in order to understand best methods for maximising use of MRI scanners; and (3) investigation of prognostic algorithms to calculate probability of a specified event using high-quality prospective studies, involving defined populations, randomly selected and clearly identified samples, and with blinding of investigators.

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# Contents

<b>Glossary</b>	<b>ix</b>
<b>List of abbreviations</b>	<b>xi</b>
<b>Scientific summary</b>	<b>xiii</b>
<b>Chapter 1 Introduction</b>	<b>1</b>
Background	1
Types of cancer	4
Pathophysiology of bone metastasis	7
Clinical manifestation of spinal metastases	9
Investigations	10
Treatment	12
Current service cost	17
Summary	18
<b>Chapter 2 Methodology</b>	<b>19</b>
Search strategies	19
Search restrictions	19
Data extraction strategy	20
Quality assessment strategy	20
<b>Chapter 3 Results</b>	<b>23</b>
Result of searches	23
Description of included studies	26
Quality assessment	26
Summary of overall quality assessment	35
Summary of systematic review evidence	35
Data synthesis	35
General considerations	35
Studies in which the whole sample population was diagnosed with prostate cancer	36
Studies in which the whole sample population was diagnosed with breast cancer	46
Studies in which the whole sample population was diagnosed with lung cancer (non-small cell lung cancer or small cell lung cancer)	58
Studies in which the population was diagnosed with a variety of cancers	65
Summary of studies involving a variety of cancers	90
Expert opinion paper	90
Overall summary of results	92
<b>Chapter 4 Discussion</b>	<b>95</b>
Summary of background	95
Summary of methods	95
Summary of principal findings	95
Prognostic factors by cancer type	98
Strengths and limitations of this review	102
Research needs	102

<b>Chapter 5 Conclusions</b>	<b>105</b>
Natural history	105
Prognostic studies	105
Imaging modalities	105
Clinical importance of spinal metastases	106
<b>Acknowledgements</b>	<b>107</b>
<b>References</b>	<b>109</b>
<b>Appendix 1</b> Record of searches undertaken	<b>119</b>
<b>Appendix 2</b> Assessment of risk of bias in prognostic studies (Hayden <i>et al.</i> )	<b>123</b>
<b>Appendix 3</b> Quality assessment	<b>127</b>
<b>Appendix 4</b> Included papers at full sift ( $n = 31$ )	<b>129</b>
<b>Appendix 5</b> Reasons for exclusion at full sift ( $n = 305$ )	<b>131</b>
<b>Appendix 6</b> Quality assessment forms: extracted data for each study	<b>147</b>
<b>Appendix 7</b> Data extraction tables	<b>181</b>
<b>Appendix 8</b> Quality assessment results	<b>243</b>
<b>Appendix 9</b> Cost information relative to the treatment of spinal metastases	<b>245</b>
<b>Appendix 10</b> Short report protocol	<b>247</b>

# Glossary

**Aetiology** Study of the factors involved in the development of a disease.

**Biochemical** Involving chemical processes in living organisms.

**Biopsy** Sampling of tissue from a specific area of the body (e.g. the prostate) to check for abnormalities such as cancer.

**Brachytherapy** Form of radiation therapy involving radioactive seeds that emit radiation while implanted to help destroy the cancer.

**Cancer** Growth of abnormal cells in the body in an uncontrolled manner.

**Epidemiology** Study of the causes, distribution and control of disease in populations.

**Grade** Degree of severity of a cancer.

**Heterogeneous (heterogeneity)** A diverse mixture of different kinds or subgroups.

**Hormone therapy** Use of hormones, hormone analogues and specific surgical techniques to treat a disease.

**Natural history** The timeline of a morbid condition from onset–inception to resolution; the course of a particular disease if it is not treated or manipulated in any way.

**Prognosis** Potential clinical outlook or chance of recovery based on the status and likely course of the disease.

**Progression** Continuing growth of a cancer.

**Radiation therapy** Use of X-rays and other types of radiation to destroy malignant tissue and cells.

**Recurrence** Reappearance of disease.

**Risk** Probability or chance that a specific event will or will not happen.

**Stage** Term used to define the size and physical extent of a cancer.

**Staging** Process of determining extent of disease in a patient from all available information, e.g. Whitmore–Jewett staging classification and more detailed TNM (tumour/node/metastasis) classification.



## List of abbreviations

ADT	antiandrogen treatment	MRI	magnetic resonance imaging
AMP	adjusted for multiple primaries	MSCC	metastatic spinal cord compression
AS	age standardised	N	nodal
AUC	area under the curve	NCRI	National Cancer Research Institute
BMI	body mass index	NDFS	neurological deficit-free survival
CI	confidence interval	NHS CRD	NHS Centre for Reviews and Dissemination
CSF	cerebrospinal fluid	NHS EED	NHS Economic Evaluation Database
CT	computerised tomography	NICE	National Institute for Health and Care Excellence
CTRA	CT-based structural rigidity analysis	NSCLC	non-small cell lung cancer
DARE	Database of Abstracts of Reviews of Effects	OR	odds ratio
EA	axial load	P/PP	posterior to predicted posterior height ratio
ECOG	Eastern Cooperative Oncology Group	PP	predicted posterior height
EGFR TKI	epidermal growth factor receptor tyrosine kinase inhibitor	PET	positron emission tomography
EI	bending load	PMMA	polymethylmethacrylate
EM	epidural mass	PSA	prostate-specific antigen
EOD	extent of disease	PTH	parathyroid hormone
ESCC	epidural spinal cord compression	PTHRP	parathyroid hormone-related peptide
FRI	fracture risk index	RANKL	receptor activator of nuclear factor- $\kappa$ B ligand
HR	hazard ratio	RCT	randomised controlled trial
HTA	Health Technology Assessment	ROC	receiver operating characteristic
IG-IMRT	image-guided intensity-modulated radiotherapy	RR	relative risk
IMRT	intensity-modulated radiotherapy	rSCC	radiological spinal cord compression
IQR	interquartile range	SAS	subarachnoid space
LBC	load-bearing capacity	SCC	spinal cord compression
LR	likelihood ratio		
MESCC	metastatic epidural spinal cord compression		

## LIST OF ABBREVIATIONS

SCD	spinal cord or cauda equina displacement	$^{99}\text{Tc}^{\text{m}}$	technetium-99m
SCLC	small cell lung cancer	T10–L5	thoracolumbar and lumbar spine
SD	standard deviation	TNM	tumour/node/metastasis
SPECT	single-photon emission computerised tomography	%TO	percentage tumour occupancy
SRE	skeletal-related event	TSC	thecal sac compression
		UKCRN	UK Clinical Research Network

# Scientific summary

## Background

The spine is a common site for bone metastasis for a number of cancers. Spinal metastases may grow to cause weakness and fracture of a vertebra or compression of the spinal nerve cord. Spinal cord compression (SCC) carries a risk of paralysis of body structures below the level of compression, compromising limb movement and bladder, bowel and sexual functioning. Early targeted treatment might prevent, reduce or delay serious unwanted outcomes. Diagnostic methods include plain radiography, myelography, magnetic resonance imaging (MRI), computerised tomography (CT), radionuclide bone scanning (scintigraphy with technetium-99m-labelled diphosphonates), single-photon emission CT and positron emission tomography (PET).

These might serve several purposes: (1) to inform the choice about potential pre-emptive intervention(s) so as to avoid or delay complication and more radical surgical intervention; (2) to bring forward radical interventions before patient health deteriorates too far; and (3) to categorise patients into those more or less suitable for earlier or later radical intervention. However, there is uncertainty about the effectiveness of these diagnostic techniques.

## Main question

To undertake a systematic review to examine the natural history of metastatic spinal lesions and to identify patients at high risk of vertebral fracture and SCC.

## Methods

Searches were undertaken from inception to June 2011 in 13 electronic bibliographic databases (e.g. MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, etc.). Evidence was also retrieved through contact with experts, scrutiny of references of included studies, and other relevant resources. The search strategy covered the concepts of metastasis, the spine and adults. No study type or publication type restrictions were applied, as all types of study involving all languages were screened for potential inclusion. The titles and abstracts of retrieved studies were examined for inclusion by two reviewers independently. Disagreement was resolved by retrieval of the full publication and consensus agreement. Included studies involved adult patients with vertebral metastases, at risk of developing (or who had developed) metastatic spinal cord compression, vertebral collapse or progression of vertebral collapse. Natural history was taken to mean the progression of spinal metastases from inception to resolution independent of the influence of intervention. Diagnostic/prognostic methods included clinical features and/or imaging technologies. Full data were extracted independently by one reviewer. All included studies were reviewed by a second researcher with disagreements resolved by discussion. A quality assessment instrument was used to assess bias in six domains: study population, attrition, prognostic factor measurement, outcome measurement, confounding measurement, and account and analysis. Data were tabulated and discussed in a narrative review.

## Results

### Searches

In all, 2425 potentially relevant articles were identified; 31 met the inclusion criteria. Seventeen studies reported retrospective data, 10 were prospective studies, three were other study designs and one was a systematic review. There were no randomised controlled trials (RCTs). The approximate overall number of

participants was 7888 and 5782 were included in analyses. Sample sizes analysed ranged from 41 to 859. Cancers reported on were: lung ( $n = 3$ ), prostate ( $n = 6$ ), breast ( $n = 7$ ), mixed cancers ( $n = 13$ ) and unclear ( $n = 1$ ).

### *Quality assessment*

Included studies were generally of poor methodological quality and suffered from missing data, lack of transparency and clarity of reporting, particularly regarding participant selection. No studies tested the performance of identified risk factors in a cohort independent of the one in which the factors had been identified. Almost all made use of medical records and/or stored scan images rather than using data collection techniques specifically designed for research purposes.

### *Summary of findings of included studies*

We did not identify any epidemiological study with a primary aim of investigating the natural history of spinal metastases. Most studies looked at factors associated with survival. Identification of prognostic factors for intermediate outcomes (SCC or vertebral collapse) was often an incidental objective. Ninety-three prognostic factors were reported as statistically significant in predicting risk of vertebral fracture or SCC in the 30 included primary studies.

Consideration of quantitative results from the studies does not easily allow generation of a coherent numerical summary: studies were heterogeneous, especially with regard to population, results were not consistent between studies and study results almost universally lacked corroboration from other independent studies. Below we summarise the major findings; these should be viewed with caution while bearing in mind the caveats regarding quality of studies and the general lack of replication of results.

### *Summary of prostate cancer studies*

None of the included prostate cancer studies provided a description of the natural history of spinal metastases.

Only 409 patients were included in the six prostate cancer studies identified, and the underlying populations, diagnostic interventions methodology and transparency of reporting of these studies varied. This made interpretation of findings difficult. Selection bias was a potential problem in almost all studies, particularly because they all used routine medical records for data collection. In the prostate cancer studies, high tumour grade, high metastatic load and long time on hormone therapy were associated with increased risk of SCC. Studies reported that the more spinal metastases that were present, and the longer a patient was at risk, the greater the chance of clinically occult SCC. It was suggested that the time a patient is on hormone therapy may be a proxy for risk of occult compression.

In one investigation of castration-resistant metastatic prostate cancer, risk of SCC before death was 24% and was 2.37 times greater with high-grade cancer than with low-grade cancer (Gleason score  $\geq 7$  compared with  $< 7$ ) ( $p = 0.003$ ). A further investigation reported that patients with six or more bone lesions were at greater risk of SCC than those with fewer than six lesions [odds ratio (OR) 2.9, 95% confidence interval (CI) 1.012 to 8.35;  $p = 0.047$ ]. Among these patients, median time from initial MRI for suspected SCC to development of neurological deficit was 896 days (95% CI 13 to 986 days).

However, prostate cancer studies were heterogeneous, results were not consistent between studies and study results almost universally lacked corroboration from further independent studies.

Results from the prostate cancer studies also imply that:

- Patients with a high-risk bone scan may benefit from MRI screening of the spine aimed at early detection and treatment of occult subarachnoid space compression/SCC.
- 'Total involvement of vertebra', according to scintigraphy, appears to be highly discriminatory for subsequent SCC.

### Summary of breast cancer studies

None of the studies described the natural history of spinal metastases derived from breast cancer.

The seven included studies were disparate in terms of population, imaging procedures and study aims, and some provided limited information on these factors. In an early study, a positive test result from myelography for suspected epidural SCC was associated with a positive bone scan ( $p < 0.001$ ), bone pain ( $p < 0.001$ ), and paraesthesia ( $p = 0.009$ ). Among breast cancer patients who underwent CT for suspected SCC, multiple logistic regression identified four independent variables predictive of a positive test: bone metastases  $\geq 2$  years (OR 3.0, 95% CI 1.2 to 7.6;  $p = 0.02$ ); metastatic disease at initial diagnosis (OR 3.4, 95% CI 1.0 to 11.4;  $p = 0.05$ ); objective weakness (OR 3.8, 95% CI 1.5 to 9.5;  $p = 0.005$ ); and vertebral compression fracture on spine radiograph (OR 2.6, 95% CI 1.0 to 6.5;  $p = 0.05$ ). A Japanese study of breast cancer patients following primary surgery using Cox's regression analysis reported that the risk of developing bone metastases was associated with tumour/node/metastasis (TNM) tumour stage [hazard ratio (HR) 1.615, 95% CI 1.322 to 1.973;  $p < 0.0001$ ]; N (nodal) stage classification (HR 2.128, 95% CI 1.381 to 3.279;  $p = 0.0006$ ); presence of metastases to axillary lymph nodes ( $p = 0.0006$ ); and the presence of metastases in important organs (HR 7.502, 95% CI 5.100 to 11.036;  $p < 0.0001$ ). Of patients who developed skeletal metastases, 82% exhibited spinal metastases and 14% of these developed paralysis. The median time between detection of skeletal metastases and development of SCC was 4.4 (range 2–72) months.

A consideration of quantitative results from the breast cancer studies does not easily allow generation of a coherent numerical summary; as with prostate cancer, studies were heterogeneous, especially with regard to populations, results were not consistent between studies and, almost universally, study results lacked independent corroboration.

The following results should therefore be viewed with caution:

- A positive bone scan, back pain, paraesthesia and bladder/bowel dysfunction at the time of myelography were more common in patients with a positive myelogram than in those with a negative myelogram.
- Objective weakness in patients with suspected SCC was predictive for SCC but estimates of sensitivity and specificity for this were low.
- Stratification of patients suspected of SCC according to the number of independent risk factors (see above: e.g. stage, grade, duration of risk and bone metastasis) identified a high-risk group with an 85% probability of CT-positive SCC.
- TNM classification stages were identified as risk factors in one study.
- Longer survival was a risk factor for vertebral fracture and for SCC.
- Two biomechanical studies examined in vitro power of vertebral load-bearing capacity estimates for predicting vertebral fracture and were reported to have superior specificity to an alternative method; however, this is, of course, not practicable in the clinical setting.

Results from time-to-event analyses are difficult to generalise because of the different populations studied and the uncertainty regarding representativeness.

### Summary of lung cancer studies

The three included studies used retrospective methods and routinely collected case note data. Two studies investigated patients with non-small cell lung cancer (NSCLC) and recruited a substantial number of participants (642 with advanced disease and 273 with bone metastases).

Among patients with advanced NSCLC who received chemotherapy, the occurrence of skeletal-related events (SREs; i.e. fracture, SCC, requirement for bone surgery or radiotherapy, or hypocalcaemia causing death or requiring emergency treatment) was reported to be associated with the load of bone metastases (OR 3.08, 95% CI 1.60 to 5.94 for single bone metastasis; OR 4.27, 95% CI 2.66 to 6.86 for multiple

bone metastases). Among patients with more than one bone metastasis, the median time from start of chemotherapy to occurrence of first SRE was 19.7 months (95% CI 14.5 to 24.9 months). In another study of patients with advanced small cell lung cancer with skeletal metastases, multivariate analysis identified 'ever smoked' as significantly associated with risk of a SRE (OR 2.8, 95% CI 1.32 to 6.00).

For lung cancer, findings included:

- The greater the number of bone metastases, the greater is the risk of a SRE.
- There was an increased likelihood of SREs with smoking, lack of history of treatment with epidermal growth factor receptor tyrosine kinase inhibitors, poor Eastern Cooperative Oncology Group (ECOG) status and non-adenocarcinoma.

Again prognostic factors identified were not validated in other independent populations.

### *Summary of studies involving a variety of cancers*

Thirteen studies investigated mixed primary tumour types. Patients with breast, prostate and lung cancers provided the majority of participants; however, it is important to note that the relative contribution of different tumour types varied considerably from study to study. A very broad range of factors was investigated. Among patients who received surgery for SCC a retrospective analysis identified that vertebral body compression fractures were associated with presurgery chemotherapy (OR 2.283, 95% CI 1.064 to 4.898;  $p = 0.03$ ), primary breast cancer (OR 4.179, 95% CI 1.457 to 11.983;  $p = 0.008$ ), thoracic involvement (OR 3.505, 95% CI 1.343 to 9.143;  $p = 0.01$ ) and anterior cord compression (OR 3.213, 95% CI 1.416 to 7.293;  $p = 0.005$ ). In another study, thecal sac compression was associated with abnormal neurological examination (OR 3.0, 95% CI 1.6 to 10.4;  $p = 0.004$ ), stage IV cancer at initial diagnosis (OR 2.8, 95% CI 1.40 to 7.7;  $p = 0.006$ ), known vertebral metastases (OR 2.8, 95% CI 1.4 to 8.2;  $p = 0.008$ ) and middle or upper back pain (OR 2.7, 95% CI 1.4 to 9.1;  $p = 0.010$ ).

Findings common to several of these mixed cancer studies included:

- Primary tumour type was a risk factor for vertebral collapse and SCC recurrence in three studies.
- Patient health status was a factor in SCC recurrence.
- Degree of tumour occupancy of the vertebral body was predictive for fracture.
- Two studies identified combinations of risk factors to predict individual SCC risk with high probability – five factors delivered a probability of 87% and combination of three or four factors gave a probability of 81%.
- An empirical algorithm for prediction of fracture in vertebrae harbouring predominantly lytic metastases was found potentially useful, as were other proposed models.

Missing data, lack of transparency and clarity of reporting, particularly regarding participant selection, mean that in general the validity of findings was uncertain. No studies tested the performance of identified predictors or risk factors in an independent cohort.

## **Discussion**

We undertook a systematic review to examine the natural history of metastatic spinal lesions and to identify patients at high risk of vertebral fracture and SCC. We identified 31 studies in three different cancer areas of which 13 studies had populations with several different cancers represented.

### *Overall summary of results*

We did not identify any epidemiological study with a primary aim of investigating the natural history of spinal metastases.

The evidence presented in this report suggests that the greater the extent of invasion of any one vertebra by metastases, the more likely spinal fracture is to occur. In addition, the more spinal metastases present and the longer a patient is at risk, the greater the chance of SCC. There is an increased risk of developing SCC if a cancer has already spread to the bones. Clinicians are unlikely to have been unaware of these factors and much of the research reported here appears to add little to current knowledge. Several included studies, with populations with a mix of cancer types, identified cancer type itself as a significant factor in predicting SCC, but it remains difficult to determine the difference in risk as a result of the type of cancer (e.g. breast, lung or prostate cancer) and these studies are liable to suffer from residual bias.

Three studies attempted to combine risk factors into algorithms predictive for occurrence of an event. These appeared to have modest discriminatory power but were not tested in independent samples.

Included studies were of poor methodological quality and made use of medical records and/or stored scan images rather than using data collection techniques specifically designed for research purposes.

Imaging methods used for detection of and screening for SCC and/or vertebral fracture have changed over the duration of the studies described. Formal comparison of different imaging procedures was rarely undertaken and we found no RCTs. It is clear that investigations now favour MRI and CT over myelography only and/or plain radiography. Bone scanning (e.g. scintigraphy) were widely employed but PET was not used in any of the included studies. The development and routine availability of machines with faster throughput and better performance (e.g. resolution) may change practice.

The considerable variability in the prognostic factor categories, the quality of studies, the lack of studies for some categories and changes in practice over the time period to which the studies relate have all made it difficult to provide clear conclusions as to which factors might currently offer the most potential to identify patients at high risk of vertebral fracture and SCC.

### **Strengths and limitations**

We identified a large volume of literature and all papers were read and sifted by two reviewers. We used a rigorous search strategy in a large number of databases. A large number of papers were sifted at full paper stage. Nevertheless, our  $\kappa$ -statistic at 0.74 was acceptable. Owing to the poor reporting of the natural history we are unable to draw any conclusions on this aspect of the review. As far as prognostic factors are concerned, heterogeneity precluded the use of meta-analysis.

### **Implications for research**

There is a need for:

1. Prospective randomised designs of the clinical effectiveness and cost-effectiveness of identification and subsequent treatment of patients at high risk of vertebral collapse and SCC. These trials should be undertaken for diagnostic methods such as bone scintigraphy and particularly for serial MRI, to identify patient groups who are most likely to benefit from early detection and treatment, and the value of, and optimal frequency of MRI screening for populations.
2. Service Delivery and Organisation research on MRI and scanning (in tandem with research studies on use of MRI to monitor progression) in order to understand best methods for maximising use of MRI scanners (e.g. to investigate variation in need, and optimal location, throughput and staffing, etc.).
3. Investigation of prognostic algorithms designed to calculate the probability of a specified event using high-quality prospective studies, involving defined populations, randomly selected and clearly identified samples, and with blinding of investigators.
4. Higher-quality prospective studies to investigate and confirm previous findings on risk factors for progression or spinal collapse, as opposed to survival. These could usefully feed into work on prognostic algorithms.
5. Methodological research to improve prognosis research.

**Implications for clinical practice**

The major factors that should be taken into account when considering a patient for further investigation and potential treatment when at risk of SCC, progression or spinal collapse have not altered from those identified in 2008 NICE guideline 75.

**Conclusions**

This report has identified a large number of studies reporting limited evidence on risk factors for progression or spinal collapse for patients with spinal metastases. Evidence is generally of poor quality. Rigorous research is now needed on best diagnostic methods for patients with spinal metastases to identify those patients at high risk of vertebral fracture and SCC.

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# Chapter 1 Introduction

When a cancer spreads to a new and different site in the body it very often locates in the bony skeleton. The commonest place for these new cancers in bone is in one or more vertebrae, in which case they are called spinal metastases. Sometimes these spinal metastases do not cause symptoms; however, they can be a source of severe pain or weakness in the vertebrae, which may fracture. Spinal metastases may grow so that the spinal nerve cord that runs through the length of the vertebral column is compressed. In this report we concentrate mainly on bony metastases in the spine. Although rarer, metastases may also grow in the extradural space, causing metastatic spinal cord compression (SCC).<sup>1</sup>

When vertebrae fracture, the spine may become bent or twisted, making everyday movements more difficult, and there is a danger that vertebral fracture and collapse may also cause compression of the spinal cord. Compression of the spinal cord carries with it the risk of paralysis of body structures below the level of compression. If it were possible to predict which vertebrae were more likely to fracture, then early targeted treatment might prevent, reduce or delay such events and the serious unwanted outcomes that can result.

This report aimed to examine the natural history of metastatic spinal lesions and to identify patients at high risk of progression or spinal collapse. The use of these technologies might serve several purposes: (1) to inform the choice of potential pre-emptive intervention(s) so as to avoid or delay more radical surgical intervention; (2) to bring forward radical interventions before patients' health deteriorates to the extent that they are no longer suitable candidates for intervention; and (3) to categorise patients into those more or less suitable for earlier or later radical intervention.

The first chapter examines the different types of cancer, pathological and clinical manifestation of spinal metastases, investigations, treatment, prognosis and current service cost.

## Background

Cancer is the second most common cause of death in the UK and it constituted 29% of all deaths registered in England and Wales in 2010.<sup>2</sup> Cancer of the lung, colorectum, breast and prostate are responsible for the majority of incident cancer and cancer deaths in the UK (*Tables 1 and 2*).<sup>3,4</sup> In 2009, lung cancer and colorectal cancer were the leading causes of cancer death in both sexes (24% of all deaths in males and 21% of all deaths in females for lung cancer; 10.5% in males and 10% in females

**TABLE 1** Cause of cancer deaths in the UK: 2009

Cancer type	Male, <i>n</i> (%)	Female, <i>n</i> (%)	Total, <i>n</i> (%)
Lung cancer	19,724 (24.08)	15,265 (20.61)	34,989 (22.41)
Colorectal cancer <sup>a</sup>	8600 (10.48)	7308 (9.86)	15,908 (10.19)
Breast cancer	77 (0.09)	11,651 (15.73)	11,728 (7.51)
Prostate cancer	10,382 (12.65)	–	10,382 (6.65)
Other cancers	43,251 (52.70)	39,832 (53.80)	83,083 (53.24)
All cancer deaths	82,034	74,056	156,090

<sup>a</sup> Colorectal cancer also includes cancer of the anus.

Source: adapted from Cancer Research UK.<sup>4</sup>

**TABLE 2** Incidence of most common cancers in the UK: 2008

Cancer type	Male			Female			Overall		
	Number of new cases	European AS rate per 100,000	Rank in UK	Number of new cases	European AS rate per 100,000	Rank in UK	Number of new cases	European AS rate per 100,000	Rank in UK
Breast cancer	341	0.9	–	47,693	123.9	<b>1</b>	48,034	65.2	<b>1</b>
Lung cancer	22,846	59.4	2	17,960	38.8	2	40,806	47.8	2
Colorectal cancer <sup>a</sup>	22,097	58.5	3	17,894	37.8	3	39,991	47.2	3
Prostate cancer	37,051	97.9	<b>1</b>	–	–	–	37,051	–	4

AS, age standardised.

a Colorectal cancer also includes cancer of the anus.

Bold text (1) represents the most frequent cancers in men and women.

Source: Adapted from Cancer Research UK.<sup>3</sup>

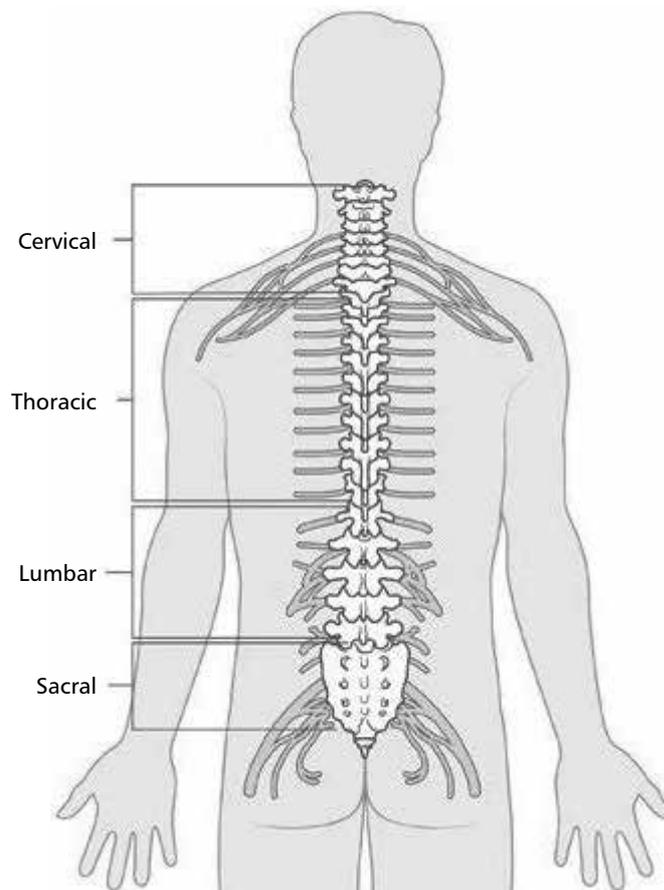
for colorectal cancer) (see *Table 1*). The second most common causes of cancer death by sex were breast cancer in women and prostate cancer in men, constituting approximately 7.5% and 6.6% of all cancer deaths in the UK, respectively.<sup>5</sup> In 2008, breast cancer (15%) was the most commonly diagnosed cancer in the UK followed by cancer of the lung (13.2%), the colorectum (12.9%) and then the prostate (12%).<sup>4</sup>

In most cases, death occurs as a result of metastases and complications rather than the primary tumour.<sup>6</sup> The most common site of metastases is the liver, followed by lung and bone.<sup>7,8</sup> Approximately 70% of all bone metastases are in the spine.<sup>8</sup> It is reported that 60–70% of patients with systemic cancer develop spinal metastasis, although only 10% are symptomatic.<sup>9</sup> The thoracic vertebrae (60–80%) are the most frequently involved sites, followed by lumbar (15–30%) and cervical vertebrae (<10%) (*Figure 1*).<sup>7,10</sup> It is estimated that almost half of patients with spinal metastasis will have metastases at multiple levels of the spine.<sup>11</sup>

Anatomically, spinal metastases can be classed as intradural (intramedullary or extramedullary) or extradural.<sup>12</sup> Approximately 95% of extradural lesions are either pure epidural lesions (rare) or those arising initially from the vertebra but migrating to the thecal sac.<sup>7</sup>

Cancer cells spread to the spine through various mechanisms – via the arterial system, Batson's venous plexus or cerebrospinal fluid (CSF) and directly from paraspinal disease.<sup>10</sup> In most cases, the posterior ventral body is the initial site of involvement. In >90% of patients, spinal metastases are extradural, most often arising in the vertebral column and then extending into the epidural space. Spinal metastases very rarely involve the intradural and intramedullary regions of the spine.<sup>10</sup>

The average time from original diagnosis of cancer to development of spinal metastases has been estimated to be 32 months and the average time from detection of spinal metastases to spinal compression approximately 27 months.<sup>13</sup> It is reported that median overall survival of patients with spinal metastases is 7 months (ranging between 3 and 16 months), although in those with epidural metastases median overall survival is between 3 and 6 months. Overall survival depends mainly on type of primary tumour.<sup>8</sup> Two-year survival rate is lowest for lung cancer (≈9%) but higher for breast and prostate cancer (≈44%).<sup>8</sup> It has been estimated that only between 10% and 20% of patients with spinal metastases are alive 2 years after diagnosis.<sup>8</sup>



**FIGURE 1** Spinal cord. Reproduced with permission from CancerHelp UK, the patient information website of Cancer Research UK. URL: <http://cancerhelp.cancerresearchuk.org>.

Although spinal metastases can occur in any age group, they are most commonly seen in individuals aged between 40 and 70 years.<sup>10</sup> It has been suggested that the incidence of spinal metastasis is comparatively higher in males than in females probably because of higher incidence of prostate cancer relative to breast cancer.<sup>10</sup>

Spinal metastases can lead to significant morbidity and reduction in quality of life owing to SCC, which can result in para- or quadriplegia, severe bone pain and pathological fractures.<sup>7,10</sup> Between 5% and 20% of patients with spinal metastases develop metastatic SCC during the course of their disease.<sup>8,14</sup> An early study estimated average survival for patients with SCC to be between 3 and 7 months, with a 36% probability of survival to 12 months.<sup>13</sup> Therefore, early diagnosis of spinal metastases is important.<sup>15</sup> It can help clinicians to manage disease and delay complications.<sup>15</sup> However, there are disputes regarding the specificity and sensitivity of the different diagnostic techniques currently available.<sup>8</sup> Some authors have also developed different models that can be used to predict collapse of the metastatic vertebrae.

The current review aims to explore the natural history of metastatic spinal lesions and to evaluate evidence on technologies for identifying patients at high risk of vertebral fracture and SCC.

## Types of cancer

### Breast cancer

Breast cancer is the most common cancer among women in the UK. Approximately 48,000 women were diagnosed with breast cancer in 2008 (see *Table 2*).<sup>4</sup> The European age-standardised (AS) incidence rate

for breast cancer was reported as 124 per 100,000 in the UK in 2008.<sup>3</sup> Using the adjusted for multiple primaries (AMP) method, Cancer Research UK reported the lifetime risk of breast cancer to be one in eight for women and one in 1014 for men.<sup>16</sup>

Although there are a number of risk factors, increasing age is one of the most important.<sup>16</sup> Approximately 81% of breast cancer cases were diagnosed in those aged >50 years and almost half occurred between 50 and 69 years of age.<sup>16</sup>

Bone is the most common site for metastases in breast cancer.<sup>17</sup> It is suggested that cancer cells metastasise directly to the bone via blood from some anatomical sites. Some studies have found that venous blood from the breast drains to the vena cava and also into a vertebral venous plexus.<sup>18</sup> The latter drains blood to the skeletal system, and this partly explains the likelihood of spread to bones.<sup>18</sup> There are other factors that influence the pattern of metastases, such as the molecular and cellular biological characteristics of breast cancer cells and of the tissues of the metastatic sites.<sup>19</sup>

The extent of the disease is measured using the tumour/node/metastasis (TNM) classification. In this classification, 'T' refers to the size of the tumour, 'N' refers to spread of the tumour to lymph nodes and 'M' refers to distant metastases.<sup>20</sup> The treatment and prognosis of patients with breast cancer depend on the extent of the disease.<sup>20</sup> There are three types of receptors expressed on breast cancer cells, namely oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2.<sup>20</sup> Treatment of patients also depends on these receptors.<sup>20</sup>

Approximately 70% of patients with metastatic breast cancer will have bone metastases.<sup>19</sup> A retrospective study of all patients with histologically confirmed diagnosis of carcinoma of the breast attending the Clinical Oncology Unit at Guy's Hospital in London reported that approximately 69% of the patients had radiological evidence of skeletal metastases before death.<sup>21</sup> Another large population-based cohort study in Denmark carried out over 9 years (between 1999 and 2007) reported a lower incidence rate of bone metastases. Researchers estimated the overall and annual incidence of bone metastases and skeletal-related events (SREs) in newly diagnosed breast cancer patients.<sup>22</sup> The authors found that 0.5% of patients had bone metastases at the time of primary diagnosis. The 1-year, 3-year and 5-year cumulative incidences of bone metastases among these patients were found to be 1.9% [95% confidence interval (CI) 1.7% to 2.0%], 3.4% (95% CI 3.2% to 3.6%) and 4.7% (95% CI 4.4% to 4.9%), respectively.<sup>22</sup> One study conducted in Canada reported a similar incidence rate of bone metastases. This study included a cohort of women ( $n = 1608$ ) with invasive breast cancer treated in a hospital between 1987 and 1997 to evaluate the patterns of metastatic spread in different types of breast cancer. In this study, the risk of developing bone metastases within 10 years after diagnosis was 7–9% for all types of breast cancer.<sup>23</sup>

Median survival from diagnosis of bone metastases from breast cancer is measurable in years; in contrast median survival from lung cancer is measured in months.<sup>18</sup> The prognosis for breast cancer is mainly dependent on co-existing non-osseous metastatic disease. In a retrospective study of 859 patients with bone metastases from breast cancer seen at one hospital between 1975 and 1991, a median survival of 34 months was reported in those with only bone metastases compared with a median survival of 5.5 months in those with bone and liver metastases.<sup>24</sup> Subsequent occurrence of extraosseous metastases in those with breast cancer and metastases confined to bone significantly affects survival. Median survival in those who developed extraosseous metastasis was 1.6 years compared with the median survival of 2.1 years in those with no extraosseous metastasis ( $p < 0.001$ ).<sup>25</sup>

Ten-year survival in patients with early-stage breast cancer who are diagnosed early is approximately 85%, because of advances in combination therapy.<sup>19</sup> Those who survive are thought to go through repeated periods of remission and progression.<sup>19</sup> The progression stage is responsible for significant morbidity, which may manifest itself clinically as pain, pathological fractures, SCC and hypercalcaemia. The occurrence of these events is seen to be highly influenced by whether or not patients are on treatment.

Walkington and Coleman<sup>19</sup> found that the skeletal events occurred more frequently if the patients were not receiving bone-targeted therapies.

### Lung cancer

Lung cancer is the second most commonly diagnosed cancer in the UK after breast cancer (see *Table 2*).<sup>4</sup> In 2008, approximately 40,806 new cases of lung cancer were diagnosed.<sup>4</sup> The European AS incidence rate for lung cancer in the UK was found to be 47.8 per 100,000 in 2008.<sup>3</sup> Using the AMP method, Cancer Research UK calculated the risk of lung cancer to be 1 in 14 for men and 1 in 19 for women.<sup>26</sup> The incidence is reported to be high in Scotland and northern England and lower in Wales, the Midlands and southern England.<sup>26</sup> Cigarette smoking is the most important risk factor for lung cancer.<sup>27</sup> The National Institute for Health and Care Excellence (NICE)<sup>27</sup> reported that since the 1970s there has been a 25% reduction in the number of men who smoke, whereas the number of women smoking has increased considerably, leading to an increased number of deaths among women.<sup>27</sup> Therefore, if the cause of death is considered according to sex, then in 2009 lung cancer was the number one cause of cancer deaths in women, followed by breast and colorectal cancer (see *Table 1*).<sup>5</sup>

Lung cancer is rare in those aged <40 years and the risk increases after this age, with 87% of cases in people aged >60 years.<sup>26</sup> Incidence rates are highest in those aged 80–84 years.<sup>26</sup>

Histologically, lung cancer can be categorised into two types: approximately 20% are small cell lung cancer (SCLC) and the remaining 80% are non-small cell lung cancer (NSCLC).<sup>27</sup> There are three main types of NSCLC, namely squamous cell carcinoma, adenocarcinoma and large cell carcinoma, constituting approximately 35%, 27% and 10% of all NSCLC, respectively.<sup>27</sup> In those who smoke cigarettes, all four types of lung cancer are common, whereas, in those who do not smoke, adenocarcinoma is common.<sup>26</sup> Adenocarcinoma is now the most common type of lung cancer seen in North America, and it has been suggested that this could be due to the increasing reduction in cigarette smoking and a change in pathological classification.<sup>28</sup> In Europe, squamous cell carcinoma is the most common type of lung cancer.<sup>26</sup>

Approximately 22% of all cancer deaths in the UK are caused by lung cancer.<sup>5</sup> In England and Wales, the 1-year survival rates of cancer in men and women are 27% and 30%, respectively, while the 5-year survival rates are 7% and 9%, respectively.<sup>26</sup> Survival rate is low compared with other cancers, mainly because lung cancer is often diagnosed at an advanced stage.<sup>26</sup> It has been estimated that the 5-year survival rate for those diagnosed with stage 1A NSCLC would be 54–80% whereas for those in stage 1B it would be 38–65%.<sup>26</sup>

Bone is a common site of metastasis in lung cancer. It is reported that approximately 15–30% of patients with lung cancer will have bone metastases.<sup>29</sup> Approximately 30–40% of patients with advanced lung cancer will develop bone metastases during the course of their disease, resulting in a significant negative impact on both morbidity and survival.<sup>30</sup>

### Prostate cancer

Prostate cancer is the most incident cancer in men<sup>3</sup> and the second most common cause of deaths in men (see *Tables 1 and 2*).<sup>5</sup> In 2008, approximately 37,051 men were diagnosed with prostate cancer in the UK.<sup>4</sup> The European AS incidence rate was 97.9 per 100,000 in 2008.<sup>3</sup> Approximately 13% of cancer deaths in 2009 were due to prostate cancer.<sup>5</sup> Using the current probability method, Cancer Research UK found that in 2008 the lifetime risk in the UK of being diagnosed with prostate cancer was 1 in 9.<sup>31</sup>

Incidence rates of prostate cancer have increased over time, and it has been suggested that this is the result of better detection techniques and testing methods.<sup>31,32</sup> One study stated that, if men lived long enough, all of them would be likely to die with histological evidence of the disease present.<sup>33</sup> However, in fact only about 3% of men die of prostate cancer.<sup>32</sup>

Prostate cancer risk increases with increasing age. Incidence rates are almost five times higher in men aged 75–79 years than in those aged 55–59 years (751 per 100,000 vs. 155 per 100,000 of population).<sup>31</sup>

Prostate cancer survival depends on stage of disease. Five-year survival rate in men with localised disease is >90%, whereas in those with metastatic disease it is approximately 30%.<sup>34</sup>

Factors such as TNM classification stage, Gleason score and prostate-specific antigen (PSA) levels are used as predictive factors in prostate cancer.<sup>32</sup> The TNM classification is the most important of them.<sup>32</sup> It is used to stage the disease: T stage is used to indicate the extent of primary tumour, N stage is used to indicate if the disease has spread to local lymph nodes and M stage is used to describe the absence or presence of distant metastasis.<sup>32</sup> Based on this classification, if the cancer is found to have spread to lymph nodes and distant sites, then the prognosis is poor.<sup>32</sup>

Gleason score is an international grading system used to grade biopsy specimens histologically on the basis of architectural differentiation of tumour cells which, in turn, can predict lymph node metastases.<sup>32</sup> A score of  $\geq 7$  indicates that the tumour has metastasised to lymph nodes and the prognosis is poor.<sup>32</sup>

Prostate-specific antigen is a protein released by both normal and malignant prostate cells.<sup>32,35</sup> As serum PSA levels can rise in a number of conditions other than malignancy, such as infection and benign enlargement of the prostate,<sup>32,35</sup> it has been suggested that PSA testing is not a good marker for this condition.<sup>32,35</sup>

The prostate is a small gland located below the bladder and in front of the rectum that helps in production of fluid for semen.<sup>36</sup> It is divided into several zones but cancer mainly originates from the peripheral area. It is estimated that approximately 95% of prostate cancers are adenocarcinoma.<sup>33</sup>

Prostate cancer is caused by genetic mutation.<sup>37</sup> Owing to mutation, control of normal proliferation and differentiation of prostate cells is lost, and this in turn leads to abnormal accumulation of a large number of abnormal cells.<sup>37</sup> These cells accumulate and become a localised tumour. In the majority of cases, it takes many years for a cancer to become large enough to be detected clinically and even longer to spread either locally or to distant sites. Progression of the prostate tumour is dependent on androgen levels, especially levels of testosterone and dihydrotestosterone. Therefore, to delay progression, antiandrogen treatment (ADT) is given. This leads to chemical castration, which can hinder tumour growth. Over time genetic mutation may ensue and the tumour may become even more or less susceptible to androgen levels.<sup>38</sup> The tumour may continue to grow even when blood testosterone levels are low or negligible. Tumours that respond to ADT are known as castration-sensitive prostate cancer, and those that no longer respond are known as castration-resistant prostate cancer. The latter is also known as hormone-resistant prostate cancer.

### **Other solid tumours**

The other most important cancer in the UK is colorectal cancer. In 2008, approximately 39,991 new cases were registered (22,097 in males and 17,894 in females).<sup>4</sup> Colorectal cancer is the second most common cause of cancer deaths in the UK,<sup>5</sup> and 10% of all cancer deaths in 2009 were due to colorectal cancer (see *Table 1*).<sup>5</sup> It is reported that approximately 25% of patients with colorectal cancer have metastatic disease at the time of initial presentation.<sup>39</sup> The staging of colorectal cancer is undertaken using the Dukes' classification and more recently using the TNM classification.<sup>40</sup> Survival depends on stage of disease. Five-year survival is >90% in those diagnosed with Dukes' stage A disease compared with 7% in those diagnosed at a later stage.<sup>40</sup> Usually cancers of the colorectum metastasise to liver and peritoneum.<sup>41</sup> In 6–10% of cases, the cancer may metastasise to bone.<sup>41,42</sup> Cancers of thyroid, kidney and bladder have also all been found to metastasise to bone (*Table 3*).<sup>18</sup>

## Pathophysiology of bone metastasis

Bone is one of the commonest sites for metastasis in cancer.<sup>8,10</sup> Post-mortem examination of patients dying with a diagnosis of breast or prostate cancer revealed that about 70% had evidence of metastatic bone disease.<sup>43</sup> High percentages have also been observed for thyroid, kidney and lung carcinomas.<sup>18</sup>

### Mechanism of metastasis

There are three mechanisms by which a cancer can disseminate in the body: (1) direct seeding of body cavities or surfaces, (2) lymphatic spread and (3) haematogenous spread.<sup>44</sup> Direct dissemination of tumour cells is rare. It can, however, occur during surgery.<sup>45</sup> A direct seeding of body cavities and surfaces may occur when a tumour penetrates into a natural cavity. Most commonly involved is the peritoneal cavity, although other cavities such as the pleural, pericardial, subarachnoid and joint space can also be affected. Ovarian carcinoma is the best example of this type of metastasis, in which cancer cells spread to the peritoneal surface as a result of serosal invasion or perforation by cancer.<sup>46</sup>

The initial dissemination of cancer occurs via the lymphatic system following the natural route of lymphatic drainage to local lymph nodes, which can act to prevent onward spread for a while.<sup>44</sup> For example, breast cancer disseminates into the axillary, infraclavicular and supraclavicular nodes.<sup>47</sup> Lung cancer of the major respiratory passages usually spreads to the perihilar tracheobronchial and mediastinal nodes.<sup>48</sup> In some cases, local lymph nodes may be spared because of venous–lymphatic anastomoses or because of obliteration of the lymphatic pathway by inflammation or radiation; however, this can lead to lymphoedema.<sup>49</sup>

The most important method of spread to bone is via the circulatory system, particularly the venous system.<sup>11</sup> The retrograde venous route is probably the most important cause of metastasis to vertebrae.<sup>11</sup> There is a communication between veins of the breast and the plexus of Batson in the thoracic region and therefore cancers of the breast and lungs often metastasise to thoracic vertebrae.<sup>11</sup> Lungs drain their blood through pulmonary veins to the left side of the heart, which can therefore disseminate lung cancer cells to all parts of the body.<sup>11</sup> The prostate drains through the pelvic plexus into the lumbar region so cancers of the prostate metastasise to lumbosacral vertebrae.<sup>11</sup> Cancer of the bowel metastasises first to liver and lungs via the portal and caval system, respectively.<sup>11</sup>

Some cancers such as renal cell carcinomas and hepatocellular carcinomas invade veins directly.<sup>50,51</sup> In renal cell carcinomas, cancer invades the renal vein, after which it grows within the vein up to the inferior vena cava.<sup>51</sup> In hepatocellular carcinomas, cancer often penetrates portal and hepatic radicles and then grows to penetrate the main venous channels.<sup>50</sup>

### Organ-specific metastasis

There are certain cancers that show an organ-specific pattern of spread. For example, cancers of breast and prostate usually metastasise to bone.<sup>52</sup> In order to explain this propensity of certain cancers to metastasise to specific organs, a 'seed and soil' hypothesis, first explained by Paget in 1889, is used.<sup>53</sup>

**TABLE 3** Incidence of bone metastasis from different primary tumours

Primary tumour	Incidence of bone metastases	
	Roodman 2004 <sup>29</sup>	Coleman 2006 <sup>18</sup> (post-mortem examination)
Breast	≈70% with advanced disease	73%
Prostate	≈70% with advanced disease	68%
Others	15–30% in cancers of lung, colon, stomach, bladder, uterus, rectum, thyroid and kidney	Thyroid: 42%; kidney: 35%; lung: 36%; gastrointestinal: 5%

Paget suggested that distribution of secondary growth does not happen by chance, but a relationship between tumour cells (referred to as 'seed') and host cells (referred to as 'soil') is the main reason why certain types of cancer metastasise to specific organs.<sup>52,53</sup> Blood flow in red marrow is very high and so it provides considerable opportunity for tumour cells to metastasise (seeding). Factors such as growth factors, hormones and cytokines provide a suitable environment for tumour growth/metastasis to take root in bone.<sup>54,55</sup> Another surgeon, James Ewing, challenged Paget's hypothesis and suggested that this type of metastasis occurs as the result of a certain circulatory pattern between cancer and specific organs.<sup>52</sup> Currently it is acknowledged that both hypotheses are important in understanding the pathogenesis of organ-specific metastasis.<sup>52</sup>

### **Molecular mechanism**

Metastatic bone diseases are often classified as osteolytic or osteoblastic; however, lesions can be made up of both components, i.e. osteoclasts and osteoblasts.<sup>29,55,56</sup> Osteoclasts originate from precursor cells of the monocyte-macrophage lineage whereas osteoblasts arise from mesenchymal stem cells.<sup>29</sup> The following description is based on the review by Roodman.<sup>29</sup>

In an individual with no cancer, bone remodels itself via a synchronised process of osteoblast and osteoclast activity on trabecular surfaces and within the Haversian system.<sup>29</sup> First, resorption of bone by osteoclast occurs and then new bone is formed at the same location by osteoblasts.<sup>29</sup> However, when tumour cells metastasise to bones, this normal remodelling sequence is disrupted and, depending on the type of cancer, either osteoblastic or osteoclastic activity becomes predominant. In breast cancer, osteolytic lesions are predominant although at least a quarter of lesions are thought to be osteoblastic.<sup>29</sup> In prostate cancer, most lesions are osteoblastic in nature. It should, however, be noted that a lesion can contain both osteoblasts and osteoclasts.<sup>55</sup> The difference between the two types of lesions is evident only during radiological examinations: osteoclastic lesions appear lytic, osteoblastic lesions appear sclerotic and, when both components are present, lesion appears mixed.<sup>57</sup>

In normal bone, several systemic hormones and locally produced cytokines are responsible for the formation and activity of osteoclasts and osteoblasts.<sup>29</sup> For these cells to develop properly, a suitable microenvironment is necessary, which is provided by macrophage colony-stimulating factor and receptor activator of nuclear factor- $\kappa$ B ligand (RANKL).<sup>29</sup> RANKL is a type of tumour necrosis factor present on the surface of osteoblasts and stromal cells.<sup>29</sup> Factors such as parathyroid hormone (PTH), 1,25-dihydroxyvitamin D<sub>3</sub>, prostaglandins and interleukins stimulate the formation of osteoclasts by increasing the expression of RANKL.<sup>29</sup> RANKL binds the RANK receptor on osteoclast precursors and forms osteoblasts via the nuclear factor- $\kappa$ B and Jun N-terminal kinase pathways.<sup>29</sup> Another type of tumour necrosis factor receptor, osteoprotegerin (known as decoy receptor), is also present in the bone marrow. It inhibits the differentiation and resorption of osteoclasts. The ratio of RANKL and osteoprotegerin regulates the formation and activity of osteoblasts.<sup>29</sup> The differentiation of osteoblasts is less well understood than that of osteoclasts.<sup>29</sup> Runx-2 (core-binding factor  $\alpha$ 1), a transcription factor, is important for differentiation of osteoblasts. It stimulates genes related to osteoblastic differentiation. Factors such as PTH, prostaglandins, cytokines, platelet-derived growth factor, corticosteroids and interleukins regulate the formation of osteoblasts.<sup>29</sup>

Once cancer cells reach bone marrow, production of osteoclasts is increased. This increment is initiated by a factor called PTH-related peptide (PTHrP) produced by tumour cells.<sup>29</sup> When released, PTHrP binds to a receptor that is the same as that for PTH, called PTHR1, which activates RANKL on marrow stromal cells. The receptor then increases production of osteoclasts, which cause bone resorption.<sup>29</sup> This cycle supports tumour growth in the bone.<sup>55</sup> PTHrP is secreted by breast cancer cells, prostate cancer cells and other solid tumours.<sup>29</sup> During bone resorption, growth factors (transforming growth factor- $\beta$ ) and calcium stored in the bone matrix are released.<sup>29,55</sup> The transforming growth factor- $\beta$  released during bone resorption further stimulates production of the PTHrP by the cancer cells.<sup>29</sup> This type of osteoclastic metastasis is predominantly seen in breast cancer. Other factors that also induce osteoclastic activity in breast cancer

patients are interleukin 6, prostaglandin E<sub>2</sub>, macrophage colony-stimulating factor, interleukin 1 and tumour necrosis factor- $\alpha$ .<sup>29</sup>

The mechanism and factors involved in osteoblastic metastasis are not well known.<sup>29</sup> In prostate cancer, a large number of fibroblastic growth factors have been found. Another growth factor, endothelin-1, is found at increased levels in patients with prostate cancer and is also found in breast cancer patients. Both fibroblastic growth factors and endothelin-1 have been found to stimulate bone formation *in vivo*<sup>29,58</sup> and are also shown to cause osteoblastic activity in prostate cancer. In prostate cancer, other factors are also found to contribute to bone metastasis.<sup>29</sup> PC3 (prostate cancer) cells produce a factor similar to urokinase-type plasminogen activator, which increases bone metastasis.<sup>29</sup> PSA is a factor that blocks tumour-induced bone resorption and also activates growth factors such as insulin-like growth factors I and II or transforming growth factor- $\beta$  released during bone metastasis.<sup>29</sup>

In summary, several signalling pathways operate in controlling bone formation and breakdown and these are influenced by the activity of metastatic cells.

## Clinical manifestation of spinal metastases

Spinal metastases can lead to a considerable number of complications.<sup>57</sup> They may cause bone pain, fractures, motor or sensory dysfunction and also symptoms associated with systemic disease.<sup>59</sup> On examination, a patient may show signs of systemic disease such as weight loss and anaemia.<sup>57,59</sup> Patients may also show signs of nerve root impingement or SCC.<sup>59</sup> In some, a palpable mass may also be found, especially in the case of large sacral metastases.<sup>59</sup>

Pain is the most common manifestation in patients with spinal metastasis.<sup>10,57,59</sup> It is estimated that approximately 80–95% of patients will complain of pain.<sup>10,57,59</sup> However, pain will be the initial symptom of spinal metastasis in only about 10% of patients.<sup>59</sup> Patients with spinal metastases can have one of the three types of pain, i.e. local pain, mechanical pain or radicular pain.<sup>10,59</sup> It is believed that local pain occurs as a result of periosteal stretching or increasing length of the spine or enlargement of epidural venous plexuses.<sup>10,59</sup> This pain is often termed 'night' or 'nocturnal' pain as the patient feels better during activity.<sup>10,59</sup> It is aggravated on percussion or palpation and is often described as 'gnawing' or 'aching' pain.<sup>10,59</sup> It is often relieved by taking anti-inflammatory medication or corticosteroids.<sup>59</sup> Mechanical pain results from instability of the spine, which happens when metastases affect the vertebral body of the spine. The strain to support muscles and tendons increases under these conditions.<sup>59</sup> Therefore, mechanical pain is aggravated during movement and activity.<sup>10,59</sup> This pain, in contrast to nocturnal pain, is relieved only by lying down, often on one side. Stabilisation of the spine using braces or fixators can improve a patient's quality of life remarkably.<sup>59</sup> Radicular pain occurs when a tumour compresses or invades nerve roots and can also result from pathological fractures.<sup>10,59</sup> Pain is usually sharp, shooting or stabbing in nature<sup>59</sup> and often radiates towards limb, chest or upper abdomen.<sup>18</sup> An intense or burning type of pain is felt when a nerve root is impeded by intradural extramedullary metastases.<sup>59</sup>

Motor dysfunction is the second most commonly found clinical manifestation in patients with spinal metastasis.<sup>10,59</sup> It is estimated that approximately 35–75% of patients will present with this dysfunction.<sup>10</sup> Again this happens as the result of direct compression of nerves and nerve roots by tumour or fragments of bones resulting from pathological fracture.<sup>59</sup> This causes myelopathy, radiculopathy or sometimes a combination of both, which clinically manifests itself as a weakness of muscles.<sup>59</sup> Patients may also complain of heaviness at their extremities and when clinically examined, motor dysfunctions will be found.<sup>10,59</sup>

Some patients may also present with sensory dysfunction; however, motor dysfunction and pain in the corresponding dermatomes are always present.<sup>10,59</sup> Sensory dysfunctions include anaesthesia, hyperaesthesia and paraesthesia.

### Metastatic spinal cord compression

Metastatic spinal cord compression (MSCC) is the most serious complication that can occur in patients with spinal metastasis.<sup>60</sup> It is defined as 'compression of the dural sac and its contents (spinal cord and/or cauda equina) by an extradural tumour mass' (Figure 2).<sup>60</sup>

It is estimated that approximately 10 people per 100,000 per year will develop this complication.<sup>60</sup> It is a critical condition that requires emergency care to prevent loss of neurological function and to reverse established deficits.<sup>61</sup> Surgical indications can include bony compression and spinal instability.<sup>62</sup>

The patient can have a range of symptoms. Approximately 60–85% of patients will have weakness of muscles.<sup>59</sup> In addition, patients may have autonomic disturbances that include abnormalities of bowel, bladder and sexual function.<sup>59,60</sup> Initially, patients will often present with numbness and anaesthesia of the parts distal to the metastases.<sup>18</sup> Symptoms such as urinary retention, incontinence and impotence occur late in the disease.<sup>18</sup> The most common autonomic abnormality found in patients with MSCC is bladder dysfunction, often clinically presenting as urinary retention.<sup>59</sup> The degree of bladder dysfunction is directly associated with the degree of motor dysfunction. If a patient with motor dysfunction is not treated, they may progress to complete paralysis.<sup>59</sup>

## Investigations

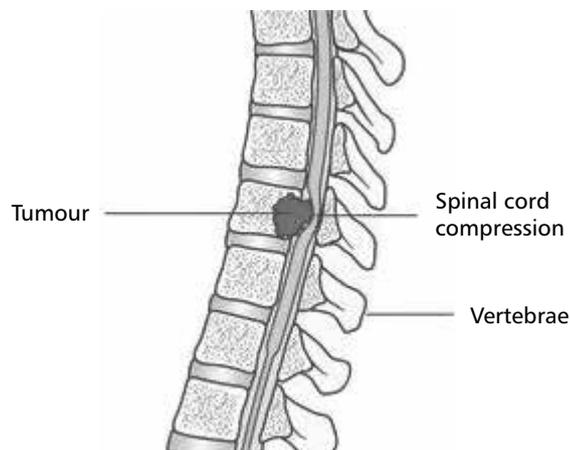
### Diagnosis

Patients with suspected spinal metastasis should be evaluated with a detailed medical history, clinical examination and laboratory tests.<sup>8,59,63</sup>

Spinal metastases may be asymptomatic and detected during routine examination, but suspicious clinical examination or suggestive symptoms are more likely to lead to investigation and detection. Patients can have a plethora of symptoms, which include pain, weight loss, weakness, and neurological and organ dysfunction.<sup>59</sup> Details of different types of pain have been described in previous sections. The laboratory examination includes blood cell counts, urine examination, liver function, creatinine level and PSA.<sup>59,63</sup>

### Imaging and detection

In those patients undergoing surgery or other interventions, assessment of bowel and bladder function, motor weakness and sensory deficits is important as they determine outcomes such as healing and risk



**FIGURE 2** A tumour causing SCC. Reproduced with permission from CancerHelp UK, the patient information website of Cancer Research UK. URL: <http://cancerhelp.cancerresearchuk.org>.

of infection.<sup>63</sup> Imaging technologies such as ultrasonography and computerised tomography (CT) of the abdomen and chest may be helpful in localising primary neoplasms.

Biopsy of the tumour and examination of the CSF are more useful when the source of the primary tumour is unknown.<sup>8,59</sup> The CT-guided needle biopsy is safe and a reliable method.<sup>59</sup> However, where lesions are small, it may not be possible to collect an appropriate sample.<sup>8</sup> In these patients an open biopsy is better.<sup>8</sup>

A broad range of imaging techniques is available to the clinician, for example plain radiography, myelography, magnetic resonance imaging (MRI), CT, radionuclide bone scan, single-photon emission CT (SPECT) and positron emission tomography (PET).<sup>63</sup> MRI of the entire spinal axis is likely to be the gold standard for evaluation of vertebral metastasis.<sup>64,65</sup> MRI of the entire spinal axis provides images of masses, distortion of CSF spaces and various metastases and therefore is better than CT.<sup>10</sup> However, CT with sagittal, coronal and three-dimensional reconstruction allows detailed evaluation of the bony anatomy of the spine, allowing preoperative and intraoperative surgical planning and postoperative consideration.<sup>66,67</sup> In addition, CT also provides images of vertebral arteries, and the characteristics, extent and overall instability of a fracture. It has been suggested that CT usually complements the findings of MRI.<sup>10</sup> Myelography may be used in patients who are unable to undergo MRI because of metallic implants or foreign bodies.<sup>8</sup>

There is active discussion in the literature regarding which method or combination of methods (e.g. integrated CT/PET) is most useful and appropriate; nevertheless, no method achieves 100% sensitivity or specificity in identification of patients at high risk of vertebral collapse and SCC. It has been reported that if lesions are examined using three methods, i.e. plain radiography, CT and MRI, then sensitivity and specificity ranges between 85% and 100%.<sup>8</sup>

Plain radiography can be useful in identifying vertebral body collapse, pedicle erosion, osteoblastic and osteolytic lesions, and pathological fracture–dislocation.<sup>68,69</sup> However, it is not a reliable diagnostic tool for a number of reasons: (1) vertebral body collapse is frequently seen in non-neoplastic conditions, (2) 30–40% of bone must be eroded before lesions are visible on plain radiography, and (3) in most cases, lesions are seen only after half of the vertebral body is affected. Despite these problems it is estimated that approximately 90% of patients with symptomatic disease show abnormal changes on plain radiography.<sup>70,71</sup>

Other imaging techniques such as bone scan, SPECT and PET with <sup>18</sup>F-fluorodeoxyglucose are used to diagnose and evaluate vertebral metastases. PET with <sup>18</sup>F-fluorodeoxyglucose has been found by some investigators to be as accurate as MRI.<sup>72</sup>

There appear to be no guidelines that recommend specific imaging modalities; however, NICE clinical guideline 75, for diagnosis and management of adults at risk of or with MSCC, states that MRI should be undertaken very soon after diagnosis or suspected diagnosis.<sup>15</sup> The guideline reports that in patients in whom MRI is contraindicated, CT with three-plane reconstruction should be performed. Finally, the guideline states that plain radiography should not be used to confirm or exclude the diagnosis of spinal metastases or MSCC.<sup>15</sup> In cases of spinal pain suggestive of spinal metastases, NICE states that MRI should be carried out as early as possible to deploy definitive treatment within 1 week of developing these symptoms. However, in cases of spinal pain suggestive of MSCC or neurological function deterioration, MRI should be undertaken within 24 hours as this is a medical emergency<sup>15</sup> (see *Figure 3*).

## Treatment

The treatment of metastatic spinal tumours typically involves multiple interventions such as surgery, medical therapy and radiation.<sup>63</sup> Interdisciplinary collaboration is essential to allow each patient's treatment to be tailored to the overall prognosis,<sup>8</sup> and therefore treatment of these patients involves a

variety of specialties, namely medicine, surgery, oncology, neurology and rehabilitation medicine.<sup>59</sup> Owing to the heterogeneity of tumour pathology, patients' condition and the anatomical extent of disease, it remains difficult to provide a consensus about treatment. As therapy is not curative, treatment, in most cases, is focused on improving a patient's quality of life and restoring neurological function or preventing further deterioration, reducing pain and stabilising the spine mechanically.<sup>59,63</sup> Radiation therapy and different forms of surgery are the primary methods for treating SCC. High-dose steroids are administered with radiation treatment and tapered gradually with completion of treatment.<sup>61</sup> Surgical interventions include decompression and fixation of the spinal joints.<sup>62,73</sup>

### **National Institute for Health and Care Excellence clinical guideline for management of spinal cord compression**

In November 2008, NICE issued a clinical guideline for the diagnosis and management of adults at risk of or with MSCC.<sup>15</sup> The guidelines contained treatment algorithms for patients with symptoms suggestive of spinal metastases. The guideline proposed the patient treatment pathways shown in *Figure 3*.

Treatment of patients with spinal metastases and MSCC can be broadly divided into three pathways.<sup>15</sup>

#### **Treatment of patients with spinal metastases and prevention of metastatic spinal cord compression**

Patients with painful spinal metastases should be offered conventional analgesics, i.e. non-steroidal anti-inflammatory drugs. Those patients with intractable pain should be considered for specialist pain care that includes invasive procedures and neurosurgical interventions. Patients with spinal metastases from breast and prostate cancer should be offered bisphosphonates to alleviate pain and reduce the risk of pathological fracture/collapse of the spine. Those patients with non-mechanical spinal pain should be given single-fraction palliative radiotherapy. This should also be considered in those who are completely paralysed. In asymptomatic patients, radiotherapy should not be administered.

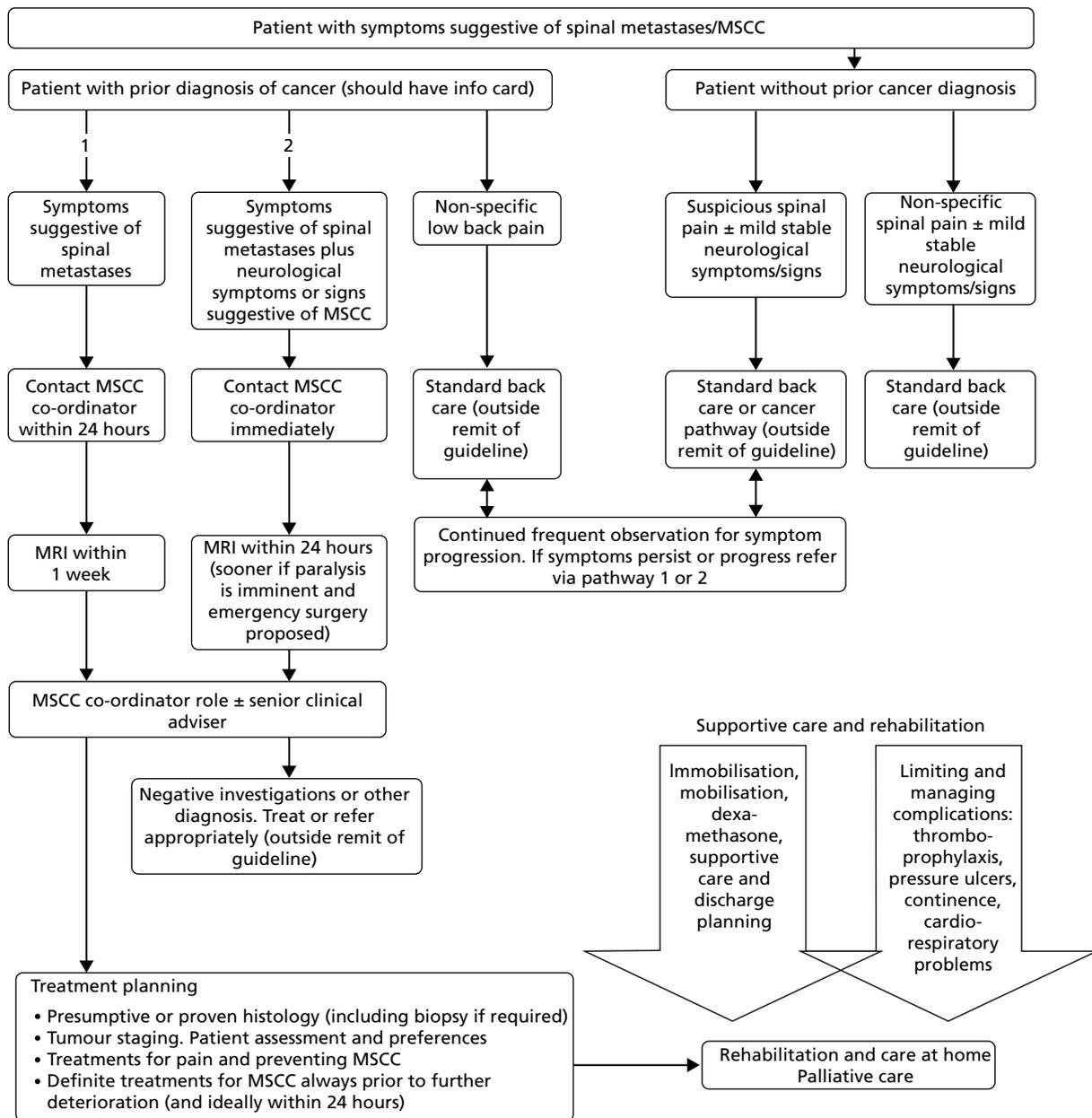
Two vertebral augmentation techniques, vertebroplasty and kyphoplasty, should be considered in those with mechanical spinal pain resistant to conventional analgesics and no evidence of MSCC or spinal instability.

Surgery should be preferred when there is evidence of progressive disease mainly to prevent MSCC. It should also be considered in those with spinal metastases and mechanical pain resistant to conventional analgesics and in those with evidence of spinal instability.

#### **Treatment of threatened spinal cord in patients with metastatic spinal cord compression**

In patients with severe mechanical pain suggestive of spinal instability or those with neurological symptoms or signs suggestive of MSCC, the spine should be stabilised. Patients should be monitored regularly, especially during sitting from supine to 60 degrees. If patients continue to deteriorate, then they should revert back to the lying position or to the position in which there is minimal pain/neurological symptoms. In those patients not suitable for definitive treatment, the aim of the treatment should be helping the patient to achieve a comfortable position and mobilisation. This is usually achieved by using orthoses.

Corticosteroids should be given to all patients with MSCC unless contraindicated. Dexamethasone at 16 mg as a loading dose should be given followed by a short course of 16 mg dexamethasone daily until definitive treatment is employed. After definitive treatment, the dose of dexamethasone should be reduced gradually over 5–7 days and then stopped. In those patients in whom symptoms have deteriorated, the dose of dexamethasone can be increased temporarily.



**FIGURE 3** Patient treatment pathways for diagnosis and management of adults at risk of or with MSCC. Adapted from Metastatic spinal cord compression: Diagnosis and management of adults at risk of or with metastatic spinal cord compression. 2008. Available from: <http://guidance.nice.org.uk/CG75/Guidance/pdf/English> (accessed April 2011).<sup>15</sup>

### Definitive treatment of metastatic spinal cord compression

The definitive treatment should be given as early as possible, ideally within 24 hours of the diagnosis of MSCC. Before this, diagnosis of primary location of the tumour should be made. In addition, an attempt should be made to study the extent of the disease. A scoring system such as the Tokuhashi scoring system and the American Society of Anesthesiologists grading for overall patient condition should be used to assess whether surgery is appropriate.

### Surgery

Surgery should be considered only if it would increase the patient's survival by >3 months. The aim of this treatment is to decompress the spinal cord and stabilise the spine. Posterior decompression alone should be used only in cases of isolated epidural tumour or neural arch metastases without bony instability. In

those in whom metastasis involves the vertebral body and who are therefore at increased risk of spinal instability, posterior decompression by internal fixation, with or without bone grafting, should be carried out. Reconstruction of the vertebral body should be carried out in patients with MSCC and vertebral body involvement who are expected to survive <1 year, whereas in those expected to survive >1 year, reconstruction of the vertebral body with anterior bone graft should be undertaken. In rare circumstances such as solitary renal or thyroid metastasis following complete staging, en bloc excisional surgery should be carried out.

### **Radiotherapy**

Patients unsuitable for surgery should receive radiotherapy within 24 hours, 7 days a week. Fractionated radiotherapy is the definitive treatment of choice for patients with epidural tumour without neurological dysfunction, mechanical pain or spinal instability. It is also an appropriate first-line treatment for patients with good prognosis. Radiotherapy should not be given to patients with MSCC who are waiting for surgery but fractionated radiotherapy should be offered to all patients postoperatively once their wound has healed.

### **Supportive care and rehabilitation**

Supportive care includes thromboprophylaxis, management of pressure ulcers, bladder and bowel continence, circulatory and respiratory functions and access to specialist rehabilitation care at home.<sup>15</sup>

### **Radiation**

The aim of radiation is to alleviate pain and to prevent recurrence and tumour growth.<sup>74</sup> It is indicated when the spine is stable, if the tumour is radiosensitive and the patient's neurological condition is stable, or if the patient is in poor medical condition or has a life expectancy <3–6 months and has had complete paraplegia for >24 hours.<sup>74</sup>

According to a recent review,<sup>74</sup> conventional external beam radiation is the most commonly used radiotherapy in patients with spinal metastasis. Often radiotherapy is used in combination with surgical treatment as this is useful in preventing local recurrence.<sup>74</sup> It should, however, be noted that radiation adversely affects surgical outcomes by delaying wound healing and/or delaying fusion of the joints. Thus, radiation is now usually not given before surgery. It is given either as a single fraction or as multiple fractions. Usually it is administered in 10 fractions, which is equivalent to 3000 cGy.<sup>74</sup>

Patients aged <65 years with radio-resistant tumours and with signs of MSCC are treated with surgery and adjuvant radiotherapy. The latter is used to prevent local recurrence of the tumour.<sup>74</sup> Currently, in those with low-grade compression, a single-fraction treatment is given.<sup>74</sup>

Recently, new approaches, such as intensity-modulated radiotherapy (IMRT),<sup>75</sup> or stereotactic body radiotherapy, have been suggested for the treatment of vertebral metastases.<sup>76</sup>

### **Systemic therapies**

#### **Corticosteroids**

Intravenous or oral corticosteroids have been found to provide improvement or resolution of neurological symptoms and pain in patients with epidural spinal metastases.<sup>63</sup> It should be noted that there is no standard dosage regimen for corticosteroids. They are often used before surgery.<sup>63</sup>

In patients with MSCC undergoing surgical decompression, corticosteroids are often used in combination with radiotherapy.<sup>74</sup>

#### **Bisphosphonates and denosumab**

Bisphosphonates are known to impair osteoclastic activity and so they reduce tumour-related resorption of bone.<sup>10,57</sup> Currently, bisphosphonates are used to alleviate metastatic bone pain and to reduce SREs

such as pathological fractures, hypercalcaemia and MSCC. Bisphosphonates are also used to reduce the frequency of surgery and radiation therapy.<sup>10,57</sup> Bisphosphonates such as pamidronate (Aredia®; Novartis Pharmaceuticals Corporation), clodronate (Bonefos®, Clasteon®, Loron®; Bayer), ibandronate (Bondronat®; F. Hoffmann-La Roche Ltd), alendronate (Fosamax®; Merck Sharp & Dohme Corporation) and zoledronate (Aclasta®; Novartis) have all been found to be effective in the treatment of hypercalcaemia.<sup>57</sup> Although radiotherapy is the main treatment for reducing bone pain, bisphosphonates can be used as an alternative therapy, which in turn will considerably reduce the frequency of radiotherapy.<sup>10,57</sup> The effect of bisphosphonates on pain is not dependent on the nature or type of the tumour (i.e. sclerotic or lytic).<sup>57</sup> The efficacy of these drugs has been seen in breast cancer, multiple myeloma and other osteolytic metastases.<sup>57</sup> Although bisphosphonates have been found to be effective in preventing skeletal-related complications, they are not so effective in reducing pain in patients with prostate cancer.<sup>77</sup>

Recently, monoclonal antibody therapy with denosumab, a specific inhibitor of RANKL, has been found to be effective in delaying and preventing SREs.<sup>77</sup>

### Chemotherapy

The benefits of chemotherapy are limited in spinal metastases, as patients are usually at a late stage of disease.<sup>57</sup> Chemotherapy can be given on its own or in combination with surgery and hormonal therapy.<sup>10</sup>

### Radioisotopes

Radioisotopes are administered systematically and act as local radiation therapy to the spine.<sup>10</sup>

Radioisotopes include strontium-89 and rhenium-186. Although radioisotopes are found to reduce pain in patients with spinal metastases, these can cause irreversible bone marrow suppression and, for this reason, they are recommended for use in those with good marrow function and in whom no other treatment is available.<sup>10</sup>

### Hormonal therapies

Hormonal therapies are a major treatment modality for metastatic breast and prostate cancer. As an example, a new drug, abiraterone (Zytiga®; Janssen), has recently been developed which has improved outcomes in men with metastatic castration-resistant prostate cancer.<sup>78,79</sup>

### Surgery

The main aims of surgery are to remove the tumour, to achieve spinal stability and to reconstruct the vertebral column.<sup>7</sup> Surgery may also help with diagnosing the origin of the tumour and in relieving neurological symptoms.<sup>7</sup> In those with solitary renal cell carcinoma metastases, surgery can increase disease-free survival.<sup>80</sup> Current indications for surgery are (1) radioresistant tumour such as renal or colon carcinoma, (2) evidence of neurological function deterioration or tumour progression despite radiotherapy, (3) radiological images showing fragments of bone in the spinal canal, (4) spine instability due to fracture and causing pain and neurological deficit, (5) neurological deficit for >24 hours, or significant MSCC, and (6) life expectancy of at least 3 months.<sup>7,74</sup>

Different scoring systems have been developed to select patients who will benefit from surgery such as those developed by Tokuhashi *et al.*<sup>81</sup> Prognostic predictions for these patients after surgery can also be made using these scoring systems.<sup>81</sup> Details of this have been given below (see *Prognosis*).

The surgical approach to remove a tumour or to decompress neurons in spinal metastases depends on various elements such as the spinal segment involved and the location and histological characteristics of the tumour.<sup>59</sup> In most cases, metastases occur in the vertebral body of the spine and therefore an anterior approach has been used by many surgeons to remove the tumour, and to decompress and then stabilise the spine.<sup>74</sup> An anterior approach is appropriate if the cervical spine is involved. Other approaches such as anterolateral cervical with sternotomy or thoracotomy are preferred when the upper thoracic spine is affected.<sup>82</sup> During these techniques great vessels in the thorax can obstruct access to the spine and newer approaches have been developed such as transpedicular posterior or posterolateral approaches.

### Vertebral augmentation

Two techniques, percutaneous vertebroplasty and kyphoplasty, initially developed for treatment of painful vertebral haemangiomas, are now used effectively in treating painful pathological fractures caused by metastatic spinal disease.<sup>59</sup> Vertebroplasty involves an injection of polymethylmethacrylate (PMMA) into the compression fracture whereas in kyphoplasty an inflatable balloon is placed in the vertebral body and PMMA is injected.<sup>83,84</sup> Although these interventions can lead to significant pain reduction and greater mobility,<sup>83,84</sup> they are contraindicated in SCC because of pathological fractures as they do not relieve cord compression.<sup>59</sup> Complications of these techniques include leakage of PMMA, misplacement of PMMA and haematogenous embolisation of PMMA to the lungs.<sup>59</sup>

### Prognosis

Several types of prognostic studies have been undertaken to explore the prognosis of spinal metastases. These studies will be the focus of this current short report. Prognostic studies serve several purposes, for example to inform choice of potential pre-emptive intervention(s) so as to avoid or delay more radical surgical intervention; to bring forward radical interventions before patients' health deteriorates to the extent that they are no longer suitable candidates for interventions; and to categorise patients into those more or less suitable for earlier or later radical intervention.

Prognostic studies comprise four types:

- attempts to determine the risk factors that allow prediction of overall survival (e.g. scoring schemes such as those of Tokuhashi *et al.*<sup>85</sup> and Tomita *et al.*<sup>86</sup>)
- the identification of patients most suitable for surgical intervention; some of these studies are specific for metastases derived from particular primary tumours (e.g. lung, breast)
- attempts to identify risk factors important in determining the survival of patients after surgical intervention for SCC and/or vertebral compression fracture(s)<sup>87</sup> (e.g. vertebrectomy and reconstruction, vertebroplasty, kyphoplasty, radiofrequency ablation)
- assessment of risk factors using clinical or imaging technologies for progression of metastatic spinal metastases to SCC and/or to vertebral compression fracture(s).<sup>88,89</sup>

Early studies by Yamashita *et al.*<sup>90</sup> documented longer survival in patients with spinal or pelvic metastatic cancer lesions compared with those with appendicular lesions or both. Tokuhashi *et al.*<sup>81</sup> developed a scoring system involving six parameters to determine survival after surgery for metastatic spinal tumours: (1) general condition; (2) number of vertebral metastases; (3) number of metastases to internal organs; (4) number of metastases to extraspinal bone; (5) primary site; and (6) severity of spinal cord injury. Scores of 9 out of a possible 12 indicated a good prognosis for patients whereas scores <5 indicated a worse prognosis.<sup>81</sup> Tomita *et al.*<sup>86</sup> developed a similar scoring system based on (1) primary tumour site, (2) presence of visceral metastases and (3) number of bone metastases. In contrast to Tokuhashi *et al.*,<sup>81</sup> in this system, a lower score indicates a better prognosis.<sup>86</sup>

van der Linden *et al.*<sup>91</sup> analysed response to radiotherapy in a cohort of patients with painful spinal metastases and without neurological impairment. Patient characteristics such as Karnofsky performance score, primary tumour site, number of visceral metastases, etc., were studied for their prognostic value in predicting survival. The points were awarded as follows: (1) 2, 1 and 0 points were given for Karnofsky performance score of 80–100, 50–70 and 10–40, respectively; (2) 3, 2, 1 and 0 points were given for breast cancer, prostate cancer, lung cancer and other types of cancer, respectively; and (3) in the presence of visceral metastases 1 point was given, and 0 points if they were absent. Three prognostic groups were formed: Group A with scores between 0 and 3, Group B with scores between 4 and 5, and Group C with a total score of 6. The median overall survival in Groups A, B and C was found to be 3 months, 9 months and 18.7 months, respectively. Patients in Group C had breast cancer with good performance and no metastases to organs.<sup>91</sup>

Sioutos *et al.*<sup>92</sup> studied a cohort of patients with spinal metastases from solid tumours and epidural compression of the spinal cord who underwent surgical decompression of the spinal cord and radiotherapy. Patient characteristics such as anatomical site of primary carcinoma, preoperative neurological deficit, extent of disease, number of vertebral metastases, site of cord compression and age were explored if they predicted survival. In the study, it was found that patients with renal cell carcinoma survived longer than those with breast, prostate, lung or colon cancer. Patients with single vertebral body metastasis survived comparatively longer than those with multiple vertebral body metastases. The presence of leg strength between 0/5 and 3/5, lung or colon cancer, and multiple vertebral metastases all had a negative impact on survival; however, factors such as extent of disease, age and location of tumour had no apparent impact on overall survival of patients.<sup>92</sup>

Ambulatory status, age <60 years and single vertebral segment involvement have also been found to be independent predictors of good outcome.<sup>92–95</sup> Furthermore, Weigel *et al.*<sup>95</sup> reported a significant association between a postoperative Karnofsky scale and duration of survival.

Bauer and Wedin<sup>96</sup> studied survival of patients with spinal metastases after surgery. The survival of the patient was found to be associated with metastatic load, location of tumour and presence of pathological fracture. On multivariate regression analysis, some factors such as pathological fracture, metastasis to brain or viscera, and lung cancer were found to be negative prognostic factors while single skeletal metastases and breast or kidney cancer were positive variables.<sup>96</sup>

All of these scoring systems relate to survival, which is not one of the outcome measures included in this current review. According to a recent review, they have recently been assessed as having limited predictive value.<sup>8</sup>

## Current service cost

### *Economic impact of skeletal complications*

There is a large burden on health-care resources from bone metastases and their complications. The cost also increases because of the multidisciplinary approach required to manage such patients. For example, Botteman *et al.*<sup>97</sup> used NHS perspective costs to compare relative cost and cost-effectiveness of commonly used bisphosphonates versus no therapy for the management of SREs in breast cancer patients with bone metastasis and receiving chemotherapy or hormone therapy. The authors took different types of costs into consideration such as hospital cost (including cost of vertebral fracture, non-vertebral fracture, hypercalcaemia, radiotherapy, orthopaedic surgery), community care cost, monthly cost of bone pain (including cost of medical consultant, palliative care nurse, district nurse, social work assistant) and cost of drugs.<sup>97</sup> The paper reports a mean cost of £18,662 over the mean survival of 2 years with no bisphosphonate therapy, and states that the use of bisphosphonates can be cost-saving and cost-effective in reducing SREs without influencing survival. The mean cost of using zoledronic acid over the mean survival of 2 years was £16,396.<sup>97</sup>

Another study showed that zoledronic acid may be cost-effective in lung cancer patients with bone metastases, with the mean drug cost (£1473) being slightly lower than costs associated with additional SREs (£1562) incurred in an untreated population.<sup>98</sup>

Recently denosumab, a monoclonal antibody, has been found to prevent and delay SREs.<sup>77</sup> In the UK, it is currently indicated for the prevention of osteoporotic fractures in postmenopausal women<sup>99</sup> and for the treatment of bone loss associated with hormone ablation in men with prostate cancer.<sup>100</sup> The recommended dose is 60 mg every 6 months via subcutaneous injection. It is available as Prolia<sup>®</sup> manufactured by Amgen (Thousand Oaks, CA, USA) and costs £183 for a 1-ml (60 mg/ml) prefilled syringe.<sup>100</sup> On 18 November 2010, the US Food and Drug Administration approved denosumab (trade name Xgeva<sup>®</sup>, Amgen) for the prevention of SREs in patients with bone metastases from solid tumours.<sup>101</sup>

For this, the recommended dose of denosumab is 120 mg every 4 weeks subcutaneously,<sup>101</sup> giving an annual cost of approximately £4770 in the UK.

A retrospective observational study reported high costs of treating SREs in lung cancer.<sup>102</sup> Of 534 patients identified with lung cancer and bone metastases, 295 (55%) experienced one or more SREs over a mean follow-up of 5.6 months, whereas 25% of patients had two or more SREs. Costs of treatment of SREs were estimated to be approximately \$9500. Total medical care costs were almost \$28,000 in patients with SREs and were significantly higher than in patients without SREs ( $p < 0.001$ ). Radiation therapy accounted for 55% of the treatment cost (compared with 25% for bone surgery), and 54% of costs were due to inpatient hospitalisation.<sup>102</sup>

These examples most importantly show that the management of a patient with malignant skeletal metastases is associated with appreciable consumption of resources.

## Summary

Metastases to the spine occur commonly in commonly occurring cancers, such as breast, prostate and colorectal cancers.

Spinal metastases can lead to significant morbidity and reduction in quality of life due to SCC, which can result in paraplegia or quadriplegia, severe bone pain and pathological fractures. An early study estimated average survival for patients with SCC to be between 3 and 7 months, with a 36% probability of survival to 12 months. Spinal metastases are costly. Early diagnosis is important, helping clinicians to manage disease and delay complications. There is uncertainty about the specificity and sensitivity of the different diagnostic techniques currently available. Prognostic models have been developed to predict overall survival.

## Chapter 2 Methodology

A protocol was produced and approved by the Health Technology Assessment (HTA) Programme before the start of this review. It is available on the HTA Programme website ([www.hta.ac.uk/project/2553.asp](http://www.hta.ac.uk/project/2553.asp)).

### Search strategies

The search aimed to identify all references relating to the natural history of metastatic spinal lesions and the identification of patients at high risk of vertebral fracture and SCC through the use of various technologies. The search strategy involved searching electronic bibliographic databases; contact with experts in the field; and scrutiny of references of included studies. An iterative procedure was used to develop the search strategy, with input from clinical advisors, an experienced information specialist and previous HTA and systematic reviews (e.g. Cooper *et al.*,<sup>103</sup> National Collaborating Centre for Cancer<sup>15</sup> and Sutcliffe *et al.*<sup>104</sup>). Copies of the search strategies used in the main electronic databases are provided in *Appendix 1*.

The searches were undertaken in June 2011. Searches were performed in MEDLINE; MEDLINE In-Process & Other Non-Indexed Citations; EMBASE; Cochrane Database of Systematic Reviews; CENTRAL; Database of Abstract of Reviews of Effects (DARE); NHS Economic Evaluation Database (EED); HTA databases [NHS Centre for Reviews and Dissemination (CRD)]; Science Citation Index and Conference Proceedings (Web of Science); UK Clinical Research Network (UKCRN) Portfolio Database; Current Controlled Trials; and ClinicalTrials.gov.

The search strategy covered the concepts of metastases, spine and adults (see *Appendix 1*) and was intentionally kept broad to cover natural history, diagnostic and prognostic factors.

In addition, the reference lists of relevant articles were checked and various health services research-related resources were consulted via the internet. These included HTA organisations, guideline-producing bodies, generic research and trials registers. Citation searches of included studies were undertaken using the Web of Science citation search facility. The reference lists of included studies, and relevant review articles were also checked.

### Search restrictions

No study type or publication type restrictions were applied, as all types of study involving all languages were screened for potential inclusion.

### Inclusion of relevant studies

Titles and abstracts of retrieved studies were examined for inclusion by two reviewers independently. Disagreement was resolved by retrieval of the full publication and consensus agreement. The following inclusion and exclusion criteria were used.

### Study design

Randomised controlled trials (RCTs), systematic reviews, prospective or retrospective case series, cohort or case-control studies (case studies were excluded).

### Population

Adult patients with vertebral metastases at risk of developing (or who have developed) MSCC, vertebral collapse or progression of vertebral collapse.

### Intervention/technologies

Diagnostic/prognostic methods, including clinical features and/or imaging technologies [MRI, CT, PET, technetium-99m (<sup>99</sup>Tc<sup>m</sup>) scintigraphy, radiography], and natural history.

### Comparator

None or another diagnostic/prognostic method.

### Outcomes

Spinal cord compression, vertebral compression, vertebral collapse or progression of vertebral collapse.

### Exclusion criteria

- Animal models and post-mortem studies.
- Preclinical and biological studies.
- Editorials, opinions.
- Reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality.
- Studies not in English, French and German.
- Studies where a majority of patients (>50%) are suffering from multiple myeloma.
- Studies predicting overall survival as the only outcome measure.

### Data extraction strategy

The full data were extracted independently by one reviewer using a data extraction form informed by the NHS CRD<sup>105</sup> and previous HTAs involving prognosis (e.g. Sutcliffe *et al.*;<sup>104</sup> see *Appendix 3*). All included studies were reviewed by a second researcher, and any disagreements were resolved by discussion. Further discrepancies were resolved by discussion, with involvement of a third reviewer when necessary. Summary tables were developed that list all clinical assessments, imaging and other technologies that may inform prognosis of metastatic spinal lesions reported in the literature, with details of their prognostic value, where adequate information was available. In view of the early publication date of some included studies, and in the context of a short report, it was not considered feasible to contact authors for data or for clarification. Data have been extracted from relevant copyright figures and used to redraw graphs; as this procedure is not exact these graphs are used for illustrative purposes only.

### Quality assessment strategy

Quality assessment of included studies was informed using the guidelines suggested by Hayden *et al.*<sup>106</sup> as appropriate for prognosis studies (see *Appendix 2*) and modified as necessary according to Sutcliffe *et al.*<sup>104</sup> (further details are provided below and in *Appendix 3*).

Hayden *et al.*<sup>106</sup> appraised how authors of reviews of prognostic studies had assessed study quality and provided recommendations as to the domains that should be included, and also the questions that might contribute to the assessment of each domain. Domains proposed by Hayden *et al.*<sup>106</sup> to assess potential biases in prognostic studies were (1) study population; (2) study attrition; (3) prognostic factor measurement; (4) outcome measurement; (5) confounding measurement and account; and (6) analysis.

Within each of these categories, Hayden *et al.*<sup>106</sup> proposed a series of additional questions to help assess the extent of possible biases. In line with the previous HTA work undertaken by Sutcliffe *et al.*,<sup>104</sup> we have

adapted these questions for the current disease area, the types of studies available, and also to clarify the meaning of each question in the context of the short report. The resulting quality assessment tool is provided in *Appendix 3*. Systematic reviews were quality assessed using an adapted checklist proposed by the NHS CRD<sup>105</sup> (see *Appendix 3*).

In total there were 16 questions; they included an overall question on the conclusion for each domain. Each question was scored as yes (Y), no (N), partly clear (P), unsure (UN) or not applicable (NA). The quality of each study was assessed by at least two of the three members of the research team (PS, MC, DS). Regular discussion meetings were arranged to resolve uncertainty between reviewers who completed the quality assessment. The third team member attended the meetings when agreement could not be reached.

The following section provides a brief summary of issues used to appraise the quality under each of the domains proposed by Hayden *et al.*<sup>106</sup>

### **Study population**

We assessed whether a study reported sufficient information on the principal factors known to affect patient prognosis so that it would be clear to which population the results were applicable.<sup>104</sup>

### **Treatment**

The reporting of the principal treatment and diagnostic or prognostic tool and also the proportion of patients who had had treatment were evaluated.

### **Recruitment dates**

The time period during which patients were recruited was established.

### **Baseline characteristics**

Known prognostic factors were included, for example whether there were differences between studies in terms of the stages of the cancers.

### **Study attrition**

Following preliminary scoping work, it became apparent that many included studies would be retrospective; therefore, the assessment of attrition was likely to be relevant to this short report. The total number of patients from the study population and reasons for patient exclusion were noted.

### **Prognostic factor measurement**

This domain was assessed in terms of whether a well-defined and reproducible method of extraction and measurement was reported. In particular, whether the authors provided a description of the measurement of the factors prognostic of MSCC, vertebral collapse or progression of vertebral collapse.

### **Outcome measurement**

This domain was assessed in terms of whether the outcomes were clearly defined by the authors.

### **Confounding measurements**

This domain was assessed in terms of whether the authors had provided any measurements of potential confounding factors. In particular, reviewers assessed whether bisphosphonates and tamoxifen had been clearly reported in the study population as both influence the rate of bone fracture at sites of metastases, so that if these treatments are not considered in identifying predictors they may confound treatments.

### **Analysis**

This domain was assessed in terms of whether an adequate description of the analysis and sufficient data were provided.

***Methods of analysis/synthesis***

Data were tabulated and discussed in a narrative review. Summary tables for each included paper were provided. Each tumour type was looked at separately.

## Chapter 3 Results

The following section provides a summary of the search results, a quality assessment and a detailed description of the included studies for each cancer group.

### Result of searches

#### Natural history studies

No epidemiological studies were identified that had a primary aim of evaluating the natural history of spinal metastases. In the Discussion section of this report we include an evaluation of what can be inferred about the natural history of spinal metastases from the prognostic studies we identified and which we evaluate in the following section.

#### Number of studies identified

The flow chart outlining the process of identifying relevant literature can be found in *Figure 4*. Following the removal of duplicates, the searches identified 2425 potentially relevant articles. A total of 2089 articles did not meet our inclusion criteria and were removed at title and abstract sift, leaving a total of 336 articles to be further investigated. Of these, 305 were removed at full-paper sift, resulting in 31 articles that met the inclusion criteria. *Appendix 4* lists included papers at full sift.

#### Kappa statistic

A  $\kappa$ -statistic was calculated for the sifting of the 336 articles examined at full text by the two reviewers (PS and MC). *Tables 4* and *5* provide a summary of the  $\kappa$ -statistic calculations. The resulting  $\kappa$  was 0.7033.

#### Number of studies excluded

A list of the 305 articles that were excluded at full paper sift with reasons for exclusion is provided in *Appendix 5*. *Table 6* provides a summary of the main reasons for excluding papers at full-paper sift. The most common reason for exclusion was related to outcome measures.

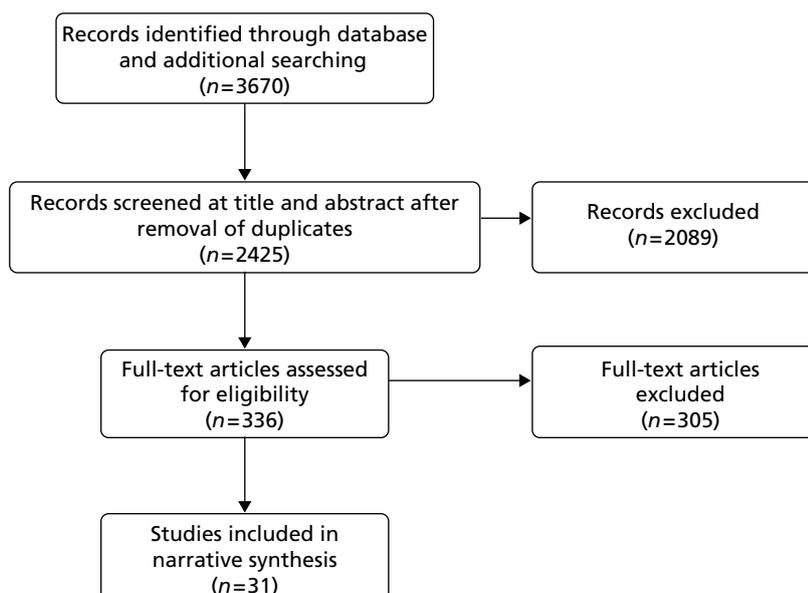


FIGURE 4 Flow diagram.

### Prognostic factors identified

A broad range of factors (93 in total) were reported as significant in prediction of MSCC; vertebral collapse or progression of vertebral collapse were reported across the 31 included studies (Table 7). Many prognostic factors were mentioned by only a small number of studies, or in some cases by a single study. It was not possible to examine the potential issues of publication bias or selective outcome reporting.

Anterior cord compression, back pain, male sex, preoperative chemotherapy, primary breast cancer and thoracic spine involvement were reported in two studies. Furthermore, the most commonly reported factor was related to tumour characteristics and was found to be significant for 11 factors in eight studies,<sup>88,89,109,110,113,117,126,129</sup> however, the definition of tumour characteristics varied between the different studies [e.g. amount of vertebral body occupied by tumour,<sup>88</sup> overall tumour size and pedicle destruction in the thoracolumbar and lumbar spine (T10–L5),<sup>89</sup> tumour size in the thoracic region,<sup>89</sup> blastic-type tumour,<sup>109</sup> lytic-type tumour,<sup>109</sup> tumour pain,<sup>109</sup> favourable tumour histology,<sup>117</sup> time interval from diagnosis of the primary tumour,<sup>113</sup> total involvement of vertebra,<sup>129</sup> tumour involvement of > 50%,<sup>110</sup> undifferentiated tumours<sup>126</sup>].

TABLE 4 Kappa statistic calculations

Category	Observer MC		Total
	+	–	
Observer PS			
+	A = 28	B = 9	A + B = 37
–	C = 11	D = 288	C + D = 299
Total	A + C = 39	B + D = 297	<b>A + B + C + D = 336</b>

TABLE 5 Kappa statistic

Agreement	Expected agreement	Kappa	SE	z	Prob > z
94.05%	79.94%	0.7033	0.0545	12.90	0.0000
SE, standard error.					

TABLE 6 Summary of reasons for exclusion at full sift (n=305)

Reasons for exclusion	n
Outcome measures did not meet inclusion criteria	266
Review	22
Abstract	6
Case reports	6
Editorial	3
Animal study	1
Letter	1

**TABLE 7** List of 93 prognostic factors reported as significant in the 31 included studies

Age	Motor deficit
Age <60 years	MRI multiple bone metastases
Alkaline phosphatase	Neurological examination (abnormal neurological examination)
Altered sensation	Neurological abnormalities
Amount of vertebral body occupied by tumour	No history of EGFR TKI therapy
Anterior cord compression <sup>a</sup>	Number of spinal metastases
Back pain <sup>a</sup>	Objective weakness
Bladder and bowel dysfunction	Older age
Blastic-type tumour	Pain (tumour, mechanical, radicular)
Bone metastases diagnosed > 1 year earlier	Paraparesis
Bone metastases previously diagnosed	Paraesthesia
Bone metastasis	Progesterone receptor status
Bone only	Positive vertebral plain films
Bone scan extent of disease score	Posterior vertebral heights
Cervical level	Preoperative chemotherapy <sup>a</sup>
Complaint of inability to walk	Preoperative radiation
Complete resection	Presence of back pain
Costovertebral joint destruction	Primary breast cancer <sup>a</sup>
Cross-sectional area within the vertebral body	Prostatic acid phosphatase
CT appearance	Performance status of 2–3
Duration of hormonal therapy before study entry	PSA
ECOG status 2/3, vertebral body fracture on most recent plain radiograph	Radicular pain
Elective surgery	Radicular weakness
Ever smoked	Sensory deficits
Extraspinal metastases	Sensory level or dermatomal loss on examination
Favourable tumour histology	Short PSA doubling time < 3 months
Focal radiographic abnormalities	Soloway grade 4
Gleason score	Stage IV cancer at initial diagnosis
Good general health status	Symmetrical fractures with fragments
Haemoglobin concentration	Thoracic spine involvement <sup>a</sup>
High PSA level at the time of initial MRI	Time interval from the diagnosis of the primary tumour
Histology of non-adenocarcinoma	Total involvement of vertebra
History of local pain	Tumour size and pedicle destruction in the thoracolumbar and lumbar spine (T10–L5)
History of radicular pain	Tumour size in the thoracic region
History of radiotherapy before chemotherapy	Tumour involvement of > 50%
History of weakness	Tumour size
Increased deep tendon reflexes	Undifferentiated tumours
Increasing number of spinal levels	Upper lumbar
Known bone metastases spinal level	Urinary and bowel symptoms
LBC/BMI	Vertebrae with > 80% body infiltration
Lesion location	Vertebral axial displacement
Lesions located between T10 and sacrum	Vertebral bulge
Log transformed PSA	Vertebral compression fracture on spine radiograph
Low number of affected vertebral bodies	Visceral metastases
Lytic lesions	Weakness or difficulty in walking
Lytic-type tumour	
Male sex <sup>a</sup>	
Metastatic disease at initial diagnosis	

ECOG, Eastern Cooperative Oncology Group; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; LBC/BMI, load bearing capacity/body mass index (kg/m<sup>2</sup>).

<sup>a</sup> Two studies reported this factor.

## Description of included studies

The following section summarises the main characteristics of the 30 included studies<sup>24,88,89,107–133</sup> which are listed in *Tables 8* and *9*. (The systematic review is to be discussed separately.)

A large proportion of the included studies evaluated retrospective data ( $n = 17$ ); however, other study designs were also reported: (1) prospective study ( $n = 11$ ); (2) case series ( $n = 1$ ); and (3) a review and modified Delphi technique ( $n = 1$ ). The reviewers reported difficulties in calculating the number of participants who were selected and analysed. The approximate overall number of participants selected in the included studies was 7888 (four studies did not provide this information<sup>110,120,121,127</sup>) and 5782 were analysed (three studies did not provide this information<sup>108,110,126</sup>). The analysed sample sizes ranged from 41 to 859. *Table 8* shows the range of male and female participants involved in these studies. The ranges of ages across studies were 7–92 years.

The types of cancers reported included lung alone ( $n = 3$ ); prostate alone ( $n = 6$ ); breast alone ( $n = 7$ ); mixed cancers ( $n = 13$ ); and unclear ( $n = 1$ ). There was often limited reporting of the mean and median ages. Use of a broad range of technologies was reported. These included CT, bone scanning, bone scintigraphy, CSF examination, chest CT, liver ultrasonography, chest radiography, intraoperative recording, isotope bone scanning, isotope bone scintigraphy, isotope tomography, liver function tests, MRI, myelography, panmyelography, patient records, X-rays, sagittal T1- and/or T2-weighted images of the spine with selected axial images, and scintigraphy images. Some technologies were unclear. Eleven studies<sup>24,88,107,111,115,117,119,125,129–131</sup> reported on medication use; for example, three studies<sup>88,125,130</sup> reported the use of bisphosphonates. There was a lack of clarity about the spinal level of involvement in 12 included studies.<sup>24,89,110,114,122,123,125,127,130,131,133</sup>

## Quality assessment

Each study was evaluated according to six subheadings (study population, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account, and analysis). An overall quality score was not provided for each paper. Rather the quality assessment tool enabled the two reviewers to identify factors for consideration when interpreting the findings from each study. *Appendix 8, Table 37* provides a summary of the 16 questions considered under the six subheadings.

### Study population

The majority of the 30 included studies<sup>24,88,89,107–133</sup> (the review by Loblaw *et al.*<sup>62</sup> is discussed separately) either adequately reported ( $n = 17$ <sup>24,109,112–116,120,121,123–126,130–133</sup>) or partly reported ( $n = 11$ <sup>88,89,107,108,111,117–119,122,128,129</sup>) the inclusion and exclusion criteria (including treatment, start/finish date, recruitment). However, two studies<sup>110,127</sup> did not provide sufficient information on inclusion and exclusion criteria.<sup>110,127</sup> The baseline study sample (i.e. individuals entering the study) was adequately described for key characteristics ( $n = 17$ <sup>88,89,107,108,115,116,119–121,123,125,126,128,130–133</sup>) or partly described ( $n = 8$ <sup>24,111–114,117,122,124</sup>) among the included papers. A further five studies<sup>109,110,118,127,129</sup> provided limited information on the characteristics of the sample (e.g. sampling frame). Overall, in 11 studies<sup>115,116,120,121,123,125,126,130–133</sup> the population of interest was sufficiently represented on key characteristics to limit potential bias, with partial bias in a further 17 studies.<sup>24,88,89,109,111–114,117–119,122,124,128,129</sup> Two studies<sup>110,127</sup> provided such limited information on overall study population that the potential for bias could not be assessed.

### Study attrition

The majority of studies ( $n = 27$ <sup>24,88,89,107,108,111–133</sup>) reported exclusions due to missing data at baseline, although two studies did not ( $n = 2$ <sup>109,110</sup>), and in one case the reviewers were unsure.<sup>127</sup> Compared with missing data reported at baseline, fewer studies reported ( $n = 22$ <sup>24,88,89,107,111–116,119–126,129–133</sup>) or partly reported ( $n = 1$ <sup>122</sup>) exclusions at follow-up. Some studies did not provide any details about exclusions from

trials because of missing data at follow-up ( $n = 3^{108-110}$ ) and this was not considered appropriate in two studies<sup>117,118</sup> or the reviewers were unsure.<sup>127,128</sup> None of the studies reported a clear statement as to the possible effect on the results from missing data. Overall, study quality related to the loss to follow-up was considered adequate in the majority of studies ( $n = 23^{88,89,107,111-121,123-126,129-133}$ ), partly adequate in four studies ( $n = 4^{24,108,122,128}$ ), not adequate ( $n = 2^{109,110}$ ), or reviewers were unsure ( $n = 1^{127}$ ). The quality of reporting the study attrition was adequate and many studies provided details about exclusions for missing data at baseline and follow-up.

### Prognostic factor measurement

A clear definition of prognostic factors was provided (e.g. extraction method, measurement described) in the majority of studies ( $n = 22^{88,89,107,108,112,116,118,133}$ ). For eight studies the definition of prognostic factors was only partly reported.<sup>24,109-111,113-115,117</sup> There was excellent reporting of the specified instrument and personnel for measurement of predictive factors in 27 studies.<sup>88,89,107-109,111-117,119-133</sup> In three studies, this was only partly reported.<sup>24,110,118</sup> Continuous variables or appropriate cut-off points were reported in two studies ( $n = 2^{88,129}$ ) and partly reported in 14.<sup>89,109,110,115,117,120-123,126,130-133</sup> Three studies did not provide sufficient information about the continuous variables or appropriate cut-off points.<sup>24,118,119</sup> In six studies<sup>107,108,124,125,127,128</sup> there was a lack of clarity about continuous variables or appropriate cut-off points, and this was not applicable in five studies.<sup>111-114,116</sup> There was a lack of reporting of blinding across the majority of studies ( $n = 29^{88,89,107-123,125-133}$ ) or reporting of blinding was unclear ( $n = 1^{124}$ ). Overall, in five studies<sup>88,120,125,129,131</sup> measurement of prognostic factors of interest was sufficient to limit bias. In 25 studies<sup>24,89,107-119,121-124,126-128,130-133</sup> the prognostic factor(s) of interest were only 'partly' measured to limited potential bias. Therefore, the majority of included studies provided incomplete reporting of prognostic factor measurement.

### Outcome measurement

A large number of studies provided an adequate ( $n = 20^{88,89,107,108,112,115,116,118,120-123,125-133}$ ) or partly adequate ( $n = 10^{24,109-111,113-115,117,119,124}$ ) definition of the outcomes measured (SCC, vertebral compression, vertebral collapse or progression of vertebral collapse).

### Confounding measurement and account

Four studies<sup>88,107,109,123</sup> adequately met and six studies<sup>115,117,120,125,130,131</sup> partly met the criteria for whether or not confounding factors (e.g. bisphosphonate use) had appropriately been accounted for. A further 18 studies<sup>24,89,108,110-114,116,118,121,122,124,126-128,132,133</sup> provided insufficient information or the information was unclear ( $n = 2^{119,129}$ ). In general, there was poor reporting of the possible confounding measures and how they were accounted for.

### Analysis

There was sufficient presentation of data to assess the adequacy of analysis in 19 studies<sup>24,88,107-109,112,115-117,119-123,125,128,131-133</sup> and to partly assess the adequacy of analysis in 11 studies.<sup>89,110,111,113,114,118,124,126,127,129,130</sup> For a large proportion of the included studies the selected statistical analysis was considered adequate ( $n = 22^{24,88,89,107-109,112,113,115,117,120-128,131-133}$ ) or partly adequate ( $n = 5^{110,114,116,129,130}$ ) for the design of the study. Statistical analysis was not considered adequate in three studies.<sup>111,118,119</sup> Overall, the quality of the statistical analysis was considered appropriate in the majority of included studies.

Table 10 provides a summary of the summed quality assessment for the overall questions (see Appendix 6 – shaded boxes). Five studies were considered to be of high quality<sup>88,120,123,125,131</sup> as they scored 'yes' on five of the six overall quality assessment questions. Five studies were considered to be of poor quality<sup>24,110,111,114,119</sup> as they scored 'yes' on one or none of the six overall quality assessment questions. Twenty studies<sup>89,107-109,112,113,115-118,121,122,124,126,127-130,132,133</sup> were considered to be of intermediate quality because they scored 'yes' on between two and four of the six overall quality assessment questions.

TABLE 8 Summary of main sample characteristics of included studies (n = 30)

Author, year	Sample selected (n)	Sample analysed (n)	Study design	Mean age (years)	Median age (years)	Range age (years)	Male (n)	Female (n)
Bayley 2001 <sup>107</sup>	68	68	Prospective study	NR	71	50–84	68	0
Bernat 1983 <sup>108</sup>	133	Unclear	Retrospective data comparison study	NR	61	7–85	77	56
Chaichana 2009 <sup>109</sup>	216	162	Retrospective review	58	NR	NR	95	67
Fisher 2010 <sup>110</sup>	NA	NA	Modified Delphi technique	NA	NA	NA	NA	NA
Goldman 1989 <sup>111</sup>	616	610	Retrospective analysis of records	Unclear	Unclear	Unclear	Unclear	Unclear
Harrison 1985 <sup>112</sup>	78	78	Retrospective case series	51	51	22–75	0	78
Helweg-Larsen 2000 <sup>113</sup>	153	153	Prospective study	NR	Females = 64 (36–88) years; males = 71 (26–92) years	26–92	78	75
Helweg-Larsen 1995 <sup>114</sup>	107	107	Prospective study	NR	66	34–91	53	54
Huddart 1997 <sup>115</sup>	69	69	Retrospective analysis of patient records	NR	NR	NR	NR	NR
Husband 2001 <sup>116</sup>	280	201	Prospective study	NR	67	23–89	158	122
Klekamp 1998 <sup>117</sup>	101	106	Prospective study	62	NR	NR	NR	NR
Kuban 1986 <sup>118</sup>	41	41	Case series	NR	68	50–90	611	0
Levack 2002 <sup>119</sup>	319	319	Prospective observational study	NR	65	NR	203	116
Lu 1998 <sup>120</sup>	Unclear	93	Retrospective analysis/study	NR	52.9	29.8–77.3	0	93
Lu 2005 <sup>121</sup>	Unclear	134	Prospective study	NR	61.5	30.9–84.8	NR	NR

Author, year	Sample selected (n)	Sample analysed (n)	Study design	Mean age (years)	Median age (years)	Range age (years)	Male (n)	Female (n)
McCloskey 1993 <sup>122</sup>	100 controls and 163 women	100 controls and 163 women	Prospective study criteria	59	NR	30–75	0	263
Oka 2006 <sup>123</sup>	695	695	Retrospective cohort study	53.1	NR	24–88	4	691
Plunkett 2000 <sup>24</sup>	1437	859	Retrospective analysis/study	Unclear	Unclear	Unclear	Unclear	Unclear
Rose 2009 <sup>88</sup>	62	62	Prospective study	62	Unclear	Unclear	38	24
Roth 2004 <sup>124</sup>	560	72	Retrospective study design	NR	NR	NR	34	38
Sekine 2009 <sup>125</sup>	642	642	Retrospective study	NR	Patients without SREs = 61 years; Patients with SREs = 59.5 years	Patients without SREs = 24–86 years; Patients with SREs = 26–77 years	402	240
Shah 2003 <sup>126</sup>	213	Unclear	Retrospective cohort study	58	NR	20–90	26	27
Snyder 2005 <sup>127</sup>	Unclear	106	Prospective study	NR	NR	NR	0	106
Snyder 2009 <sup>128</sup>	94	94	Prospective observational	55	NR	NR	0	94
Soerjbalie-Maikoe 2004 <sup>129</sup>	84	84	Retrospective observational	NR	NR	NR	84	0
Sun 2011 <sup>130</sup>	1166	273	Retrospective observational	NR	NR	Unclear	60.1%	39.9%
Talcott 1999 <sup>131</sup>	258	258	Retrospective cohort	NR	56.5	18–83	39%	61%
Taneichi 1997 <sup>89</sup>	53	53	Retrospective study	59.7	NR	43–80	NR	NR
Venkitaraman 2007 <sup>132</sup>	150	150	Retrospective study	NR	69	50–88	150	0
Venkitaraman 2010 <sup>133</sup>	130	130	Retrospective study	NR	70	50–88	130	0

NA, not applicable; NR, not reported.

TABLE 9 Summary of main cancer, intervention, treatment and spinal level characteristics of included studies (n = 30)

Author, year	Cancers	Interventions	Medications	Spinal level				Other
				Cervical	Thoracic	Lumbar		
Bayley 2001 <sup>107</sup>	Prostate	Bone scans, radiographs, sagittal T1-weighted spin-echo sequence	Hormone therapy, analgesics, acetaminophen, non-steroidal anti-inflammatory medications, narcotic analgesics	3	20	8		Clinically occult SAS compression/SCC was identified in 22 patients. SAS compression alone in 12 patients and frank compression of the spinal cord or cauda equina in 10 patients. Nine of 22 patients had SAS compression/SCC at two discontinuous vertebral levels
Bernat 1983 <sup>108</sup>	Lung, breast, prostate, lymphoma, colon/rectal, melanoma, kidney and ureter, bladder, other, unknown	CSF examination, radiography, vertebral radiographs, bone scans, and myelograms	NR	9% of 47	50% of 47 (23 or 24)	Sacral 31% of 47		15 cauda equina
Chaichana 2009 <sup>109</sup>	Lung, breast, prostate, renal, haematopoietic, thyroid, gastrointestinal, melanoma and non-renal genitourinary system	MRI, CT, intraoperative recordings	NR	35	114	49		Cervicothoracic 22; thoracolumbar 24
Fisher 2010 <sup>110</sup>	Unclear	Unclear	NR	Unclear	Unclear	Unclear		Unclear
Goldman 1989 <sup>111</sup>	Small cell lung cancer	Laminectomy and decompression of spinal cord, chest radiography, liver function tests, liver ultrasound scan, isotope bone scan and isotope or CT	Dexamethasone, chemotherapy with doxorubicin (Adriamycin®) and methotrexate	17	61	Unclear		Thoracic or thoracic and lumbar spine in 61 cases and lumbosacral spine alone in 43 cases

Author, year	Cancers	Interventions	Medications	Spinal level			
				Cervical	Thoracic	Lumbar	Other
Harrison 1985 <sup>112</sup>	Breast	Patient records, prior bone scans, skeletal radiographs, myelography, panmyelography	NR	M+ 17/42 M- 11/36	M+ 33/42 M- 15/36	M+ 33/42 M- 12/36	M- bone 19/36
Helweg-Larsen 2000 <sup>113</sup>	Breast carcinoma, prostatic carcinoma, NSCLC, small cell lung cancer, solid tumours	Myelographic evidence, MRI scanning	NR	7 (4%) cases	102 (67%) cases	0	Lumbosacral in 44 (29%) cases
Helweg-Larsen 1995 <sup>114</sup>	Breast, adenocarcinoma of the prostate, tumour of the lung and other solid tumours	Myelography alone or myelography combined with postmyelography, CT	NR	Unclear	Unclear	Unclear	Unclear
Huddart 1997 <sup>115</sup>	Prostate	Myelography with or without MRI/CT; plain radiography	High-dose steroids, hormone therapy if not hormone resistant, radiotherapy	5	57	20	
Husband 2001 <sup>116</sup>	Breast, prostate, bronchus, haematological, urinary tract, gastrointestinal tract, unknown primary, other	Plain radiographs of the whole spine	NR	15	160	71	
Kiekamp 1998 <sup>117</sup>	Breast, prostate, thyroid, kidney, unknown primary tumour, lung, colon, melanoma, urogenital tract, pleura mesothelioma, teratoma, gallbladder	Plain radiographs, CT, myelography, MRI	'Adjuvant' therapy administered postoperatively to 60% (radiation ± hormone therapy/chemotherapy)	12	62	24	
Kuban 1986 <sup>118</sup>	Biopsy-proved adenocarcinoma of the prostate	Radioisotopic bone scans, plain films and myelograms	NR	12	21	14	Cervical and thoracic 1 (2.4%); cervicothoracic junction 1 (2.4%); thoracic and lumbar 2 (4.9%)

continued

TABLE 9 Summary of main cancer, intervention, treatment and spinal level characteristics of included studies (n = 30) (continued)

Author, year	Cancers	Interventions	Medications	Spinal level			
				Cervical	Thoracic	Lumbar	Other
Levack 2002 <sup>119</sup>	Lung, prostate and breast, gastrointestinal, haematological origin (myeloma, lymphoma, chronic lymphatic leukaemia). In 23 cases (7%) the site of primary tumour was never identified	MRI, plain films, isotope bone scintigraphy	Strong opioids	7%	68%	21%	Sacral 4%
Lu 1998 <sup>120</sup>	Breast	Spinal CT, MRI, myelography and spine radiography	NR	6%	67%	55%	Sacral 3%
Lu 2005 <sup>121</sup>	Breast, lung, prostate, non-Hodgkin's lymphoma, multiple myeloma, others	MRI of the spine, sagittal T1 - and/or T2-weighted images of the spine with selected axial images	NR	6	64	30	Sacral 6%
McCloskey 1993 <sup>122</sup>	Breast	Radiographs	NR	Unclear	Unclear	Unclear	Unclear
Oka 2006 <sup>123</sup>	Breast	Bone scintigraphy, chest radiography, chest CT, liver ultrasonography, abdominal CT, cranial CT or MRI (or any combination thereof)	NR	Unclear	Unclear	Unclear	Unclear
Plunkett 2000 <sup>24</sup>	Breast	Bone scans, radiographs, histology	Endocrine therapy	Unclear	Unclear	Unclear	Unclear
Rose 2009 <sup>88</sup>	Renal cell, melanoma, prostate, sarcoma, colorectal, cholangiocarcinoma, thyroid, NSCLC, breast, other	Spinal MRI or CT, myelography	Bisphosphonate therapy, narcotics	6	47	18	46 sites were lytic (65%), 13 were sclerotic (18%) and 12 were mixed (17%)

Author, year	Cancers	Interventions	Medications	Spinal level			
				Cervical	Thoracic	Lumbar	Other
Roth 2004 <sup>124</sup>	Breast, lung, colon, prostate, lymphoma multiple myeloma, renal, other, unknown	CT	NR	0	48	44	0
Sekine 2009 <sup>125</sup>	Advanced NSCLC	Unclear	Zoledronic acid (bisphosphonates)	Unclear	Unclear	Unclear	Unclear
Shah 2003 <sup>126</sup>	Breast, lung, prostate, renal, undifferentiated, others	MRI	NR	6	16	16	Whole spine 79; thoracolumbar 39; cervicothoracic 8
Snyder 2005 <sup>127</sup>	Metastatic breast cancer to the spine	Transaxial CT	NR	Unclear	Unclear	Unclear	Unclear
Snyder 2009 <sup>128</sup>	Breast	Axial CT	NR	Unclear	Unclear	Unclear	Unclear
Soergjbalie-Maikoe 2004 <sup>129</sup>	Prostate	Bone scintigraphy, scintigraphy images	Hormone therapy, estramustine (Estracyt®; Pharmacia)	2	14	6	
Sun 2011 <sup>130</sup>	NSCLC	Unclear	Bisphosphonates: pamidronate, zoledronic acid	Unclear	Unclear	Unclear	Unclear
Talcott 1999 <sup>131</sup>	Breast, NSCLC, prostate, sarcoma, other	CT, myelography, MRI	Palliative radiotherapy, prior hormonal and chemotherapies	Unclear	Unclear	Unclear	Unclear
Taneichi 1997 <sup>89</sup>	Breast, lung, prostate, renal, hepatocellular, gastric, colon, malignant meningioma, malignant fibrous histiocytoma, rhabdomyosarcoma, leiomyosarcoma, malignant lymphoma, ureter cancer, adrenal cancer, unknown	CT of the spine	NR	Unclear	Unclear	Unclear	Unclear
Venkitaraman 2007 <sup>132</sup>	Prostate	MRI	NR	Unclear	20	21	Unclear
Venkitaraman 2010 <sup>133</sup>	Prostate	MRI	NR	Unclear	Unclear	Unclear	Unclear

M+, presence of distant metastases; M-, absence of distant metastases; NR, not reported; SAS, subarachnoid space.

**TABLE 10** Sum of quality assessments based on overall questions for the six subheadings

Author, year	Yes	Partly	No	Unsure	NA
Lu 1998 <sup>120</sup>	5	1	0	0	0
Oka 2006 <sup>123</sup>	5	1	0	0	0
Rose 2009 <sup>88</sup>	5	1	0	0	0
Sekine 2009 <sup>125</sup>	5	1	0	0	0
Talcott 1999 <sup>131</sup>	5	1	0	0	0
Bayley 2001 <sup>107</sup>	4	2	0	0	0
Lu 2005 <sup>121</sup>	4	1	1	0	0
Shah 2003 <sup>126</sup>	4	1	1	0	0
Venkitaraman 2007 <sup>132</sup>	4	1	1	0	0
Venkitaraman 2010 <sup>133</sup>	4	1	1	0	0
Harrison 1985 <sup>112</sup>	3	2	1	0	0
Huddart 1997 <sup>115</sup>	3	3	0	0	0
Husband 2001 <sup>116</sup>	3	2	1	0	0
Soerdjbalie-Maikoe 2004 <sup>129</sup>	3	2	0	1	0
Sun 2011 <sup>130</sup>	3	3	0	0	0
Taneichi 1997 <sup>89</sup>	3	2	1	0	0
Bernat 1983 <sup>108</sup>	2	3	1	0	0
Chaichana 2009 <sup>109</sup>	2	3	1	0	0
Helweg-Larsen 2000 <sup>113</sup>	2	3	1	0	0
Klekamp 1998 <sup>117</sup>	2	4	0	0	0
Kuban 1986 <sup>118</sup>	2	2	2	0	0
McCloskey 1993 <sup>122</sup>	2	3	1	0	0
Roth 2004 <sup>124</sup>	2	3	1	0	0
Snyder 2005 <sup>127</sup>	2	1	2	1	0
Snyder 2009 <sup>128</sup>	2	3	1	0	0
Goldman 1989 <sup>111</sup>	1	3	2	0	0
Helweg-Larsen 1995 <sup>114</sup>	1	4	1	0	0
Levack 2002 <sup>119</sup>	1	3	1	1	0
Plunkett 2000 <sup>24</sup>	1	4	1	0	0
Fisher 2010 <sup>110</sup>	0	3	3	0	0

NA, not applicable.

## Summary of overall quality assessment

This section has shown that the included studies varied in terms of quality on ratings of study population, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account, and analysis. Study populations were adequately reported although none of the included studies provided a statement of the possible effect on the results of missing data. Loss to follow-up and study attrition information reported were considered adequate in the majority of studies but for a large number of studies ratings for the measurement of prognostic factors of interest were considered only 'partly' adequate to limit potential bias. None of the included studies provided information about blinding of investigators (e.g. clinical outcomes assessors), representing a considerable weakness in methodology. A large number of studies provided a clear definition of the outcome, although there was a lack of consistency in the type and definitions of outcomes reported. There was poor reporting of possible confounding factors (e.g. bisphosphonate use) and, when they were reported, how confounders were accounted for. The quality of the statistical analysis was considered appropriate in the majority of included studies.

## Summary of systematic review evidence

The only review included in the current short report was undertaken by Loblaw *et al.*<sup>62</sup> The Critical Appraisal Skills Programme (CASP) systematic review checklist<sup>134</sup> was used to critically appraise the quality of the review (see *Appendix 6* for full details). In summary, the review aimed to address a large number of questions, which resulted in a broad range of study designs being included. It was difficult to determine whether all the included studies met the authors' inclusion criteria. No quality assessment was undertaken of the included papers and data from the studies were not clearly displayed to allow a clear comparison. MRI was the preferred imaging technique and conclusions were proposed that treatment for patients with MSCC should consider pretreatment ambulatory status, comorbidities, technical surgical factors, the presence of bony compression and spinal instability, potential surgical complications, potential radiotherapy reactions and patient preferences. Given the limited discussion of the populations in each included study and the lack of quality assessment, it is difficult to draw strong conclusions as to the application of these findings. Although the review discussed issues related to adverse events, there was a lack of consideration of the costs of treatment diagnosis and management of malignant extradural SCC, and the consequential outcomes of false-positive and false-negative predictions or diagnoses.

## Data synthesis

The heterogeneous nature of the studies precluded the use of meta-analysis. One of the main sources of heterogeneity was in the measures of outcome, as is commonly found.<sup>135</sup>

## General considerations

The primary aim of many of the included studies was to identify prognostic factors for survival; the analysis of influential factors for intermediate outcomes, such as SCC or vertebral collapse, was often an incidental objective.

A large number of included studies enrolled patients who had different primary tumours; more than five types of cancer were included in some studies. Several of these mixed cancer studies (e.g. breast, prostate, colorectal, etc.) indicate that the type of primary tumour might itself be a prognostic factor for SCC and/or vertebral collapse. As the factors influencing development of spinal metastases, and of the

unwanted outcomes that develop from them, can be expected to differ between various primary cancers, the interpretation of results from these 'mixed tumour' studies is problematic. The relative importance of identified prognostic factors may reflect only that the characteristics of the most frequent cancers in the sample analysed are potentially subject to both lead time and length time bias because of differential rates of diagnosis, progression and growth of different cancers.

## Studies in which the whole sample population was diagnosed with prostate cancer

*Bayley et al. (2001)*<sup>107</sup>

### Relevant aim

The aim of this study was to identify risk factors for occult subarachnoid space (SAS) compression or SCC in patients judged to be at risk according to clinical, radiography or bone scan parameters. Occult SAS compression or SCC was established using MRI.

### Design and method

This study investigated outpatients with metastatic prostate cancer at a single Canadian hospital ( $n = 68$ ). All had previous evidence of spinal metastases, but had no neurological indication or signs of SAS compression or SCC; 64 out of 68 had received continuous hormone therapy and 61 had hormone-refractory disease (indicated by rising PSA levels). The authors described the sample as cross-sectional; however, as patients were approached at the physicians' discretion, the sample was probably one of convenience. All patients were examined by bone scintigraphy within 1 week of study entry. Follow-up ranged from 1 to 47 months (median 8 months). Thirty patients underwent plain radiographic examination: 22 for back pain and eight at the physicians' discretion. The timing of radiography was not reported.

### Results

MRI was used to identify patients with occult SAS compression/SCC; the timing of the MRI was not stated. The criteria used to establish occult compression are shown in *Box 1*.

Occult compression was identified in 22 out of 68 patients; all cases were due to direct extension of tumour from the vertebral body. Ten patients had frank compression of the cauda equina or the spinal cord, and 12 of the SAS alone. Nine of 22 had compression at two separate vertebral levels. The disposition of compressions was cervical in three patients, thoracic in 20 patients and lumbar in eight patients. Plain radiographs were not informative for detection of occult compression.

Clinically evident SCC developed during follow-up in 4 of the 46 patients in whom no occult compression was apparent at MRI (the authors quote actuarial risk at 1 and 2 years using Kaplan–Meier analysis; however, with only four events it is unlikely that this analysis is meaningful). The 22 patients with occult

#### **BOX 1** Summary of the MRI criteria used to establish occult compression

##### **Criteria used for MRI-established occult compression of the subarachnoid space or spinal cord**

- Impingement of the SAS by metastatic tumour involving vertebrae
- Distortion or collapse of vertebrae with impingement of the SAS by bone fragments
- Frank compression of spinal cord or cauda equina by either of the above

compression were treated with appropriate radiotherapy; the post-MRI occurrence of neurological compression in these 22 patients was not reported.

Logistic regression was used to identify risk factors for occult SAS compression/SCC. Of the candidate factors examined in univariate regression, haemoglobin, duration of continuous hormone therapy before study entry and bone scan extent of disease (EOD) score (extent of disease according to number of bone metastases according to the Soloway *et al.* method<sup>136</sup>) were significantly associated with occult compression ( $p = 0.04$ ,  $p = 0.03$  and  $p = 0.015$ , respectively), whereas no association was found for Gleason score, alkaline phosphatase, PSA, prostatic acid phosphatase, presence of back pain or use of narcotic analgesics. In multivariate regression, only EOD and duration of hormone therapy were significantly associated with occult compression ( $p = 0.02$  and  $p = 0.04$ , respectively).

### Author conclusion

Heavy load of spinal metastases, as indicated by scintigraphy, and duration of continuous treatment with hormone therapy are predictive factors for presence of occult SAS compression or SCC. Such patients, although lacking neurological abnormality and signs of compression, would probably benefit from early MRI for occult compression, which if positive for compression should be followed by radiotherapy treatment before the development of symptomatic compression.

### Reviewer conclusions

Patients with a high-risk bone scan may benefit from MRI of the spine aimed at early detection and treatment of occult SAS compression/SCC. The reported results are as would be intuitively expected, so the more spinal metastases that are present and the longer a patient is at risk, the greater the chance of clinically occult SCC. The time a patient is on hormone therapy is a proxy for how long he or she is at risk of occult compression. The quantitative estimates of risk probably do not add much value to this conclusion other than suggesting that spinal load is more influential than time at risk; it can be hypothesised that time at risk interacting with the individual patient's propensity for metastases to reach the spine will govern the spinal load. What this study does not address is the probability that occult SCC becomes patently symptomatic SCC, and how long after occult SCC is detected this occurs.

### Huddart *et al.* (1997)<sup>115</sup>

#### Relevant aim

The aim of this study was to identify risk factors for recurrence of SCC at an old or new site in prostate cancer patients with previous diagnosis of SCC.

#### Design and method

The main focus of this retrospective study was to identify prognostic factors for survival and for good response to therapy, after diagnosis of SCC in prostate cancer patients with SCC treated at the Royal Marsden Hospital between 1984 and 1992. Sixty-nine patients with SCC were identified from a review of medical records of (1) participants in a previous study of hormone-resistant prostate cancer; (2) those who had undergone spinal MRI; and (3) those who had undergone spinal irradiation. The total number of records reviewed was not stated. SCC was established by myelography or MRI in 66 patients and from plain radiographs in three patients. No information was provided about patients with negative assessments for suspected SCC. Thirteen of 69 patients had SCC at presentation; the median time from diagnosis of prostate cancer to detection of SCC in the remaining 56 patients was 586 days. Most patients ( $n = 52$ ) had received hormone therapy. Evidence of vertebral collapse at the site of cord compression was present in 24 patients. MRI identified more patients with multiple sites of SCC than did myelography. Fifty-seven patients were given radiotherapy after SCC diagnosis and 13 received surgery.

#### Results

Neurological relapse (from various causes including 13 second occurrences of SCC) was observed in 20 out of 69 patients. A second SCC at the same site occurred in eight patients and at a new site in five patients.

None of the following potentially predictive factors were associated with the occurrence of neurological relapse: presenting characteristics; haemoglobin; the number of lesions evident by bone scan; hormonal status or method of diagnosis; radiation dose for first SCC. The paper provides a Kaplan–Meier analysis of the cumulative probability of neurological relapse. The methodology used for this was unclear and no ‘at risk’ table was provided; one interpretation is that all 69 patients were included and many were censored at time of death if no relapse had occurred.

### Author conclusions

No significant factor was identified for risk of future relapse. An early improvement in motor power is a strong predictor of subsequent functional improvement. MRI detects additional sites of asymptomatic SCC which makes it the investigation of choice.

### Reviewer conclusions

No significant predictive factor was identified for risk of future relapse (i.e. second SCC) but the sample was so small that there was little power in the analysis. The actuarial analysis of time to relapse was difficult to interpret because of a lack of methodological detail and ambiguity about the equivalence of SCC and neurological relapse.

### *Kuban et al. (1986)*<sup>118</sup>

#### Relevant aim

The aim was to determine and analyse, with reference to primary tumour stage and differentiation at diagnosis, the interval between primary diagnosis and SCC, the interval between radiographic evidence of bony metastasis and cord impingement, and the survival period after spinal cord compromise.

#### Design and method

Forty-one patients with biopsy-proven adenocarcinoma of the prostate who presented with MSCC, or who subsequently developed MSCC, were identified from a total of 611 prostate cancer patients seen at a single centre over a period from 1975 to 1983. Mean and median age was 68 (range 50–90) years. Primary tumours were classified according to a modified Gleason system and patients were classified according to the Fowler–Whitmore staging system. SCC was established by myelography ( $n = 36$ ) and by clinical findings ( $n = 5$ ), and by bone scan- or plain radiography-detected lesions at the level of compression. Of the 41 patients with SCC, 3, 11 and 27 were classified as stages A, B and C at the time of diagnosis of the primary tumour. The spinal locations of the SCCs were reported as follows: cervical, two patients; thoracic, 21 patients; lumbar, 14 patients; cervical and thoracic, one patient; cervicothoracic junction, one patient; thoracic and lumbar, two patients.

#### Results

The median time between primary diagnosis and SCC was 24 months, with 5 out of 41 patients presenting with SCC; there was no clear relationship with tumour grade at diagnosis. The median time from detection of bone metastases to SCC was 15.5 months, with 6 out of 41 patients having bone metastases first observed at the diagnosis of SCC. A second SCC developed in six patients during follow-up, at 6, 6, 8, 19, 21 or 23 months after the first SCC.

#### Author conclusions

Overall, tumour stage and differentiation were poor predictors of prognosis once a diagnosis of cord compression was established. MSCC secondary to adenocarcinoma of the prostate most frequently occurs in a thoracic location in patients with poorly differentiated disease at diagnosis. The mechanism of cord involvement appears to begin with osseous vertebral metastasis, progressing to extradural compromise with a median interval that is independent of tumour grade. The prognosis following spinal cord involvement remains dismal in the majority of cases.

## Reviewer conclusions

This paper did not look at predictive factors of SCC other than tumour grade at diagnosis of primary tumour and this had no detectably significant influence on median time to SCC detection. Kaplan–Meier analysis was not used.

## Soerdjbalie-Maikoe et al. (2004)<sup>129</sup>

### Relevant aim

The study aimed to determine if high-resolution bone scintigraphy at the time of diagnosis of hormone-refractory metastatic prostate cancer has added prognostic value compared with prevailing PSA concentrations and tumour staging (Gleason grading) for SCC-free survival. The authors were also interested in prognosis for overall survival.

### Design and method

This was a retrospective study of 84 patients with histologically confirmed diagnosis of hormone-resistant metastatic prostate cancer (treatments had included orchidectomy, luteinising hormone-releasing hormone agonist or antiandrogens). Hormone treatment was stopped for 23 patients. Patients were followed up till death. Tumours were assessed according to Gleason grading. Various criteria were used to establish hormone refractoriness. Palliative care treatments included radiotherapy, radionuclide therapy (<sup>89</sup>Sr), nitrogen-containing bisphosphonate olpadronate and analgesia.

Whole-body high-resolution bone scintigraphy was undertaken using <sup>99</sup>Tc<sup>m</sup>-labelled methylene-diphosphonate. Bone scans were scored according to the Soloway scoring system; in addition, metastasis of vertebrae was classified according to degree of involvement as total or partial. Scintigrams were interpreted by two independent observers. Observations were related to subsequent development of SCC established clinically according to impaired motor or sensory function confirmed by MRI or CT at the appropriate spinal level. 'Skeletal event-free survival' was defined as survival without SCC.

Kaplan–Meier analysis of overall survival and of SCC-free survival was undertaken with Cox regression to investigate the relationship between the relative risk (RR) of SCC according to variables including PSA (log-transformed), serum alkaline phosphatase (log-transformed), Soloway grade, age, degree of vertebral involvement and Gleason score.

### Results

Mean survival after hormone refractoriness was 8.6 [standard deviation (SD) 10.6] months. Twenty of 84 patients developed SCC 3 days to 10 months after refractoriness was established. Six patients experienced SCC at lumbar level, and 14 at thoracic level; four of the latter also had SCC at another level, two at lumbar level and two at cervical level.

Mean Gleason score was 7.5. When Gleason score was dichotomised to  $\geq 7$  or  $< 7$ , the former was found to be significantly associated with shorter SCC-free survival and overall survival (median 6.1 vs. 12.3 months;  $p < 0.05$ ). Median overall survival of patients with Gleason scores  $\geq 7$  and  $< 7$  was 6.8 months and 12.7 months, respectively ( $p < 0.03$ ). RR (Gleason  $\geq 7$  vs.  $< 7$ ) was 1.89 (95% CI 1.02 to 3.53) for mortality and 1.76 (95% CI 0.95 to 3.28) for SCC-free survival. RRs remained significant after adjusting for confounders: RR = 2.33 ( $p = 0.013$ ) for mortality and RR = 2.37 ( $p = 0.003$ ) for SCC.

Serum PSA and alkaline phosphatase activity were elevated in all patients (mean values of  $511 \pm 1035 \mu\text{g/l}$  and  $402 \pm 503 \text{ U/l}$ , respectively). Log-transformed PSA concentrations were significantly predictive of SCC-free survival (RR = 1.21, 95% CI 1.07 to 1.36;  $p = 0.003$ ) and survival (RR = 1.17, 95% CI 1.04 to 1.32;  $p = 0.01$ ) but log-transformed serum alkaline phosphatase activity and age were not.

The unadjusted RR for SCC was significantly associated with Soloway grade ( $p = 0.031$ ), i.e. patients with heavier metastatic skeletal load were more likely to sustain SCC (the reported results are summarised in

Table 11). However, after adjustment for confounders (PSA and alkaline phosphatase concentrations and age), statistical significance was greatly reduced to  $p = 0.35$  (similarly, for survival,  $p = 0.008$  became  $p = 0.09$  after adjustment).

The unadjusted RR for SCC-free survival among Soloway grade 4 patients was significantly greater than that for grade 1 patients (this also applied for overall survival).

For the 'new method' of assessing total or partial vertebral involvement at progression, the sensitivity and specificity were 0.90 and 0.94, respectively (based on  $2 \times 2$  table values shown in Table 12 derived from table 2 of published paper). The positive predictive value for a totally involved vertebra was therefore 82% and the positive likelihood ratio (LR) was 14.4. The SCC pre-test probability of  $\approx 0.24$  is raised to a post-test probability of  $\approx 0.82$  by a positive total involvement test.

### Author conclusions

The data demonstrate that bone scintigraphy performed at the time of development of refractoriness to hormone therapy is of high predictive value for inherent risk of subsequent SCC.

### Reviewer conclusions

There is no indication of how the 84 patients were selected. It is possible that different patients received various treatments likely to influence the probability of SCC (e.g. bisphosphonates), but it is not clear if these were accounted for in Cox regression analyses. Although the 'total involvement of vertebra' according to scintigraphy appeared to be highly sensitive and specific for subsequent SCC, the study lacks sufficient rigour to be confident of this result; in particular, participant selection was unclear, progression criteria were not defined precisely and no details were given of the method of discriminating total from partial vertebral involvement except that two independent assessors were involved. The frequency of investigator disagreements was not reported, and the level of concordance and how investigator

**TABLE 11** Influence of metastatic load on unadjusted RR for overall survival and SCC-free survival

Soloway grade <sup>a</sup>	Patients, <i>n</i>	RR survival (95% CI)	<i>p</i> -value	RR SCC-free survival (95% CI)	<i>p</i> -value
0					
1	11	1		1	
2	23	2.29 (1.03 to 5.07)		1.96 (0.89 to 4.29)	
3	24	1.85 (0.84 to 4.07)		1.72 (0.79 to 3.75)	
4	26	3.66 (1.67 to 8.06)		3.03 (1.40 to 6.56)	
			0.008		0.031

a 0, no metastases; 1, <6 metastases; 2, 6–20 metastases; 3, >20 metastases; 4, 'superscan' (diffuse increased uptake in axial skeleton without a focal lesion) or >75% of skeleton affected by metastatic process.

**TABLE 12** Accuracy of test for vertebral involvement at bone scan in predicting subsequent SCC

Soloway grade <sup>a</sup>	SCC	No SCC	Total
Total involvement	18	4	22
Partial involvement	2	60	62
Total	20	64	84

a 0 = no metastases; 1, <6 metastases; 2, 6–20 metastases; 3, >20 metastases; 4, 'superscan' (diffuse increased uptake in axial skeleton without a focal lesion) or >75% of skeleton affected by metastatic process.

Note: sensitivity =  $18/20 = 90\%$ ; specificity =  $60/64 = 94\%$ .

disagreement was handled were not mentioned. It is not altogether clear whether the assessment was conducted before or after SCC was determined to have occurred, and whether scintigraphy assessors and MRI/CT assessors were reciprocally blind to each other's results.

### Venkitaraman et al. (2007)<sup>132</sup>

#### Relevant aim

The aim of the study was to identify clinical factors that predict a high risk for SCC in metastatic prostate cancer patients with MRI-suspected overt or occult SCC who have no functional neurological deficit.

#### Design and method

This was a retrospective study based on a single institution's medical records of 570 consecutive patients with prostate cancer who underwent MRI of the spine between January 2001 and May 2005. Patients with skeletal metastases were included if their MRI indicated SCC in the absence of neurological deficit. Patients were excluded if they had experienced previous SCC. In all, 150 patients were included. Their median age was 69 (range 50–88) years, 112 out of 150 were hormone refractory, median time since diagnosis was 41.3 (range 3.13–213) months and from start of hormone treatment was 26.8 (range 0.1–157.5) months. Gleason scores ranged from 6 to 10 (G6,  $n = 23$ ; G7,  $n = 36$ ; G8,  $n = 26$ ; G9,  $n = 29$ ; G10,  $n = 9$ ). Back pain was present in 72% of patients.

Whole-spine MRI was conducted and patients were classified as (1) 'overt SCC', defined as involvement or compression of either the spinal cord or the cauda equina 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; or (3) no SCC. Categories (1) and (2) were considered together as radiological SCC (rSCC).

Binary univariate and multivariate logistic regression were used to identify independent clinical risk factors for rSCC.

#### Results

Of the 150 patients, 41 (27.33%) had rSCC, 24 (16%) had overt rSCC and 17 (11.3%) had occult rSCC. Seven patients had rSCC at multiple non-contiguous sites; 20 had compression in the thoracic spinal level and 21 in the lumbosacral region.

On univariate analysis, significant determinants of rSCC were found to be extensive bone metastases (six or more bone lesions;  $p = 0.005$ ) and back pain ( $p = 0.002$ ), whereas 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 ( $p = 0.855$ ) did not predict rSCC. Univariate regression results are summarised in *Table 13*.

On multivariate analysis, back pain [odds ratio (OR) 5.1, 95% CI 1.44 to 18.25;  $p = 0.012$ ] and extensive bone metastasis (OR 2.9, 95% CI 1.01 to 8.35;  $p = 0.047$ ) were significant independent predictors of rSCC. One variable, PSA at the time of MRI (median PSA 402 vs. 98 ng/ml), was significantly different in the patients who had overt SCC and those who had occult SCC [hazard ratio (HR) 1.005, 95% CI 1.001 to 1.009;  $p = 0.014$ ].

#### Author conclusions

A significant proportion (27.3%) of patients with metastatic prostate cancer may harbour overt or occult SCC in the absence of functional neurological deficit. MRI of the spine for the early diagnosis of SCC may be considered useful in patients with extensive skeletal metastasis and back pain.

#### Reviewer conclusions

Magnetic resonance imaging of the spine in patients with extensive skeletal metastasis and back pain but lacking neurological deficit may lead to early detection of SCC. Since 72% of the selected population

**TABLE 13** Univariate regression analysis of potential risk factors for occurrence of SCC in patients with suspected compression but without neurological deficit

Factor	<i>n</i>	OR (95% CI)	<i>p</i> -value
Back pain			
No	42	1	0.002
Yes	108	7.05 (2.04 to 24.36)	
Extensive bone metastasis			
No, < 6 lesions	45	1	0.005
Yes, ≥6 lesions	104	4.24 (1.54 to 11.67)	
Age (years)			
< 70	76	1	0.97
≥70	74	0.97 (0.47 to 1.99)	
Haemoglobin below normal (<13 g/dl)			
No	57	1	0.61
Yes	86	1.21 (0.57 to 2.56)	
Calcium (mmol/l)			
< 2.27	66	1	0.32
≥2.27	74	0.69 (0.33 to 1.44)	
Initial PSA (ng/ml)			
< 52	70	1	0.68
≥52	73	1.17 (0.56 to 2.44)	
PSA at MRI (ng/ml)			
< 71	75	1	0.85
≥71	75	0.94 (0.46 to 1.92)	
Hormone refractory			
No	38	1	0.16
Yes	112	1.93 (0.77 to 4.81)	
T stage			
< T3	19	1	0.19
≥T3	103	2.40 (0.65 to 8.84)	
N stage			
N0	58	1	0.19
N1	40	0.51 (0.19 to 1.38)	
Composite Gleason score			
< 8	61	1	0.34
≥8	64	0.68 (0.31 to 1.49)	
Primary Gleason grade			
< 4	41	1	0.36
≥4	84	0.68 (0.31 to 1.54)	

**TABLE 13** Univariate regression analysis of potential risk factors for occurrence of SCC in patients with suspected compression but without neurological deficit (*continued*)

Factor	n	OR (95% CI)	p-value
Metastasis at diagnosis			
No	67	1	0.53
Yes	83	0.80 (0.39 to 1.64)	
Serum alkaline phosphatase			
No	42	1	0.93
Yes	104	0.97 (0.44 to 2.14)	
Time from diagnosis			
< 3.4 years	76	1	0.52
≥ 3.4 years	74	1.27 (0.62 to 2.61)	
Time from start of hormone therapy			
< 2 years	70	1	0.96
≥ 2 years	80	1.02 (0.50 to 2.09)	

had back pain, and rSCC may occur in patients without back pain (although relevant data were not provided), it appears that MRI of all patients with extensive skeletal metastases might represent a factor for consideration.

### Venkitaraman et al. (2010)<sup>133</sup>

#### Relevant aim

The authors' stated aims were to determine the optimal frequency of MRI of the spine required to detect clinically occult rSCC and to determine the incidence of neurological deficit in patients with metastatic prostate cancer. The rSCC was defined as involvement or compression of either the spinal cord or the cauda equina by an epidural or an intramedullary mass/lesion, or metastatic disease causing impingement, indentation or loss of definition of the thecal sac.

#### Design and method

This was a retrospective study based on a single institution's medical records of 570 consecutive patients with prostate cancer who underwent MRI of the spine between January 2001 and May 2005. Initial MRI was requested by the physician when patients were considered at high risk of SCC. These appear to be the same patients as those in Venkitaraman *et al.* 2007.<sup>132</sup> From these 570, 130 patients (median age 70 years, range 50–88 years) with castration-resistant disease and skeletal metastases in whom MRI was indicative of suspected clinically occult SCC (i.e. an absence of neurological deficit) were included. Patients were excluded if they had experienced previous SCC. Median times since diagnosis and the start of hormone treatment were 1355 (range 219–6412) days and 917 (range 100–3332) days, respectively. The selection criteria differed from those in the previous 2007 study in that some patients in the latter were not hormone refractory. Median follow-up after initial MRI was 11 (range 1–50) months. Patients with rSCC received radiotherapy to the site of the lesion and some received bisphosphonate treatment as indicated by the treating physician.

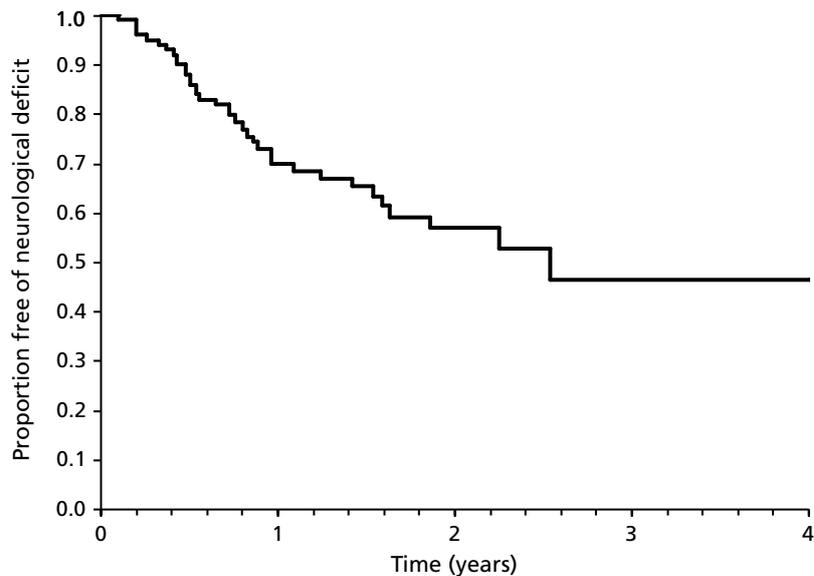
Kaplan–Meier analysis was used to investigate neurological deficit-free survival (NDFS) (i.e. the time to development of neurological deficit); those patients who did not develop neurological deficit were censored at time of death or at end of follow-up. Cox's multivariate regression was used to identify

influential risk factors for neurological deficit. The following variables were tested: rSCC during first MRI; PSA level at the time of initial MRI; PSA doubling time; radiotherapy; and back pain.

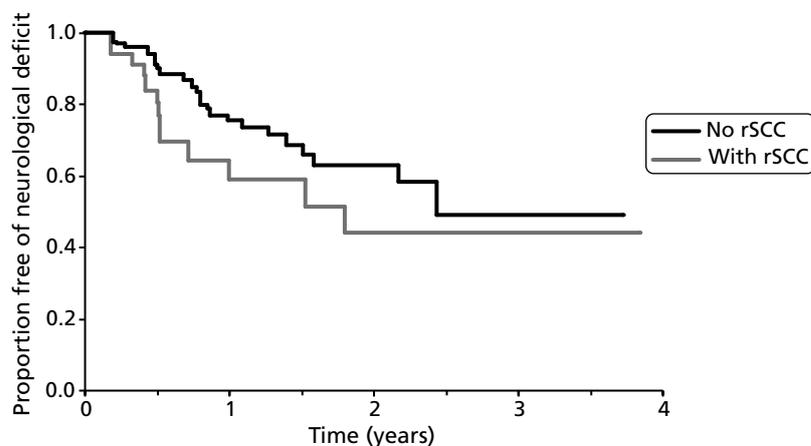
## Results

Median overall survival was 416 (95% CI 23 to 987) days.

The median time to development of neurological deficit was 896 (95% CI 13 to 986) days (*Figure 5*). Thirty-seven (28.5%) of the 130 patients had rSCC at initial MRI. When patients were dichotomised into those with ( $n = 37$ ) or without ( $n = 93$ ) rSCC at the first MRI, the latter exhibited slower development of deficit (*Figure 6*) but this did not reach statistical significance ( $p = 0.103$  by log-rank test); median times were 657 (95% CI 23 to 1103) days and 896 (95% CI 13 to 986) days, respectively.



**FIGURE 5** Time to development of neurological deficit after initial MRI (patients' initial MRI requested because of physicians' judgement of a high risk of SCC). Patients were censored either at the time of death or at the time of last follow-up for surviving patients who had not developed neurological deficit. Data read from published graph (Venkitaraman 2010<sup>133</sup>).



**FIGURE 6** Time to development of neurological deficit according to rSCC at initial MRI. Patients were censored either at the time of death or at the time of last follow-up for surviving patients who had not developed neurological deficit. Data read from published graph (Venkitaraman 2010<sup>133</sup>).

Of the 37 patients who had rSCC during initial MRI, 10 developed a repeat rSCC on MRI follow-up after a median time of 161 (95% CI 63 to 259) days. In 6 out of 10 of these patients, recurrence was at the same site as initial rSCC and radiotherapy. Six of the 37 patients (16.2%) developed irreversible paraparesis on follow-up.

Of the 93 patients without rSCC at initial MRI, 20 (21.5%) developed SCC during follow-up. The median time to development of an rSCC for patients with no rSCC on initial MRI was 283 (95% CI 229 to 337) days, and 8 out of 93 (8.6%) developed paraparesis during follow-up.

High PSA level at the time of initial MRI (HR 2.04, 95% CI 1.05 to 3.96;  $p = 0.035$ ) and short PSA doubling time (<3 months) (HR 0.40, 95% CI 0.19 to 0.79;  $p = 0.009$ ) were found to significantly predict adverse NDFS on univariate analysis, but rSCC on initial MRI ( $p = 0.11$ ), radiotherapy ( $p = 0.1$ ) and back pain ( $p = 0.059$ ) did not attain statistical significance. On multivariate analysis, only a rapid PSA doubling time (<3 months) independently predicted future neurological deficit ( $p = 0.042$ ).

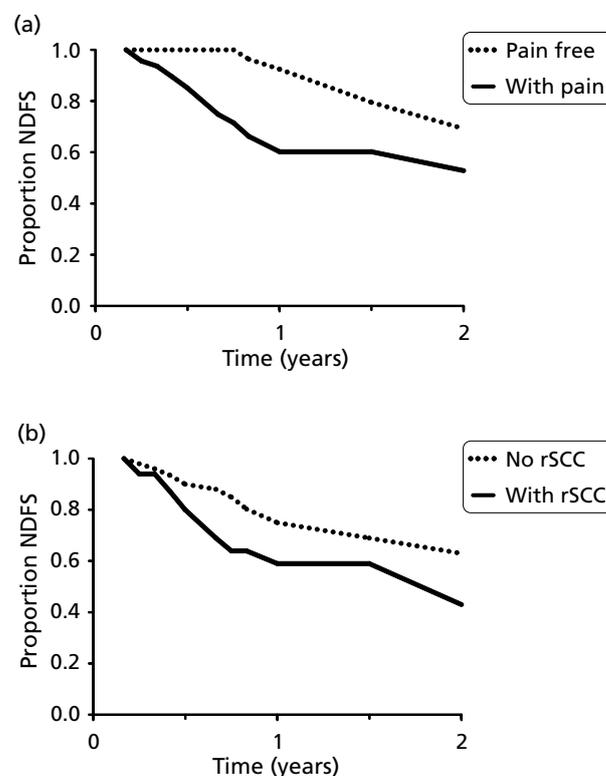
The authors tabulated the actuarial NDFS at several time points for patients with and without back pain and for patients with and without rSCC at initial MRI. These data are summarised graphically in *Figure 7*.

### Author conclusions

Imaging by MRI of the spine can be used to detect asymptomatic rSCC in patients with castration-resistant prostate cancer. Serial estimations are required to maintain a low incidence of clinical SCC. If serial MRI is to be used to detect rSCC in 90% of patients before the development of neurological signs, the optimum frequency for scanning depends on the subset of patients studied.

### Reviewer conclusions

The study findings are consistent with the fairly obvious conclusion that, among castration-resistant prostate cancer patients lacking neurological deficit, those in whom MRI is suggestive of occult SCC (i.e.



**FIGURE 7** Actuarial deficit-free survival according to (a) back pain and (b) rSCC at initial MRI.

with rSCC) will develop neurological deficit sooner than those patients whose MRI scan is negative for occult SCC. Only 37 (28%) of patients had occult SCC so the study lacked power. Rapid escalation of serum PSA was found to be associated with increased risk of neurological deficit.

### Summary of prostate cancer studies

None of the included prostate cancer studies provided a description of the natural history of spinal metastases.

The six included studies varied in methodology and transparency, and this resulted in difficulties in interpreting the findings reported. In particular, it was often difficult to ascertain how study samples were selected. In three studies (those by Bayley *et al.*<sup>107</sup> and Venkitaraman *et al.*<sup>132,133</sup>) patient participation depended on physicians' decisions (e.g. regarding requirement for MRI), but the criteria for decision-making were not clear. In the study by Huddart *et al.*,<sup>115</sup> an investigation conducted at the same centre as the Venkitaraman studies<sup>132,133</sup> but a decade earlier, participants had been diagnosed with SCC; however, it was not clear if this was a subsample of such patients at the centre or a complete set. The report of Soerdjbalie-Maikoe *et al.*<sup>129</sup> gave no information regarding sampling frame. In the study by Kuban *et al.*<sup>118</sup> both sampling frame and selection procedure were fully described.

Patient populations differed with regard to degree of progression of their prostate cancer so that looking for coherence of results across studies should be undertaken with caution. In the study by Bayley *et al.*,<sup>107</sup> patients had metastatic prostate cancer with neurological deficit. In two studies (Kuban *et al.*<sup>118</sup> and Huddart *et al.*<sup>115</sup>) metastatic patients with SCC were examined. Venkitaraman *et al.*<sup>132</sup> investigated patients with SCC but no neurological deficit, whereas in two studies (Venkitaraman *et al.*<sup>133</sup> and Soerdjbalie-Maikoe *et al.*<sup>129</sup>) patients had progressed to become castration resistant. A further complication arises because previous and current treatments and the timing of their implementation, likely to affect the natural progression of the spinal metastases and to influence the identity of potential prognostic factors, varied between studies.

All studies used medical records to ascertain measures of and presence of risk factors. These records were not collected for the purposes of the studies according to a structured framework that was applied equitably to each participant. Furthermore, the completeness of information content within the records was indeterminate. The six studies together included only 409 patients.

The results from these studies imply that patients with a high-risk bone scan may benefit from MRI of the spine aimed at early detection and treatment of occult SAS compression/SCC. The more spinal metastases present, and the longer a patient is at risk, the greater the chance of clinically occult SCC. The time a patient is on hormone therapy may be a proxy for how long he or she is at risk of occult compression. 'Total involvement of vertebra', according to scintigraphy, appeared to be highly discriminatory for subsequent SCC.<sup>129</sup> Other studies reported no significant predictive factors for risk of future relapse (i.e. second SCC). Time-to-event analyses were difficult to generalise because of the different populations studied and uncertainty regarding their representativeness. The validity of the risk factors identified in these studies did not appear to have been tested in an independent population selected according to similar criteria.

## Studies in which the whole sample population was diagnosed with breast cancer

### Harrison *et al.* (1985)<sup>112</sup>

#### Relevant aim

The aim of this study was to determine the correlation of specific symptoms and signs with epidural spinal cord compression (ESCC) in patients suspected of having ESCC, and to compare the roles of skeletal radiographs, radionuclide scans and CSF analyses in the diagnosis of SCC.

## Design and method

This was a retrospective study based on case records from a single centre. Consecutive patients with a positive diagnosis of breast cancer from records dated between January 1977 and July 1982 were selected if they had received myelography for suspected SCC secondary to metastatic breast cancer. The number with suspected SCC who did not receive myelography was not reported.

## Results

In 42 of the 78 included patients (age range 22–75 years), myelography was positive for ESCC (with complete block in 21); myelography was negative in 36 patients. In all 42 myelogram-positive patients, bone scans were also positive for spinal metastases, and most had three or more of these at different sites. Bone scans were positive for spinal metastases in 11 of the 36 patients with negative myelograms. Seven of the patients with a negative myelogram were found not to have metastatic disease.

There was no statistical difference between myelogram-positive and myelogram-negative groups in the distribution of spinal metastases as detected by bone scan or in the proportion with visceral metastases (Table 14). The distribution of spinal metastases in patients not undergoing myelography is unknown. The distribution of various signs and symptoms of SCC between patients with positive and negative myelograms indicated that back pain, paraesthesias and bladder/bowel dysfunction were more common in the myelogram-positive group ( $p \leq 0.05$  by chi-squared test; Table 15). The number of metastatic sites (0, 1, 2,  $\geq 3$ ) and the type of dominant site (bone, visceral, soft tissue, none) were also significantly associated with a positive myelogram. Plain radiographs were analysed in only 13 of the 36 patients with negative myelograms and therefore comparison between groups based on radiographic findings is unlikely to be meaningful.

**TABLE 14** Frequency of variables in patients with positive and negative myelograms

Variable	Positive myelogram ( <i>n</i> = 42 patients)	Negative myelogram ( <i>n</i> = 36 patients)	<i>p</i> -value from statistical test <sup>a</sup> for difference
Positive bone scan	42/42	19/36	<0.001
Positive bone scan for spinal metastases	42/42	16/36	<0.001
Cervical involvement	17/42	11/36	0.149
Thoracic involvement	33/42	15/36	0.484
Lumbar involvement	33/42	12/36	0.418
Visceral metastases			
Liver	6/42	5/36	0.96
Lung	13/42	10/36	0.76
Brain	3/42	6/36	0.29
Signs and symptoms of ESCC			
Back pain	39/42	20/36	<0.001
Radicular pain	24/42	13/36	0.06
Paraesthesias	24/42	10/36	0.009
Extremity weakness	28/42	22/36	0.61
Bladder/bowel dysfunction	18/42	8/36	0.05

a Fisher's exact test or chi-squared test.

### Author conclusion

Specific signs and symptoms may predict SCC. Back pain, radicular pain, paraesthesias and even bladder and bowel dysfunction are seen in patients without cord lesions. Myelography remains the most precise tool for diagnosing spinal cord lesions.

### Reviewer conclusions

In a comparison of patients in whom myelography for suspected ESCC was positive or negative, chi-squared tests indicated that a positive bone scan, back pain, paraesthesia and bladder/bowel dysfunction at the time of myelography were more common in patients with a positive myelogram than those with a negative myelogram. The discriminatory power of these signs or symptoms to distinguish patients with or without ESCC was poor because they were common in both groups.

*Lu et al. (1998)<sup>120</sup> (see also Talcott et al., 1999)<sup>131</sup>*

### Relevant aim

The aim of this study was to examine potential clinical neurological and oncological risk factors for CT-established SCC in breast cancer patients with suspected SCC.

### Design and method

This was a retrospective study of 123 episodes of suspected SCC encountered at a single centre over a 2.5-year period from 1985 to 1988. In all, 405 episodes of suspected SCC were recorded; the number of breast cancer patients among these was not reported. Sixty-three episodes were excluded for various reasons including radiotherapy to the suspected site of SCC within 1 year of the index CT scan. Of the remaining 342 episodes, 146 occurred in breast cancer patients; 23 episodes were excluded because of incomplete medical records. The 123 included episodes involved 93 patients with a median age of 52.9 (range 29.8–77.3) years, of whom 98% had previously established metastatic disease and 89% had skeletal involvement. The spinal level of the suspected episodes was reported as lumbar 38%, thoracic 35%, cervical 18%, sacral 1% and various combinations (8%).

All patients received CT scans; problematic cases were examined with MRI when this became available. Bone scans were performed in 99% of episodes and plain spinal radiography was undertaken in 72%.

Univariate analysis (Fisher's exact test) was used to test for association of potential clinical, neurological and oncological factors predictive of SCC. Stepwise multivariable logistic regression was used to identify independent risk factors for SCC and Kaplan–Meier analysis examined survival of SCC-positive and -negative patients after the index CT scan.

### Results

Of 123 episodes (93 patients), the index CT scan revealed spinal cord (or cauda equina) displacement in 14 (11%), thecal sac compression (TSC) without displacement in 19 (16%), epidural cancer without displacement or compression in 21 (17%) and epidural cancer in 69 (56%). Depending on the definition of clinically important metastatic ESCC, the authors estimate that the CT scan was positive in between 11% and 44% of episodes (any epidural disease). In their analysis of predictors, the authors took clinically important metastatic ESCC to be TSC or thecal compression (equivalent to 33 of 123 episodes, 27%).

In univariate analysis, predictors for a positive CT index scan for clinically important metastatic ESCC were: known bone or vertebral metastases for  $\geq 1$  year; metastatic breast cancer at initial diagnosis; previous spine radiotherapy; objective weakness; increased deep tendon reflexes; and abnormal plantar reflex. These were weak predictors; the best was objective weakness with specificity of only 67% and positive predictive value of 40%. Given these data it is possible to populate a  $2 \times 2$  table for this predictor, as shown in *Table 15*.

Some variables tested occurred so infrequently in the population that they could not reach statistical significance as predictors.

In multiple logistic regression analysis, four independent predictors of TSC were identified as follows: known bone metastases  $\geq 2$  years (OR 3.0, 95% CI 1.2 to 7.6;  $p = 0.02$ ); metastatic disease at initial diagnosis (OR 3.4, 95% CI 1.0 to 11.4;  $p = 0.05$ ); objective weakness (OR 3.8, 95% CI 1.5 to 9.5;  $p = 0.005$ ); and vertebral compression fracture on spine radiograph (OR 2.6, 95% CI 1.0 to 6.5;  $p = 0.05$ ). These four predictors stratified episodes into subgroups with widely varying risk of positive TSC scans, ranging from 12% (no risk factors) to 85% ( $\geq 3$  risk factors) as shown in *Table 16*. Of the 123 episodes, 11% were associated with three or more risk factors relative to a prevalence of 27% for TSC.

### Author conclusions

The results suggest that evaluation of breast cancer patients with suspected SCC might include clinical information about disease course, in addition to neurological examination and previous imaging studies. If confirmed, these predictors may help clinicians to assess risk in this patient population.

### Reviewer conclusions

A combination of three or four of the four identified risk factors predicted TSC with a probability of 85% in this population of breast cancer patients. In the current context the presence of any two of these would probably lead to physicians requesting MRI examination, and so their predictive utility would appear to be limited as these patients are obvious cases for further imaging examination. The study by Talcott *et al.*<sup>131</sup> examined CT scans for suspected SCC over the same period (1985–8) at the same institute; Talcott *et al.* included several primary cancers, of which breast cancer represented 42% of 258 patients ( $n = 108$ ); it appears that data for most or all of the patients in Lu *et al.*<sup>120</sup> were also included in the Talcott study.<sup>131</sup>

**TABLE 15** Objective weakness as predictor of clinically important metastatic SCC

Variable	TSC	No TSC	Total
Positive for objective weakness	20	30	50
Negative for objective weakness	13	60	73
Total	33	90	123

Specificity =  $60/90 = 66.7\%$ ; positive predictive value =  $20/50 = 40\%$ ; sensitivity =  $20/33 = 60.6\%$ ; positive likelihood ratio = 1.818. Pre-test probability of SCC = 27%; pre-test odds of SCC =  $33/90 = 0.366$ ; post-test odds = 0.666 ( $1.818 \times 0.366$ ); post-test probability of SCC = 40%.

**TABLE 16** Probability of TSC according to number of pre-test risk factors present

Number of significant predictors	Number of episodes	Number of episodes with TSC	Number of episodes with no TSC	LR with TSC/without TSC	Post-test probability of TSC <sup>a</sup>
0	33 (0.27)	4 (0.12)	29 (0.32)	0.376	0.121
1	52 (0.42)	9 (0.27)	43 (0.48)	0.571	0.173
2	25 (0.20)	9 (0.27)	16 (0.18)	1.534	0.360
3 or 4	13 (0.11)	11 (0.33)	2 (0.02)	15.00	0.850
Total	123 (1.0)	33 (1.0)	90 (1.0)		

<sup>a</sup> Pre-test probability =  $33/123$  (26.8%); pre-test odds =  $33/90$ ; post-test odds =  $(33/90) \times \text{LR}$ ; post-test probability =  $\text{post-test odds} / (1 + \text{post-test odds})$ .

*McCloskey et al. (1993)<sup>122</sup>***Relevant aim**

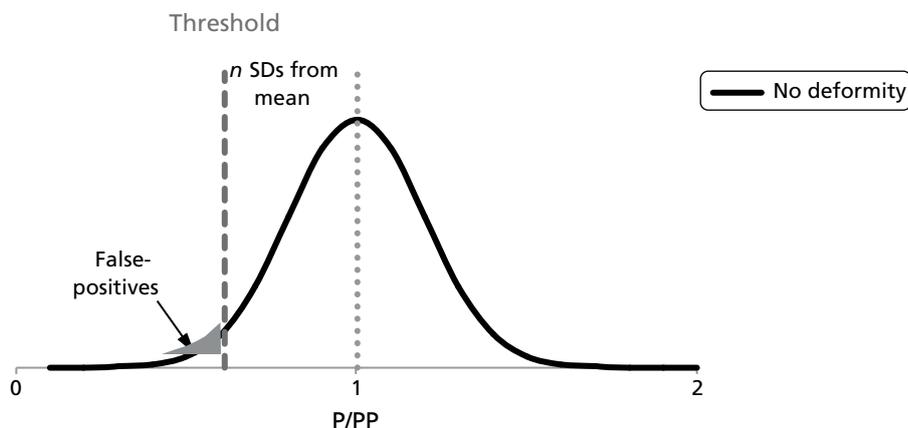
The aim was to develop a radiological method to assess vertebral deformity in women and to employ the method to estimate the incidence and prevalence of vertebral deformity in a population of women with breast cancer.

**Design and method**

This study used radiographs of the spinal vertebrae of 100 randomly selected normal women (aged 45–50 years) to measure the anterior, posterior and central heights of vertebrae T4 to L5; these measures were termed A, P and C. The predicted posterior height (PP) of a given vertebra was estimated using the mean  $p$ -values for adjacent vertebrae (for the population of 100 women). The predicted height for each vertebra (for 100 women) could then be compared with its measured height (for 100 women) to give a ratio and its SD. For the posterior height, this was termed the posterior to predicted posterior height (P/PP) ratio. All P/PP ratios were very close to unity (listed as 1.000) and SDs were mostly in the range 0.04–0.06 and varied somewhat between each specific vertebra. This indicated that estimating the predicted height of a vertebra from the heights of normal adjacent vertebrae was a reasonably accurate procedure. The ratios A/P and C/P and their SDs were also calculated. The authors tested the within- and between-observer reproducibility of the procedure and judged that it was satisfactory.

The ratios P/PP, A/P and C/P were plotted in a normal probability plot and each was shown to have a normal distribution. Given these ratios and their normal distributions, the authors defined criteria for the presence of deformity in a given vertebra in terms of how many SDs the ratios for a scrutinised vertebra departed from the mean observed among the 100 normal women (taking the SD specific for that vertebra as determined for the 100 normal women). The number of standard variations required (e.g. 2.5, 3, 3.5, 4, 4.5) could be varied in determining the presence or absence of deformity and so various cut-off thresholds for deformity could be investigated. Criteria for four types of deformity (central collapse, anterior wedge, posterior wedge and crush deformity) were defined in terms of the combination of ratios required to be satisfied according to appropriate SDs for different cut-offs.

An estimate of the specificity of a particular cut-off threshold was made by examining the vertebrae of the 100 normal women and assuming a prevalence of zero and that a vertebra below the mean according to the defined threshold represented a false-positive (Figure 8 and cell B in Table 17). This allowed the population of cells B and D in the  $2 \times 2$  table and thence the calculation of specificity.



**FIGURE 8** Illustration of the proportion of false-positives among normal vertebrae at a defined threshold.

**TABLE 17** Two by two table for specificity of test in normal women assuming zero prevalence

	Deformity present	Deformity absent	
Test positive	A	B	
Test negative	C	D	
Total	0	100	100

Vertebrae of 163 women with breast cancer (aged 30–75 years) and with skeletal metastases were examined and classified according to the presence of vertebral deformity using A/P, C/P, P/PP ratio criteria and five SD cut-offs ranging from 2.5 to 4.5. After 6 months the vertebrae were re-examined in 121 of these women and newly developed deformities were estimated. These evaluations allowed estimates of point prevalence and 6-month incidence rates of vertebral deformity for this population. For the breast cancer population false-positives (cell B in *Table 17*) were defined as those with ratios above the mean (for normal women) by a defined number of SDs (depending on the threshold cut-off).

## Results

For normal vertebrae the P/PP ratio was normally distributed with a mean of 1.00; SDs of the P/PP ratio varied from vertebra to vertebra, suggesting the need to use site-level criteria in determining the presence of deformity. The SDs for the P/PP ratio were similar whether the PP was made using measures from one or from four adjacent vertebrae (un-deformed). Using a cut-off of 3 standard deviations, the prevalence of vertebral deformity in women with breast cancer and skeletal metastases was 46%.

## Author conclusions

The technique developed for assessment of vertebral deformities is robust and rapid, and has minimal effects on sensitivity while maximising specificity. The method was able to detect minor vertebral deformities, which subsequently progress, and there is a close relationship between existence of deformities and subsequent rate of deformity in breast cancer.

## Reviewer conclusions

Radiography coupled with vertebral measurements and the use of the criteria developed by the authors allowed specific detection of vertebral deformity in women with breast cancer and skeletal metastases. Such detection before the development of frank neurological involvement could be useful. Radiography of the spine is not now used in the comprehensive way reported in this study and whether the procedures developed could be applied using CT or MRI images is uncertain; however, the loss of 'length' dimension in a diseased vertebra, relative to the value of that dimension expected from measurement of healthy adjacent vertebrae, is currently used to determine if fracture is present.

## Oka et al. (2006)<sup>123</sup>

### Relevant aim

This study attempted to identify prognostic factors for bone metastases.

### Design and method

The main focus of this study was to provide basic data on the incidence of bone and spinal metastases and SCC of Japanese breast cancer patients treated with endocrine therapy or chemotherapy following primary surgery in a single institution and to calculate the survival rate after breast surgery, bone or spinal metastasis, and paralysis due to cord compression, using the Kaplan–Meier analysis.

This was a retrospective study of 695 patients with breast cancer (four men, 691 women) who underwent radical surgery at a single centre between January 1990 and December 1996; mean age at surgery was

53.1 (range 24–88) years. Forty-two patients had other concurrent cancer. One hundred and three patients had visceral metastases at baseline and 592 had no visceral metastases.

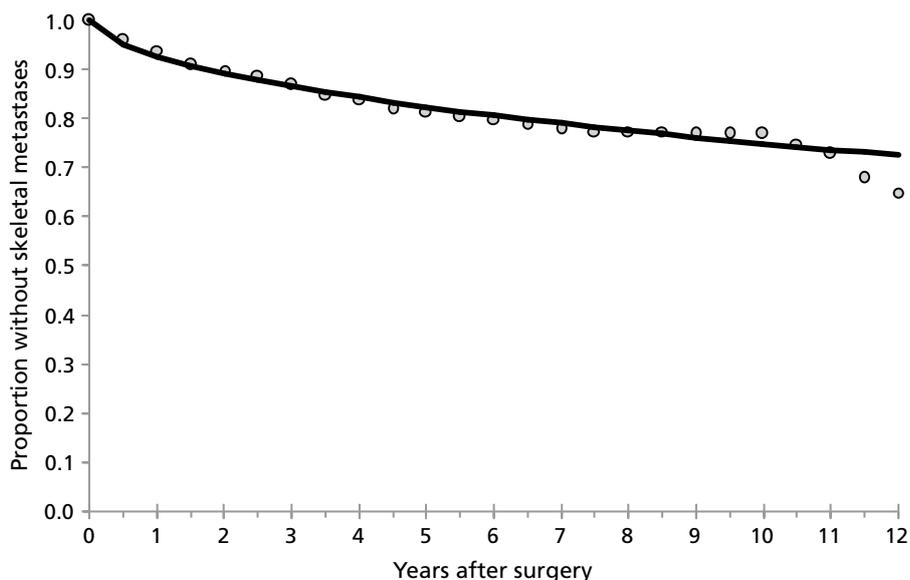
Various imaging methods were employed including bone scintigraphy, chest radiography, chest CT, liver ultrasonography, abdominal CT, cranial CT and MRI (or any combination of these). A Cox proportional hazards model was used to identify prognostic factors for the development of skeletal metastases.

## Results

Bone metastases were observed in 148 patients at the end of the observation period (all received chemotherapy; 44 patients received endocrine therapy before the metastases). The survival of these patients after surgery was much worse than that of the 547 patients who did not develop skeletal metastases (5-year survival 45.8% vs. 89.9%). The interval between surgical treatment and the development of bone metastases ranged from 0 to 130 months (median 19 months). Kaplan–Meier analysis indicated that after surgical treatment of breast cancers, bone metastases developed in 18.1% of the patients over 5 years and in 24.7% of the patients over 10 years (*Figure 9*).

The risk factors for development of bone metastases identified using Cox's regression were tumour stages evaluated by TNM classification (HR 1.615, 95% CI 1.322 to 1.973;  $p < 0.0001$ ); nodal (N) stage classification (HR 2.128, 95% CI 1.381 to 3.279;  $p = 0.0006$ ); the presence or absence of metastases to axillary lymph nodes ( $p = 0.0006$ ); and the presence or absence of metastases to important organs (HR 7.502, 95% CI 5.100 to 11.036;  $p < 0.0001$ ). By the end of the observation period spinal metastases were observed in 121 of the 148 patients who developed skeletal metastases, and 17 out of 121 of these developed paralysis due to SCC. The time between detection of skeletal metastases and development of SCC ranged from 2 to 72 months with a median of 4.4 months.

The study investigated factors prognostic for survival after surgery and survival after development of skeletal metastases. Postsurgery prognostic factors included tumour stages evaluated by TNM classification (HR 1.346, 95% CI 1.099 to 1.648;  $p = 0.004$ ); N stage classification (HR 1.524, 95% CI 1.030 to 2.257;  $p = 0.03$ ); the presence or absence of metastases to axillary lymph nodes ( $p = 0.03$ ); presence or absence of metastases to important organs (HR 3.356, 95% CI 2.226 to 5.060;  $p < 0.0001$ ); presence or absence of oestrogen receptors (HR 1.686, 95% CI 1.102 to 2.580;  $p = 0.02$ ); presence or absence of progesterone



**FIGURE 9** Time to development of skeletal metastases after surgery for breast cancer. Data read from published graph (Oka 2006<sup>123</sup>); Weibull distribution fitted to the first 10.5 years of data. Number at risk at t0 assumed to be 605.

receptors (HR 1.954, 95% CI 1.274 to 2.997;  $p = 0.002$ ); and the presence or absence of bone metastases (HR 3.704, 95% CI 2.415 to 5.682;  $p < 0.0001$ ).

Prognostic factors for survival after development of bone metastases included the presence or absence of metastases to important organs (HR 2.379, 95% CI 1.484 to 3.815;  $p = 0.0003$ ) and the presence or absence of progesterone receptors (HR 2.689, 95% CI 1.553 to 4.657;  $p = 0.0004$ ). Statistically, there were no factors significantly associated with the prognosis of breast cancer patients with paralysis due to cord compression (only 17 patients available for analysis).

### Author conclusions

To detect predictive factors of long survival after paralysis and establish indications for surgery, a comparative study among large groups of patients with paralysis and with different backgrounds is needed.

### Reviewer conclusions

Risk factors for the development of skeletal metastases were tumour stage (TNM classification), N stage classification, metastases to axillary lymph nodes and visceral metastases. The prognostic factors for survival after development of bone metastases were visceral metastases and presence of progesterone receptors.

### Plunkett et al. (2000)<sup>24</sup>

#### Relevant aim

The aim was to identify factors that predict complications from skeletal disease in patients with bone metastases from advanced breast cancer.

This was a retrospective study of breast cancer patients with bone metastases identified between 1975 and 1991 at one centre. Of 1437 patients so identified, 111 were followed up elsewhere and 460 were diagnosed elsewhere and their records contained too little information for inclusion in the study. The notes for 7 patients (0.5%) were not found. The remaining 859 patients were included. Patients were divided into four groups according to sites of disease at the time of diagnosis of bone metastases as follows: (1) bone metastases only ( $n = 243$ , 28%); (2) bone and soft tissue disease only ( $n = 268$ , 31%); (3) bone and pleuropulmonary disease, with or without soft tissue disease ( $n = 237$ , 28%); (4) bone and liver metastases, with or without soft tissue or pleuropulmonary disease ( $n = 111$ , 13%). Patients were monitored with scintigraphy and radiography; myelography was not mentioned.

#### Results

The time from diagnosis of skeletal metastases to vertebral fracture was shortest in the bone-only group ( $p < 0.0017$ ). *Figure 10* illustrates the shape of the reported Kaplan–Meier plots for each group. In addition, patients with bone-only disease developed SCC more rapidly than patients in other groups ( $p = 0.01$ ). Thirty-six patients with bone-only disease at diagnosis of bone metastases (15%) developed cord compression compared with 2–6% of patients in the other groups. Bone scan evidence of metastases in the spine did not predict for subsequent development of cord compression.

Survival from diagnosis of bone metastases was significantly greater for patients with bone disease only at diagnosis of skeletal metastases ( $p < 0.001$ ), and was shortest for patients with concomitant liver metastases (median survival 5.5 months).

There were no differences between the groups in the time to pathological long bone fractures. However, since patients with bone disease only at diagnosis of skeletal disease lived longest, most fractures occurred in this group. Of a total of 243 such patients, 42 (17%) developed a pathological long bone fracture (i.e. 1 in 5.8 patients), compared with 5 of 111 shorter-lived patients with bone and liver disease (5%) (i.e. 1 in 22.2 patients).

### Author conclusions

The results suggest that patients with disease confined to the skeleton at the diagnosis of bone metastases are most likely to develop skeletal-related complications from advanced breast cancer. Such patients may benefit most from treatment with bisphosphonates.

### Reviewer conclusions

The study does not give detailed information regarding participants such as age or time since diagnosis. In breast cancer patients diagnosed with bone metastases, longer survival is a risk factor for vertebral fracture and for SCC, and longer survival is associated with lack of disease at sites additional to the skeleton, especially liver disease and to a lesser extent pleuropulmonary disease.

### Snyder et al. (2005)<sup>127</sup>

#### Relevant aim

The aim was to investigate if prognostic factors identified ex vivo using structural rigidity analysis of transaxial CT image data predict in vivo vertebral fracture in cancer patients with spinal metastases more effectively than contemporary clinical and radiographic guidelines published by Taneichi *et al.*<sup>89</sup>

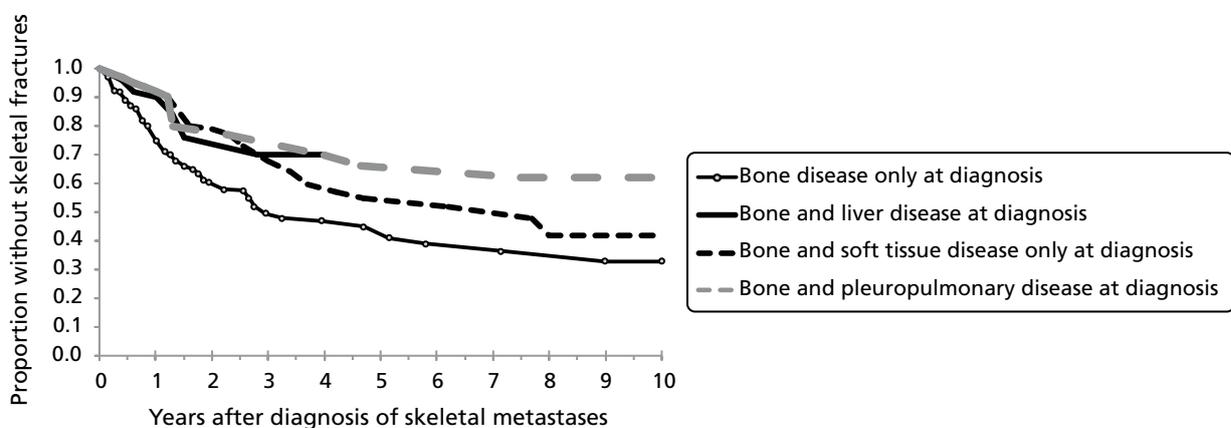
#### Design and method

This study describes the development of the authors' biomechanical model for prediction of fracture. The model estimates the load-bearing capacity of vertebrae using transaxial CT scans. It was tested in 106 women with breast cancer metastatic to the spine who were followed up for 4 months after CT scan to monitor vertebral fracture (4 months was selected as a sufficiently short period for the influence of any tumour progression that might occur to minimally affect risk).

The fracture risk index (FRI) was calculated for each vertebra between T8 and L5 using two different load scenarios for each patient: (1) lifting a 10-kg mass and (2) rising from a chair. A FRI > 1 predicts that fracture would occur during the applied load condition. The accuracy of FRI was compared with the radiographic criteria according to the Taneichi *et al.* guidelines,<sup>89</sup> which predict fracture on the basis of size and location estimates of the spinal tumour. Investigators blinded to the predictions used MRI and radiography to establish the incidence of actual fractures using standard criteria.

#### Results

Over the 4-month period, 10 out of 106 patients suffered one or more new vertebral fractures. Both the CT-based structural rigidity analysis and the Taneichi criteria predicted that these 10 patients were at increased fracture risk (sensitivity = 100% for either method, threshold set so there are no false-negatives).



**FIGURE 10** Time to development of skeletal fracture according to patient's subgroup.

However, the CT rigidity analysis was better at predicting which patients would not fracture an affected vertebra (specificity = 49% when FRI > 1 for lifting a 10-kg mass) compared with the Taneichi CT criteria (specificity = 20%). With sensitivity at 100%, negative predictive ratios are not calculable (infinitely large). The calculated positive LRs were modest for both methods (1.96 and 1.25, respectively), as also were the positive predictive ratios (0.17 and 0.11).

When the load-carrying capacity of the vertebra was normalised by the patient's body mass index (BMI; kg/m<sup>2</sup>) and the threshold for predicting vertebral fracture set to achieve 100% sensitivity, the specificity for predicting no vertebral fracture was improved to 69% (i.e. a false-positive rate of 31%). This is illustrated in purely diagrammatic form in *Figure 11*. The negative LR becomes 0.25 and positive LR 3.2.

By logistic regression the estimated RR for fracture based on FRI > 1 was 4.2 (95% CI 1.4 to 12.8;  $p < 0.001$ ). When controlling for BMI (kg/m<sup>2</sup>), the adjusted RR for fracture based on FRI > 1 was 7.9 (95% CI 1.8 to 34.5;  $p < 0.001$ ).

### Author conclusions

A CT-based structural rigidity analysis was as sensitive but significantly more specific than the best radiographic guidelines for estimating metastatic cancer vertebral fracture risk.

### Reviewer conclusions

The paper has inadequate information in terms of patient population. The number of events (10 patients with fractures) was small. The study compares sensitivity and specificity of CT-based structural rigidity analysis against available guidelines (Taneichi *et al.*<sup>89</sup>); neither method performed well in this population.

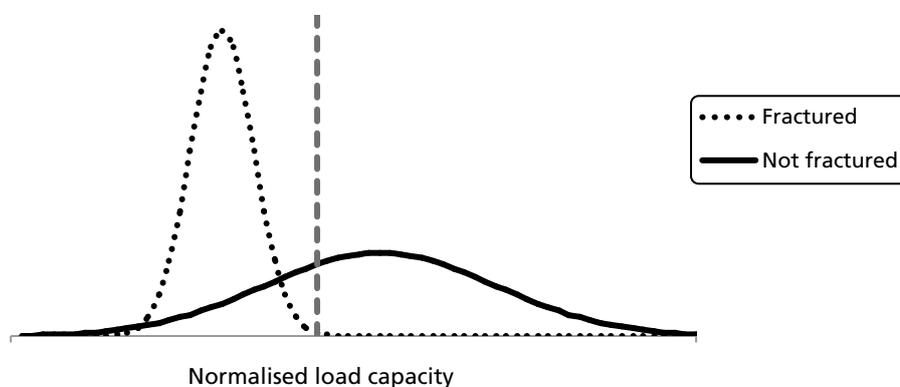
### Snyder *et al.* (2009)<sup>128</sup>

#### Relevant aim

These authors aimed to compare CT-based structural rigidity analysis with current standards for prediction of spinal fracture in women with breast cancer with spinal metastases. The current standard is implied to be plain radiography used with an empirically derived logistic regression analysis based on size and location of vertebral metastases observed by axial CT scanning (Taneichi's algorithm).

#### Design and method

The records of 1024 breast cancer patients at a single institute were reviewed to identify study participants. Ninety-four patients were included; patients were excluded if records indicated neural compromise (due to metastases in brain or spinal cord), withdrawal, relocation, death, previous fracture at metastatic or adjacent site, surgical treatment for impending fracture or fractured bones due to significant



**FIGURE 11** Diagrammatic representation of threshold set to 100% sensitivity and 69% specificity. The dashed vertical line represents the load capacity threshold for discriminating predicted fracture and non-fracture.

trauma. Fifty-one per cent of included patients were postmenopausal, many with co-existent osteopenia. It was unclear when CT and radiographic examinations were conducted relative to time of selection into the study.

Axial CT scans were used to estimate rigidity, a product of bone tissue modulus and geometry. It had been previously established (in an ex vivo study) that the force needed to fracture vertebrae is proportional to the weakest cross-section through the affected bone; thus, the scans were used to identify the cross-sectional structural rigidity with weakest resistance to axial (EA), or bending (EI) loads (that is the minimal axial load and bending load rigidities for each vertebra). From this, the load-bearing capacity (LBC) of the vertebra in combined axial compression and forward bending was also estimated using 'beam theory'. The LBC was standardised on BMI ( $\text{kg/m}^2$ ) (LBC/BMI). The rate of fractures over the next 4 months was recorded by independent investigators.

## Results

The value for each of the four parameters (EI, EA, LBC, LBC/BMI) in each of the 247 vertebrae was estimated. There were 11 fractures over 4 months (236 vertebrae did not fracture). Fractures were distributed as shown in *Table 18*.

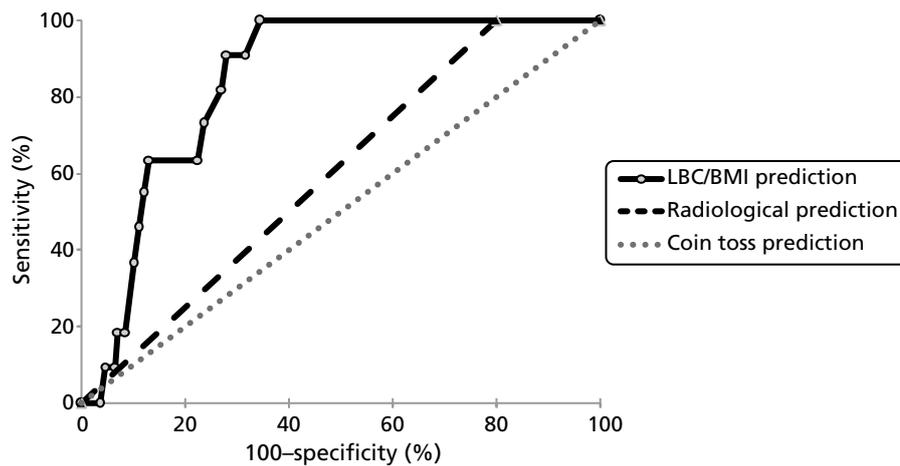
The value for each of the four parameters in each of the 247 observed vertebrae was calculated. From these values, for each parameter the maximum value for the 11 fractured vertebrae was selected as the diagnostic threshold for that parameter. For example, for LBC/BMI, the maximum value among fractured vertebrae was 46.5. As all other fractured vertebrae had values  $<46.5$ , using this as the threshold meant that all fractures would be detected; the resulting sensitivity was 100%. Of the 236 unfractured vertebrae, 74 also had a LBC/BMI  $<46.5$ , giving a specificity of 68.6%  $[(236-74)/236]$ , which was reported as 70%, possibly based on patients rather than vertebrae]. Should a successful treatment be available that prevented fracture, these results imply a number needed to treat of  $\approx 7.7$ .

Using the same procedure for LBC, EI and EA, the specificities were 44%, 53% and 55% (all sensitivities at 100%), respectively. Using Taneichi's algorithm and sensitivity set at 100%, specificity was only 20% (i.e. very many false-positives).

The authors provided a receiver operating characteristic (ROC) curve for LBC/BMI showing how sensitivity and specificity were affected by changing (reducing) the value of the cut-off (*Figure 12*). Hence, as cut-off fell below 46.5,  $<100\%$  of the fractures were detected, but there were fewer false-positives and so specificity improved. The area under the ROC curves was estimated using a binomial semi-parametric model. The results were Taneichi, 0.6; LBC, 0.82; EI, 0.80; EA, 0.68; LBC/BMI, 0.84. Corresponding  $p$ -values for the comparison with chance (tossing a coin; area under the curve = 0.5) were 0.25, 0.001, 0.001, 0.002 and  $<0.001$ , respectively.

**TABLE 18** Distribution of spinal segments included in the study

Group	Vertebral level	Number involved	Number fractured	Percentage fractured
1	T8	33	0	0
2	T9–L1	93	10	11
3	L2–L5	82	1	1
4	L5	39	0	0
Total	T8–L5	247	11	4



**FIGURE 12** Receiver operating characteristic curves for LBC/BMI and radiological prediction. Data read from published graph (Synder 2009<sup>128</sup>).

### Author conclusions

The CT-based structural rigidity analysis is as sensitive as, and significantly more specific than, current radiographic criteria for predicting vertebral fracture in breast cancer.

### Reviewer conclusions

Patient selection was not fully described; it is possible that sensitivities and specificities could vary depending on stage of vertebral invasion by metastases, so selection of participants is important. From T8 to L5 for 94 women provides at least 658 potential vertebrae examined; 247 were used for parameter calculations, but it was not reported how these were selected (i.e. whether these were all those identified with metastases or a proportion of them). It is unclear if the patients in this study overlapped with those in the Snyder 2005<sup>127</sup> study considered above. There were only 11 events (fractures); to retain 100% sensitivity with more events would probably require moving the threshold to a higher value, thereby probably increasing the rate of false-positives and reducing specificity.

### Summary of breast cancer studies

None of the studies described the natural history of spinal metastases derived from breast cancer.

The seven included studies were disparate in terms of population, imaging procedures and study aims. In the study by Harrison *et al.*,<sup>112</sup> participants with suspected SCC underwent myelography and an attempt was made to identify risk factors associated with positive and negative myelography tests. Lu *et al.*<sup>120</sup> examined 93 patients with suspected SCC and identified clinical and oncological features associated with a positive CT scan for SCC. Oka *et al.*<sup>123</sup> searched for risk factors associated with development of bone metastases in 695 breast cancer patients, and another study (Plunkett *et al.*<sup>24</sup>) looked for factors associated with skeletal events in breast cancer patients with bone metastases. McCloskey *et al.*<sup>122</sup> investigated how dimensional measures (e.g. vertebral height) made in vertebrae with metastases and in adjacent intact vertebrae could be used in the diagnosis of vertebral fracture/collapse, while the two biomechanical studies (Snyder *et al.*<sup>127,128</sup>) examined the power of vertebral LBC estimates for predicting vertebral fracture, comparing the specificity of the method with that of Taneichi *et al.*<sup>89</sup>

The results from Harrison *et al.*<sup>112</sup> imply that a positive bone scan, back pain, paraesthesia and bladder/bowel dysfunction at the time of myelography were more common in patients with a positive myelogram than in those with a negative myelogram. Another study, by Lu *et al.*,<sup>120</sup> found that objective weakness in patients with suspected SCC was predictive for SCC; however, the calculated estimates of sensitivity and specificity were very modest. Stratification of patients suspected of having SCC according to the number

of independent risk factors identified a high-risk group with an 85% probability of CT-positive SCC. Oka *et al.*<sup>123</sup> identified T stage (TNM classification), N stage classification, metastases to axillary lymph nodes and visceral metastases as risk factors for the development of skeletal metastases. In breast cancer patients diagnosed with bone metastases, one study, by Plunkett *et al.*,<sup>24</sup> observed that longer survival was found to be a risk factor for vertebral fracture and for SCC.

According to Snyder *et al.*,<sup>127,128</sup> the 'vertebral load bearing capacity algorithm' developed by the authors had superior specificity to the method used by Taneichi *et al.*<sup>89</sup> for predicting vertebral collapse.

The included studies generally provided limited information about the patient population and selection criteria. Results from time-to-event analyses are difficult to generalise because of the different populations studied and uncertainty regarding their representativeness.

### Studies in which the whole sample population was diagnosed with lung cancer (non-small cell lung cancer or small cell lung cancer)

#### *Sekine et al. (2009)*<sup>125</sup>

##### Relevant aim

The stated aim was to identify the risk factors for SREs in patients with advanced NSCLC.

##### Design and method

This was a retrospective study of 642 NSCLC patients. According to the report, for inclusion in the study, patients required a histological or cytological diagnosis of NSCLC, stage IV disease or postoperative recurrence with distant metastases, and 'no prior chemotherapy' or 'chemotherapy prescribed by the National Cancer Center Hospital between 2000 and 2006'. These criteria may therefore have excluded patients who received certain sorts of chemotherapy not prescribed by the National Cancer Center Hospital between 2000 and 2006. However, all 642 patients were described as having received first-line chemotherapy as follows: platinum based,  $n = 429$ ; gefitinib (Iressa<sup>®</sup>, AstraZeneca),  $n = 117$ ; third-generation monotherapy,  $n = 47$ ; non-platinum doublets,  $n = 9$ . Patients were excluded if they had postoperative local recurrence without distant metastases. Forty-three patients received zoledronic acid (Aclasta<sup>®</sup>; Novartis) either before ( $n = 26$ ) or after ( $n = 17$ ) the development of SREs.

At initial diagnosis 399 had no bone metastases, 63 had a single bone metastasis and 180 had multiple bone metastases. Disease progression was observed in 580 out of 642 patients; the initial site of progression was bone in 78 and other than bone in 502.

SREs were defined as (1) pathological fractures, (2) SCC, (3) requirement for radiation therapy, (4) requirement for surgery to the bone, (5) requirement for radiological intervention to the bone, and (6) hypercalcaemia of malignancy that was either fatal or required emergency treatment. Association of baseline characteristics with development of SREs was examined in univariate analysis and multivariate logistic regression. Cox's proportional hazards model was used to identify risk factors for time to event. Kaplan–Meier analysis was used to investigate the time to first SRE after commencement of chemotherapy.

##### Results

A total of 118 (18.4%) patients developed SREs during or after initial chemotherapy (107 required radiotherapy to bone, five developed hypercalcaemia of malignancy, three developed compression fracture of vertebrae, two required surgical treatment of the bone and one underwent radiofrequency ablation therapy to bone).

**TABLE 19** Univariate analysis of association of SREs and patient characteristics

Characteristics	Patients without SREs		Patients with SREs		p-value
	n	%	n	%	
Number of patients	524	81.6	118	18.4	
Sex					
Male	325	80.8	77	19.2	0.53
Female	199	82.9	41	17.1	
Age, median (range)	61	24–86	59.5	26–77	0.083
Performance status					
0	163	82.7	34	17.3	0.68
1	335	81.5	76	18.5	
2–3	26	76.5	8	23.5	
Histology					
Adenocarcinoma	419	80.6	101	19.4	0.16
Non-adenocarcinoma	105	86.1	17	13.9	
Bone metastases					
None	358	89.7	41	10.3	<0.001
Single	46	73.0	17	27.0	
Multiple	120	66.7	60	33.3	
Radiotherapy to the bone before chemotherapy?					
No	499	82.9	103	17.1	0.001
Yes	25	62.5	15	37.5	

Note: the method for establishing performance status was not reported.

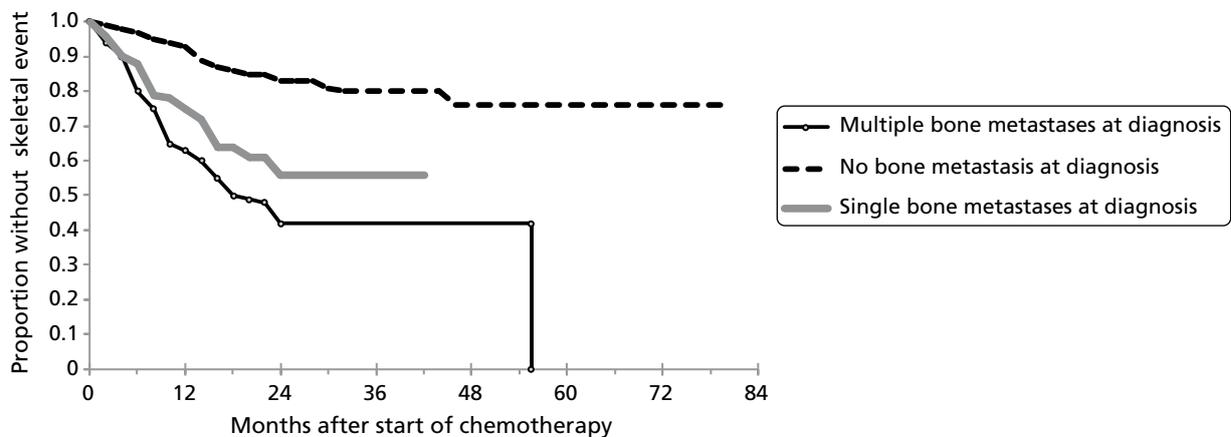
In univariate analysis the number of bone metastases (none, single or multiple) at initial diagnosis ( $p < 0.001$ ) and history of radiotherapy to bone before chemotherapy ( $p = 0.001$ ) were associated with the development of SREs, whereas sex, age, performance status and cancer histology were not (Table 19). However, multivariate analysis using a logistic regression model showed that the number of bone metastases was strongly associated with the occurrence of SREs (OR 3.08, 95% CI 1.60 to 5.94, for single bone metastasis; OR 4.27, 95% CI 2.66 to 6.86, for multiple bone metastases), whereas radiotherapy to the bone before the chemotherapy was not (OR 1.43, 95% CI 0.69 to 2.97).

Of patients who had no bone metastasis at diagnosis, only 10.3% developed SREs, whereas 27% of patients with a single bone metastasis and 33% of patients with multiple bone metastases developed SREs during their clinical course ( $p < 0.001$ ); the median follow-up for SREs was 10.4 (range 0.1–77) months.

In univariate analysis the time to development of SREs was associated with sex, performance status, number of bone metastases at diagnosis and history of radiotherapy to bone before chemotherapy. However, on multivariate analysis a history of radiotherapy to bone was not associated with the development of SREs (Table 20).

**TABLE 20** Risk factors influencing time to SREs

Analysis	HRs (95% CI)	
	Univariate	Multivariate
<b>Time to the first SRE</b>		
Sex		
Female	1	1
Male	1.47 (1.01 to 2.15)	1.44 (0.98 to 2.11)
Performance status		
0	1	1
1	1.43 (0.96 to 2.15)	1.15 (0.76 to 1.74)
2–3	3.73 (1.71 to 8.14)	2.21 (0.97 to 5.03)
Bone metastases		
None	1	1
Single	3.26 (1.85 to 5.75)	3.00 (1.68–5.35)
Multiple	4.98 (3.33 to 7.44)	4.43 (2.91 to 6.76)
Radiotherapy to the bone before chemotherapy?		
No	1	1
Yes	3.39 (1.97 to 5.86)	1.39 (0.77 to 2.49)

**FIGURE 13** Time from start of chemotherapy to first skeletal event according to bone metastases at diagnosis. Data read from published graph (Sekine 2009<sup>125</sup>). Patients with no event by end of follow-up were censored at that time.

Kaplan–Meier analysis indicated that the time to first SRE was shorter for those with multiple bone metastases at diagnosis than those with a single metastasis or none; the relationship published is illustrated in *Figure 13*.

For the analysis of SRE-free survival, a SRE or death was taken as an event and patients without an event by end of follow-up were censored. In multivariate analysis, SRE-free survival was strongly associated with performance status (compared with zero performance status: HR 1.47, 95% CI 1.15 to 1.89, for performance status 1; and OR 3.72, 95% CI 2.31 to 5.98, for performance status 2 or 3). The median SRE-free survival was 23.5 months (95% CI 18.6 to 28.5 months) in patients with performance status of 0, 13.1 months (95% CI 10.4 to 15.8 months) in patients with performance status of 1 and 5.2 months

(95% CI 1.0 to 9.4 months) in patients with performance status of 2 or 3 ( $p < 0.001$ ). To a lesser extent male sex and multiple bone metastases at diagnosis were also indicators of poor SRE-free survival.

### Author conclusions

The presence of multiple bone metastases was significantly associated with the development of SRE in patients with advanced NSCLC treated by systemic chemotherapy. The factor 'multiple bone metastases' was identified as a risk factor for the development of SREs as assessed by all three parameters, and was, therefore, considered as a definite risk factor for the development of SREs. Male sex and poor performance status may be additional risk factors for the development of SREs in these patients. Male sex and poor performance status were significant risk factors influencing the SRE-free survival, marginally significant in relation to the time to the first SRE, and not significant in relation to the presence of SRE.

### Reviewer conclusions

This was a large study with homogeneous mixed cases and more statistical power than many others. The definition of SRE included a number of clinical presentations so it is difficult to distinguish the number of occurrences related to spines. The study does not report number of spinal metastases. A small proportion of participants used bisphosphonates, a drug that prevents loss of bone mass/delayed SREs. It is probably not a surprising finding that the greater the number of bone metastases, the greater the risk of a SRE.

### Sun et al. (2011)<sup>130</sup>

#### Relevant aim

The study aimed to identify clinical factors that can predict SREs in patients with advanced NSCLC.

#### Design and method

Patients were identified from medical records of consecutive diagnoses of advanced NSCLC at a single centre between January 2006 and March 2009 ( $n = 1166$ ). From these, 273 patients with bone metastases secondary to NSCLC were identified from imaging (e.g. scintigraphy and PET) and biopsy records. Clinical data were obtained from the date of primary diagnosis to 31 October 2009; median follow-up was 11 (range 0.7–46.0) months. Of the 273 included patients, 242 were diagnosed with bone metastases at the time of NSCLC diagnosis. Bone metastases were found at multiple locations in most patients. A total of 528 locations were identified (221 to the spine).

The authors investigated the following potential risk factors for their association with SREs: sex; ever a smoker; adenocarcinoma/non-adenocarcinoma; no history of therapy with an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) such as gefitinib; Eastern Cooperative Oncology Group (ECOG) status; BMI ( $\text{kg}/\text{m}^2$ ); and age. These were evaluated in univariate analysis and multivariate logistic regression for an association with the risk of experiencing a first SRE (i.e. at least one event), for the time to first SRE using Kaplan–Meier methods, and for the risk of recurrent SREs (>21 days after the preceding event) using survival-adjusted multiple event analysis.<sup>137</sup>

#### Results

Of the 273 patients analysed, 171 experienced at least one SRE, and 46 had multiple SREs. A total of 229 SREs developed of which 65 occurred before any systemic treatment was received. The most frequent site of SREs was the spine (55.2%). The pattern of SREs was complex: radiotherapy in 169 cases (73.9%), cord compression with vertebral fracture in 14 cases (6.1%), cord compression without definitive vertebral fracture in 14 cases (6.1%), pathological fracture in 30 cases (13.1%), and one case each of prophylactic surgery for impending fracture and hypercalcaemia (0.8%).

In multivariate analysis, only 'ever smoked' was associated with significantly higher SRE risk (OR 2.8, 95% CI 1.32 to 6.00). The same result was obtained if patients who received bisphosphonate therapy were omitted from the analysis. For median time to first SRE in multivariate analysis (*Table 21*) the following

**TABLE 21** Results of analysis of risk factors for time from bone metastasis to first SRE

Characteristic	Number of patients (%)	Time to event (months)	Univariate, <i>p</i> -value	Multivariate HR (95% CI)	<i>p</i> -value
Total	273 (100)	8.9			
Sex					
Male	164 (60.1)	6.3	0.15	NA	–
Female	109 (39.9)	11.6			
Age					
50years	196 (71.8)	8.2	0.64	NA	–
<50years	77 (28.2)	10.1			
BMI (kg/m <sup>2</sup> )					
≥25	67 (24.5)	10.4	0.18	NA	
20 to <25	166 (60.8)	10.1			
<20	40 (14.7)	3.9			
Smoking					
Ever	138 (50.5)	5.2	0.004	1.75 (1.05 to 2.92)	0.03
Never	135 (49.5)	11.6			
Performance status					
ECOG 0, 1	209 (76.6)	10.0	0.23	NA	
ECOG 2, 3	64 (23.4)	5.3			
Histology					
Non-adenocarcinoma	72 (26.4)	3.1	<0.001	1.59 (1.14 to 2.22)	0.007
Adenocarcinoma	201 (73.6)	11.4			
History of EGFR TKI therapy					
No	81 (29.7)	3.3	<0.001	2.12 (1.49 to 3.00)	<0.001
Yes	192 (70.3)	11.8			

NA, not applicable.

variables were associated with shorter median time to first SRE: no history of therapy with a EGFR TKI such as gefitinib; ever smoked; and histology of non-adenocarcinoma.

The same three factors (no history of therapy with a EGFR TKI, ever smoked and histology of non-adenocarcinoma) and also ECOG status 2/3 were significantly associated with increased risk of multiple events (separated by at least 21 days) (*Table 22*).

Significantly more SREs per cycle of treatment occurred during cytotoxic therapy than during EGFR TKI therapy; however, the authors draw attention to the potential pitfall for interpretation in that systemic therapies did not necessarily precede SRE in all cases.

### Author conclusions

This study suggests that metastatic NSCLC patients with characteristics such as ever having smoked, no history of EGFR TKI therapy, poor ECOG status and non-adenocarcinoma are more likely to suffer SREs.

**TABLE 22** Results of analysis of risk factors for occurrence of multiple SREs

Characteristics	HR	95% CI	p-value
Ever a smoker (vs. never a smoker)	1.601	1.034 to 2.479	0.035
Non-adenocarcinoma (vs. adenocarcinoma)	1.498	1.116 to 2.011	0.007
Performance status ECOG 2, 3 (vs. ECOG 0, 1)	1.458	1.074 to 1.980	0.016
No history of treatment with EGFR TKI (vs. history of treatment with EGFR TKI)	1.937	1.428 to 2.627	<0.001
Female (vs. male)	1.382	0.879 to 2.170	0.161

### Reviewer conclusions

SREs appear to have been classified as pathological fracture, SCC with or without vertebral fracture, need for radiation or surgery to bone and hypercalcaemia of malignancy. The risk factors identified may well apply equally to SCC and/or vertebral fracture alone; however, this would need to be investigated using the appropriate narrower definition of an event. This is one of the few studies that considered the risk of repeated events.

### Goldman et al. (1989)<sup>111</sup>

#### Relevant aim

The aim was to undertake an analysis of medical records to define factors predictive of SCC.

#### Design and method

This was a retrospective analysis of medical records of patients who participated in an RCT that investigated the effectiveness of chemotherapy regimens for SCLC between 1982 and 1986. In this trial, participants ( $n = 616$ ) were randomised to four or eight courses of vincristine (Oncovin®, Genus), cyclophosphamide (trade names Endoxan, Cytosan, Neosar, Procytox, Revimmune) and etoposide [etoposide phosphate or VP-16 (current brand name Etopophos)]. On relapse, patients were further randomised to standard care or to further therapy with doxorubicin INN (trade name Adriamycin; also known as hydroxydaunorubicin) and methotrexate. The cases of SCC ( $n = 24$ , 3.8% of 616 patients; age range 42–64 years; 20 male) consisted of those trial participants who according to medical records had a diagnosis of SCC at the start of the trial or who developed SCC during follow-up. SCC was assessed on clinical grounds of signs and symptoms. Of the 24 with SCC, myelography was performed in only 11.

#### Results

Of 616 patients, 500 had undergone bone scanning at presentation (presumed to be study entry). Among these, scanning was judged to be positive for spinal metastases in 131 patients; 9 of these 131 patients (6.9%) had a diagnosis of SCC at some time. Hence, 15 patients (the 24 patients with SCC minus the 9) had SCC at some time but either did not have a scan or had a negative scan. If all 15 had negative scans for spinal metastases then the percentage of any-time SCC patients who had negative scans at presentation is 4.1%. This is somewhat lower than the 6.9% SCC associated with positive scans for spinal metastases. If the 15 SCC patients not detected with a positive spinal bone scan were proportionately distributed among all non-positive scan patients ( $616 - 131 = 485$ ) then percentage of any-time SCC patients providing negative scans for spinal metastases reduces to 3.1%, half that for positive scans indicating a likely association of spinal metastases with present or future SCC. Two of the patients who did not have bone scans had plain radiographs showing vertebral collapse.

Of 24 patients (3.9% of 616) who presented with back pain and a positive spinal bone scan, nine (38%) had SCC at some time. Of 32 patients presenting with cerebral metastases, 12.5% had SCC at some time. Of 87 patients who relapsed with cerebral metastases, 8% had SCC at some time.

### Author conclusion

Patients with the combination of cerebral metastases and a positive bone scan had a 25% chance of developing SCC. It may be possible to select patients who should receive radiotherapy to the spine to try to prevent the development of this complication.

### Reviewer conclusions

This is an early study with only 24 cases of SCC. Not all SCC cases were confirmed by myelography and the study may have predated wide use of CT or MRI. Multiple logistic regression was not performed and chemotherapy (some patients received very heavy loads of cytotoxic agents), a potentially influential confounder for risk of SCC, was not considered; subsequent studies have indicated that such treatments might affect frequency of SCC. The authors' conclusion regarding the combination of positive bone scan and cerebral metastases as a discriminatory risk factor should be viewed with caution. First, as cerebral metastases and SCC could occur at any time during follow-up, there is no assurance that cerebral metastases preceded SCC. Second, as shown in the  $2 \times 2$  table below (Table 23), viewed as a diagnostic test for SCC, the combination (positive bone scan for spinal metastases plus cerebral metastases) has a sensitivity of only 25% based on the reported results. The positive predictive value is 0.25. The positive LR, that is the ratio of those with SCC to those without SCC returning a positive test, is  $0.25/0.03 = 8.33$ . With a prevalence of 4.1% (24/592) this provides a probability of 0.25 (25%) of having SCC should the test result be positive (pre-test odds = 24/592; post-test odds =  $(24/592) \times 8.33 = 0.338$ ; post-test probability =  $1.338/0.338 = 0.252$ ). Patients with a positive test would therefore require further imaging before treatment decisions could be safely undertaken.

### Summary of lung cancer studies

Two of the three included studies (Sekine *et al.*<sup>125</sup> and Sun *et al.*<sup>130</sup>) investigated patients with NSCLC and recruited a substantial number of participants (642 with advanced disease and 273 with bone metastases, respectively). Sekine *et al.*<sup>125</sup> found that the greater the number of bone metastases the greater the risk of a SRE. Sun *et al.*<sup>130</sup> found that smoking, no history of treatment with EGFR TK inhibitors, poor ECOG status and non-adenocarcinoma were associated with more likely occurrence of SREs. Sun *et al.*<sup>130</sup> also considered the risk of repeated events.

In an early study by Goldman *et al.*,<sup>111</sup> 616 SCLC patients with and without SCC were investigated. A combination of cerebral metastases and a positive bone scan were reported to provide a post-test 25% probability for developing SCC, an improvement on the pre-test probability of 0.039; however, this result should be viewed with caution because it was unclear if cerebral metastases actually preceded SCC.

These were retrospective studies that depended on retrieval of information from medical records not designed for, and possibly not suitable for, the study questions addressed. Caution is needed in generalising the conclusions across and beyond the included studies. The prognostic factors identified have not been validated in other independent populations.

**TABLE 23** Positive bone scan plus cerebral metastases as a predictor of SCC

	SCC	No SCC	Total
Positive for combination	6	18	24
Negative for combination	18	574	592
Total	24	592	616

Note: sensitivity =  $6/24 = 25\%$ ; specificity =  $574/592 = 97\%$ .

## Studies in which the population was diagnosed with a variety of cancers

*Bernat et al. (1983)<sup>108</sup>*

### Relevant aim

The study aimed to identify risk factors for SCC so as to distinguish between those who would benefit from myelography and those who would not.

### Design and method

This retrospective study examined medical records of patients discharged from two hospitals during a period from 1975 to 1980 and identified patients who (1) had clinically suspected epidural compression from 'metastatic cancer' and (2) had undergone myelography to confirm or exclude the clinical diagnosis. Myelograms were considered positive for compression if  $\geq 80\%$  of the SAS was obliterated. Patient age ranged from 7 to 85 years.

A total of 133 patients were included. They had diagnoses of carcinoma, sarcoma and lymphoma as follows: lung ( $n = 40$ ), breast ( $n = 27$ ), prostate ( $n = 15$ ), lymphoma ( $n = 12$ ), colon/rectal ( $n = 6$ ), melanoma ( $n = 6$ ), kidney and ureter ( $n = 5$ ), bladder ( $n = 3$ ), other ( $n = 15$ ) and unknown ( $n = 6$ ) (two patients had primaries at two different sites).

### Results

The paper reported that 62 and 71 patients, respectively, had positive and negative myelograms. The ratio of positive to negative images varied with primary cancer; for example, 20 of 27 and 3 of 15 myelograms were positive in breast cancer and prostate cancer patients, respectively. Compressions were commonest in the thoracic region, followed by the lumbosacral and cervical regions. Of compressions to the spinal cord, 30 of 47 were complete and 17 were incomplete; there were 15 patients with primarily cauda equina compression.

Stepwise logistic regression was used to examine the association of 13 variables with a positive myelogram. The precise identity of these variables was unclear. The authors selected the following as the most influential variables ( $p$ -values were not reported): positive vertebral plain radiographs; sensory level or dermatomal loss on examination; history of local pain; older age; history of weakness; history of radicular pain; male sex; paraparesis or radicular weakness on examination. These predictors were used to calculate the predicted probability of a positive myelogram (compression) for each patient who had compression (i.e. observed compression) and for each who had no compression (observed negative myelogram). Figure 1 of the paper presented the frequency of patients with predicted probabilities of a positive myelogram ranging in 10% steps of probability from 0–0.09 to 0.9–1. Unfortunately, the number of patients with observed positive myelograms shown in the figure fell short of those reported to have positive myelograms (i.e. 62 positive myelograms reported, 53 patients in the figure); this discrepancy was not explained but it is possible the missing patients represent those with incomplete data for logistic regression.

### Author conclusion

Attempts to identify symptoms and signs that might increase diagnostic ability were not successful. Logistic regression analysis was used to separate two groups; however, overlap in scores of those with and without compression resulted in difficulty in selecting a useful cut-off point.

### Reviewer conclusions

The study sample selected is difficult to define; it will reflect different physicians' decisions about a clinical diagnosis of compression, likely to vary from study centre to study centre and perhaps through time (e.g. 30 years ago vs. now). There was a considerable mix of different cancers in the study sample; any predictive variable(s) uncovered are likely to reflect the mixed cases and would be difficult to generalise to

particular conditions or to spinal metastases in general. As different primary tumours manifest at different times, the influence of age as a predictor could relate to mixed cases rather than risk of compression. It is unclear if the type of primary tumour was explored as a predictive variable:  $p$ -values were not reported for the logistic regression and there appeared to be errors in the application of the regression results to the study population.

### *Chaichana et al. (2009)*<sup>109</sup>

#### Relevant aim

To understand factors associated with pathological vertebral body compression fractures in patients with metastatic epidural SCC [SCC caused by an epidural mass (EM)].

#### Design and method

This retrospective study examined medical records of patients who had received surgery for SCC at a single tertiary care centre between 1996 and 2007. Inclusion required MRI evidence of spinal cord displacement by an EM. Patients with more than one discrete lesion, brain metastases, cauda equina or spinal root compression were excluded.

The report implied that, of 216 patients who may have been included, data for 162 were analysed (implying a possibility of  $\approx 25\%$  missing data). Patients with vertebral fracture who did not receive surgery were not identified or quantified.

The primary cancer diagnoses among the 162 included patients were various, reported as follows: lung ( $n = 26$ , 16%), breast ( $n = 26$ , 16%), prostate ( $n = 20$ , 12%), renal ( $n = 21$ , 13%) and haematopoietic ( $n = 28$ , 17%). Other sources included thyroid, gastrointestinal, melanoma and non-renal genitourinary system. The distribution of spinal metastases was described as: cervical,  $n = 35$ ; thoracic,  $n = 114$ ; lumbar,  $n = 49$ ; cervicothoracic,  $n = 22$ ; and thoracolumbar,  $n = 24$ .

#### Results

Univariate logistic regression identified the following variables that were associated with presurgery vertebral fracture: sensory deficit ( $p = 0.02$ ), presurgery chemotherapy ( $p = 0.03$ ), primary breast cancer ( $p = 0.02$ ), thoracic involvement ( $p < 0.001$ ), number of spinal levels involved ( $p = 0.1$ ), number of spinal metastases ( $p = 0.07$ ) and anterior location ( $p = 0.005$ ). Variables found not to be associated with vertebral fracture according to univariate regression ( $p > 0.1$ ) included age, pain symptoms, motor deficit, lytic-type tumour, blastic-type tumour and extraspinal metastases. After multivariate logistic regression, presurgery chemotherapy (OR 2.283, 95% CI 1.064 to 4.898;  $p = 0.03$ ), primary breast cancer (OR 4.179, 95% CI 1.457 to 11.983;  $p = 0.008$ ), thoracic involvement (OR 3.505, 95% CI 1.343 to 9.143;  $p = 0.01$ ) and anterior cord compression (OR 3.213, 95% CI 1.416 to 7.293;  $p = 0.005$ ) were found to be independently associated with vertebral body compression fractures.

#### Author conclusion

The factors strongly associated with preoperative compression fractures include lack of sensory deficits, primary breast cancer, anterior spine metastases, thoracic spine involvement, preoperative chemotherapy and possibly preoperative radiation therapy.

#### Reviewer conclusions

The study sample selected may be unrepresentative of patients with SCC who are at risk of or who have vertebral body compression fractures, as those patients who did not receive surgery were not included; this may or may not be a sufficient proportion to bias results. A further concern is that it appears that 25% of relevant data were missing; however, the report lacks clarity on this. There was a considerable mix of different cancers in the study sample; any predictive variable(s) uncovered are likely to reflect the mixed cases. It would be difficult to generalise to particular conditions or to patients with SCC in general.

## Helweg-Larsen et al. (2000)<sup>113</sup>

### Relevant aim

The parts of this study relevant to this report were (1) an investigation of whether tumour type influenced the time from cancer diagnosis to diagnosis of spinal cord or nerve root compression and the clinical severity of the compression; and (2) the identification of prognostic factors for subsequent recurrence of compression at a second site. The authors' main aim focused on the analysis of the prognostic significance of various clinical and radiological variables for ambulatory function and survival following treatment for spinal cord or nerve root compression.

### Design and method

This was a prospective study of 153 consecutive patients recruited over a 3.5-year period if they had a diagnosis of SCC or nerve root compression due to intraspinal metastases from a known solid malignant tumour. All 153 patients had SCC or nerve root compression confirmed by myelography (some received CT imaging). Patients were followed up from diagnosis of compression to death or for a minimum of 11 months. The primary cancer diagnoses were breast carcinoma in 56 patients (37%), prostatic carcinoma in 43 (28%), NSCLC in 18 (12%), SCLC in nine (6%), and other solid tumours in 27 (17%) patients. The distribution of compressions was cervical, seven (4%) cases; thoracic, 102 (67%) cases; and lumbosacral, 44 (29%) cases.

### Results

The main results concerned predictors of overall survival and of ambulatory status after treatment for compression and these are outside the remit of this short report. The type of primary tumour was found to be a predictor of the time from diagnosis of cancer to the time of the first compression ( $p < 0.0005$  in multivariate analysis), and also of the severity of the compression in terms of patients' ambulatory status at the time of diagnosis of compression. Of the tumour types examined, the shortest time to compression was found for lung cancer and the longest for breast cancer. Kaplan–Meier analyses of this outcome were not shown.

New compression at a different site was observed in 14 of 153 patients. In an analysis that lacked power because of small sample size, it was found that primary tumour type was not a predictor of recurrence. The median time to new recurrence after the first compression was 4.5 (range 1–25.4) months.

### Author conclusions

There was a significant association ( $p = 0.016$ ) between time interval from diagnosis of primary tumour until development of SCC and type of primary tumour. Pretreatment ambulatory function of SCC patients is a main determinant for post-treatment gait function. Survival time is short, especially in non-ambulatory patients, and can be improved only by restoration of gait function in non-ambulatory patients by immediate treatment.

### Reviewer conclusions

Primary tumour type influences the time to SCC and patient walking status at time of confirmation of SCC. An inference that follows for studies with populations of mixed cancer type is that the length of time from primary diagnosis to study entry will influence the results of any analysis of prognostic factors predicting compression or vertebral fracture. There will therefore be considerable difficulties in interpretation of results from studies with a case-mix of patients with different cancer types and various delays between primary diagnosis and study entry.

**Helweg-Larsen et al. (1995)<sup>114</sup>****Relevant aim**

A stated aim of this study was to compare the risk of a recurrence of spinal cord or root compression among patients with different numbers of spinal metastases detected at the time of the diagnosis of the first compression.

**Design and method**

This was a prospective study of patients recruited over a 3.5-year period. The study included 107 consecutive patients with myelographically verified metastatic SCC or spinal root compression from a histologically verified solid tumour. The report states that all patients received radiotherapy after myelographic diagnosis, but also that 'only those epidural lesions causing neurological signs or symptoms were irradiated'. The primary cancer diagnoses were reported as breast carcinoma in 42 patients, prostatic adenocarcinoma in 28 patients, lung cancer in 21 patients and other solid tumours in 16 patients. Multiple epidural lesions were observed in 37 (35%) patients; in one patient there were four separate lesions, in eight patients there were three lesions, and in 28 there were two separate lesions.

**Results**

Recurrence of compression was observed in 8 of 107 patients. There was no difference in risk of a second compression between patients with a single metastasis at the time of the confirmatory myelogram for first compression (five recurrence events among 70 patients at risk) and those with multiple metastases at the confirmatory myelogram (three recurrence events among 37 patients at risk). The overall survival was superior for those who experienced recurrence ( $n = 8$ , median 9.2 months) than for those with no recurrence ( $n = 99$ , median 3.5 months). Unsurprisingly, this indicates that a predictor for recurrence is prolonged survival and that identifying patients with recurrence tends to select those with longer survival.

**Author conclusions**

Only symptomatic epidural metastases should be irradiated, and all patients treated should be followed regularly and observed for a second SCC.

**Reviewer conclusions**

The number of recurrence events ( $n = 8$ ) was too small to allow for meaningful investigation of prognostic factors predicting recurrence. Unsurprisingly, patients who survive longer are more at risk of recurrence.

**Husband et al. (2001)<sup>116</sup>****Relevant aim**

These authors aimed to assess indicators that might identify those patients with physician-suspected MSCC in whom MRI examination can be forgone.

**Design and method**

This was a prospective study of 280 consecutive patients, recruited over 2 years at a single centre, who underwent MRI for suspected SCC. Of 362 potentially eligible patients, 51 were excluded because they had MRI at other centres, and 31 were excluded because they did not undergo MRI for various reasons (e.g. unavailable scanner). The primary cancer diagnoses among the 280 included patients were various and reported as follows: breast 65, prostate 57, bronchus 72, haematological 23, urinary tract 21, gastrointestinal tract 13, unknown primary 12 and other 17 patients.

Patients received MRI, plain radiography and neurological assessment. The relative timing of the different imaging modalities was not reported.

## Results

The presence of focal abnormality on radiographs together with neurological signs consistent with compression at that level was taken as positive diagnosis by radiography. On this basis, 104 out of 280 patients were judged positive; however, 13 had received previous radiotherapy at that site and were classified as MRI-mandatory because of previous therapy. The remaining 91 patients were classified as MRI non-mandatory. The remaining 176 out of 280 patients were negative by radiography plus neurological signs and were classified as MRI-mandatory.

Of the 280 MRI scans undertaken, 201 were positive for MSCC (186 extradural, five intradural but extramedullary and 10 intramedullary), and 79 were negative (of these, 19 showed no MRI abnormality and 60 showed various abnormalities). MSCC was observed at one level in 161 patients, at two levels in 36 patients and in three regions in four patients. The sites at which MSCCs were observed were cervical in 15 patients, thoracic in 160 patients and lumbar/sacral in 71 patients.

The diagnostic/prognostic performance of plain radiographs plus neurological examination for the diagnosis of MSCC was compared with MRI (the latter taken as gold standard), and specificity, sensitivity and positive and negative predictive values were calculated and reported. The results were presented in table 9 of the paper. Of the 91 patients classified as 'non-mandatory MRI' based on positive radiography plus neurological signs, 89 were positive for MSCC according to MRI, leaving two as MRI negative (i.e. false-positives). Of the 189 patients classified as 'mandatory MRI' based on negative radiography plus neurological signs (or by virtue of previous treatment), 112 were positive for MSCC by MRI. This should leave 77 true-negatives (189–112) by radiography; however, the table presents this number as 87, giving a total number of patients of 290 (10 more than included in the study). The reason for this discrepancy is unclear. The text states that for this analysis 'thecal sac compression without SCC' was viewed as a negative MRI, but it appears that these patients may have been double counted. The reported sensitivity, specificity and positive and negative predictive values were 44%, 98%, 98% and 44%, respectively. Values calculated on a total of 280 patients become 97% for specificity and 41% for negative predictive value.

## Author conclusions

Although focal radiographic abnormalities with consistent neurological findings, when present, accurately predicted the presence and level of MSCC, whole-spine MRI is indicated in most patients with suspected MSCC because the additional information may alter the management plan. The primary tumour is not helpful in predicting which patients will have more than one site of compression, although this is uncommon in tumours of haematological origin.

## Reviewer conclusions

The predictive/diagnostic performance of radiography plus neurological signs was poor (sensitivity only 44%), with more false-negatives than true-positives, but with a positive predictive value of 97%. However, predictive values are highly dependent on the prevalence of the condition in the population examined; here the prevalence was 69%, which tends to strongly favour a high positive predictive value, as illustrated in *Figure 14*.

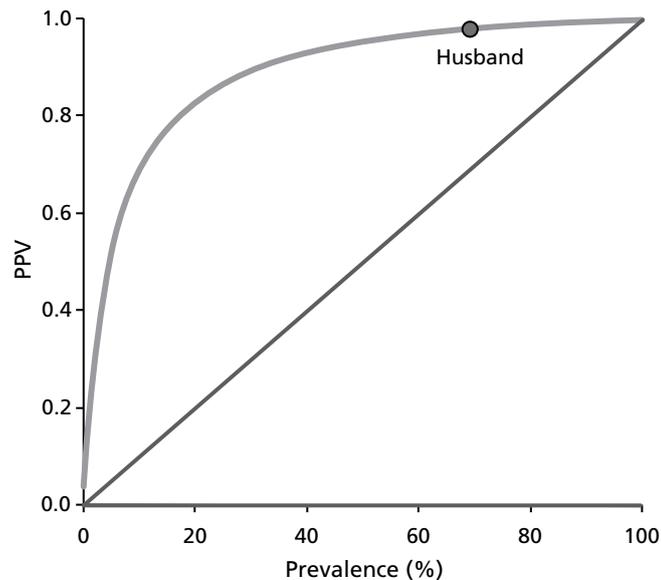
## *Klekamp and Samii (1998)<sup>117</sup>*

### Relevant aim

The aim was to identify factors that might predict local recurrent disease (i.e. of spinal metastases).

### Design and method

The main focus of this paper was to identify variables associated with prolonged survival or a favourable postoperative neurological status in patients who have received surgery for spinal metastases.



**FIGURE 14** Strong dependence of positive predictive value (PPV) on prevalence. The curve shows the relationship between prevalence and positive predictive value when sensitivity and specificity are 44% and 97%, respectively, as in the study by Husband *et al.*<sup>116</sup> The straight line is when sensitivity and specificity are both set at 50%.

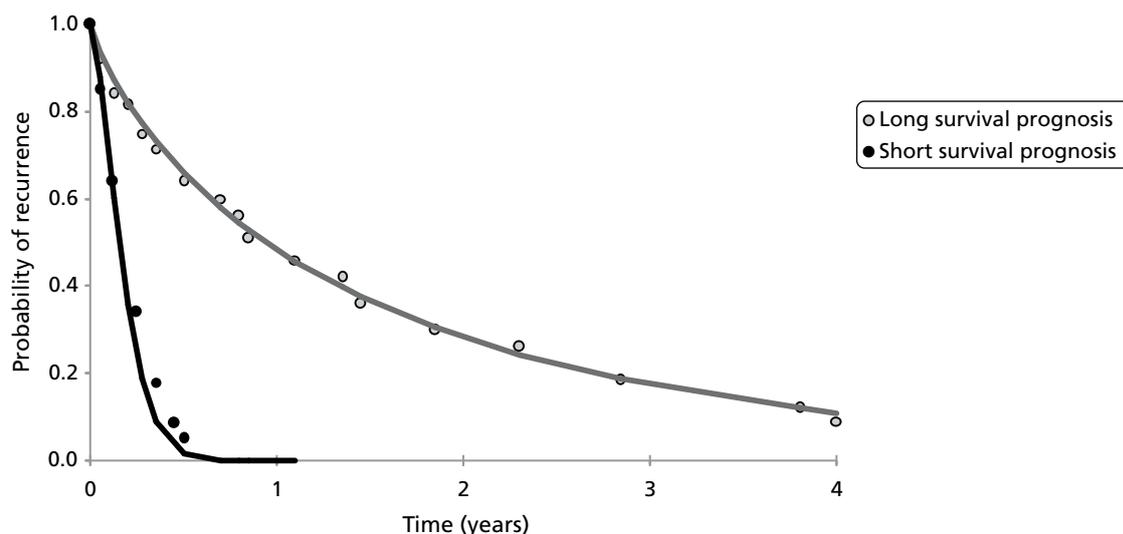
This was a prospective study of 101 patients (with a total of 106 spinal metastases) who received surgery for spinal metastases at a single hospital between 1977 and 1996. Patients were recruited from a total of 740 patients who had received spinal tumour treatment. The number of patients with spinal metastases not in receipt of surgery was unclear. The primary cancer diagnoses resulting in 106 spinal metastases were reported as breast 17, prostate 15, thyroid 9, kidney 12, unknown primary tumour 25, lung 17, colon 5, melanoma 2, urogenital tract 1, pleural mesothelioma 1, teratoma 1 and gallbladder 1. The time interval between cancer diagnosis and diagnosis of spinal metastases ranged from 2 days to 5 years (mean 4 months; SD 6 months). Spinal metastases were distributed as follows: cervical, 12 patients; thoracic, 62 patients; lumbar, 24 patients; and sacral, three patients. Various imaging methods were employed to establish the diagnosis of spinal metastasis. Health status was monitored according to the authors' published scoring system based on that of Karnofsky; scores ranged from 0 to 5.

## Results

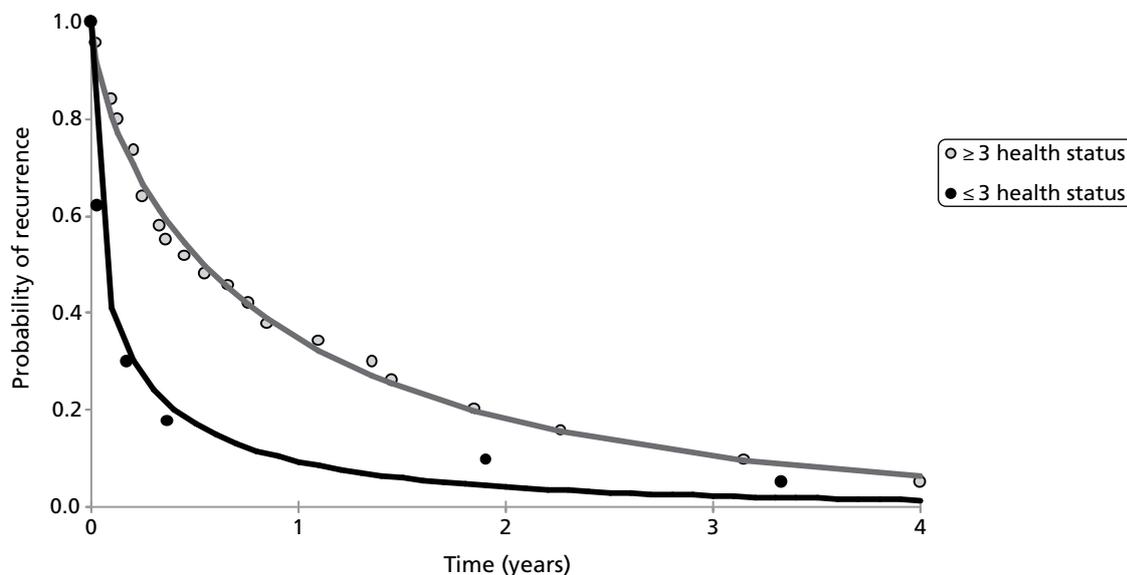
The 106 spinal metastases were subdivided according to primary tumour into 'long survival prognosis' ( $n = 53$ ; breast, prostate, thyroid, kidney) and 'short survival prognosis' ( $n = 53$ ; lung, colon, melanoma, urogenital, mesothelioma, teratoma, gallbladder). The rationale for this subdivision was not elaborated. Kaplan–Meier analysis was used to investigate time to local recurrence and multiple logistic regression was used to identify influential risk variables for recurrence.

The absolute number of postsurgery local recurrences was not reported. According to Kaplan–Meier analysis, recurrence of spinal metastases leading to neurological deterioration (implying the presence of SCC) was observed in 57.9% of spinal metastases within 6 months of surgery, 69.3% within 1 year and 96% within 4 years (no risk table was provided; it is assumed that patients who died before recurrence were censored at time of death). Figure 3 of the study depicts the time to recurrence for 'short survival prognosis' and for 'long survival prognosis' patients; time to recurrence was much shorter for the latter. The reported relationship is represented in Figure 15. It is unclear if the prognostic subgroups were specified a priori. Similarly, time to recurrence was shorter for patients with better health status ( $<3$ ) than for those with scores  $\geq 3$ . The relationship is represented in Figure 16.

Multiple logistic regression identified that long postoperative recurrence-free survival was associated with the following variables: favourable tumour histology (i.e. tumours in the long survival prognosis group



**FIGURE 15** Time to local recurrence reported by Klekamp and Samii.<sup>117</sup> Data read from graph and fitted with Weibull distributions.



**FIGURE 16** Time to local recurrence reported by Klekamp and Samii.<sup>117</sup> Data read from graph and fitted with Weibull distributions.

category), tumours at cervical spine level, low number of affected vertebral bodies, good general health status, complete resection at surgery, and elective surgery (as distinct from emergency surgery; 70% of patients received emergency surgery). Adjuvant postoperative therapy, length of history and age did not show a significant influence on local metastatic recurrence rate.

### Author conclusions

The authors' conclusions were largely based on a literature survey and concerned survival, treatment modalities and recommendations of treatment pathways as follows:

1. Patients in good health condition and living independently should undergo surgery for spinal metastasis if neurological symptoms are present. Postoperatively, adjuvant therapy should be initiated.

2. Patients with neurological symptoms but in poor condition, requiring hospitalisation for their cancerous disease independent of spinal metastasis, should not be operated on but should be offered radiotherapy and/or chemotherapy primarily.
3. Patients with spinal instability due to metastatic disease require stabilisation to achieve a satisfactory neurological outcome. However, a surgical procedure has to be tailored according to life expectancy and health status of the patient.
4. Patients without neurological symptoms or instability should undergo radiotherapy primarily.
5. Patients who deteriorate after or despite primary radiotherapy may be candidates for surgery, but more complications and higher mortality rates should be expected.

### Reviewer conclusions

The patient population was very heterogeneous and the study spanned two decades, during which imaging and treatment modalities will have changed. Patients not judged suitable for surgery were excluded and therefore the study population represents physicians' judgements and may be particular to time and place. Unsurprisingly, type of primary tumour and patient's health status were identified as factors that influence the reappearance of spinal metastases after surgery. As recurrences were associated with neurological deficit it is probable that these factors will also be associated with SCC or vertebral collapse.

### Levack et al. (2002)<sup>119</sup>

#### Relevant aim

The authors aimed to quantify the incidence of clinical signs and symptoms of malignant SCC, or of cauda equina compression, among patients with confirmed diagnosis of compression and to assess the utility of various imaging procedures for the diagnosis of malignant compression. The authors focused on the nature and onset of patient symptoms relative to the time of diagnosis, and on the reasons for delays in diagnosis.

#### Design and method

This was a prospective observational study of 319 patients with SCC or cauda equina compressions (with a total of 324 compressions) recruited at three centres between January 1998 and April 1999. Compression was mostly confirmed by MRI. The primary cancer diagnoses were reported as lung, prostate and breast, together accounting for 59% of all cases. Tumours were from the gastrointestinal tract in 10% of cases (32) while 10% were of haematological origin (myeloma, lymphoma, chronic lymphatic leukaemia) and in 23 cases (7%) the site of the primary tumour was never identified. Median age was 65 years and 203 out of 319 participants were male. The spinal level of compressions was reported to be cervical in 7% of cases, thoracic in 68%, lumbar in 21% and sacral in 4%. In 55 of 324 compressions, compression of more than one site was detected. In 72 out of 319 patients, the malignant compression was the presenting symptom; the remaining 247 patients were known to have cancer at the time of compression diagnosis. Diagnoses of malignant compression were mainly made on weekdays (average of 18.3% per day for all diagnoses) whereas weekend days only accounted for 4.3% per day, implying a few days' delay in diagnosis for a proportion of patients, presumably reflecting the lack of access to MRI outside the working week.

The proportions of patients with various clinical signs and symptoms of malignant compression, and in some instances the timing of their onset, were reported; however, no formal regression analysis of predictive factors or Kaplan–Meier analyses were undertaken. Various imaging methods were employed, including plain radiography, bone scintigraphy, CT and MRI. The accuracy of different modalities for diagnosis of malignant compression was compared.

#### Results

The reported frequencies of signs and symptoms are summarised in *Table 24*.

Pain was experienced by 94% of patients. Various categories of pain were common, and pain was found not to be the predictive factor of malignant cord compression; there was considerable discordance

**TABLE 24** Summary of frequencies of signs and symptoms

Self-reported sign or symptom <sup>a</sup>	Proportion experiencing it	Timing before diagnosis
Pain (spinal nerve root or localised)	94%	Median duration 90 days (IQR 37–205 days)
Root pain	79%	
Root pain alone	35% ( <i>n</i> = 86)	
Back pain alone	44% ( <i>n</i> = 110)	
Progressive pain and latterly severe	84% ( <i>n</i> = 197)	
Pain rated as 'worst imagined pain'	29%	
Unable to walk at diagnosis	18%	
Falls before diagnosis	Common	
Weakness before diagnosis	85% ( <i>n</i> = 210)	Median duration 20 days (IQR 7–132 days)
Altered sensation before diagnosis	68% ( <i>n</i> = 168)	Median duration 12 days (IQR 4–41 days)
Problem passing urine	56% ( <i>n</i> = 139)	
Urinary incontinence	15%	
Frequency	6%	
Urgency	3%	
Hesitancy	14%	
Bowel problems	74% ( <i>n</i> = 183)	
Constipation (possibly opioid-related)	64% ( <i>n</i> = 164)	
First relevant symptom	100%	Median duration 66 days (IQR 37–205 days)
<b>Clinical assessment<sup>b</sup></b>		
Weakness	84% ( <i>n</i> = 272)	
Sensory abnormality	58% ( <i>n</i> = 187)	
Abnormality at noted level	52% ( <i>n</i> = 169)	

IQR, interquartile range.

a Information mainly based on interviews with 248 of 261 consenting patients and gained retrospectively after diagnosis of compression.

b Information based on hospital examination of 324 compressions among 319 patients.

between the spinal level of pain and the structural level of compression. Eighteen per cent of patients were unable to walk by the time a diagnosis was made. There was no association between ability to walk and the patient's self-reported pain level ( $p = 0.99$ ). Most clinical indicators were so common in this sample that they had little potential power as predictors.

The clinical level of sensory abnormality corresponded poorly with the level of cord compression identified on MRI scans. Considering the whole study population of 324 compressions, a sensory level was of value in identifying the level of compression in only 16%.

Factors contributing to delays in diagnosis of compression included slow general practitioner referral for patients not already known to have cancer, delay in referral after first appearance of signs or symptoms [median 66 days; interquartile range (IQR) 37–205 days], and delay between referral and definitive diagnosis (median 15 days; IQR 3–66 days). The rate of diagnosis of malignant cord compression increased through the week and was maximal on a Friday and low on weekend days.

Plain radiographs were obtained for 57% of compressions before diagnosis. Vertebral collapse (defined as  $\geq 50\%$  loss of vertebral height) was seen in 60 out of 187 (32%) plain films, yielding a sensitivity of only 32%. In 39 of these, the level of compression was confirmed on MRI. Hence, correctly predicted compression level was found in only 21% of radiographs. The most common request was for lumbar spine radiography, whereas the commonest site of compression was the thoracic spine.

Bone scintigraphy for back pain was performed in 139 patients. In 49, spinal hotspots suggestive of extensive bone destruction were identified, and in 26 of these the site corresponded to the level of compression as identified by MRI, yielding a true-positive rate of only 19% (26/139).

### Author conclusions

Patients who developed spinal metastases were at risk of irreversible spinal cord damage. Weakness and sensory abnormalities were reported late and identified even later, despite patients having reported pain for a considerable time. Plain films and bone scans accurately predicted 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 was MRI. Certain categories of patients are at risk of malignant cord compression, in particular, patients who are already known to have cancer when they first develop pain or who are  $>50$  years of age, and those with breast or prostate cancer with known bone metastases.

### Reviewer conclusions

The paper looked at clinical symptoms, clinical signs and different technologies. The clinical symptoms and signs examined were found to be common in the selected population and therefore lacked discriminatory predictive power. MRI was judged to be the best available technology for detecting malignant compression and, relative to MRI, both plain radiography and bone scintigraphy were judged to perform badly.

### Loblaw et al. (2005)<sup>62</sup>

#### Relevant aim

One aim was to identify and to assess the utility predictive models for MSCC, and similarly to compare imaging modalities for investigation of suspected MSCC (for previous more detailed discussion of concerns in relation to quality considerations for this systematic review, see *Summary of systematic review evidence*).

#### Design and method

The study was a systematic review that focused on the following seven questions concerning malignant SCC: (1) What are the clinical symptoms of MSCC? (2) What is the optimal approach for investigating suspected MSCC? (3) Is there a role for systemic corticosteroids in the management of MSCC, and if there is, what is the optimal dose? (4) What are the indications for surgery in the management of MSCC? (5) What are the indications for radiotherapy in the management of MSCC? (6) Is there an optimal dose prescription for radiotherapy? and (7) What are the treatment options for recurrent MSCC in an area previously irradiated?

#### Results

Fifty published studies were included and were reviewed by narrative description. Those publications that considered predictors of SCC or of vertebral collapse are discussed elsewhere in this short report.

Six studies were reviewed that addressed the relative utility of myelography and MRI for the investigation of suspected MSCC. These indicated that whole-spine MRI should be used for patients.

### Author conclusions

Predictive risk models may help to define patients at higher risk of developing cord compression, but optimal screening strategy for a population and intervention have not been elucidated. Back pain was not predictive of MSCC. Treatment for patients with MSCC should consider presence of bony compression

and spinal instability comorbidities, pretreatment ambulatory status, technical surgical factors, potential radiotherapy reactions, patient preferences and potential surgical complications.

### Reviewer conclusions

Different factors such as inability to walk, increased deep tendon reflexes, compression fractures on radiographs of the spine, bone metastases present, bone metastases diagnosed > 1 year earlier and age < 60 years were found to be of some predictive value for MSCC. Back pain was found not to be predictive of MSCC.

### Lu et al. (2005)<sup>121</sup>

#### Relevant aim

The aim was to identify independent clinical predictors of MRI-established SCC in cancer patients through the analysis of potential risk factors.

#### Design and method

This prospective study was a review of cancer patients with suspected SCC who were evaluated by MRI at two centres over the period from July 1998 to March 1999. Inclusion required consent by the physician ordering MRI. The patients included in the study had pathologically confirmed cancer diagnosis, no metastatic epidural cancer over the previous 12 months, age  $\geq 18$  years, and gave consent to a brief interview within 7 days of the scan. The patient interviews were conducted by one physician and focused on numerous factors experienced before MRI. Interviews were also conducted with the physicians ordering the scans; most patients were not blind to the results of the MRI. Of 167 eligible episodes of suspected SCC, a total of 136 episodes of suspected SCC among 134 patients were investigated by interview. The primary cancer diagnoses were reported as breast ( $n = 33$ ; 24%), lung ( $n = 33$ ; 24%), prostate ( $n = 21$ ; 15%), non-Hodgkin's lymphoma ( $n = 8$ ; 6%), multiple myeloma ( $n = 6$ ; 4%) and others ( $n = 35$ , 26%). Median age was 61.5 (range 30.9–84.8) years.

Univariate analysis using Fisher's exact test was used to estimate the association of variables with a positive MRI test for SCC. Multivariate stepwise logistic regression was used to identify significant independent predictors of SCC.

#### Results

Clinically important metastatic epidural SCC was defined as any TSC with or without spinal cord displacement. MRI demonstrated 50 episodes of TSC reported at the following spinal levels: cervical 6%; thoracic 64%; lumbar 30%; sacral 6%. Vertebral metastases without TSC were seen in 46 episodes and no vertebral metastases in 40 episodes. In univariate analysis, back pain was not associated with TSC (92% of episodes were associated with back pain). Four independent variables predictive of TSC were identified by multivariate regression as follows: abnormal neurological examination (OR 3.0, 95% CI 1.6 to 10.4;  $p = 0.004$ ); stage IV cancer at initial diagnosis (OR 2.8, 95% CI 1.4 to 7.7;  $p = 0.006$ ); known vertebral metastases (OR 2.8, 95% CI 1.4 to 8.2;  $p = 0.008$ ); and middle or upper back pain (OR 2.7, 95% CI 1.4 to 9.1;  $p = 0.010$ ). These four 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), as summarised in *Table 25*. Only 19% of the episodes were associated with three or four risk factors relative to a prevalence of TSC of 36.7%.

Among the episodes not associated with abnormal neurological examination ( $n = 100$ ), middle or upper back pain and stage IV cancer at initial diagnosis were found to be independent predictive variables. In this population these variables stratified patients experiencing episodes into subgroups with varying risks of TSC, ranging from 11% (no risk factors) to 69% (both risk factors), as summarised in *Table 26*. Only 13% of episodes in this population exhibited both risk factors.

**TABLE 25** Probability of TSC according to number of pre-test risk factors present (all episodes)

Number of significant predictors	Number of episodes	Number of episodes with TSC	Number of episodes with no TSC	LR with TSC/without TSC	Post-test probability of TSC <sup>a</sup>
0	26 (0.19)	2 (0.04)	24 (0.28)	0.143	0.077
1	38 (0.28)	7 (0.14)	31 (0.36)	0.388	0.184
2	46 (0.34)	20 (0.40)	26 (0.30)	1.534	0.435
3 or 4	26 (0.19)	21 (0.42)	5 (0.05)	15.00	0.808
Total	136 (1.0)	50 (1.0)	86 (1.0)		

a Pre-test probability = 50/136 (36.7%); pre-test odds = 50/86; post-test odds = (50/86) × LR; post-test probability = post-test odds / (1 + post-test odds).

**TABLE 26** Probability of TSC according to number of pre-test risk factors present in patients with normal neurological examination

Number of significant predictors	Number of episodes	Number of episodes with TSC	Number of episodes with no TSC	LR with TSC/without TSC	Post-test probability of TSC <sup>a</sup>
0	36 (0.36)	4 (0.14)	32 (0.46)	0.292	0.111
1	51 (0.51)	17 (0.57)	34 (0.49)	1.163	0.333
2	13 (0.13)	9 (0.30)	4 (0.06)	5.25	0.692
Total	100 (1.0)	30 (1.0)	70 (1.0)		

a Pre-test probability = 30/100 (30%); pre-test odds = 30/70; post-test odds = (30/70) × likelihood ratio; post-test probability = post-test odds / (1 + post-test odds).

### Author conclusions

The results confirmed earlier retrospective studies indicating that evaluation of cancer patients with suspected SCC should be based on clinical information that includes cancer-related history, symptom data and presence of pertinent neurological signs. Predictors may help clinicians to assess risk in this patient population.

### Reviewer conclusions

The selected population included several different types of cancers and so the four identified risk factors need to be tested in both similar and different mixed case populations to determine the generalisability of the findings. The primary tumour type and treatment with bisphosphonates or other interventions (except radiotherapy to the level of suspected SCC) which might influence the identity of predictive variables do not appear to have been included in the regression analyses.

### Rose et al. (2009)<sup>88</sup>

#### Relevant aim

The aim of this study was to evaluate prospectively the probability of vertebral fracture in patients who have received single-dose image-guided intensity-modulated radiotherapy (IG-IMRT) for spinal metastases, and also to identify risk factors for such fracture.

#### Design and method

Image-guided-intensity-modulated radiotherapy is a recently developed therapeutic option for patients with spinal tumours. The authors noticed that a number of patients sustained vertebral fractures after

IG-IMRT so they undertook a prospective study to monitor the incidence and risk factors for post-therapy fracture. The study included 71 lesions occurring in 62 patients given IG-IMRT for spinal tumours. The primary cancer types for the 71 lesions were reported as follows: renal cell,  $n = 14$ ; melanoma,  $n = 9$ ; prostate,  $n = 9$ ; sarcoma,  $n = 7$ ; colorectal,  $n = 6$ ; cholangiocarcinoma,  $n = 5$ ; thyroid,  $n = 5$ ; non-small cell lung,  $n = 5$ ; breast,  $n = 4$ ; and other,  $n = 7$ . The spinal distributions of the treated lesions were reported as follows: cervical,  $n = 6$ ; thoracic,  $n = 47$ ; and lumbosacral,  $n = 18$ . The treated sites were classified on CT appearance as lytic ( $n = 46$ ; 65%), sclerotic ( $n = 13$ ; 18%) or mixed ( $n = 12$ ; 17%). The sites were also classified according to the percentage of the vertebral body occupied by the lesion, as follows: 0–20% of the vertebral body occupied,  $n = 26$  lesions (37%); 21–40% occupied,  $n = 18$  (25%); 41–60% occupied,  $n = 10$  (14%); 61–80% occupied,  $n = 7$  (10%); and >80% occupied,  $n = 10$  lesions (14%).

After IG-IMRT patients were followed up using MRI at 2 months and then at 3-month to 4-month intervals. Multiple logistic regression and Cox's proportional hazard models were used to identify factors associated with fracture. Kaplan–Meier analysis was used to determine time to fracture. Fractures were classified as new or progressive; a progressive fracture represented a worsening, after IG-IMRT, of a lesion in which vertebral deformity or end-plate infraction existed at the time of IG-IMRT therapy. The following potential risk factors for fracture were examined: location of the lesion; size of the lesion (tumour occupancy in vertebral body); type of lesion (lytic, sclerotic or mixed); appearance of the lesion in CT; obesity; local kyphosis; bisphosphonate use; IG-IMRT radiation dose; presence of baseline fracture; and histology of fracture.

## Results

Fracture progression was found in 27 vertebral bodies (39%). Multivariate logistic regression analysis showed that CT appearance (lytic or sclerotic/mixed), lesion location and amount of vertebral body occupied by tumour independently predicted fracture progression. Lesions located between T10 and the sacrum were 4.6 times more likely to fracture than were lesions above T10 (95% CI 1.1 to 19.7 times more likely). Lytic lesions were 6.8 times more likely to fracture than were sclerotic and mixed lesions (95% CI 1.4 to 33.3 times more likely). As the amount of vertebral body occupied by tumour increased, the odds of fracture increased.

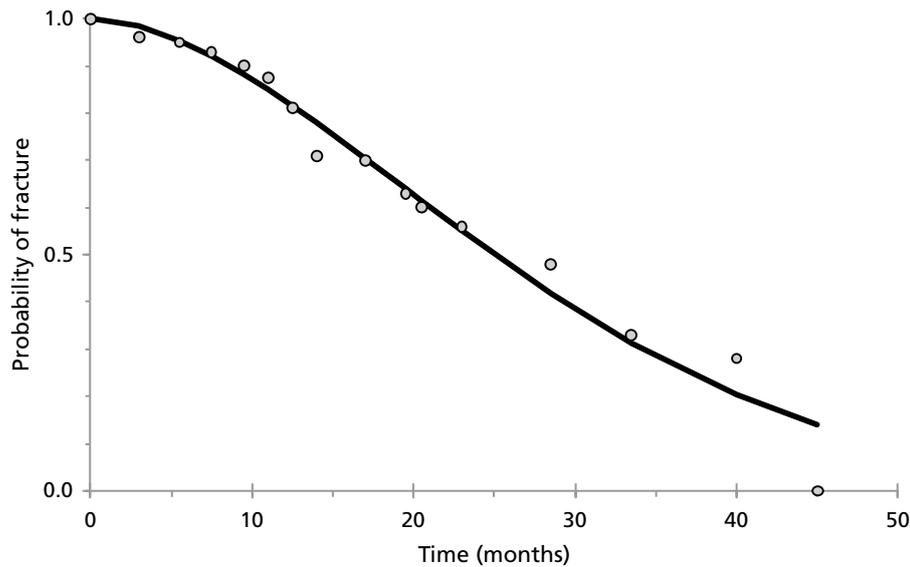
Obesity, local kyphosis, bisphosphonate use, baseline presence of vertebral deformity and IG-IMRT radiation dose were not associated with increased risk of fracture. The presence of baseline fracture was not associated with new fracture development or progression. There was no clear correlation between histology and risk of fracture.

Median time to fracture taken from the Kaplan–Meier analysis was reported to be 25 months. *Figure 17* illustrates the relationship and shows data read from the graph. A Weibull fit generated a median time to fracture of 25.02 months.

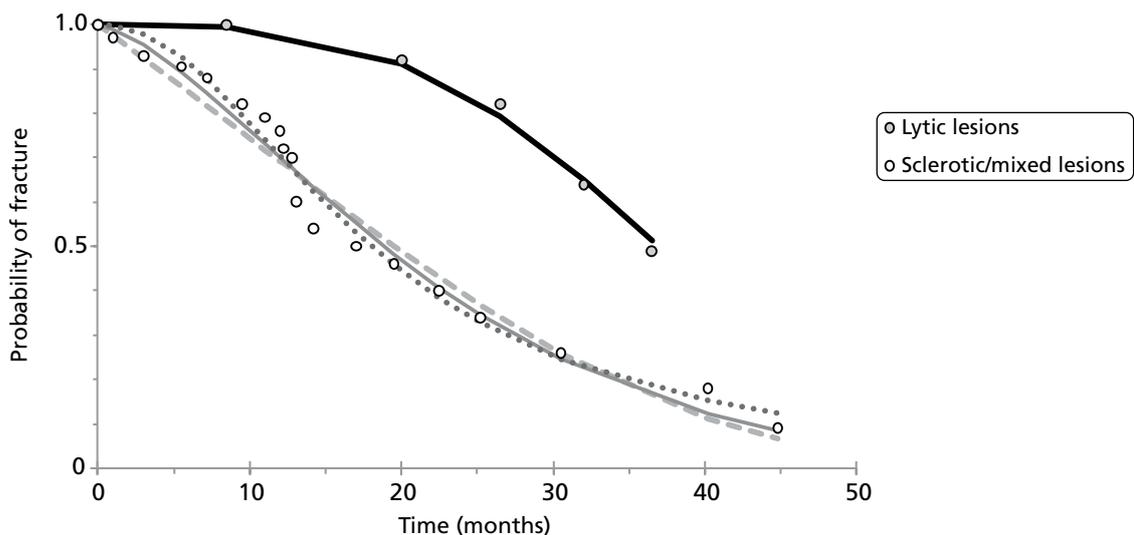
The median time to fracture for lytic lesions was reported to be 19 months, whereas the median time in sclerotic or mixed lesions was 32 months ( $p < 0.05$ ). *Figure 18* illustrates the time-to-event relationship and shows data read from the published graph. Weibull fits generated median times to fracture of 18.9 months for lytic lesions and 36.9 months for sclerotic/mixed lesions.

By stratifying lesions according to location, median time to fracture changed significantly. The median time to fracture with lesions between T10 and the sacrum was 20 months, and for lesions located higher in the spine it was 35 months ( $p < 0.05$ ). Stratification according to the amount of the vertebral body occupied by the lesion also resulted in significantly different fracture probability functions ( $p < 0.02$ ).

In the multivariate proportional hazards regression model, only lytic appearance (HR 3.8, 95% CI 1.3 to 11.4) and lesions that occupied 41–60% of the vertebral body (HR 3.9, 95% CI 1.1 to 14.2) were associated with a statistically significant increase in the HR.



**FIGURE 17** Time to progressive fracture. Data read from graph (Rose 2009<sup>80</sup>). Solid line represents a Weibull distribution fit to extracted data.



**FIGURE 18** Time to fracture for lytic and sclerotic or mixed lesions. Data read from published graph (Rose 2009<sup>80</sup>). Numbers at risk assumed to be 46 and 25, respectively, and numbers of events assumed to be 23 and four, respectively. Solid lines represent fits using Weibull distributions; dashed line uses a Gompertz distribution and dotted line a log-log distribution.

The Karnofsky performance status at final follow-up was 80%. The median change in Karnofsky performance status among patients with fracture progression was 10%, and among patients without fracture progression was 0% ( $p < 0.03$ ).

### Author conclusions

The study identifies a high risk of vertebral fracture after single-fraction IG-IMRT to spinal metastases. Lytic disease involving >40% of the vertebral body and location at or below T10 confers a high risk of fracture, the presence of which yields significantly poorer clinical outcomes.

## Reviewer conclusions

The study explores fracture risk after single-fraction IG-IMRT treatment. Risk of progressive fracture after IG-IMRT was appreciable; poor prognosis for fracture appeared to be associated with lytic lesions, those occupying >40% of the vertebral body and greater load on the deformed vertebra (as indicated by greater risk for lesions below T10). This was a small study with potentially very important findings but because of quality considerations its validity is difficult to evaluate.

## Roth et al. (2004)<sup>124</sup>

### Relevant aim

The study aimed to assess the predictive utility of biomechanically derived models to accurately predict the risk of vertebral burst fracture in the metastatic spine, and to generate simple methods to obtain the required data needed to make such risk assessment of burst fracture.

### Design and method

This was a retrospective study of all cancer patients seen at a single centre between September 1998 and November 2001 who, on the basis of available CT imaging, were considered to have osteolytic metastases of the thoracic or lumbar spine. Vertebrae were classified as not fractured or as bearing burst or wedge fractures.

Of 560 potentially eligible patients with spinal metastases, 117 had suitable CT imaging and, of these, 72 (34 male and 38 female) harboured osteolytic spinal metastases (48 thoracic and 44 lumbar) and were included. Of the 92 metastatic vertebrae, 21 (23%) harboured fractures (17 burst fractures and four compression fractures), and 71 (77%) were not fractured. The primary cancer diagnoses were reported as follows: breast,  $n = 23$ ; lung,  $n = 7$ ; colon,  $n = 3$ ; prostate,  $n = 5$ ; lymphoma,  $n = 6$ ; multiple myeloma,  $n = 5$ ; renal,  $n = 4$ ; other,  $n = 10$ ; and unknown,  $n = 9$ .

The following estimates were made for each vertebra: vertebral body volume; minimal cross-sectional area; tumour volume (as a percentage of the vertebral body volume); apparent bone mineral density; tumour volume in the pedicle (dichotomised as intact or involved) and intervertebral disc quality (dichotomised as healthy or degenerated); pressure load based on patient weight, activity level and apparent cross-sectional area of the vertebra; and estimated proportion of body weight above the vertebral level. Loading rate, dichotomised as high or normal, was also recorded. For fractured vertebrae the minimal sectional area was estimated from that of adjacent intact vertebrae. The data estimates were used in biomechanical models, developed in a previous study, so as to determine the risk of burst fracture for each vertebra. The predicted outcome could then be compared with the known presence or absence of a burst fracture.

### Results

The most accurate predictor of burst fracture was a model of vertebral bulge using only the spinal load-bearing capacity (constant pressure load). At an appropriate threshold (5.04, with a margin of 0.37) this had sensitivity and specificity of 1 for distinguishing burst-fractured vertebrae from unfractured or wedge-fractured vertebrae, and in logistic regression a Hosmer–Lemeshow test value of 1. Burst fracture prediction using vertebral axial displacement and tumour size were also good predictors. None of the models performed well at distinguishing unfractured from fractured (burst or wedge) vertebrae.

### Author conclusions

Fracture prediction was optimised using the vertebral bulge model considering only load-bearing capacity with a specificity, sensitivity and CI of 1 to yield a clear threshold for burst fracture risk. Fracture prediction in the other two models, vertebral axial displacement considering only load-bearing capacity and tumour size, was also strong, with receiver-operator curve values of 0.992 and 0.988, respectively. The predictive power of these models can provide useful clinical information for prophylactic decision-making.

### Reviewer conclusions

As indicated by the authors, the operator inputs required to undertake the modelling described are considerable and the methods used required relatively sophisticated digital scanning equipment, which may not be widely available. The development of automated systems may be required for the necessary data collection to become routine. Although prediction of burst fractures was impressive, the number of samples included was small and the validity of the results needs testing in a larger sample and in different populations.

### *Shah et al. (2003)*<sup>126</sup>

#### Relevant aim

The aim of this study was to identify risk factors for metastatic vertebral fracture and epidural impingement.

#### Design and method

This was a retrospective study of metastatic cancer patients with spinal metastases. Patients were excluded if the primary tumour was a myeloma, lymphoma or other tumour of haematopoietic origin, if MRI was carried out within 30 days of a surgical intervention or if MRI demonstrated a metallic implant.

A random sampling method was reported and was used to select two samples from a population of MRI-evaluated patients with spinal metastases seen at one university hospital between October 1992 and June 1998. The first sample was used to estimate the incidence of vertebral fracture and risk factors for fracture; the second sample was selected from patients who presented with vertebral fracture and was used to investigate progression from normal shape, patterns of fracture and progression to epidural impingement.

The first sample comprised 53 patients (mean age 58 years, SD 26 years; 26/53 male) with images by MRI of 756 vertebrae. The primary tumours were reported as follows: breast,  $n = 14$  patients (26.4%); lung,  $n = 13$  (24.5%); prostate,  $n = 9$  (17%); renal,  $n = 7$  (13.2%); undifferentiated,  $n = 3$  (5.7%); and others,  $n = 7$  (13.2%). Metastatic lesions were observed in 253 out of 756 vertebrae (33.4%). In 114 of these, an isolated zone of lysis or of osteoblastic new bone could be identified; these lesions were classified as circumscribed. Of circumscribed lesions, 104 (91.2%) were confined to the vertebral body (excluding arch and pedicles). The metastatic lesions were observed most commonly among lumbar and posterior thoracic vertebrae.

The second sample comprised 67 patients presenting with vertebral fractures (113 fractured vertebrae). Twenty-two fractures were found to have no metastatic infiltration and were not analysed further, leaving a final sample of 91 fractured vertebrae.

#### Results

The risk of vertebral fracture among infiltrated vertebrae was greatest for upper lumbar (L1–L3) vertebrae relative to other vertebrae (RR 1.95, 95% CI 1.12 to 3.38;  $p = 0.017$ ), and for undifferentiated tumours relative to other tumours (RR 7.36, 95% CI 2.69 to 20.12;  $p = 0.001$ ). Prostate metastases were associated with the smallest risk of fractures (RR 0.21, 95% CI 0.082 to 0.535;  $p = 0.001$ ).

MRI follow-up identified 23 normally shaped vertebrae that progressed to fracture. According to a Cox's proportional hazards model, greater fracture risk was noted in vertebrae with >80% vertebral body infiltration relative to less infiltration (HR 4.60, 95% CI 1.66 to 12.71).

The number of spinal levels affected by metastasis was weakly correlated with the number of fractured vertebrae in an individual patient ( $r = 0.325$ ). There was no significant correlation between metastatic involvement of one or both pedicles with fractures ( $p = 0.43$ ).

Fractures were classified by the authors as (1) symmetrical compression wedge fracture (with 'delta fragments'); (2) symmetrical compression fracture with no 'delta fragments'; (3) lateral compression fracture; or (4) anterior compression fracture. Those classified as wedge fractures had a greater tendency to progress to migration into the epidural space.

### Author conclusions

Fracture risk was greatest for upper lumbar and undifferentiated tumours. Fracture risk was substantially increased in vertebrae with >80% body infiltration, and symmetrical fractures with fragments were associated with the greatest risk of epidural impingement.

### Reviewer conclusions

The reported results are perhaps unsurprising in that those vertebrae tending to bear greater load and sustaining greater metastatic infiltration are more likely to fracture. Similarly, fractures generating bony fragments might be expected to cause more serious epidural penetration. The finding that risk of fracture appears to vary with primary tumour diagnosis is of interest for this report in that it implies that results with mixed cancer type populations might be viewed as largely reflecting the proportional contribution of the different cancer types.

### Talcott et al. (1999)<sup>131</sup>

#### Relevant aim

The aim was to examine potential clinical neurological and oncological risk factors for CT-established SCC in metastatic cancer patients with suspected SCC.

#### Design and method

This was a retrospective study of medical and CT scan records accumulated between 1 February 1985 and 30 September 1988 at a single centre. Patients were included if a CT scan had been conducted for clinically suspected SCC (where SCC = SCC or cauda equina syndrome); this was termed the index scan. Patients were excluded if CT was not carried out for suspected SCC or if they had a previous diagnosis of SCC.

Of 405 index scans identified from records, 342 (in 258 patients) were included for analysis. The reasons for exclusion of 63 scans were reported. Mean age at study entry was 56.5 years. Primary tumour diagnosis was reported as breast in 42% of patients; NSCLC in 14%; prostate in 9%; sarcoma in 5%; and other in 30%.

The time period, study centre, number of index scans identified and the number excluded ( $n = 63$ ) correspond to the Lu *et al.* 1998 study<sup>120</sup> (described earlier); however, Lu *et al.* investigated only breast cancer patients (number reported as 93). Talcott *et al.* report on 258 patients, of whom 42% had diagnosis of breast cancer ( $n = 108$ ); it is likely that most of the breast cancer patients in this study are identical to those reported by Lu *et al.*<sup>120</sup>

The spinal level of the suspected episodes was reported as L3 or L4 in 43% of 342 index scans and T13 in 30% of 342 index scans. Uncertain scans (<5%) were followed up by myelography or MRI. Most patients received imaging before the index CT, mostly to document metastases to bone, especially spine. Plain film radiographs immediately preceded 250 of the 342 index scans; vertebral lesions (lytic 29%, blastic 16%, mixed 20%) were seen in 68% of the plain films and compression fractures were seen in 30%.

#### Results

Twenty-two variables were examined in univariate or multivariate logistic regression for association with SCC. Several definitions of SCC were employed: TSC; spinal cord or cauda equina displacement (SCD); TSC + SCD; EM; SCD + TCD + EM.

**TABLE 27** Variables associated with SCC (TSC or SCD) at index CT or within a 90-day follow-up

Variable	Patients with SCC if variable is		OR (95% CI)	p-value
	Present	Absent		
Bone metastases previously diagnosed	27	8	4.1 (1.7 to 9.8)	0.002
Vertebral body fracture on most recent plain radiograph	42	18	3.3 (1.9 to 5.7)	<0.0005
Increased deep tendon reflexes	43	20	3 (1.6 to 5.6)	0.001
Complaint of inability to walk	39	21	2.4 (1.3 to 4.7)	0.008
Bone metastases diagnosed 1 year prior	34	18	2.4 (1.4 to 4.0)	0.001
Bone metastases diagnosed 90 days prior	30	15	2.3 (1.4 to 4.0)	0.002
Bone metastases diagnosed 2 years prior	37	20	2.3 (1.3 to 4.2)	0.006
Bone metastases diagnosed 6 months prior	31	17	2.2 (1.3 to 3.7)	0.003
Prior radiotherapy elsewhere in the spine	37	20	2.3 (1.3 to 4.1)	0.005
Spine metastases diagnosed 6 months prior	32	17	2.3 (1.4 to 3.8)	0.001
Spine metastases diagnosed 90 days prior	31	16	2.3 (1.4 to 3.8)	0.002
Spine metastases previously diagnosed	27	14	2.2 (1.2 to 4.2)	0.01
Spine metastases diagnosed 1 year prior	34	19	2.2 (1.3 to 3.7)	0.003
Spine metastases diagnosed 2 years prior	36	21	2.1 (1.1 to 3.9)	0.022
Prior radiotherapy at the suspected spinal site	38	22	2.2 (1.1 to 4.7)	0.04
Complaint of bowel or bladder dysfunction	37	21	2 (1.1 to 4.2)	0.02
Any vertebral body lesion on most recent plain radiograph	30	17	2.1 (1.2 to 3.6)	0.004
Vertebral body lytic lesion on most recent plain radiograph	32	19	2.1 (1.2 to 3.4)	0.006
Abnormal plantar reflex	35	21	2 (1.1 to 3.7)	0.02
Weakness on physical examination	31	18	2 (1.2 to 3.3)	0.008
Complaint of sensory loss	33	21	1.9 (1.1 to 3.3)	0.02
Sensory deficit on physical examination	31	21	1.8 (1.0 to 3.0)	0.04

**TABLE 28** Variables associated with TSC at index CT or within 90 days

Variable	OR (95% CI)	p-value
Vertebral body fracture on most recent plain radiograph	2.7 (1.6 to 5.1)	<0.0005
Bone metastases previously diagnosed	2.6 (1.0 to 6.7)	0.05
Complaint of inability to walk	2.3 (1.1 to 4.7)	0.02
Increased deep tendon reflexes	2.3 (1.2 to 4.6)	0.02
Bone metastases diagnosed 1 year prior	1.8 (1.0 to 3.2)	0.04
Age <60 years	1.8 (1.0 to 3.2)	0.05

A positive diagnosis at index scan depended on the formal definition of SCC used. For TSC, 29 out of 342 scans were positive; for SCD, 43 out of 342; for EM only, 52 out of 342; for TSC + SCD, 72 out of 342; for TSC + SCD + EM, 124 out of 342; and for TSC + SCD at index or within the 90-day follow-up, 80 out of 342. If local radiation at the site of suspected SCC within 90 days of a negative index CT, as an indication of SCC, then 169 out of 342 (49%) index scan episodes were positive. The reported associations of variables with SCC in univariate logistic regression is summarised in *Table 27*.

In multivariate logistic regression six variables were significantly associated with TSC at index or during 90 days of follow-up. These are summarised in *Table 28*.

The authors counted the number of these six risk factors present in each patient and related this to the occurrence of TSC at index scan or within 90 days. The results are summarised in *Table 29* together with the post-test probability of having TSC. According to these results, the 23% pre-test probability of TSC (within 90 days of the index scan) is raised to 87% for a patient who exhibits five risk factors.

### Author conclusions

The clinical history of patients' cancer contributes independently to risk assessment. The prevalence of SCC depends on definition used and whether short-term clinical follow-up is included.

### Reviewer conclusions

The authors' main conclusion is justified. The 23% prevalence of TSC among the CT index scans may not be surprising because patients were selected for suspected SCC. Several of the risk factors identified were also probably unsurprising as they included vertebral fracture on most recent radiograph (250 of the 342 index scans were immediately preceded by plain radiograph and fracture is known to be highly associated with SCC); previously diagnosed bone metastases (these may have progressed for a long time before the index scan, and although breast cancer and other patients may have osteoporosis, which might independently lead to bone fractures, it is unlikely that SCC will occur without bone metastasis in this selected population); complaint of inability to walk (a well-known symptom of SCC); increased deep tendon reflex; and age <60 years. Spinal imaging has advanced since this study was conducted (1985–8) so that some of the findings might be interpreted differently in the current context.

**TABLE 29** Probability of TSC according to number of pre-test risk factors present

Total risk factors	Patients in group	Number with TSC (%)	Number without TSC (%)	LR (with TSC/without TSC)	Post-test probability of TSC
0	24	1 (4)	23 (96)	0.1424	0.042
1	63	6 (10)	57 (90)	0.3447	0.095
2	121	25 (21)	96 (79)	0.8529	0.207
3	92	21 (23)	71 (77)	0.9687	0.228
4	27	14 (52)	13 (48)	3.5269	0.519
5	15	13 (87)	2 (13)	21.2875	0.867
Total	342	80 (23)	262 (77)		

*Taneichi et al. (1997)*<sup>89</sup>**Relevant aim**

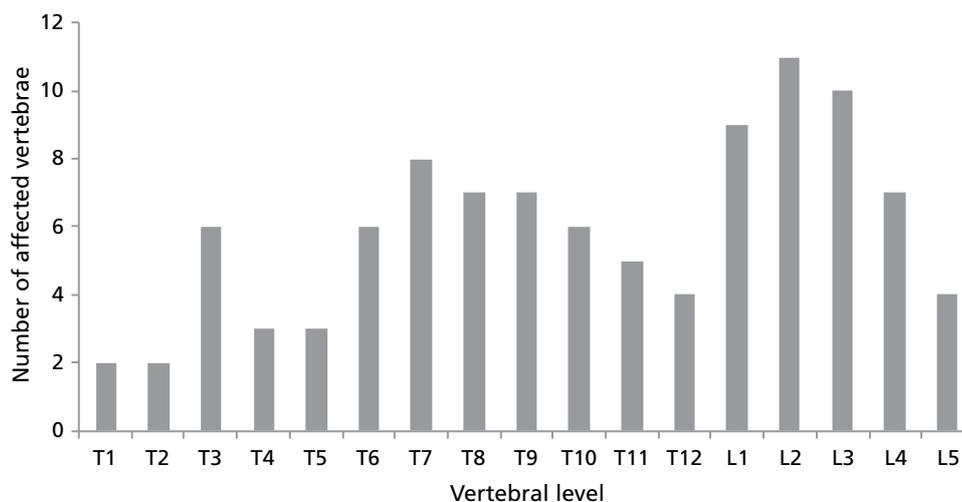
In an attempt to accurately diagnose impending collapse of vertebrae with metastatic invasion, the authors determined the risk factors for vertebral collapse, estimated the predicted probability of collapse under various states of metastatic vertebral involvement and established criteria for impending collapse.

**Design and method**

Fifty-three patients, with ( $n = 40$ ) or without vertebral collapse, harbouring 100 thoracic or lumbar metastatic tumours were studied. The patients' average age was 59.7 years (SD 8.8, range 43–80 years). The sampling frame was not reported but it is implied that patients visited a single centre. The vertebrae were selected if they satisfied the following conditions: they contained purely or predominantly osteolytic metastatic lesions; there were no end-plate fractures in adjacent vertebrae; tomography (sagittal and coronal plane) and CT had been performed within 1 week of an initial plain radiographic examination, and images were judged to be qualified for detailed analysis; and radiographic examinations were performed before biopsy, radiation therapy or surgical treatment (e.g. laminectomy).

A variety of primary cancers were reported to be associated with the 100 vertebrae, as follows: renal cell carcinoma,  $n = 17$ ; breast,  $n = 15$ ; prostate,  $n = 15$ ; hepatocellular,  $n = 13$ ; lung,  $n = 8$ ; oesophageal,  $n = 4$ ; thyroid,  $n = 3$ ; gastric,  $n = 3$ ; colon,  $n = 2$ ; melanoma,  $n = 2$ ; fibrous sarcoma,  $n = 1$ ; rhabdosarcoma,  $n = 1$ ; leiomyosarcoma,  $n = 1$ ; lymphoma,  $n = 1$ ; ureter,  $n = 1$ ; adrenal,  $n = 1$ ; and unknown,  $n = 12$ . The distribution of affected vertebrae was as shown in *Figure 19* and was reported as equally split between T4 to T10 ( $n = 50$ ) and T11 to L4 ( $n = 50$ ).

The potential risk factors for vertebral collapse examined reflected size and disposition of the metastatic lesion in the affected vertebra. Four factors were estimated. Factor [1] was the percentage tumour occupancy (% TO) of the vertebral body. To estimate %TO the CT images were examined using computer software so as to gain measures of A, the most extensive cross-sectional area of the tumour, and B, the cross-sectional area of the adjacent unaffected vertebra measured in the same plain as A. The %TO then =  $100 \times A/B$ ; if A in the affected vertebra could not be reasonably measured then the intact part of the vertebral body C was measured, and a value for A was obtained indirectly as  $B-C$ . Factors [2], [3] and [4] were dichotomised according to CT image estimates of the presence of destruction of, respectively, the pedicle, the posterior elements (not including the pedicle); and the costovertebral joint (T vertebrae only).



**FIGURE 19** Distribution of metastatically affected vertebrae in the study by Taneichi *et al.*<sup>89</sup>

Vertebral collapse was defined as (1) a vertebra with fractures of the end-plate adjacent to the osteolytic lesion, and (2) a vertebra with reduction of vertebral body height because of pathological fractures of the anterior and/or lateral cortex of the vertebral body. Vertebral body height was considered to be reduced when the height of the affected vertebral body was <90% of the estimated original height. This was calculated from an average of the corresponding measurements at adjacent unaffected levels above and below the metastatic vertebra.

The authors developed a multivariate logistic regression model to determine the associations between the occurrence of vertebral collapse and the four risk factors. The predicted probability of vertebral body collapse in various states of metastatic vertebral involvement was estimated using the developed model. A set of criteria for 'impending vertebral body collapse' was suggested.

## Results

There were no differences between T and L groups in the frequency of risk factors in collapsed and intact vertebrae, nor in the %TO of collapsed vertebrae (*Table 30*).

The results of multivariate logistic regression for the T and L group vertebrae are summarised in *Tables 31* and *32*.

For group T vertebrae, the strongest association was between costovertebral joint destruction and vertebral collapse (OR 10.17;  $p = 0.021$ ). The tumour size (%TO) was also associated with the risk of vertebral collapse ( $p = 0.032$ ) with an OR of 2.44 for every 10% increment in %TO. Destruction of the pedicle and other posterior elements was not associated with collapse (OR 1.73;  $p = 0.703$ , and OR 1.17;  $p = 0.886$ , respectively).

For group L, the two most important risk factors for vertebral body collapse were %TO (OR of every 10% increment in %TO 4.35;  $p = 0.002$ ) and pedicle destruction (OR 297.08;  $p = 0.009$ ). Destruction of the posterior elements was inversely correlated with the risk of collapse (OR 0.03;  $p = 0.027$ ).

Based on these results the authors developed the following equations to describe the probability of vertebral collapse in group T and group L:

$$\text{Probability of T collapse} = [\exp(\text{odds of collapse})] / [1 + \exp(\text{odds of collapse})]$$

$$\text{Odds of T collapse} = (0.089 \times [1] + 0.646 \times [2] + 0.161 \times [3] + 2.319 \times [4]) - 4.597$$

where [1], [2], [3] and [4] refer to risk factors listed in *Table 32* and take values [1], 0–100 and [2], [3] and [4], 0 or 1.

**TABLE 30** Frequency of risk factors in group T and group L intact and collapsed vertebrae

	Groups T1 to T10		Groups T11 to L5	
	Present	Absent	Present	Absent
Vertebral body collapse	24	26	26	24
[1] %TO (SD)	40.8 (24.8)		40.3 (24.1)	
[2] Pedicle destruction	15	35	14	36
[3] Posterior element destruction	22	28	12	38
[4] Costovertebral joint destruction	28	22	-	-

**TABLE 31** Summary of logistic regression results for the T group of vertebrae

Risk factor	OR	95% CI	p-value
[1] %TO			
10% increment	2.44	1.07 to 5.55	0.032
20% increment	5.93	1.14 to 30.77	
30% increment	14.44	1.22 to 170.65	
[2] Pedicle destruction	1.73	0.10 to 28.75	0.703
[3] Posterior element destruction	1.17	0.13 to 10.63	0.886
[4] Costovertebral joint destruction	10.17	1.43 to 72.45	0.021

**TABLE 32** Summary of logistic regression results for the L group of vertebrae

Risk factor	OR	95% CI	p-value
[1] %TO			
10% increment	4.35	1.73 to 10.93	0.002
20% increment	18.92	3.00 to 119.39	
30% increment	82.27	5.19 to 1305.53	
40% increment	357.81	8.98 to 14,254.10	
[2] Pedicle destruction	297.08	4.11 to 21,474.90	0.009
[3] Posterior element destruction	0.03	0.00 to 1.00	0.027

Probability of L collapse =  $[\exp(\text{odds of collapse})] / [1 + \exp(\text{odds of collapse})]$

Odds of L collapse =  $(0.147 \times [1] + 5.694 \times [2] - 3.609 \times [3] - 5.492)$

where [1], [2] and [3] refer to risk factors.

Examples of the reported predicted probabilities of fracture for the T group, calculated according to the equation above, are shown in *Table 33*.

Similar reported predicted probabilities of fracture for the L group are shown in *Table 34*.

On the basis of these predictors, the criteria of impending collapse in group T were defined by the authors as (1) 50–60% (%TO) involvement of the vertebral body with no destruction of the other structures; and (2) 25–30% (%TO) involvement of the vertebral body with costovertebral joint destruction. In group L, the criteria were defined as (1) 35–40% (%TO) involvement of the vertebral body with no destruction of the other structures; and (2) 20–25% (%TO) involvement of the vertebral body with destruction of the posterior elements including the pedicle.

### Author conclusions

With respect to the timing and occurrence of vertebral collapse, there is a distinct discrepancy between the thoracic and thoracolumbar or lumbar spine. When a prophylactic treatment is required, the optimum timing and method of treatment should be selected according to the level and extent of the metastatic vertebral involvement.

**TABLE 33** Predicted probability of fracture for T group vertebrae according to different states of metastatic involvement

T group vertebral type	Value	% involvement							
%TO	[1] value	30	60	30	60	30	60	30	60
Costovertebral	[4] value	0	0	1	1	1	1	1	1
Pedicle	[2] value	0	0	0	0	1	1	1	1
Posterior	[3] value	0	0	0	0	0	0	1	1
Reported odds									
Odds T collapse		-1.927	0.743	0.392	3.062	0.938	3.769		
Exp (odds T collapse)		0.1456	2.1022	1.4799	21.370	2.5548	43.336		
1 + exp (odds T collapse)		1.1456	3.1022	2.4799	22.370	3.5548	44.336		
Probability of fracture		0.127083	0.677652	0.596764	0.955298	0.718695	0.977445		
Results by factor									
Factor	[1]	[2]	[3]	[4]	Constant				
Coefficient	0.089	0.546	0.161	2.319	4.597				

**TABLE 34** Predicted probability of fracture for L group vertebrae according to different states of metastatic involvement

L group vertebral type	Value	% involvement							
%TO	[1] value	20	30	40	40	60	5	20	
Pedicle	[2] value	0	0	0	1	1	1	1	
Posterior	[3] value	0	0	0	0	1	1	1	
Reported odds									
Odds L collapse		-2.552	-1.082	0.388	6.082	5.413	-2.672	-0.467	
Exp (odds L collapse)		0.077926	0.338917	1.47403	437.9041	224.3035	0.069114	0.62688	
1 + exp (odds L collapse)		1.077926	1.338917	2.47403	438.9041	225.3035	1.069114	1.62688	
Probability of fracture		0.072	0.253	0.596	0.998	0.995	0.064	0.385	
Results by factor									
Factor	[1]	[2]	[3]	Constant					
Coefficient	0.147	5.694	3.609	5.492					

## Reviewer conclusions

This study is more complete than many in that it develops empirical equations for prediction of fracture. The study selected only intraspinal tumour-related factors as risk factors for collapse; extraspinal factors such as age and sex were not considered. Any effect exerted from different primary types was not explored. Intraspinal factors such as costovertebral joint destruction and tumour size in the thoracic region were found to be significant risk factors. Factors such as tumour size and pedicle destruction were found to be significant risk factors in the thoracolumbar and lumbar spine. The equations developed need testing prospectively in different populations with spinal metastases.

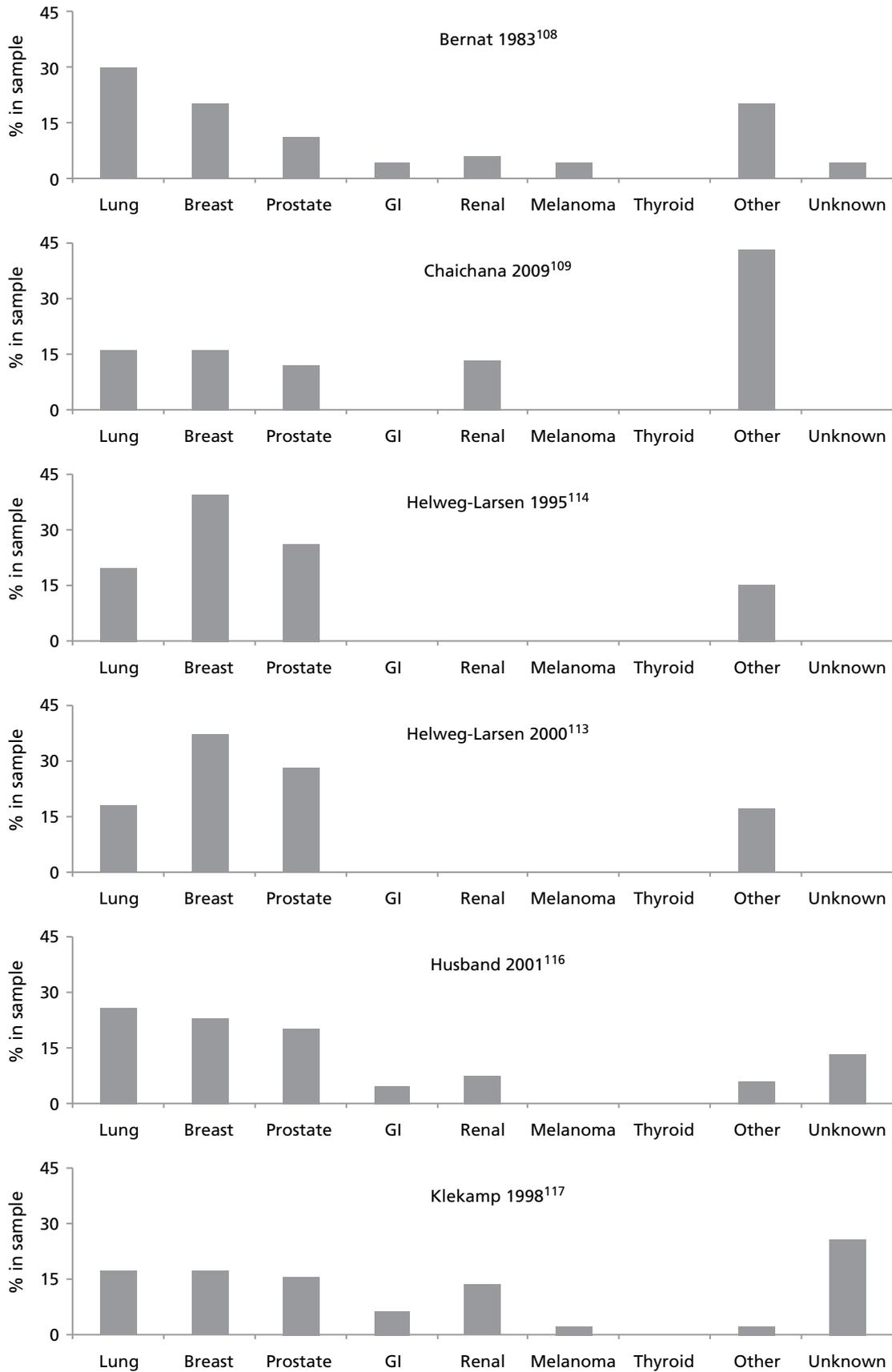


FIGURE 20 The frequency of different cancers in the included case-mix studies. GI, gastrointestinal.

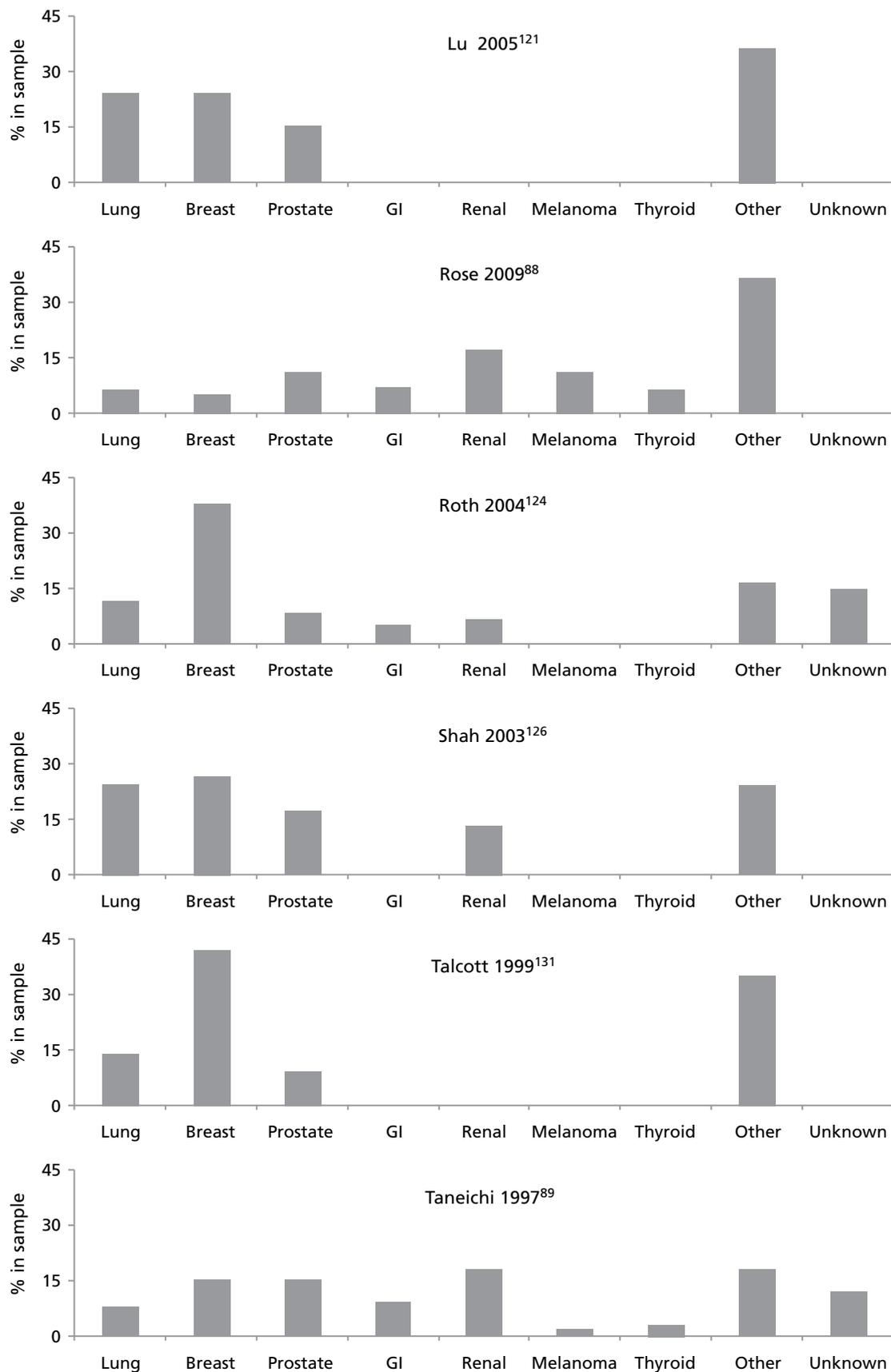


FIGURE 20 The frequency of different cancers in the included case-mix studies. GI, gastrointestinal. (continued)

## Summary of studies involving a variety of cancers

There were 13 studies in which the sample was constructed from participants with a variety of different primary tumour types. The variation in samples in this regard is summarised in *Figure 20*. The study by Levack *et al.*<sup>119</sup> provided insufficient detail to determine the frequency of each major tumour type. In most studies, patients with breast, prostate and lung cancers constituted the majority of participants; however, this was not invariably so and the relative contribution from these three common cancer types was variable from study to study. Attempts to identify symptoms and signs that might increase diagnostic ability were not always successful in the included studies (e.g. Levack *et al.*<sup>119</sup>). Because of the very broad range of factors investigated (see *Table 7*), this summary focuses on clinically significant findings common to several studies.

Two studies (Chaichana *et al.*<sup>109</sup> and Shah *et al.*<sup>126</sup>) found that primary tumour type was a risk factor for vertebral collapse. Similarly, three studies (Helweg-Larsen *et al.*,<sup>114</sup> Helweg-Larsen *et al.*<sup>113</sup> and Klekamp *et al.*<sup>117</sup>) found that primary tumour type was a risk factor for SCC recurrence, and Klekamp *et al.*<sup>117</sup> found that patient health status was also influential. Three studies (Roth *et al.*,<sup>124</sup> Rose *et al.*<sup>88</sup> and Taneichi *et al.*<sup>89</sup>) all found that degree of tumour occupancy of the vertebral body was predictive for fracture.

Two studies (Lu *et al.*<sup>121</sup> and Talcott *et al.*<sup>131</sup>) were able to identify risk factors which in combination in a single individual predicted SCC with high probability (five factors present delivered a probability of 87%<sup>131</sup> and combination of three or four factors gave a probability of 81%<sup>121</sup>). Taneichi *et al.*<sup>89</sup> constructed an empirical algorithm for prediction of fracture in vertebrae harbouring predominantly lytic metastases. CT images were used to estimate tumour occupancy of the vertebral body and the presence or absence of various manifestations of vertebral damage. Two predictive models were developed, one for T4 to T10 and one for T11 to L4. The proposed models gave potential utility but were not widely used in the included studies. According to a citation index the paper has been cited 53 times since publication.

Missing data and a lack of transparency and clarity in reporting, particularly regarding participant selection, mean that in general the validity of findings was uncertain. No studies tested the performance of identified risk factors in a cohort independent of that in which the factors had been identified.

An inference that follows from the finding that risk of fracture appears to vary with primary tumour diagnosis is that the mix of cancer types in these case-mix studies, and the length of time from primary diagnosis to study entry, will influence the results of any analysis of prognostic factors. This leads to considerable difficulty interpreting the results from these studies. Potential confounding effects of primary tumour type, age and treatment with bisphosphonates or other interventions should have been considered when attempting to identify predictive variables.

## Expert opinion paper

### *Fisher et al. (2010)*<sup>110</sup>

#### Relevant aim

A stated objective of this study was 'To use an evidence-based medicine process using the best available literature and expert opinion consensus to develop a comprehensive classification system to diagnose neoplastic spinal instability'. The authors comment that spinal stability may be defined as the ability of the spine to maintain its degree of motion while simultaneously preventing pain, neurological deficit and abnormal angulation.

## Design and method

The authors (34 members of a Spine Oncology Study Group) used evidence provided by two systematic reviews undertaken by members of the group, and attempted to integrate this with expert opinion through a modified Delphi technique to generate through consensus of best evidence and expert opinion a classification system to define neoplastic spinal instability. The outcome was a spinal instability scoring system (Spine Instability Neoplastic Score). The authors believe that the Spine Instability Neoplastic Score, together with a patient's overall prognosis and physical condition, should be taken into account when considering interventions (e.g. surgery) that might be appropriate.

**TABLE 35** Spine Instability Neoplastic Score components and their associated scores (data taken verbatim from published table, Fisher 2010<sup>110</sup>)

Component	Score	Commentary
<b>Spine location</b>		
Junctional (occiput–C2, C7–T2, T11–L1, L5–S1)	3	Spine location is scored based on global variations in the spinal architecture. Junctional regions include occipitocervical (C0–C2), cervicothoracic (C7–T2), thoracolumbar (T11–L1) and lumbosacral (L5–S1) regions. Mobile segments include those not in the junctional regions and those that do not articulate with the rib cage. Semi-rigid segments are non-junctional segments in the thoracic region that articulate with the rib cage. Rigid segments are parts of the non-junctional sacral spine (S2–S4)
Mobile spine (C3–C6, L2–L4)	2	
Semi-rigid (T3–T10)	1	
Rigid (S2–S5)	0	
<b>Pain relief with recumbence and/or pain with movement/loading of the spine</b>		
Yes	3	Mechanical or postural pain is scored in this section. Relief with recumbency supports a structural or mechanical component
No (occasional pain but not mechanical)	1	
Pain-free lesion	0	
<b>Bone lesion quality</b>		
Lytic	2	This category is meant to describe spinal alignment between motion segments that are affected by tumour. Scoring of de novo deformity such as kyphosis and/or scoliosis requires knowledge of prior imaging or may be assessed with upright compared with supine radiographs
Mixed lytic/blastic	1	
Blastic	0	
<b>Radiographic spinal alignment score</b>		
Subluxation/translation present	4	This category is meant to describe spinal alignment between motion segments that are affected by tumour. Scoring of de novo deformity such as kyphosis and/or scoliosis requires knowledge of prior imaging or may be assessed with upright compared with supine radiographs
De novo deformity (kyphosis/scoliosis)	2	
Normal alignment	0	
<b>Vertebral body collapse score</b>		
<50% collapse	3	Presence and extent of vertebral body height collapse are used to assign a contribution of the score to the anterior and middle columns
>50% collapse	2	
No collapse with >50% body involved	1	
None of the above	0	
<b>Posterolateral involvement of spinal elements (facet, pedicle, or costovertebral joint fracture or replacement with tumour)</b>		
Bilateral	3	The 'posterolateral elements of the spine' component of the score allows contribution from the posterior elements including pedicles, facets and costovertebral joints. Bilateral involvement is scored as greater than double the contribution of unilateral involvement because of the destabilising nature of its effects
Unilateral	1	
None of the above	0	

One systematic review was referenced as 'in press': (1) Fehlings MD, Furlan J, Bilsky M, *et al.* Defining oncologic instability of the cervical spine can the available evidence guide clinical practice? *Spine* (in press). This study was not retrieved in our searches. A study by Weber *et al.*<sup>52</sup> was excluded from this short report because the outcome measures did not meet the inclusion criteria (see *Appendix 5*). Most of the studies included in the Weber systematic review were conducted with animal models, cadaver vertebrae or computer modelling and were not concerned with testing prognostic variables in humans with spinal metastases.

### Results

The authors developed a Spine Instability Neoplastic Score for a series of variables that may be present in a particular patient. The variables were classified under six categories and are summarised in *Table 35*.

### Author conclusions

The Spine Instability Neoplastic Score was found to be a comprehensive classification system with content validity that could potentially guide clinicians in identifying when patients with neoplastic disease of the spine may benefit from surgical consultation. The Spine Instability Neoplastic Score might aid surgeons in assessing the key components of spinal instability due to neoplasia and may become a prognostic tool for surgical decision-making when put in context with other key elements such as neurological symptoms, extent of disease, prognosis, patient health factors, oncological subtype and radiosensitivity of the tumour.

### Reviewer conclusions

It is difficult to discern how the findings of the systematic reviews fed into the study findings. In essence, this study is an expert opinion piece, and as such its quality is difficult to gauge using conventional assessment procedures. As with other studies included in this short report, the potentially prognostic variables identified require testing quantitatively in appropriate relevant populations; the clear difference between this study and others is that the prognostic variables deemed important have been identified on the basis of evidence synthesis by expert opinion.

## Overall summary of results

No studies were identified that primarily aimed at describing the natural history of spinal metastases. It was not possible to examine the full text of all 2425 retrieved studies; consequently, natural history descriptions might exist but the titles (and abstracts) of such publications failed to reveal this fact readily. Because progression of spinal metastases will be influenced by the many different interventions that can affect host bone and/or resident metastases, and because spinal metastases vary according to tumour type and the general condition of the patient, we think a description of a natural history of spinal metastases is problematic. The relatively poor imaging methods available in early studies, in which interventions were minimal, means that it is unlikely that these would provide representative cohorts of patients and findings generalisable to current practice.

Imaging methods used for detection of SCC and/or vertebral fracture changed over the duration of the studies described. Formal comparison of different imaging procedures was rarely undertaken. We found no RCTs. It is clear that investigators favoured MRI and CT over myelography and/or plain radiography. Bone scans were widely employed but PET was not used in any of the included studies. The development and routine availability of machines with faster throughput and better performance (e.g. resolution) may change practice.

The included studies provided some evidence regarding factors that influence the risk of vertebral fracture and/or SCC. In general, these risk factors were unsurprising and would be familiar to clinicians charged with the care of patients with spinal metastases. They included the following: the number of spinal metastases (or skeletal metastases); the time of exposure to spinal metastases (i.e. survival); type of primary tumour and whether the spinal metastasis is lytic or blastic; the degree of occupancy of the vertebral

body by the metastasis and its distribution. Some studies (e.g. Taneichi *et al.*,<sup>89</sup> Snyder *et al.*<sup>128</sup> and Roth *et al.*<sup>124</sup>) attempted to combine risk factors into a decision rule that developed a probability for occurrence of an event. These appeared to have modest discriminatory power and were not tested by the authors in a population independent of that in which they were developed. Generally, the included studies made use of medical records and/or stored scan images to identify and quantify potential risk factors, and this information had not been collected specifically for the reported investigation.



## Chapter 4 Discussion

The present report aimed to examine the natural history of metastatic spinal lesions and to identify patients at high risk of vertebral fracture and SCC. We did not find any epidemiological evidence with a primary aim of evaluating the natural history of spinal metastases. This review therefore focused on studies of spinal metastatic disease and candidate prognostic factors to predict undesirable outcomes for individuals or their vertebrae.

### Summary of background

The overall effects of MSCC can be devastating. Spinal metastases can lead to significant morbidity and reduction in quality of life due to SCC or collapse. Compression of the spinal cord carries with it the risk of paralysis of body structures below the level of compression. If it were possible to predict which vertebrae were more likely to fracture, then early targeted treatment might prevent, reduce or delay such events and the serious unwanted outcomes that might result. There are many diagnostic methods available, including plain radiography, myelography, MRI, CT, radionuclide bone scan, SPECT and PET. However, uncertainty surrounds the effectiveness of these diagnostic techniques.

### Summary of methods

Evidence was retrieved through searches during June 2011 in 13 electronic bibliographic databases, contact with experts in the field, scrutiny of references of included studies, and checking various health-service research-related resources. The search strategy covered the concepts of metastatic spinal lesions, adults, natural history, outcomes, technologies and prognosis. No study type or publication type restrictions were applied, as all types of study involving all languages were screened for potential inclusion. The titles and abstracts of retrieved studies were examined for inclusion by two reviewers independently. Disagreement was resolved by retrieval of the full publication and consensus agreement. Included studies involved adult patients with vertebral metastases at risk of developing (or who had developed) MSCC, vertebral collapse or progression of vertebral collapse and involved diagnostic/prognostic methods, including clinical features and/or imaging technologies. The full data were extracted independently by one reviewer. All extracted data were reviewed by a second researcher, and any disagreements were resolved by discussion. A quality assessment instrument was used to assess bias in six domains: study population, attrition, prognostic factor measurement, outcome measurement, confounding measurement, and account and analysis. Data were tabulated and discussed in a narrative review. Summary tables for each included paper were provided. Each tumour type was looked at separately.

### Summary of principal findings

#### Searches

Comprehensive searches identified 2425 potentially relevant articles. Of these, 30 primary studies and one systematic review met the inclusion criteria. Seventeen studies reported retrospective data, 10 were prospective studies and three were other study designs. There were no RCTs. The approximate overall number of participants selected was 7888 and sample sizes analysed ranged from 41 to 859. Types of cancers reported were lung alone ( $n = 3$ ), prostate alone ( $n = 6$ ), breast alone ( $n = 7$ ), mixed cancers ( $n = 13$ ) and unclear ( $n = 1$ ). We did not identify any epidemiological studies with a primary aim of investigating the natural history of spinal metastases.

### Quality assessment

Five studies were considered to be of relatively high quality<sup>88,120,123,125,131</sup> as they scored 'yes' on five of the six overall quality assessment questions developed for this review. Two additional studies are recognised by the reviewers to be of particular relevance and of reasonable quality, those by Venkitaraman *et al.*<sup>133</sup> and Taneichi *et al.*<sup>89</sup>

### Limitations in the evidence base

We identified some key limitations with the evidence in this review including:

- limited information about the patient population and selection criteria
- poor reporting of methods for estimating values for prognostic factors
- failure to justify missing data or perform sensitivity analyses around the effects of missing data
- limited reporting of multivariate models
- time-to-event analyses failed to indicate numbers at risk at different time intervals
- failure to consider potentially influential confounders for risk of SCC (e.g. primary tumour type) and treatments (e.g. with bisphosphonates).

There was a lack of coherence of potential predictive factors investigated between research groups. Across studies there was a lack of consistent methodology with regard to sampling procedure, populations (disease stage), treatments received for primary cancer or metastases, or definitions of outcome measures.

Further sources of uncertainty result from the small number of participants in the majority of studies and the small number of studies between which populations were comparable.

### Natural history

We were unable to draw strong conclusions on natural history because of the limited information available.

The natural history of progression of skeletal metastasis suggests that all patients with occult SCC on MRI, if untreated, may progress to develop neurological deficit.<sup>133</sup> The risk of SCC and of the recurrence of cord compression increases with longer survival.

If the natural history of a condition is taken to be a description of how it progresses in the absence of influential interventions then the available information does not allow a precise or detailed description of the natural history of spinal metastases. Factors contributing to this situation include the following:

- (a) Many interventions, encompassing a wide variety of actions, have been developed and employed for treatment of primary tumours and specifically for skeletal metastases. These, to a greater or lesser extent, alter the natural progression of spinal metastases; they may inhibit or block the progressive growth of the metastasis, or they may alter bone metabolism (e.g. tamoxifen, bisphosphonates, denosumab, cytotoxic drugs, radiation) so that unwanted sequelae are more or less likely.
- (b) Early studies on the natural progression of spinal metastases in which the influence of interventions may be minimal are unlikely to provide samples that are currently useful. This is partly because imaging has changed and also because clinical practice at that time would tend to identify more advanced cases.
- (c) Spinal metastases can arise from a wide variety of primary cancer types and so do not represent a single entity. The natural history of metastases is likely to reflect characteristics of the primary tumour from which they arise. Some of the mixed cancer studies included in this report show that the type of primary tumour may be important for the development of SCC and/or vertebral collapse from spinal metastases.

The primary aim of many of the included studies was to identify prognostic factors for survival, the analysis of influential factors for intermediate outcomes; SCC or vertebral collapse was often an incidental objective.

### **Prognostic factors for vertebral collapse or spinal cord compression**

In the 30 primary studies a total of 93 prognostic factors were reported as statistically significant in predicting the risk of progression and/or spinal collapse. The considerable variability in the prognostic factor categories, the quality of studies, the lack of studies for some categories, and changes in practice over the time period to which the studies relate have all made it difficult to provide clear conclusions as to which factors might currently offer the most potential to identify patients at high risk of vertebral fracture and SCC.

The evidence presented in this report suggests that the greater the extent of invasion of any one vertebra by metastases, the more likely spinal fracture is to occur, and the more spinal metastases present and the longer a patient is at risk, the greater the chance of SCC. In addition, there is an increased risk of developing SCC if a cancer has already spread to the bones. Clinicians are likely to have been aware of these factors and much of the research reported here appears to add little to current knowledge. Several included studies with mixed case populations identified cancer type as a significant factor in predicting SCC, but it remains difficult to determine a precise increment in risk as a result of the type of cancer (e.g. breast, lung or prostate cancer) and these studies are liable to suffer from both length and lead-time bias.

A broad range of factors was associated with preoperative compression fractures and MSCC. These included sensory deficits, primary breast cancer, anterior spine metastases, inability to walk, increased deep tendon reflexes, longer time interval from diagnosis of primary tumour until development of SCC, longer-surviving patients, type of primary tumour, thoracic spine involvement, preoperative chemotherapy, tumour size and pedicle destruction, focal radiographic abnormalities with consistent neurological findings, patient's health status and, possibly, preoperative radiation therapy.

Some specific prognostic factors were only identified by a few studies (or in some cases by a single study). The most commonly reported factor was related to tumour characteristics and was found to be significant for 11 factors in eight studies,<sup>88,89,109,110,113,117,126,129</sup> however, the definition of tumour characteristics varied between the different studies [e.g. amount of vertebral body occupied by tumour,<sup>88</sup> overall tumour size and pedicle destruction in the thoracolumbar and lumbar spine (TH10-15),<sup>89</sup> tumour size in the thoracic region,<sup>89</sup> blastic-type tumour,<sup>109</sup> lytic-type tumour,<sup>109</sup> tumour pain,<sup>109</sup> favourable tumour histology,<sup>117</sup> time interval from diagnosis of the primary tumour,<sup>113</sup> total involvement of vertebra,<sup>129</sup> tumour involvement of >50%,<sup>110</sup> undifferentiated tumours<sup>126</sup>].

In addition to the 93 prognostic factors reported as statistically significant in one or more of the 30 included studies, a further large number of potential prognostic factors were identified in the included studies.

As far as diagnostic interventions were concerned, MRI was reported to be the best available technology for detecting malignant compression and, relative to MRI, plain radiography and bone scintigraphy were judged to perform badly.

## Prognostic factors by cancer type

### Summary of prostate cancer studies

None of the included prostate cancer studies provided a description of the natural history of spinal metastases.

The six included studies varied in methodology and transparency, and this resulted in difficulties in interpreting the findings reported. In particular, it was often difficult to ascertain how study samples were selected. In three studies (by Bayley *et al.*<sup>107</sup> and Venkitaraman *et al.*<sup>132,133</sup>) patient participation depended on physicians' decisions (e.g. regarding requirement for MRI), but the criteria for decision-making were not clear. In Huddart *et al.*,<sup>115</sup> an investigation conducted at the same centre as the Venkitaraman studies,<sup>132,133</sup> but a decade earlier, participants had been diagnosed with SCC; however, it was not clear if this was a subsample of such patients at the centre or a complete set. The report of Soerdjbalie-Maikoe *et al.*<sup>129</sup> gave no information regarding sampling frame. In Kuban *et al.*<sup>118</sup> both sampling frame and selection procedure were fully described.

Patient populations differed with regard to degree of progression of their prostate cancer so that looking for coherence of results across studies should be undertaken with caution. In the study by Bayley *et al.*<sup>107</sup> patients had metastatic prostate cancer with neurological deficit. In two studies (by Kuban *et al.*<sup>118</sup> and Huddart *et al.*<sup>115</sup>) metastatic patients with SCC were examined. Venkitaraman *et al.*<sup>132</sup> investigated patients with SCC but no neurological deficit, whereas in two studies (by Venkitaraman *et al.*<sup>133</sup> and Soerdjbalie-Maikoe *et al.*<sup>129</sup>) patients had progressed to become castration resistant. A further complication arises because previous and current treatments and the timing of their implementation, both of which are likely to affect the natural progression of the spinal metastases and to influence the identity of potential prognostic factors, varied between studies.

All studies used medical records to ascertain measures of and presence of risk factors. These records are not collected for the purposes of the studies according to a structured framework that was applied equitably to each participant. Furthermore, the completeness of information content within the records was indeterminate. The six studies together included only 409 patients.

In one investigation of castration-resistant metastatic prostate cancer, risk of SCC before death was 24% and was 2.37 times greater with high-grade cancer than with low-grade cancer (Gleason score  $\geq 7$  compared with  $< 7$ ) ( $p = 0.003$ ). A further investigation reported that patients with six or more bone lesions were at greater risk of SCC than those with fewer than six lesions (OR 2.9, 95% CI 1.012 to 8.35;  $p = 0.047$ ). For these patients median time from initial MRI for suspected SCC to development of neurological deficit was 896 days (95% CI 13 to 986 days).

The results from these studies imply the following:

- Patients with a high-risk bone scan may benefit from MRI investigations of the spine aimed at early detection and treatment of occult SAS compression/SCC.
- The more spinal metastases present, and the longer a patient is at risk, the greater the chance of clinically occult SCC.
- The time a patient is on hormone therapy may be a proxy for how long they are at risk of occult compression.
- 'Total involvement of vertebra', according to scintigraphy, appeared to be highly discriminatory for subsequent SCC (Soerdjbalie-Maikoe *et al.*<sup>129</sup>).
- Time-to-event analyses were difficult to generalise because of the different populations studied and uncertainty regarding their representativeness.
- The validity of the risk factors identified in these studies did not appear to have been tested in an independent population selected according to similar criteria.
- No significant predictive factors were identified for risk of future relapse (i.e. second SCC).

### Summary of breast cancer studies

None of the studies described the natural history of spinal metastases derived from breast cancer.

The seven included studies were disparate in terms of population, imaging procedures and study aims. Harrison *et al.*'s participants<sup>112</sup> with suspected SCC underwent myelographic imaging and an attempt was made to identify risk factors associated with positive and negative myelograms. Lu *et al.*<sup>120</sup> examined 93 patients with suspected SCC and identified clinical and oncological features associated with a positive CT scan for SCC. Oka *et al.*<sup>123</sup> searched for risk factors associated with development of bone metastases in 695 breast cancer patients and another study (by Plunkett *et al.*<sup>24</sup>) looked for factors associated with skeletal events in breast cancer patients with bone metastases. McCloskey *et al.*<sup>122</sup> investigated how dimensional measures (e.g. vertebral height) made in vertebrae with metastases and in adjacent intact vertebrae could be used in the diagnosis of vertebral fracture/collapse while the two biomechanical studies (by Snyder *et al.*<sup>127,128</sup>) examined the power of vertebral load-bearing capacity estimates for predicting vertebral fracture, comparing the specificity of the method with that of Taneichi *et al.*<sup>89</sup>

In the early study by Harrison *et al.*<sup>112</sup> a positive myelogram for suspected epidural SCC was associated with a positive bone scan ( $p < 0.001$ ), bone pain ( $p < 0.001$ ) and paraesthesias ( $p = 0.009$ ). Among breast cancer patients who underwent a CT for suspected SCC, multiple logistic regression identified four independent variables predictive of a positive test: bone metastases  $\geq 2$  years (OR 3.0, 95% CI 1.2 to 7.6;  $p = 0.02$ ); metastatic disease at initial diagnosis (OR 3.4, 95% CI 1.0 to 11.4;  $p = 0.05$ ); objective weakness (OR 3.8, 95% CI 1.5 to 9.5;  $p = 0.005$ ); and vertebral compression fracture on spine radiograph (OR 2.6, 95% CI 1.0 to 6.5;  $p = 0.05$ ). A Japanese Cox's regression study of breast cancer patients following primary surgery indicated that the risk of developing bone metastases was associated with TNM T stage (HR 1.615, 95% CI 1.322 to 1.973;  $p < 0.0001$ ); N stage classification (HR 2.128, 95% CI 1.381 to 3.279;  $p = 0.0006$ ); presence of metastases to axillary lymph nodes ( $p = 0.0006$ ); and the presence of metastases in important organs (HR 7.502, 95% CI 5.100 to 11.036;  $p < 0.0001$ ). Of patients who developed skeletal metastases, 82% exhibited spinal metastases, and 14% of these developed paralysis. The median time between detection of skeletal metastases and development of SCC was 4.4 (range 2–72) months.

A consideration of quantitative results from the breast cancer studies does not easily allow generation of a coherent numerical summary; as with prostate cancer, studies were heterogeneous especially with regard to populations, results were not consistent between studies, and almost universally, study results lacked independent corroboration.

The results summarised below should therefore be viewed with caution:

- A positive bone scan, back pain, paraesthesia and bladder/bowel dysfunction at the time of myelography were more common in patients with a positive myelogram than in those with a negative myelogram (Harrison *et al.*<sup>112</sup>).
- Objective weakness in patients with suspected SCC was predictive for SCC, although calculated estimates of sensitivity and specificity were very modest (Lu *et al.*<sup>120</sup>).
- Stratification of patients suspected of SCC according to the number of independent risk factors identified a high-risk group with an 85% probability of CT-positive SCC (Lu *et al.*<sup>120</sup>).
- TNM classification stages were identified as risk factors – N stage classification, metastases to axillary lymph nodes and visceral metastases for the development of skeletal metastases (Oka *et al.*<sup>123</sup>).
- Longer survival was found to be a risk factor for vertebral fracture and for spinal cord compression (Plunkett *et al.*<sup>24</sup>).
- The 'vertebral load bearing capacity algorithm' developed by Snyder *et al.*<sup>127,128</sup> was reported as having superior specificity to the method used by Taneichi *et al.*<sup>89</sup> for predicting vertebral collapse.

The included studies generally provided limited information about the patient population and selection criteria. Results from time-to-event analyses are difficult to generalise because of the different populations studied and uncertainty regarding their representativeness.

### Summary of lung cancer studies

Two of the three included studies (by Sekine *et al.*<sup>125</sup> and Sun *et al.*<sup>130</sup>) investigated patients with NSCLC and recruited a substantial number of participants (642 with advanced disease and 273 with bone metastases). Goldman *et al.*<sup>111</sup> studied SCLC.

Among patients with advanced NSCLC who received chemotherapy, the occurrence of SREs (i.e. fracture, SCC, requirement for bone surgery or radiotherapy, or hypocalcaemia causing death or requiring emergency treatment) was reported to be associated with the load of bone metastases (OR 3.08, 95% CI 1.60 to 5.94 for single bone metastasis; OR 4.27, 95% CI 2.66 to 6.86 for multiple bone metastases). Among patients with more than one bone metastasis, the median time from start of chemotherapy to occurrence of first SRE was 19.7 months (95% CI 14.5 to 24.9 months). Another study of advanced SCLC patients with skeletal metastases multivariate analysis identified 'ever smoked' as significantly associated with risk of a SRE (OR 2.8, 95% CI 1.32 to 6.00).

Findings included:

- The greater the number of bone metastases, the greater the risk of a SRE (Sekine *et al.*<sup>125</sup>).
- Smoking, no history of treatment with EGFR TKIs, poor ECOG status and non-adenocarcinoma were associated with more likely occurrence of SREs (Sun *et al.*<sup>130</sup>).
- For patients with and without SCC, a combination of cerebral metastases and a positive bone scan were reported to provide a post-test 25% probability for developing SCC, an improvement on the pre-test probability of 0.039. However, this result should be viewed with caution because it was unclear if cerebral metastases actually preceded SCC (Goldman *et al.*<sup>111</sup>).

These were retrospective studies that depended on retrieval of information from medical records not designed for and possibly not suitable for the study questions addressed. Caution is needed in generalising the conclusions across and beyond the included studies. The prognostic factors identified have not been validated in other independent populations.

### Summary of studies involving a variety of cancers

Thirteen studies<sup>88,89,108,109,113,114,116,117,119,121,124,126,131</sup> investigated mixed primary tumour types. Patients with breast, prostate and lung cancers provided the majority of participants; however, it is important to note that the relative contribution of different tumour types varied considerably from study to study. A very broad range of factors was investigated. The variation in samples in this regard is summarised in *Figure 20*. The study by Levack *et al.*<sup>119</sup> provided insufficient detail to determine the frequency of each major tumour type in the sample. In most studies patients with breast, prostate and lung cancers provided the majority of participants; however, this was not invariably so, and the relative contribution from these three common cancer types was variable from study to study. Attempts to identify symptoms and signs that might increase diagnostic ability were not always successful in the included studies (e.g. the study by Levack *et al.*<sup>119</sup>). Because of the very broad range of factors investigated (see *Table 7*) this summary focuses on significant findings common to several studies.

Among patients who received surgery for SCC, a retrospective analysis identified that vertebral body compression fractures were associated with presurgery chemotherapy (OR 2.283, 95% CI 1.064 to 4.898;  $p = 0.03$ ), primary breast cancer (OR 4.179, 95% CI 1.457 to 11.983;  $p = 0.008$ ), thoracic involvement (OR 3.505, 95% CI 1.343 to 9.143;  $p = 0.01$ ) and anterior cord compression (OR 3.213, 95% CI 1.416 to 7.293;  $p = 0.005$ ). In another study, TSC was associated with abnormal neurological examination (OR 3.0, 95% CI 1.6 to 10.4;  $p = 0.004$ ), stage IV cancer at initial diagnosis (OR 2.8, 95% CI 1.40 to 7.7;  $p = 0.006$ ), known vertebral metastases (OR 2.8, 95% CI 1.4 to 8.2;  $p = 0.008$ ) and middle or upper back pain (OR 2.7, 95% CI 1.4 to 9.1;  $p = 0.010$ ).

Findings common to several of these mixed cancer studies included:

- Primary tumour type was a risk factor for vertebral collapse in two studies (by Chaichana *et al.*<sup>109</sup> and Shah *et al.*<sup>126</sup>).
- Primary tumour type was also a risk factor for SCC recurrence in three studies (by Helweg-Larsen *et al.*<sup>113,114</sup> and Klekamp and Samii<sup>117</sup>).
- Patient health status was also a factor in SCC recurrence (by Klekamp and Samii<sup>117</sup>).
- Degree of tumour occupancy of the vertebral body was predictive for fracture in the studies by Roth *et al.*,<sup>124</sup> Rose *et al.*<sup>88</sup> and Taneichi *et al.*<sup>89</sup>.
- Two studies (by Lu *et al.*<sup>121</sup> and Talcott *et al.*<sup>131</sup>) were able to identify risk factors which in combination in a single individual predicted SCC with high probability – five factors present delivered a probability of 87%<sup>131</sup> and a combination of three or four factors gave a probability of 81%.<sup>12</sup>
- Taneichi *et al.*<sup>89</sup> constructed an empirical algorithm for prediction of fracture in vertebrae harbouring predominantly lytic metastases, which was found to be potentially useful, as were other proposed models.

Missing data and a lack of transparency and clarity in reporting, particularly regarding participant selection, mean that in general the validity of findings was uncertain. No studies tested the performance of identified risk factors in a cohort independent of that in which the factors had been identified.

An inference that follows from the finding that risk of fracture appears to vary with primary tumour diagnosis is that the mix of cancer types in these studies, and the length of time from primary diagnosis to study entry, will influence the results of any analysis of prognostic factors. This leads to considerable difficulty interpreting the results from these studies. Potential confounding effects of primary tumour type, age and treatment with bisphosphonates or other interventions should have been considered when attempting to identify predictive variables.

### Overall evaluation of the results

We did not identify any epidemiological study with a primary aim of investigating the natural history of spinal metastases. Because the progression of spinal metastases, from inception to complications, will be influenced by the use of the many different interventions that can affect host bone and/or resident metastases, and because spinal metastases vary according to tumour type and the general condition of the patient, a description of a natural history of spinal metastases is problematic. Relatively poor imaging methods were available in the early studies and interventions were minimal. This means that these studies are likely to provide unrepresentative cohorts with spinal metastases detected at late stages of development.

Imaging methods used for detection of SCC and/or vertebral fracture have changed over the duration of the studies described. Formal comparison of different imaging procedures was rarely undertaken and we found no RCTs. It is clear that investigations now favour MRI and CT over myelography only and/or plain radiography. Bone scans were widely employed but PET was not used in any of the included studies. The development and routine availability of machines with faster throughput and better performance (e.g. resolution) may change practice.

The included studies provided some evidence regarding factors that influence the risk of vertebral fracture and/or SCC. In general, these risk factors were unsurprising and would be familiar to clinicians charged with the care of patients with spinal metastases. They include the following: number of spinal metastases (or skeletal metastases); the time of exposure to spinal metastases (i.e. survival); type of primary tumour and whether the spinal metastasis is lytic or blastic; and the degree of occupancy of the vertebral body by the metastasis and its distribution. Three studies attempted to combine risk factors into a decision rule that developed a probability for occurrence of an event. These appeared to have modest discriminatory power but were not tested by the authors in a population independent of that in which they were

developed. Generally, included studies were of poor methodological quality and made use of medical records and/or stored scan images rather than using data collection techniques specifically designed for research purposes.

### Strengths and limitations of this review

Many bibliographic databases were searched and a large volume of literature was sifted by two reviewers. We used a rigorous search strategy in a large number of databases to identify research papers. Reviewers had difficulties in determining whether or not a paper met the inclusion criteria at abstract level and therefore a large number of papers needed to be sifted at full-paper stage. Nevertheless, our  $\kappa$ -statistic at 0.74 was acceptable. We have summarised a large volume of research. We used a detailed quality assessment process using a dedicated prognostic factors quality assessment framework developed by one of our team and an in-depth analysis (where possible) by cancer type.

Unfortunately, the relatively poor quality and methodology of the papers retrieved, coupled with the variability of underlying patient populations investigated, makes it difficult to draw overall and generalisable conclusions about development of vertebral fracture and SCC. It was not possible to examine the full text of all 2425 retrieved studies; consequently, natural history descriptions might exist but the titles (and abstracts) of such publications failed to reveal this fact readily. At full paper it was difficult to identify relevant information related to the prediction of spinal collapse. The sifting process was time-consuming as it required detailed scrutiny and evaluation of a large number of papers.

It is a weakness that owing to lack of reports of the natural history we are unable to draw any conclusions on this aspect of the review. As far as prognostic factors are concerned, the heterogeneity between studies prevented the use of meta-analysis and again, because of this it is difficult to summarise findings.

### Research needs

Clear conclusions cannot currently be drawn from the evidence to identify patients at high risk of vertebral fracture and SCC, either clinically or using imaging investigations. Prospective clinical studies are needed to define those patients who are more likely to present with fractures and to establish functional outcomes and cost-effectiveness of identification and treatment of these patients. MRI is often used for diagnosing SCC and it would be useful to know which patients are at high risk of SCC and are most likely to benefit from early detection and treatment.

In the absence of good predictors, repeated imaging using MRI to monitor progression may offer the best route to identifying patients who can benefit from intervention. Venkitaraman *et al.*<sup>133</sup> proposed further research to investigate the statistically significant positive effect of early detection of SCC using serial screening MRI. They suggested that the effect of early treatment on neurological function and on survival in metastatic castration-resistant prostate cancer patients needed to be explored with a prospective randomised study involving a quality of life and health economic analysis. The NICE guidelines on SCC also state that MRI screening for SCC in asymptomatic high-risk patients is a promising area for further clinical research.<sup>15</sup> The evidence presented in this short report also supports this conclusion. We would suggest that research on the optimal frequency for MRI screening would also be beneficial.

Personal communication (Professor Charles Hutchinson, University of Warwick, 2011, personal communication) from our clinical expert has suggested that  $\approx 10\%$  of patients with metastases of the spine are currently re-imaged using MRI. (This information is taken from a database of 24,991 MRI patients' images obtained over the last 5 years in one large hospital in the UK; 1175 patients had metastatic disease of the spine and 125 had repeat scans.) This proportion of patients suggests that the practice of re-imaging is current and it is likely to be increasing. However, given that MRI is an expensive and

sometimes limited resource,<sup>107</sup> it may be useful to undertake Service Delivery and Organisation research on MRI scans and scanning (in tandem with research studies on use of MRI to monitor progression) to understand the best methods for maximising use of MRI scanners (e.g. to investigate variation in need, and optimal location, throughput and staffing, etc.).

Several included studies involved prognostic algorithms (see Lu *et al.*,<sup>120</sup> Talcott *et al.*,<sup>131</sup> and Taneichi *et al.*<sup>89</sup>) designed to calculate the probability of a specified event. These findings could be explored further in high-quality prospective studies, involving defined populations, randomly selected and clearly identified samples, and with blinding of investigators.

A very broad range of factors was associated with preoperative compression fractures and MSCC, including lack of sensory deficits; primary breast cancer; anterior spine metastases; inability to walk; increased deep tendon reflexes; time interval from diagnosis of primary tumour until development of SCC; longer surviving patients; type of primary tumour; thoracic spine involvement; preoperative chemotherapy; tumour size and pedicle destruction; focal radiographic abnormalities with consistent neurological findings; patient's health status; and possibly preoperative radiation therapy. Many of the included studies focused on specific regions of the spine (e.g. cervical and thoracolumbar). These results are not necessarily generalisable to all regions of the spine and should be treated with caution. Higher-quality prospective studies would be valuable on these risk factors of progression or spinal collapse, as opposed to survival, and these could usefully feed into work on prognostic algorithms.

Methodologically, suggestions for improving primary<sup>135,138</sup> and secondary<sup>139,140</sup> prognosis research are increasingly being reported. Furthermore, the statistical interpretations of prognostic findings, in terms of survival, are being considered.<sup>141</sup> There have been a number of publications reporting the development, validation and impact of prognostic models.<sup>142–147</sup> Recently, Henriksson *et al.*<sup>148</sup> developed a new risk equation from a Swedish cohort and carried out external validation in a smaller UK data set of patients waiting for coronary artery surgery. A lifetime time horizon was used and risk of cardiovascular events was extrapolated from the Swedish data using a Markov model. Although the authors recognise that the risk score requires further validation and refinement, this provides a useful example of how researchers might consider assessing cost-effectiveness of prognostic factors with decision models to enable prioritisation of patients waiting for treatment.<sup>148</sup> Importantly, the authors recognised several limitations that might be considered in further research; for example, the RR estimates for specific factors might be inflated because of publication bias or because of inadequate adjustment for the routinely recorded factors known to relate to prognostic factors and outcomes.

The Cochrane Prognosis Methods Group has also been highly influential in the conduct of systematic reviews of prognosis (see <http://prognosismethods.cochrane.org/>, accessed 1 December 2011).<sup>149</sup> This group has recognised that there are many issues particularly pertinent for systematic reviews of prognosis, for example (1) lack of clarity with indexing of studies for bibliographic searches; (2) low quality of primary studies; (3) poor reporting; and (4) difficulties in pooling results across research designs, analyses and presentations of results. All these factors have implications for future primary and secondary research of spinal metastases and risks of spinal collapse and fracture.

### Ordered summary of research needs

There is a need for:

1. prospective randomised designs to establish clinical and quality of life outcomes and cost-effectiveness of identification and treatment of patients at high risk of vertebral collapse and SCC, using bone scintigraphy and serial MRI to identify patient groups who are most likely to benefit from early detection and treatment, and the value and optimal frequency of MRI screening for populations
2. Service Delivery and Organisation research on MRI scans and scanning (in tandem with research studies on use of MRI to monitor progression) to understand best methods for maximising use of MRI scanners (e.g. to investigate variation in need, and optimal location, throughput and staffing, etc.)

3. investigation of prognostic algorithms designed to calculate the probability of a specified event using high-quality prospective studies, involving defined populations, randomly selected and clearly identified samples, and with blinding of investigators
4. higher-quality prospective studies to investigate and confirm previous findings on risk factors for progression or spinal collapse, as opposed to survival – these could usefully feed into work on prognostic algorithms
5. methodological research to improve prognosis research.

### *Implications for clinical practice*

This review has provided data on a large number of prognostic factors. Some may warrant further consideration although the weak discriminatory power of most is not encouraging for clinicians wishing to use the research in practice to guide selection for surgery or other interventions. A patient's likelihood of development of severe neurological complications is the most important consideration and there is potential for rapid and/or sustained improvement in quality of life after timely intervention. In the absence of good predictors, repeated imaging (e.g. MRI) to monitor progression may offer the best route to identifying patients who can benefit in this way. Spinal instability is a key component in treatment decision-making for spinal oncology patients, although it is poorly defined in the literature and there is a lack of current guidelines to support definition of the degree of spinal instability in the setting of spinal metastases.<sup>110</sup> However, in making surgical treatment decisions, stability is only one factor in the process. General health, tumour histology, overall prognosis, duration of disease symptomatology, neurology and patient choice clearly warrant consideration.

The major factors which should be taken into account when considering a patient for further investigation and potential treatment when at risk of SCC, progression or spinal collapse have not altered from those identified in 2008 NICE guideline 75.<sup>15</sup>

Our clinical experts have directed us to the cost information provided in the NICE guideline 75.<sup>15</sup> For further details on cost, see *Appendix 9*.

## Chapter 5 Conclusions

This report has identified a large number of potentially relevant factors reported across 31 studies but the evidence base is generally poor. There was a lack of consistency in methodology and rigour in studies reported. There was limited evidence from studies with a primary aim of investigating risk factors for progression or spinal collapse, with more focus within studies directed at predictive factors for overall survival. There was a lack of sample frame definition and selection, variations in the stage of disease, mixed cancers, reliance on retrospective data with no RCTs and a repeated failure to test risk factors in another population. Although we have identified many limitations in the current evidence base, these findings should be considered carefully when developing further research in this area.

### Natural history

Our extensive sifting of retrieved studies failed to identify appropriate studies. A definition of the natural history of a medical condition is 'The timeline of a morbid condition from onset–inception to resolution; the course of a particular disease if it is not treated or manipulated in any way' (<http://medical-dictionary.thefreedictionary.com/natural+history+of+disease>, accessed December 2011). A description of the progression of spinal metastases from inception to the development of undesirable sequelae, un-influenced by interventions, is problematic because these patients receive many types of intervention that affect both tumour characteristics and the structure and biochemistry of host bone. Changes over time mean that very early studies in which intervention may have been minimal would no longer be useful because of inadequacies in the frequency and resolution of imaging modalities.

### Prognostic studies

The quality of studies was generally limited. No RCTs were identified and study designs were such that the results were susceptible to biases (especially selection bias) and analyses were susceptible to confounding from unrecorded or unanalysed variables.

The body of evidence provided by the studies was not strong; very many potentially prognostic variables were investigated, but testing of these beyond the population in which they were developed was minimal. In those investigations that developed prognostic algorithms, or risk probabilities according to stratification of risk factors, it appeared that the discriminatory performance of the models was modest.

### Imaging modalities

It is clear from many studies that the current clinical consensus favours MRI and CT imaging modalities for the investigation of SCC and vertebral fracture. Myelography appears reserved for 'difficult' cases and plain radiography for preliminary investigation. Formal comparison of modalities was not convincingly undertaken among the included studies. Bone scintigraphy was widely used in the studies included in this review and may be the method of choice for readily establishing the load of spinal and other bone metastases, but there is no evidence currently to support this. In practice the choice of imaging modality may well be influenced by availability of appropriate instruments at the time required. The development and routine availability of machines or practices with increased or faster throughput and better performance (e.g. resolution) may change practice.

## Clinical importance of spinal metastases

Early diagnosis and treatment of SCC is essential for the preservation of neurological function.<sup>107</sup> However, diagnosis of SCC is frequently not established until significant neurological deficit is present, by which time functional recovery may be difficult. At this stage treatment may need to be undertaken as an emergency, often with reduced efficiency and at increased cost. Therefore, early diagnosis of SCC before the development of symptoms may allow for treatment to preserve neurological function in some patients who might otherwise be left with significant problems. This may in turn result in more efficient management of diagnostic and therapeutic staff and facilities, and reduce long-term costs of caring for disabled patients. However, none of the identified studies discussed costs or cost-effectiveness.

The included studies, and many other publications discussed in the introduction of this report, testify to the serious consequences that may arise from spinal metastases and the impact of these on the quality of life of patients. We consider that further research is needed in this area. The desirability of good predictors of unwanted sequelae from spinal metastases is clear; however, this review suggests that good-quality evidence on either natural history or on technologies for identifying patients at high risk of vertebral fracture and SCC does not currently exist.

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## Contributions of authors

**Paul Sutcliffe** (Senior Research Fellow) and **Martin Connock** (Senior Research Fellow) co-ordinated the review.

**Rachel Court** (Information Specialist) developed the search strategy and undertook searches.

**Paul Sutcliffe** and **Martin Connock** screened the search results; they screened retrieved papers against inclusion criteria, appraised the quality of papers and abstracted data from papers.

**Paul Sutcliffe**, **Martin Connock** and **Ngianga-Bakwin Kandala** (Principal Research Fellow) analysed the data.

**Deepson Shyangdan** (Research Fellow), **Paul Sutcliffe** and **Martin Connock** wrote the report.

**Aileen Clarke** (Professor of Public Health & Health Services Research) provided advice on design and analysis, wrote the summary and provided comments on the report.

## About Warwick Evidence

Warwick Evidence is a Health Technology Assessment Group, located in Warwick Medical School, working in close collaboration with the NHS to support the further development of knowledge-based health services. Warwick Evidence brings together experts in clinical effectiveness and cost-effectiveness reviewing, health economics and modelling.



## References

1. Gilbert RW, Kim JH, Posner JB. Epidural spinal cord compression from metastatic tumor: diagnosis and treatment. *Ann Neurol* 1978;**3**:40–51. <http://dx.doi.org/10.1002/ana.410030107>
2. Office for National Statistics. *Statistical bulletin: births and deaths in England and Wales, 2010*. URL: [www.ons.gov.uk/ons/rel/vsob1/death-reg-sum-tables/2009--final--births-and-deaths-summary-tables-stats-bulletin---2009.pdf](http://www.ons.gov.uk/ons/rel/vsob1/death-reg-sum-tables/2009--final--births-and-deaths-summary-tables-stats-bulletin---2009.pdf) (accessed 11 December 2011).
3. Cancer Research UK. *Latest UK cancer incidence (2008) and mortality (2008) summary*. 2011. URL: [http://info.cancerresearchuk.org/prod\\_consump/groups/cr\\_common/@nre/@sta/documents/generalcontent/cr\\_072108.pdf](http://info.cancerresearchuk.org/prod_consump/groups/cr_common/@nre/@sta/documents/generalcontent/cr_072108.pdf) (accessed 9 December 2011).
4. Cancer Research UK. *CancerStats incidence 2008 – UK*. 2011. URL: [http://info.cancerresearchuk.org/prod\\_consump/groups/cr\\_common/@nre/@sta/documents/generalcontent/cr\\_072111.pdf](http://info.cancerresearchuk.org/prod_consump/groups/cr_common/@nre/@sta/documents/generalcontent/cr_072111.pdf) (accessed 9 December 2011).
5. Cancer Research UK. *Deaths from common cancers – UK mortality statistics*. 2011. URL: <http://info.cancerresearchuk.org/cancerstats/mortality/cancerdeaths/> (accessed 9 December 2011).
6. Singh S, Singh G. Fundamental concepts. Overview. In Singh G, Rabbani SA, editors. *Bone metastasis: experimental and clinical therapeutics*. New York, NY: Humana Press Inc.; 2005. pp. 3–12. <http://dx.doi.org/10.1385/1-59259-892-7:003>
7. Bartels RHMA, van der Linden YM, van der Graaf WTA. Spinal extradural metastasis: review of current treatment options. *CA Cancer J Clinicians* 2008;**58**:245–59. <http://dx.doi.org/10.3322/CA.2007.0016>
8. Delank KS, Wendtner C, Eich HT, Eysel P. The treatment of spinal metastases. *Dtsch Arzt Int* 2011;**108**:71–U27.
9. Tse V. *Spinal metastases and metastatic disease to the spine and related structures*. 2009. URL: <http://emedicine.medscape.com/article/1157987-overview> (accessed April 2011).
10. Harel R, Angelov L. Spine metastases: current treatments and future directions. *Eur J Cancer* 2010;**46**:2696–707. <http://dx.doi.org/10.1016/j.ejca.2010.04.025>
11. Maccauro G, Spinelli MS, Mauro S, Perisano C, Graci C, Rosa MA. Physiopathology of spine metastasis. *Int J Surg Oncol* 2011;**1**–8. <http://dx.doi.org/10.1155/2011/107969>
12. Perrin RG, Laxton AW. Metastatic spine disease: epidemiology, pathophysiology, and evaluation of patients. *Neurosurg Clin N Am* 2004;**15**:36573. <http://dx.doi.org/10.1016/j.nec.2004.04.018>
13. Boogerd W, Vandersande JJ. Diagnosis and treatment of spinal-cord compression in malignant disease. *Cancer Treat Rev* 1993;**19**:129–50. [http://dx.doi.org/10.1016/0305-7372\(93\)90031-L](http://dx.doi.org/10.1016/0305-7372(93)90031-L)
14. Rades D, Stalpers LJ, Veninga T, Schulte R, Hoskin PJ, Obralic N, et al. Evaluation of five radiation schedules and prognostic factors for metastatic spinal cord compression. *J Clin Oncol* 2005;**23**:3366–75. <http://dx.doi.org/10.1200/JCO.2005.04.754>
15. National Institute for Health and Care Excellence (NICE), National Collaborating Centre for Cancer. *National Institute for Health and Care Excellence clinical guideline 75. Metastatic spinal cord compression: Diagnosis and management of adults at risk of or with metastatic spinal cord compression*. 2008. URL: <http://guidance.nice.org.uk/C975/Guidance/pdf/English> (accessed April 2011).
16. Cancer Research UK. *Breast cancer – UK incidence statistics*. 2011. URL: <http://info.cancerresearchuk.org/cancerstats/types/breast/incidence/> (accessed 8 December 2011).

17. Bendre M, Gaddy D, Nicholas RW, Suva LJ. Breast cancer metastasis to bone: it is not all about PTHrP. *Clin Orthop Relat Res* 2003;**415**:S39–S45. <http://dx.doi.org/10.1097/01.blo.0000093844.72468.f4>
18. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. *Clin Cancer Res* 2006;**12**:6243s–9s. <http://dx.doi.org/10.1158/1078-0432.CCR-06-0931>
19. Walkington L, Coleman RE. Advances in management of bone disease in breast cancer. *Bone* 2011;**48**:80–7. <http://dx.doi.org/10.1016/j.bone.2010.05.037>
20. Cancer Research UK. *Types of treatment for breast cancer*. URL: [www.cancerresearchuk.org/cancer-help/type/breast-cancer/treatment/which-treatment-for-breast-cancer](http://www.cancerresearchuk.org/cancer-help/type/breast-cancer/treatment/which-treatment-for-breast-cancer) (accessed 8 December 2011).
21. Coleman RE, Rubens RD. The clinical course of bone metastases from breast cancer. *Br J Cancer* 1987;**55**:61–6. <http://dx.doi.org/10.1038/bjc.1987.13>
22. Jensen AO, Jacobsen JB, Norgaard M, Yong M, Fryzek JP, Sorensen HT. Incidence of bone metastases and skeletal-related events in breast cancer patients: a population-based cohort study in Denmark. *BMC Cancer* 2011;**11**:29. <http://dx.doi.org/10.1186/1471-2407-11-29>
23. Dent R, Hanna WM, Trudeau M, Rawlinson E, Sun P, Narod SA. Pattern of metastatic spread in triple-negative breast cancer. *Breast Cancer Res Treat* 2009;**115**:423–8. <http://dx.doi.org/10.1007/s10549-008-0086-2>
24. Plunkett TA, Smith P, Rubens RD. Risk of complications from bone metastases in breast cancer: implications for management. *Eur J Cancer* 2000;**36**:476–82. [http://dx.doi.org/10.1016/S0959-8049\(99\)00331-7](http://dx.doi.org/10.1016/S0959-8049(99)00331-7)
25. Coleman RE, Smith P, Rubens RD. Clinical course and prognostic factors following bone recurrence from breast cancer. *Br J Cancer* 1998;**77**:336–40. <http://dx.doi.org/10.1038/bjc.1998.52>
26. Cancer Research UK. *Lung cancer – UK incidence statistics*. 2011. URL: <http://info.cancerresearchuk.org/cancerstats/types/lung/incidence/> (accessed 9 December 2011).
27. National Institute for Health and Care Excellence (NICE), National Collaborating Centre for Cancer. *National Institute for Health and Care Excellence clinical guideline 121 – lung cancer. The diagnosis and treatment of lung cancer*. London: NICE; 2011.
28. Charloux A, Quoix E, Wolkove N, Small D, Pauli G, Kreisman H. The increasing incidence of lung adenocarcinoma: reality or artefact? A review of the epidemiology of lung adenocarcinoma. *Int J Epidemiol* 1997;**26**:14–23. <http://dx.doi.org/10.1093/ije/26.1.14>
29. Roodman GD. Mechanisms of bone metastasis. *N Engl J Med* 2004;**350**:1655–64. <http://dx.doi.org/10.1056/NEJMra030831>
30. Al Husaini H, Wheatley-Price P, Clemons M, Shepherd FA. Prevention and management of bone metastases in lung cancer: a review. *J Thorac Oncol* 2009;**4**:251–9. <http://dx.doi.org/10.1097/JTO.0b013e31819518fc>
31. Cancer Research UK. *Prostate cancer – UK incidence statistics*. 2011. URL: <http://info.cancerresearchuk.org/cancerstats/types/prostate/incidence/> (accessed 9 December 2011).
32. National Institute for Health and Care Excellence (NICE), National Collaborating Centre for Cancer. *National Institute for Health and Clinical Excellence Clinical guideline 58 – prostate cancer: diagnosis and treatment*. London: NICE; 2008.
33. Selley S, Donovan J, Faulkner A, Coast J, Gillatt D. Diagnosis, management and screening of early localised prostate cancer. *Health Technol Assess* 1997;**1**(2).
34. Cancer Research UK. *Prostate cancer – survival statistics*. 2010. URL: <http://info.cancerresearchuk.org/cancerstats/types/prostate/survival/> (accessed 9 December 2011).

35. Thompson IM, Ankerst DP, Chi C, Goodman PJ, Tangen CM, Lucia MS, *et al.* Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. *J Natl Cancer Inst* 2006;**98**:529–34. <http://dx.doi.org/10.1093/jnci/djj131>
36. Cancer Research UK. *Treating prostate cancer*. URL: [www.cancerresearchuk.org/cancer-help/type/prostate-cancer/treatment/](http://www.cancerresearchuk.org/cancer-help/type/prostate-cancer/treatment/) (accessed 8 December 2011).
37. Mimeault M, Mehta PP, Hauke R, Batra SK. Functions of normal and malignant prostatic stem/progenitor cells in tissue regeneration and cancer progression and novel targeting therapies. *Endocr Rev* 2008;**29**:234–52. <http://dx.doi.org/10.1210/er.2007-0040>
38. Balk SP, Knudsen KE. AR, the cell cycle, and prostate cancer. *Nucl Recept Signal* 2008;**6**:e001.
39. National Institute for Health and Care Excellence (NICE), National Collaborating Centre for Cancer. *Clinical guideline 131 – colorectal cancer. The diagnosis and management of colorectal cancer*. London: NICE; 2011.
40. Cancer Research UK. *Bowel cancer – survival statistics*. 2009. URL: <http://info.cancerresearchuk.org/cancerstats/types/bowel/survival/> (accessed 9 December 2011).
41. Sundermeyer ML, Meropol NJ, Rogatko A, Wang H, Cohen SJ. Changing patterns of bone and brain metastases in patients with colorectal cancer. *Clin Colorectal Cancer* 2005;**5**:108–13. <http://dx.doi.org/10.3816/CCC.2005.n.022>
42. Kanthan R, Loewy J, Kanthan SC. Skeletal metastases in colorectal carcinomas: a Saskatchewan profile. *Dis Colon Rectum* 1999;**42**:1592–7. <http://dx.doi.org/10.1007/BF02236213>
43. Galasko CSB. The anatomy and pathways of skeletal metastases. In Weiss L, Gilbert HA, editors. *Bone metastasis*. Boston, MA: G.K. Hall; 1981. p. 49.
44. Stacker SA, Baldwin ME, Achen MG. The role of tumor lymphangiogenesis in metastatic spread. *FASEB J* 2002;**16**:922–34. <http://dx.doi.org/10.1096/fj.01-0945rev>
45. Schoppmeyer K, Fruhauf N, Oldhafer K, Seeber S, Kasimir-Bauer S. Tumor cell dissemination in colon cancer does not predict extrahepatic recurrence in patients undergoing surgery for hepatic metastases. *Oncol Rep* 2006;**15**:449–54.
46. Carmignani CP, Sugarbaker TA, Bromley CM, Sugarbaker PH. Intraperitoneal cancer dissemination: mechanisms of the patterns of spread. *Cancer Metastasis Rev* 2003;**22**:465–72. <http://dx.doi.org/10.1023/A:1023791229361>
47. Eubank WB, Mankoff DA, Vesselle HJ, Eary JF, Schubert EK, Dunnwald LK, *et al.* Detection of locoregional and distant recurrences in breast cancer patients by using FDG PET. *Radiographics* 2002;**22**:5–17.
48. Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. *Chest* 1997;**111**:1718–23. <http://dx.doi.org/10.1378/chest.111.6.1718>
49. Robless P, Lim J, Geroulakos G. Lymphoedema. *Surgery* 2010;**28**:268–72.
50. Chung JW, Park JH, Han JK, Choi BI, Han MC. Hepatocellular carcinoma and portal vein invasion: results of treatment with transcatheter oily chemoembolization. *AJR Am J Roentgenol* 1995;**165**:315–21.
51. Skinner DG, Pritchett TR, Lieskovsky G, Boyd SD, Stiles QR. Vena caval involvement by renal cell carcinoma. Surgical resection provides meaningful long-term survival. *Ann Surg* 1989;**210**:387–92. <http://dx.doi.org/10.1097/0000658-198909000-00014>
52. Chambers AF, Groom AC, MacDonald IC. Dissemination and growth of cancer cells in metastatic sites. *Nat Rev Cancer* 2002;**2**:563–72. <http://dx.doi.org/10.1038/nrc865>

53. Paget S. The distribution of secondary growths in cancer of the breast. 1889. *Cancer Metastasis Rev* 1989;**8**:98–101.
54. Coussens LM, Werb Z. Inflammation and cancer. *Nature* 2002;**420**:860–7. <http://dx.doi.org/10.1038/nature01322>
55. Weillbaecher KN, Guise TA, McCauley LK. Cancer to bone: a fatal attraction. *Nat Rev Cancer* 2011;**11**:411–25. <http://dx.doi.org/10.1038/nrc3055>
56. Smith HS. Painful osseous metastases. *Pain Physician* 2011;**14**:E373–E403.
57. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev* 2001;**27**:165–76. <http://dx.doi.org/10.1053/ctrv.2000.0210>
58. Dunstan CR, Boyce R, Boyce BF, Garrett IR, Izbicka E, Burgess WH, *et al*. Systemic administration of acidic fibroblast growth factor (FGF-1) prevents bone loss and increases new bone formation in ovariectomized rats. *J Bone Miner Res* 1999;**14**:953–9. <http://dx.doi.org/10.1359/jbmr.1999.14.6.953>
59. Sciubba DM, Petteys RJ, Dekutoski MB, Fisher CG, Fehlings MG, Ondra SL, *et al*. Diagnosis and management of metastatic spine disease. A review. *J Neurosurg Spine* 2010;**13**:94–108. <http://dx.doi.org/10.3171/2010.3.SPINE09202>
60. Kilbride L, Cox M, Kennedy CM, Lee SH, Grant R. Metastatic spinal cord compression: a review of practice and care. *J Clin Nursing* 2010;**19**:1767–83. <http://dx.doi.org/10.1111/j.1365-2702.2010.03236.x>
61. Sejpal SV, Bhate A, Small W. Palliative radiation therapy in the management of brain metastases, spinal cord compression, and bone metastases. *Semin Intervent Radiol* 2007;**24**:363–74. <http://dx.doi.org/10.1055/s-2007-992324>
62. 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;**23**:2028–37. <http://dx.doi.org/10.1200/JCO.2005.00.067>
63. Ecker RD, Endo T, Wetjen NM, Krauss WE. Diagnosis and treatment of vertebral column metastases. *Mayo Clin Proc* 2005;**80**:1177–86. <http://dx.doi.org/10.4065/80.9.1177>
64. Cook AM, Lau TN, Tomlinson MJ, Vaidya M, Wakeley CJ, Goddard P. Magnetic resonance imaging of the whole spine in suspected malignant spinal cord compression: impact on management. *Clin Oncol (R Coll Radiol)* 1998;**10**:39–43. [http://dx.doi.org/10.1016/S0936-6555\(98\)80111-8](http://dx.doi.org/10.1016/S0936-6555(98)80111-8)
65. Loughrey GJ, Collins CD, Todd SM, Brown NM, Johnson RJ. Magnetic resonance imaging in the management of suspected spinal canal disease in patients with known malignancy. *Clin Radiol* 2000;**55**:849–55. <http://dx.doi.org/10.1053/crad.2000.0547>
66. Ohmori K, Kawaguchi Y, Kanamori M, Ishihara H, Takagi H, Kimura T. Image-guided anterior thoracolumbar corpectomy: a report of three cases. *Spine (Phila Pa 1976)* 2001;**26**:1197–201.
67. Tacke J, Klein HM, Bertalanffy H, Mayfrank L, Thron A, Gilsbach JM, *et al*. Clinical significance of three-dimensional helical CT in neurosurgery. *Minim Invasive Neurosurg* 1997;**40**:30–5. <http://dx.doi.org/10.1055/s-2008-1053411>
68. Algra PR, Heimans JJ, Valk J, Nauta JJ, Lachniet M, Van KB. Do metastases in vertebrae begin in the body or the pedicles? Imaging study in 45 patients. *AJR Am J Roentgenol* 1992;**158**:1275–9.
69. Asdourian PL, Weidenbaum M, Dewald RL, Hammerberg KW, Ramsey RG. The pattern of vertebral involvement in metastatic vertebral breast cancer. *Clin Orthop Relat Res* 1990;**250**:164–70.
70. Stark RJ, Henson RA, Evans SJ. Spinal metastases. A retrospective survey from a general hospital. *Brain* 1982;**105**:189–213. <http://dx.doi.org/10.1093/brain/105.1.189>

71. Rodichok LD, Harper GR, Ruckdeschel JC, Price A, Roberson G, Barron KD, *et al.* Early diagnosis of spinal epidural metastases. *Am J Med* 1981;**70**:1181–8. [http://dx.doi.org/10.1016/0002-9343\(81\)90825-1](http://dx.doi.org/10.1016/0002-9343(81)90825-1)
72. Schirrmester H, Glatting G, Hetzel J, Nussle K, Arslanemir C, Buck AK, *et al.* Prospective evaluation of the clinical value of planar bone scans, SPECT, and (18)F-labeled NaF PET in newly diagnosed lung cancer. *J Nucl Med* 2001;**42**:1800–4.
73. Prasad D, Schiff D. Malignant spinal-cord compression. *Lancet Oncol* 2005;**6**:15–24.
74. Eleraky M, Papanastassiou I, Vrionis FD. Management of metastatic spine disease. *Curr Opin Support Palliat Care* 2010;**4**:182–8. <http://dx.doi.org/10.1097/SPC.0b013e32833d2fdd>
75. Inoue T, Oh RJ, Shiomi H. New approach for treatment of vertebral metastases using intensity-modulated radiotherapy. *Strahlenther Onkol* 2011;**187**:108–13. <http://dx.doi.org/10.1007/s00066-010-2187-1>
76. Chang EL, Shiu AS, Mendel E, Mathews LA, Mahajan A, Allen PK, *et al.* Phase I/II study of stereotactic body radiotherapy for spinal metastasis and its pattern of failure. *J Neurosurg Spine* 2007;**7**:151–60. <http://dx.doi.org/10.3171/SPI-07/08/151>
77. Body JJ. New developments for treatment and prevention of bone metastases. *Curr Opin Oncol* 2011;**23**:338–42. <http://dx.doi.org/10.1097/CCO.0b013e328347918b>
78. Danila DC, Morris MJ, de Bono JS, Ryan CJ, Denmeade SR, Smith MR, *et al.* Phase II multicenter study of abiraterone acetate plus prednisone therapy in patients with docetaxel-treated castration-resistant prostate cancer. *J Clin Oncol* 2010;**28**:1496–501. <http://dx.doi.org/10.1200/JCO.2009.25.9259>
79. Reid AH, Attard G, Danila DC, Oommen NB, Olmos D, Fong PC, *et al.* Significant and sustained antitumor activity in post-docetaxel, castration-resistant prostate cancer with the CYP17 inhibitor abiraterone acetate. *J Clin Oncol* 2010;**28**:1489–95. <http://dx.doi.org/10.1200/JCO.2009.24.6819>
80. Jackson RJ, Gokaslan ZL, Loh SCA. Metastatic renal cell carcinoma of the spine: surgical treatment and results. *J Neurosurg* 2001;**94**:18–24.
81. Tokuhashi Y, Matsuzaki H, Toriyama S, Kawano H, Ohsaka S. Scoring system for the preoperative evaluation of metastatic spine tumor prognosis. *Spine (Phila PA 1976)* 1990;**15**:1110–13.
82. Cohen ZR, Fourney DR, Gokaslan ZL, Walsh GL, Rhines LD. Anterior stabilization of the upper thoracic spine via an 'interaortocaval subinnominate window': case report and description of operative technique. *J Spinal Disord Tech* 2004;**17**:543–8. <http://dx.doi.org/10.1097/01.bsd.0000117541.10843.c9>
83. Fourney DR, Schomer DF, Nader R, Chlan-Fourney J, Suki D, Ahrar K, *et al.* Percutaneous vertebroplasty and kyphoplasty for painful vertebral body fractures in cancer patients. *J Neurosurg* 2003;**98**(Suppl. 1):21–30.
84. Wenger M. Vertebroplasty for metastasis. *Med Oncol* 2003;**20**:203–9. <http://dx.doi.org/10.1385/MO:20:3:203>
85. Tokuhashi Y, Ajiro Y, Umezawa N. Outcome of treatment for spinal metastases using scoring system for preoperative evaluation of prognosis. *Spine* 2009;**34**:69–73. <http://dx.doi.org/10.1097/BRS.0b013e3181913f19>
86. Tomita K, Kawahara N, Kobayashi T, Yoshida A, Murakami H, Akamaru T. Surgical strategy for spinal metastases. *Spine* 2001;**26**:298–306. <http://dx.doi.org/10.1097/00007632-200102010-00016>

87. Chaichana KL, Pendleton C, Sciubba DM, Wolinsky JP, Gokaslan ZL. Outcome following decompressive surgery for different histological types of metastatic tumors causing epidural spinal cord compression. Clinical article. *J Neurosurg Spine* 2009;**11**:56–63. <http://dx.doi.org/10.3171/2009.1.SPINE08657>
88. Rose PS, Laufer I, Boland PJ, Hanover A, Bilsky MH, Yamada J, et al. Risk of fracture after single fraction image-guided intensity-modulated radiation therapy to spinal metastases. *J Clin Oncol* 2009;**27**:5075–9. <http://dx.doi.org/10.1200/JCO.2008.19.3508>
89. Taneichi H, Kaneda K, Takeda N, Abumi K, Satoh S. Risk factors and probability of vertebral body collapse in metastases of the thoracic and lumbar spine. *Spine* 1997;**22**:239–45. <http://dx.doi.org/10.1097/00007632-199702010-00002>
90. Yamashita K, Denno K, Ueda T, Komatsubara Y, Kotake T, Usami M, et al. Prognostic significance of bone metastases in patients with metastatic prostate cancer. *Cancer* 1993;**71**:1297–302. [http://dx.doi.org/10.1002/1097-0142\(19930215\)71:4<1297::AID-CNCR2820710421>3.0.CO;2-S](http://dx.doi.org/10.1002/1097-0142(19930215)71:4<1297::AID-CNCR2820710421>3.0.CO;2-S)
91. van der Linden YM, Dijkstra SP, Vonk EJ, Marijnen CA, Leer JW, Dutch Bone Metastasis Study Group. Prediction of survival in patients with metastases in the spinal column: results based on a randomized trial of radiotherapy. *Cancer* 2005;**103**:320–8. <http://dx.doi.org/10.1002/cncr.20756>
92. Sioutos PJ, Arbit E, Meshulam CF, Galicich JH. Spinal metastases from solid tumors. Analysis of factors affecting survival. *Cancer* 1995;**76**:1453–9. [http://dx.doi.org/10.1002/1097-0142\(19951015\)76:8<1453::AID-CNCR2820760824>3.0.CO;2-T](http://dx.doi.org/10.1002/1097-0142(19951015)76:8<1453::AID-CNCR2820760824>3.0.CO;2-T)
93. Enkaoua EA, Doursounian L, Chatellier G, Mabesoone F, Aimard T, Saillant G. Vertebral metastases: a critical appreciation of the preoperative prognostic tokuhashi score in a series of 71 cases. *Spine (Phila PA 1976)* 1997;**22**:2293–8.
94. Sundaresan N, Galicich JH, Bains MS, Martini N, Beattie EJ, Jr. Vertebral body resection in the treatment of cancer involving the spine. *Cancer* 1984;**53**:1393–6. [http://dx.doi.org/10.1002/1097-0142\(19840315\)53:6<1393::AID-CNCR2820530629>3.0.CO;2-0](http://dx.doi.org/10.1002/1097-0142(19840315)53:6<1393::AID-CNCR2820530629>3.0.CO;2-0)
95. Weigel B, Maghsudi M, Neumann C, Kretschmer R, Muller FJ, Nerlich M. Surgical management of symptomatic spinal metastases. Postoperative outcome and quality of life. *Spine* 1999;**24**:2240–6. <http://dx.doi.org/10.1097/00007632-199911010-00012>
96. Bauer HC, Wedin R. Survival after surgery for spinal and extremity metastases. Prognostication in 241 patients. *Acta Orthop Scand* 1995;**66**:143–6. <http://dx.doi.org/10.3109/17453679508995508>
97. Botteman M, Barghout V, Stephens J, Hay J, Brandman J, Aapro M. Cost effectiveness of bisphosphonates in the management of breast cancer patients with bone metastases. *Ann Oncol* 2006;**17**:1072–82. <http://dx.doi.org/10.1093/annonc/mdl093>
98. Marfatia AA, Botteman MF, Foley I, Brandman J, Langer CJ. Economic value of zoledronic acid compared with placebo in the treatment of skeletal metastases in patients with solid tumors: the case of the United Kingdom (UK). ASCO Annual Meeting Proceedings (Post-Meeting Edition). *J Clin Oncol* 2007;**25**:6603.
99. National Institute for Health and Care Excellence (NICE). *NICE technology appraisal guidance 204. Denosumab for the prevention of osteoporotic fractures in postmenopausal women*. London: NICE; 2010.
100. British Medical Association and Royal Pharmaceutical Society of Great Britain. *British national formulary*. No. 61, September 2011. London: BMA and RPS; 2011.
101. U.S. Food and Drug Administration. *Denosumab (Prolia)*. 2012. URL: [www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm272420.htm](http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm272420.htm) (accessed 23 December 2011).

102. Delea TE, McKiernan J, Brandman J, Edelsberg J, Sung J, Raut M, *et al.* Impact of skeletal complications on total medical care costs among patients with bone metastases of lung cancer. *J Thorac Oncol* 2006;**1**:571–6. <http://dx.doi.org/10.1097/01243894-200607000-00012>
103. Cooper K, Meng Y, Harnan S, Ward S, Fitzgerald P. Positron emission tomography (PET) and magnetic resonance imaging (MRI) for the assessment of axillary lymph node metastases in early breast cancer: systematic review and economic evaluation. *Health Technol Assess* 2011;**15**(4).
104. Sutcliffe P, Hummel S, Simpson E, Young T, Rees A, Wilkinson A, *et al.* Use of classical and novel biomarkers as prognostic risk factors for localised prostate cancer: a systematic review. *Health Technol Assess* 2009;**13**(5).
105. Khan KS, Ter Riet G, Galnville J, Snowdon AJ, Kleijnen J. Undertaking systematic reviews of research on effectiveness. CRD's guidance for carrying out or commissioning reviews. 2nd edition. (ISBN 1900640201) CRD Report No. 4. York: NHS Centre for Reviews and Dissemination (CRD), University of York. 2001.
106. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med* 2006;**144**:427–37.
107. Bayley A, Milosevic M, Blend R, Logue J, Gospodarowicz M, Boxen I, *et al.* A prospective study of factors predicting clinically occult spinal cord compression in patients with metastatic prostate carcinoma. *Cancer* 2001;**92**:303–10. [http://dx.doi.org/10.1002/1097-0142\(20010715\)92:2<303::AID-CNCR1323>3.0.CO;2-F](http://dx.doi.org/10.1002/1097-0142(20010715)92:2<303::AID-CNCR1323>3.0.CO;2-F)
108. Bernat JL, Greenberg ER, Barrett J. Suspected epidural compression of the spinal cord and cauda equina by metastatic carcinoma. Clinical diagnosis and survival. *Cancer* 1983;**51**:1953–7. [http://dx.doi.org/10.1002/1097-0142\(19830515\)51:10<1953::AID-CNCR2820511035>3.0.CO;2-D](http://dx.doi.org/10.1002/1097-0142(19830515)51:10<1953::AID-CNCR2820511035>3.0.CO;2-D)
109. Chaichana KL, Pendleton C, Wolinsky JP, Gokaslan ZL, Sciubba DM. Vertebral compression fractures in patients presenting with metastatic epidural spinal cord compression. *Neurosurgery* 2009;**65**:267–74. <http://dx.doi.org/10.1227/01.NEU.0000349919.31636.05>
110. Fisher CG, DiPaola CP, Ryken TC, Bilsky MH, Shaffrey CI, Berven SH, *et al.* A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. *Spine* 2010;**35**:E1221–9. <http://dx.doi.org/10.1097/BRS.0b013e3181e16ae2>
111. Goldman JM, Ash CM, Souhami RL, Geddes DM, Harper PG, Spiro SG, *et al.* Spinal cord compression in small cell lung cancer: a retrospective study of 610 patients. *Br J Cancer* 1989;**59**:591–3. <http://dx.doi.org/10.1038/bjc.1989.119>
112. Harrison KM, Muss HB, Ball MR, McWhorter M, Case D. Spinal cord compression in breast cancer. *Cancer* 1985;**55**:2839–44. [http://dx.doi.org/10.1002/1097-0142\(19850615\)55:12<2839::AID-CNCR2820551222>3.0.CO;2-B](http://dx.doi.org/10.1002/1097-0142(19850615)55:12<2839::AID-CNCR2820551222>3.0.CO;2-B)
113. Helweg-Larsen S, Sorensen PS, Kreiner S. Prognostic factors in metastatic spinal cord compression: a prospective study using multivariate analysis of variables influencing survival and gait function in 153 patients. *Int J Radiat Oncol Biol Phys* 2000;**46**:1163–9. [http://dx.doi.org/10.1016/S0360-3016\(99\)00333-8](http://dx.doi.org/10.1016/S0360-3016(99)00333-8)
114. Helweg-Larsen S, Hansen SW, Sorensen PS. Second occurrence of symptomatic metastatic spinal cord compression and findings of multiple spinal epidural metastases. *Int J Radiat Oncol Biol Phys* 1995;**33**:595–8. [http://dx.doi.org/10.1016/0360-3016\(95\)00199-9](http://dx.doi.org/10.1016/0360-3016(95)00199-9)
115. Huddart RA, Rajan B, Law M, Meyer L, Dearnaley DP. Spinal cord compression in prostate cancer: treatment outcome and prognostic factors. *Radiother Oncol* 1997;**44**:229–36. [http://dx.doi.org/10.1016/S0167-8140\(97\)00112-6](http://dx.doi.org/10.1016/S0167-8140(97)00112-6)

116. Husband DJ, Grant KA, Romaniuk CS. MRI in the diagnosis and treatment of suspected malignant spinal cord compression. *Br J Radiol* 2001;**74**:15–23.
117. Klekamp J, Samii H. Surgical results for spinal metastases. *Acta Neurochir* 1998;**140**:957–67. <http://dx.doi.org/10.1007/s007010050199>
118. Kuban DA, el-Mahdi AM, Sigfred SV, Schellhammer PF, Babb TJ. Characteristics of spinal cord compression in adenocarcinoma of prostate. *Urology* 1986;**28**:364–9. [http://dx.doi.org/10.1016/0090-4295\(86\)90062-2](http://dx.doi.org/10.1016/0090-4295(86)90062-2)
119. Levack P, Graham J, Collie D, Grant R, Kidd J, Kunkler I, *et al.* Don't wait for a sensory level—listen to the symptoms: a prospective audit of the delays in diagnosis of malignant cord compression. *Clin Oncol (R Coll Radiol)* 2002;**14**:472–80. <http://dx.doi.org/10.1053/clon.2002.0098>
120. Lu C, Stomper PC, Drislane FW, Wen PY, Block CC, Humphrey CC, *et al.* Suspected spinal cord compression in breast cancer patients: a multidisciplinary risk assessment. *Breast Cancer Res Treat* 1998;**51**:121–31. <http://dx.doi.org/10.1023/A:1006002823626>
121. Lu C, Gonzalez RG, Jolesz FA, Wen PY, Talcott JA. Suspected spinal cord compression in cancer patients: a multidisciplinary risk assessment. *J Support Oncol* 2005;**3**:305–12.
122. McCloskey EV, Spector TD, Eyres KS, Fern ED, Orourke N, Vasikaran SM, *et al.* The assessment of vertebral deformity – a method for use in population studies and clinical-trials. *Osteoporos Int* 1993;**3**:138–47. <http://dx.doi.org/10.1007/BF01623275>
123. Oka H, Kondoh T, Seichi A, Hozumi T, Nakamura K. Incidence and prognostic factors of Japanese breast cancer patients with bone metastasis. *J Orthop Sci* 2006;**11**:13–19. <http://dx.doi.org/10.1007/s00776-005-0966-9>
124. Roth SE, Mousavi P, Finkelstein J, Chow E, Kreder H, Whyne CM. Metastatic burst fracture risk prediction using biomechanically based equations. *Clin Orthop Relat Res* 2004;**83**:83–90. <http://dx.doi.org/10.1097/00003086-200402000-00015>
125. Sekine I, Nokihara H, Yamamoto N, Kunitoh H, Ohe Y, Tamura T. Risk factors for skeletal-related events in patients with non-small cell lung cancer treated by chemotherapy. *Lung Cancer* 2009;**65**:219–22. <http://dx.doi.org/10.1016/j.lungcan.2008.10.026>
126. Shah AN, Pietrobon R, Richardson WJ, Myers BS. Patterns of tumor spread and risk of fracture and epidural impingement in metastatic vertebrae. *J Spinal Disord Tech* 2003;**16**:83–9. <http://dx.doi.org/10.1097/00024720-200302000-00013>
127. Snyder BD, Hipp JA, Nazarian A. *Non-invasive prediction of fracture risk due to benign and metastatic skeletal defects*. Warrendale, PA: Materials Research Society; 2005.
128. Snyder BD, Cordio MA, Nazarian A, Kwak SD, Chang DJ, Entezari V, *et al.* Noninvasive prediction of fracture risk in patients with metastatic cancer to the spine. *Clin Cancer Res* 2009;**15**:7676–83. <http://dx.doi.org/10.1158/1078-0432.CCR-09-0420>
129. Soerdjbalie-Maikoe V, Pelger RCM, Nijeholt GABL, Arndt JW, Zwinderman AH, Bril H, *et al.* Bone scintigraphy predicts the risk of spinal cord compression in hormone-refractory prostate cancer. *Eur J Nucl Med Mol Imaging* 2004;**31**:958–63. <http://dx.doi.org/10.1007/s00259-004-1479-z>
130. Sun J-M, Ahn JS, Lee S, Kim JA, Lee J, Park YH, *et al.* Predictors of skeletal-related events in non-small cell lung cancer patients with bone metastases. *Lung Cancer* 2011;**71**:89–93. <http://dx.doi.org/10.1016/j.lungcan.2010.04.003>
131. Talcott JA, Stomper PC, Drislane FW, Wen PY, Block CC, Humphrey CC, *et al.* Assessing suspected spinal cord compression: a multidisciplinary outcomes analysis of 342 episodes. *Support Care Cancer* 1999;**7**:31–8. <http://dx.doi.org/10.1007/s005200050220>

132. Venkitaraman R, Sohaib SA, Barbachano Y, Parker CC, Khoo V, Huddart RA, *et al.* Detection of occult spinal cord compression with magnetic resonance imaging of the spine. *Clin Oncol (R Coll Radiol)* 2007;**19**:528–31. <http://dx.doi.org/10.1016/j.clon.2007.04.001>
133. Venkitaraman R, Sohaib SA, Barbachano Y, Parker CC, Huddart RA, Horwich A, *et al.* Frequency of screening magnetic resonance imaging to detect occult spinal cord compromise and to prevent neurological deficit in metastatic castration-resistant prostate cancer. *Clin Oncol (R Coll Radiol)* 2010;**22**:147–52. <http://dx.doi.org/10.1016/j.clon.2009.11.007>
134. Serefhanoglu S, Goker H, Aksu S, Buyukasik Y, Sayinalp N, Haznedaroglu IC, *et al.* Spinal myeloid sarcoma in two non-leukemic patients. *Intern Med* 2010; **49**:2493–7. <http://dx.doi.org/10.2169/internalmedicine.49.3878>
135. Hemingway H, Riley RD, Altman DG. Ten steps towards improving prognosis research. *BMJ* 2009;**339**:b4184. <http://dx.doi.org/10.1136/bmj.b4184>
136. Soloway MS, Hardeman SW, Hickey D, Raymond J, Todd B, Soloway S, *et al.* Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan. *Cancer* 1988;**61**:195–202. [http://dx.doi.org/10.1002/1097-0142\(19880101\)61:1<195::AID-CNCR2820610133>3.0.CO;2-Y](http://dx.doi.org/10.1002/1097-0142(19880101)61:1<195::AID-CNCR2820610133>3.0.CO;2-Y)
137. Wei LJ, Lin DY, Weissfeld L. Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. *J Am Statistical Assoc* 1989;**84**:1065–73. <http://dx.doi.org/10.1080/01621459.1989.10478873>
138. Moons KG, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? *BMJ* 2009;**338**:b375. <http://dx.doi.org/10.1136/bmj.b375>
139. Wilczynski NL, Haynes RB. Optimal search strategies for detecting clinically sound prognostic studies in EMBASE: an analytic survey. *J Am Med Inform Assoc* 2005;**12**:481–5. <http://dx.doi.org/10.1197/jamia.M1752>
140. Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound prognostic studies in MEDLINE: an analytic survey. *BMC Med* 2004;**2**:23. <http://dx.doi.org/10.1186/1741-7015-2-23>
141. Royston P, Parmar MK, Altman DG. Visualizing length of survival in time-to-event studies: a complement to Kaplan–Meier plots. *J Natl Cancer Inst* 2008;**100**:92–7. <http://dx.doi.org/10.1093/jnci/djm265>
142. Royston P, Moons KG, Altman DG, Vergouwe Y. Prognosis and prognostic research: developing a prognostic model. *BMJ* 2009;**338**:b604. <http://dx.doi.org/10.1136/bmj.b604>
143. Altman DG, Vergouwe Y, Royston P, Moons KG. Prognosis and prognostic research: validating a prognostic model. *BMJ* 2009;**338**:b605. <http://dx.doi.org/10.1136/bmj.b605>
144. Moons KG, Altman DG, Vergouwe Y, Royston P. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. *BMJ* 2009;**338**:b606. <http://dx.doi.org/10.1136/bmj.b606>
145. Mallett S, Royston P, Waters R, Dutton S, Altman DG. Reporting performance of prognostic models in cancer: a review. *BMC Med* 2010;**8**:21. <http://dx.doi.org/10.1186/1741-7015-8-21>
146. Mallett S, Royston P, Dutton S, Waters R, Altman DG. Reporting methods in studies developing prognostic models in cancer: a review. *BMC Med* 2010;**8**:20. <http://dx.doi.org/10.1186/1741-7015-8-20>
147. Altman DG. Prognostic models: a methodological framework and review of models for breast cancer. *Cancer Invest* 2009;**27**:235–43. <http://dx.doi.org/10.1080/07357900802572110>

148. Henriksson M, Palmer S, Chen R, Damant J, Fitzpatrick NK, Abrams K, *et al.* Assessing the cost effectiveness of using prognostic biomarkers with decision models: case study in prioritising patients waiting for coronary artery surgery. *BMJ* 2010;**340**:b5606. <http://dx.doi.org/10.1136/bmj.b5606>
149. Riley RD, Ridley G, Williams K, Altman DG, Hayden J, de Vet HC. Prognosis research: toward evidence-based results and a Cochrane methods group. *J Clin Epidemiol* 2007;**60**:863–5. <http://dx.doi.org/10.1016/j.jclinepi.2007.02.004>
150. Kyzas PA, Loizou KT, Ioannidis JP. Selective reporting biases in cancer prognostic factor studies. *J Natl Cancer Inst* 2005;**97**:1043–55. <http://dx.doi.org/10.1093/jnci/dji184>
151. Altman DG. Systematic reviews of evaluations of prognostic variables. *BMJ* 2001;**323**(7306):224–8. <http://dx.doi.org/10.1136/bmj.323.7306.224>
152. Altman DG, Royston P. What do we mean by validating a prognostic model? *Stat Med* 2000;**19**:453–73. [http://dx.doi.org/10.1002/\(SICI\)1097-0258\(20000229\)19:4<453::AID-SIM350>3.0.CO;2-5](http://dx.doi.org/10.1002/(SICI)1097-0258(20000229)19:4<453::AID-SIM350>3.0.CO;2-5)
153. Braitman LE, Davidoff F. Predicting clinical states in individual patients. *Ann Intern Med* 1996;**12**:406–12.
154. Counsell C, Dennis M. Systematic review of prognostic models in patients with acute stroke. *Cerebrovasc Dis* 2001;**12**:159–70. <http://dx.doi.org/10.1159/000047699>
155. Jacob M, Lewsey JD, Sharpin C, Gimson A, Rela M, van der Meulen JH. Systematic review and validation of prognostic models in liver transplantation. *Liver Transpl* 2005;**11**:814–25. <http://dx.doi.org/10.1002/lt.20456>
156. Laupacis A, Wells G, Richardson WS, Tugwell P. Users' guides to the medical literature. V. How to use an article about prognosis. Evidence-Based Medicine Working Group. *JAMA* 1994;**272**:234–7. <http://dx.doi.org/10.1001/jama.1994.03520030076032>

# Appendix 1 Record of searches undertaken

## MEDLINE via Ovid interface

### Searched on 7 June 2011

1. Spinal Neoplasms/
2. ((spine or spinal or vertebr\* or cervical spine or cervical vertebrae or thoracic or lumbar or sacral or sacrum or coccyx) adj3 (metasta\* or lesion\* or neoplasm\* or neoplasia or tumor\* or tumour\* or cancer\* or carcinoma\* or malignan\* or adenocarcinoma\*)).mp.
3. 1 or 2
4. metast\*.mp.
5. exp Neoplasm Metastasis/
6. 4 or 5
7. 3 and 6
8. limit 7 to (english language and humans and "all adult (19 plus years)")
9. Fractures, Compression/
10. Spinal Cord Compression/
11. Polyradiculopathy/
12. Spinal Fractures/
13. exp Paralysis/
14. ((spine or spinal or vertebra\* or cord) adj5 (collapse\* or compression or fractur\* or instability)).mp.
15. compression fracture\*.mp.
16. (cauda equina or polyradicul\*).mp.
17. (paralysis or paraly?ed or plegia or paraplegi\* or hemiplegi\* or quadriplegi\* or tetraplegi\*).mp.
18. (fracture adj3 progression).mp.
19. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 8 and 19

mp. searches the fields: title, original title, abstract, name of substance word, subject heading word

## MEDLINE In-Process & Other Non-Indexed Citations via Ovid interface

### Searched on 7 June 2011

1. ((spine or spinal or vertebr\* or cervical spine or cervical vertebrae or thoracic or lumbar or sacral or sacrum or coccyx) adj3 (metasta\* or lesion\* or neoplasm\* or neoplasia or tumor\* or tumour\* or cancer\* or carcinoma\* or malignan\* or adenocarcinoma\*)).mp.
2. metast\*.mp.
3. 1 and 2
4. ((spine or spinal or vertebra\* or cord) adj5 (collapse\* or compression or fractur\* or instability)).mp.
5. compression fracture\*.mp.
6. (cauda equina or polyradicul\*).mp.
7. (paralysis or paraly?ed or plegia or paraplegi\* or hemiplegi\* or quadriplegi\* or tetraplegi\*).mp.
8. (fracture adj3 progression).mp.
9. 4 or 5 or 6 or 7 or 8
10. 3 and 9

mp. searches the fields: title, original title, abstract, name of substance word, subject heading word

## EMBASE 1980 to 2011 week 22 via Ovid interface

### Searched on 7 June 2011

1. exp spinal cord tumor/
2. ((spine or spinal or vertebr\* or cervical spine or cervical vertebrae or thoracic or lumbar or sacral or sacrum or coccyx) adj3 (metasta\* or lesion\* or neoplasm\* or neoplasia or tumor\* or tumour\* or cancer\* or carcinoma\* or malignan\* or adenocarcinoma\*)).mp.
3. 1 or 2
4. metast\*.mp.
5. exp metastasis/
6. 4 or 5
7. 3 and 6
8. limit 7 to (human and english language and adult <18 to 64 years>)
9. exp spine fracture/
10. spine instability/
11. spinal cord compression/
12. cauda equina syndrome/
13. exp paralysis/
14. ((spine or spinal or vertebra\* or cord) adj5 (collapse\* or compression or fractur\* or instability)).mp.
15. compression fracture\*.mp.
16. (cauda equina or polyradicul\*).mp.
17. (paralysis or paraly?ed or plegia or paraplegi\* or hemiplegi\* or quadriplegi\* or tetraplegi\*).mp.
18. (fracture adj3 progression).mp.
19. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 8 and 19

mp. searches the fields: title, original title, abstract, name of substance word, subject heading word

## Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Health Technology Assessment, NHS Economic Evaluation Database via The Cochrane Library interface

### Searched on 9 June 2011

- #1 MeSH descriptor Spinal Neoplasms explode all trees
- #2 ((spine or spinal or vertebr\* or cervical spine or cervical vertebrae or thoracic or lumbar or sacral or sacrum or coccyx) NEAR/3 (metasta\* or lesion\* or neoplasm\* or neoplasia or tumor\* or tumour\* or cancer\* or carcinoma\* or malignan\* or adenocarcinoma\*))
- #3 (#1 OR #2)
- #4 metast\*
- #5 MeSH descriptor Neoplasm Metastasis explode all trees
- #6 (#4 OR #5)
- #7 (#3 AND #6)
- #8 MeSH descriptor Fractures, Compression explode all trees
- #9 MeSH descriptor Spinal Cord Compression explode all trees
- #10 MeSH descriptor Polyradiculopathy explode all trees
- #11 MeSH descriptor Spinal Fractures explode all trees
- #12 MeSH descriptor Paralysis explode all trees
- #13 ((spine or spinal or vertebra\* or cord) NEAR/5 (collapse\* or compression or fractur\* or instability))
- #14 compression fracture\*
- #15 (cauda equina or polyradicul\*)

#16 (paralysis or paraly?ed or plegia or paraplegi\* or hemiplegi\* or quadriplegi\* or tetraplegi\*)

#17 (fracture NEAR/3 progression)

#18 (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)

#19 (#7 AND #18)

## Science Citation Index and Conference Proceedings via the Web of Science interface

### Searched on 14 June 2011

#11 #10 AND #4

Databases=SCI-EXPANDED, CPCI-S Timespan=All Years

#10 #9 OR #8 OR #7 OR #6 OR #5

Databases=SCI-EXPANDED, CPCI-S Timespan=All Years

#9 TS=(fracture SAME progression)

Databases=SCI-EXPANDED, CPCI-S Timespan=All Years

#8 TS=(paralysis or paraly\*ed or plegia or paraplegi\* or hemiplegi\* or quadriplegi\* or tetraplegi\*)

Databases=SCI-EXPANDED, CPCI-S Timespan=All Years

#7 TS=("cauda equina" or polyradicul\*)

Databases=SCI-EXPANDED, CPCI-S Timespan=All Years

#6 TS="compression fracture" or TS="compression fractures"

Databases=SCI-EXPANDED, CPCI-S Timespan=All Years

#5 TS=(spine or spinal or vertebra\* or cord) SAME TS=(collapse\* or compression or fractur\* or instability)

Databases=SCI-EXPANDED, CPCI-S Timespan=All Years

#4 #3 AND Language=(English)

Databases=SCI-EXPANDED, CPCI-S Timespan=All Years

#3 #2 AND #1

Databases=SCI-EXPANDED, CPCI-S Timespan=All Years

#2 TS=metasta\*

Databases=SCI-EXPANDED, CPCI-S Timespan=All Years

#1 TS=(spine or spinal or vertebr\* or "cervical spine" or "cervical vertebrae" or thoracic or lumbar or sacral or sacrum or coccyx) SAME TS=(metasta\* or lesion\* or neoplasm\* or neoplasia or tumor\* or tumour\* or cancer\* or carcinoma\* or malignan\* or adenocarcinoma\*)

Databases=SCI-EXPANDED, CPCI-S Timespan=All Years

## United Kingdom Clinical Research Network's Portfolio Database (<http://public.ukcrn.org.uk/search/>)

UKCRN searched on 14 June 2011 with no date restriction.

Topic: Cancer AND Research summary: spine spinal vertebrae vertebra vertebral thoracic lumbar sacral sacrum coccyx (n.b. "Any" selected)

Topic: Cancer AND Research summary: cervical spine (n.b. "All" selected)

Topic: Cancer AND Research summary: cervical spinal (n.b. "All" selected)

Topic: Cancer AND Research summary: cervical vertebra (n.b. "All" selected)

Topic: Cancer AND Research summary: cervical vertebral (n.b. "All" selected)

Topic: Cancer AND Research summary: cervical vertebrae (n.b. "All" selected)

## Current Controlled Trials ([www.controlled-trials.com/](http://www.controlled-trials.com/))

Current Controlled Trials database searched on 14 June 2011 with no date restriction.

(metastases OR metastatic OR metastasis) AND (spine OR spinal OR vertebrae OR vertebra OR vertebral OR cervical spine OR cervical vertebrae OR thoracic OR lumbar OR sacral OR sacrum OR coccyx)

Search can be re-run using following web address:

[www.controlled-trials.com/isrctn/search.html?srch=%28metastases+OR+metastatic+OR+metastasis%29+AND+%28spine+OR+spinal+OR+vertebrae+OR+vertebra+OR+vertebral+OR+cervical+spine+OR+cervical+vertebrae+OR+thoracic+OR+lumbar+OR+sacral+OR+sacrum+OR+coccyx%29&sort=3&dir=desc&max=50&Submit=SUBMIT](http://www.controlled-trials.com/isrctn/search.html?srch=%28metastases+OR+metastatic+OR+metastasis%29+AND+%28spine+OR+spinal+OR+vertebrae+OR+vertebra+OR+vertebral+OR+cervical+spine+OR+cervical+vertebrae+OR+thoracic+OR+lumbar+OR+sacral+OR+sacrum+OR+coccyx%29&sort=3&dir=desc&max=50&Submit=SUBMIT)

## ClinicalTrials.gov (<http://clinicaltrials.gov/>)

Clinical Trials database searched on 14 June 2011 with no date restriction.

(metastases OR metastatic OR metastasis) AND (spine OR spinal OR vertebrae OR vertebra OR vertebral OR "cervical spine" OR "cervical vertebrae" OR thoracic OR lumbar OR sacral OR sacrum OR coccyx) | fractures OR fracture OR compression OR "cauda equina" OR polyradiculopathy OR paralysis OR paralysed OR plegia OR instability OR "fracture progression"

Search can be re-run using following web address: URL: [http://clinicaltrials.gov/ct2/results?term=%28metastases+OR+metastatic+OR+metastasis%29+AND+%28spine+OR+spinal+OR+vertebrae+OR+vertebra+OR+vertebral+OR+%22cervical+spine%22+OR+%22cervical+vertebrae%22+OR+thoracic+OR+lumbar+OR+sacral+OR+sacrum+OR+coccyx%29&recr=&rslt=&type=&cond=&intr=&outc=fractures+OR+fracture+OR+compression+OR+%22cauda+equina%22+OR+polyradiculopathy+OR+paralysis+OR+paralysed+OR+plegia+OR+instability+OR+%22fracture+progression%22&lead=&spons=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&gndr=&rcv\\_s=&rcv\\_e=&lup\\_s=&lup\\_e=](http://clinicaltrials.gov/ct2/results?term=%28metastases+OR+metastatic+OR+metastasis%29+AND+%28spine+OR+spinal+OR+vertebrae+OR+vertebra+OR+vertebral+OR+%22cervical+spine%22+OR+%22cervical+vertebrae%22+OR+thoracic+OR+lumbar+OR+sacral+OR+sacrum+OR+coccyx%29&recr=&rslt=&type=&cond=&intr=&outc=fractures+OR+fracture+OR+compression+OR+%22cauda+equina%22+OR+polyradiculopathy+OR+paralysis+OR+paralysed+OR+plegia+OR+instability+OR+%22fracture+progression%22&lead=&spons=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&gndr=&rcv_s=&rcv_e=&lup_s=&lup_e=)

## Appendix 2 Assessment of risk of bias in prognostic studies (Hayden *et al.*<sup>106</sup>)

## Potential bias

## Items to be considered for assessment of potential opportunity for bias

**Study participation**

The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results

Yes  
Partly  
No  
Unsure

The source population or population of interest is adequately described for key characteristics

The sampling frame and recruitment are adequately described, possibly including methods to identify the sample (number and type used, e.g. referral patterns in health care), period of recruitment, and place of recruitment (setting and geographic location)

Inclusion and exclusion criteria are adequately described (e.g. including explicit diagnostic criteria or 'zero time' description)

There is adequate participation in the study by eligible individuals

The baseline study sample (i.e. individuals entering the study) is adequately described for key characteristics

**Study attrition**

Loss to follow-up (from sample to study) is not associated with key characteristics (i.e. the study data adequately represent the sample), sufficient to limit potential bias

Yes  
Partly  
No  
Unsure

Response rate (i.e. proportion of study sample completing the study and providing outcome data) is adequate

Attempts to collect information on participants who dropped out of the study are described

Reasons for loss to follow-up are provided

Participants lost to follow-up are adequately described for key characteristics

There are no important differences between key characteristics and outcomes in participants who completed the study and those who did not

**Prognostic factor measurement**

The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias

Yes  
Partly  
No  
Unsure

A clear definition or description of the prognostic factor measured is provided (e.g. including dose, level, duration of exposure and clear specification of the method of measurement)

Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used

The prognostic factor measure and method are adequately valid and reliable to limit misclassification bias (e.g. may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall)

Adequate proportion of the study sample has complete data for prognostic factors

The method and setting of measurement are the same for all study participants

Appropriate methods are used if imputation is used for missing prognostic factor data

## Potential bias

## Items to be considered for assessment of potential opportunity for bias

### Outcome measurement

The outcome of interest is adequately measured in study participants to sufficiently limit bias

Yes  
Partly  
No  
Unsure

A clear definition of the outcome of interest is provided, including duration of follow-up and level and extent of the outcome construct

The outcome measure and method used are adequately valid and reliable to limit misclassification bias (e.g. may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test)

The method and setting of measurement are the same for all study participants

### Confounding measurement and account

Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest

Yes  
Partly  
No  
Unsure

All important confounders, including treatments (key variables in conceptual model), are measured

Clear definitions of the important confounders measured are provided (e.g. including dose, level and duration of exposures)

Measurement of all important confounders is adequately valid and reliable (e.g. may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall)

The method and setting of confounding measurement are the same for all study participants

Appropriate methods are used if imputation is used for missing confounder data

Important potential confounders are accounted for in the study design (e.g. matching for key variables, stratification or initial assembly of comparable groups)

Important potential confounders are accounted for in the analysis (i.e. appropriate adjustment)

### Analysis

The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results

Yes  
Partly  
No  
Unsure

There is sufficient presentation of data to assess the adequacy of the analysis

The strategy for model building (i.e. inclusion of variables) is appropriate and is based on a conceptual framework or model

The selected model is adequate for the design of the study

There is no selective reporting of results



## Appendix 3 Quality assessment

The quality of conduct and reporting of prognostic studies has received some criticism.<sup>135,150,151</sup> Surveys indicate that the vast majority of such studies appear to have been undertaken on an ad hoc or opportunistic basis without a defined research question or clear protocol for the design, conduct and analysis of the study. Common weaknesses include lack of information about whether outcomes, populations and test cut-off were defined before data were collected. Selective reporting of analyses is also a common problem.<sup>150</sup> Due to these anticipated deficiencies the proposed systematic review placed emphasis on assessment of quality of primary studies attempting to incorporate quality findings into the evidence synthesis.

Factors that need to be considered in the assessment of prognostic studies include: internal validity, external validity, statistical validity, evaluation of the model and the clinical usefulness of the model.<sup>152–156</sup> As there is an element of subjectivity in quality assessment, as well as a need for attention to detail as reporting methods and formats vary widely, disagreement between reviewers is not uncommon.

Previous work in the area of prognosis undertaken by Hayden *et al.*<sup>106</sup> and Sutcliffe *et al.*<sup>104</sup> provided a useful framework for appraising study quality of the included papers. The quality assessment instrument specific to the needs of this review was adapted from these published papers to assess biases in six domains: study population, attrition, prognostic factor measurement, outcome measurement, confounding measurement, and account and analysis. The quality assessment tool identified factors that needed to be taken into account when interpreting the results of the study.

## Quality assessment form

### Assessing quality of prognostic studies on the basis of framework of potential biases

First Author:    Year:    ID:    Reviewer(s):

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/ sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]  Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]  Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results					
Study attrition	Statement as to exclusions due to missing data:  Baseline variables  Loss to follow-up  Statement as to the possible effect on the results from missing data  Loss to follow-up is not associated with key characteristics					
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement and timing described)  Specified instrument and personnel for measurement of predictive factors  Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>  Blinding: were estimators of risk factor status and of outcomes blinded?  The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias					
Outcome	Is the outcome clearly defined?					
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>					
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis  The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results					
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)						

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

Note: The above table was adapted from Sutcliffe *et al.*<sup>104</sup>

## Appendix 4 Included papers at full sift ( $n = 31$ )

### Reference

- Bayley A, Milosevic M, Blend R, Logue J, Gospodarowicz M, Boxen I, *et al.* A prospective study of factors predicting clinically occult spinal cord compression in patients with metastatic prostate carcinoma. *Cancer* 2001;**92**:303–10<sup>107</sup>
- Bernat JL, Greenberg ER, Barrett J. Suspected epidural compression of the spinal cord and cauda equina by metastatic carcinoma. Clinical diagnosis and survival. *Cancer* 1983;**51**:1953–7<sup>108</sup>
- Chaichana KL, Pendleton C, Wolinsky JP, Gokaslan ZL, Sciubba DM. Vertebral compression fractures in patients presenting with metastatic epidural spinal cord compression. *Neurosurgery* 2009;**65**:267–74<sup>109</sup>
- Fisher CG, DiPaola CP, Ryken TC, Bilsky MH, Shaffrey CI, Berven SH, *et al.* A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. *Spine* 2010;**35**:E1221–9<sup>110</sup>
- Goldman JM, Ash CM, Souhami RL, Geddes DM, Harper PG, Spiro SG, *et al.* Spinal cord compression in small cell lung cancer: a retrospective study of 610 patients. *Br J Cancer* 1989;**59**:591–3<sup>111</sup>
- Harrison KM, Muss HB, Ball MR, McWhorter M, Case D. Spinal cord compression in breast cancer. *Cancer* 1985;**55**:2839–44<sup>112</sup>
- Helweg-Larsen S, Sorensen PS, Kreiner S. Prognostic factors in metastatic spinal cord compression: a prospective study using multivariate analysis of variables influencing survival and gait function in 153 patients. *Int J Radiat Oncol Biol Phys* 2000;**46**:1163–9<sup>113</sup>
- Helweg-Larsen S, Hansen SW, Sorensen PS. Second occurrence of symptomatic metastatic spinal cord compression and findings of multiple spinal epidural metastases. *Int J Radiat Oncol Biol Phys* 1995;**33**:595–8<sup>114</sup>
- Huddart RA, *et al.* Spinal cord compression in prostate cancer: treatment outcome and prognostic factors. *Radiother Oncol* 1997;**44**:229–36<sup>115</sup>
- Husband DJ, Grant KA, Romaniuk CS. MRI in the diagnosis and treatment of suspected malignant spinal cord compression. *Br J Radiol* 2001;**74**:15–23<sup>116</sup>
- Klekamp J, Samii H. Surgical results for spinal metastases. *Acta Neurochir* 1998;**140**:957–67<sup>117</sup>
- Kuban DA, el-Mahdi AM, Sigfred SV, Schellhammer PF, Babb TJ. Characteristics of spinal cord compression in adenocarcinoma of prostate. *Urology* 1986;**28**:364–9<sup>118</sup>
- Levack P, Graham J, Collie D, Grant R, Kidd J, Kunkler I, *et al.* Don't wait for a sensory level—listen to the symptoms: a prospective audit of the delays in diagnosis of malignant cord compression. *Clin Oncol (R Coll Radiol)* 2002;**14**:472–80<sup>119</sup>
- 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;**23**:2028–37<sup>62</sup>
- Lu C, Stomper PC, Drislane FW, Wen PY, Block CC, Humphrey CC. Suspected spinal cord compression in breast cancer patients: a multidisciplinary risk assessment. *Breast Cancer Res Treat* 1998;**51**:121–31<sup>120</sup>
- Lu C, Gonzalez RG, Jolesz FA, Wen PY, Talcott JA. Suspected spinal cord compression in cancer patients: a multidisciplinary risk assessment. *J Support Oncol* 2005;**3**:305–12<sup>121</sup>
- McCloskey EV, Spector TD, Eyres KS, Fern ED, Orourke N, Vasikaran SM, *et al.* The assessment of vertebral deformity – a method for use in population studies and clinical-trials. *Osteoporos Int* 1993;**3**:138–47<sup>122</sup>
- Oka H, Kondoh T, Seichi A, Hozumi T, Nakamura K. Incidence and prognostic factors of Japanese breast cancer patients with bone metastasis. *J Orthop Sci* 2006;**11**:13–19<sup>123</sup>
- Plunkett TA, Smith P, Rubens RD. Risk of complications from bone metastases in breast cancer: implications for management. *Eur J Cancer* 2000;**36**:476–82<sup>24</sup>
- Rose PS, Laufer I, Boland PJ, Hanover A, Bilsky MH, Yamada J, *et al.* Risk of fracture after single fraction image-guided intensity-modulated radiation therapy to spinal metastases. *J Clin Oncol* 2009;**27**:5075–9<sup>88</sup>
- Roth SE, Mousavi P, Finkelstein J, Chow E, Kreder H, Whyne CM. Metastatic burst fracture risk prediction using biomechanically based equations. *Clin Orthop Relat Res* 2004;**419**:83–90<sup>124</sup>

## Reference

- Sekine I, Nokihara H, Yamamoto N, Kunitoh H, Ohe Y, Tamura T. Risk factors for skeletal-related events in patients with non-small cell lung cancer treated by chemotherapy. *Lung Cancer* 2009;**65**:219–22<sup>125</sup>
- Shah AN, Pietrobon R, Richardson WJ, Myers BS. Patterns of tumor spread and risk of fracture and epidural impingement in metastatic vertebrae. *J Spinal Disord Tech* 2003;**16**:83–9<sup>126</sup>
- Snyder BD, Hipp JA, Nazarian A. *Non-invasive prediction of fracture risk due to benign and metastatic skeletal defects*. Warrendale, PA: Materials Research Society; 2005. pp. 39–51<sup>127</sup>
- Snyder BD, Cordio MA, Nazarian A, Kwak SD, Chang DJ, Entezari V, et al. Noninvasive prediction of fracture risk in patients with metastatic cancer to the spine. *Clin Cancer Res* 2009;**15**:7676–83<sup>128</sup>
- Soerdjbalie-Maikoe V, Pelger RCM, Nijeholt GABL, Arndt JW, Zwinderman AH, Bril H, et al. Bone scintigraphy predicts the risk of spinal cord compression in hormone-refractory prostate cancer. *Eur J Nucl Med Mol Imaging* 2004;**31**:958–63<sup>129</sup>
- Sun J-M, Ahn JS, Lee S, Kim JA, Lee J, Park YH, et al. Predictors of skeletal-related events in non-small cell lung cancer patients with bone metastases. *Lung Cancer* 2011;**71**:89–93<sup>130</sup>
- Talcott JA, Stomper PC, Drislane FW, Wen PY, Block CC, Humphrey CC, et al. Assessing suspected spinal cord compression: a multidisciplinary outcomes analysis of 342 episodes. *Support Care Cancer* 1999;**7**:31–8.<sup>131</sup>
- Taneichi H, Kaneda K, Takeda N, Abumi K, Satoh S. Risk factors and probability of vertebral body collapse in metastases of the thoracic and lumbar spine. *Spine* 1997;**22**:239–45<sup>89</sup>
- Venkitaraman R, Sohaib SA, Barbachano Y, Parker CC, Khoo V, Huddart RA, et al. Detection of occult spinal cord compression with magnetic resonance imaging of the spine. *Clin Oncol (R Coll Radiol)* 2007;**19**:528–31<sup>132</sup>
- Venkitaraman R, Sohaib SA, Barbachano Y, Parker CC, Huddart RA, Horwich A, et al. Frequency of screening magnetic resonance imaging to detect occult spinal cord compromise and to prevent neurological deficit in metastatic castration-resistant prostate cancer. *Clin Oncol (R Coll Radiol)* 2010;**22**:147–52<sup>133</sup>

## Appendix 5 Reasons for exclusion at full sift (n = 305)

TABLE 36 Excluded studies

Reference	Reason for exclusion
Acikgoz B, Akkurt C, Erben A, Bertan V, Ozgen T, Ozcan O. Metastatic spinal cord tumours. <i>Paraplegia</i> 1989; <b>27</b> :359–63	Outcome measures did not meet inclusion criteria
Adib RS, Anderson JB, Ashken MH, Baumber CD, Bevis CRA, Beynon LL, <i>et al.</i> Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council trial. <i>Br J Urol</i> 1997; <b>79</b> :235–46	Outcome measures did not meet inclusion criteria
Aguilar G, Moras JL, Franco V, Barousse R, Persico S, Blasi A. How to discriminate metastatic from osteoporotic compression spinal fractures. <i>Bone</i> 2007; <b>41</b> :S12	Abstract
Alafaci C, Salpietro FM, Grasso G, Passalacqua M, Lucerna S, Romano A, <i>et al.</i> Spinal cord compression by a metastasizing thymoma. <i>Acta Neurochirur</i> 1999; <b>141</b> :215–16	Case report
Alberico, RA. Balloon kyphoplasty for multilevel spinal metastases from breast cancer. <i>J Support Oncol</i> 2007; <b>5</b> :243–6	Case reports
Algra PR, Bloem JL, Tissing H, Falke THM, Arndt JW, Verboom LJ. Detection of vertebral metastases – comparison between MR imaging and bone-scintigraphy. <i>Radiographics</i> 1991; <b>11</b> :219–32	Outcome measures did not meet inclusion criteria
Algra PR. Diagnostic-Imaging of Vertebral Metastases. <i>Rivist Neuroradiol</i> 1995; <b>8</b> :165–75	Review
Alvarez L, Perez-Higueras A, Quinones D, Calvo E, Rossi RE. Vertebroplasty in the treatment of vertebral tumors: postprocedural outcome and quality of life. <i>Eur Spine J</i> 2003; <b>12</b> :356–60	Outcome measures did not meet inclusion criteria
Ambrosiano G, Lavanga A, Vassallo P, Izzo R, Diano AA, Muto M. Vertebroplasty in the treatment of spine disease. <i>Intervent Neuroradiol</i> 2005; <b>11</b> :309–23	Outcome measures did not meet inclusion criteria
Amdur RJ, Bennett J, Olivier K, Wallace A, Morris CG, Liu CR, <i>et al.</i> A prospective, phase II study demonstrating the potential value and limitation of radiosurgery for spine metastases. <i>Am J Clin Oncol Cancer Clin Trial</i> 32.5 2009; <b>32</b> :515–20	Outcome measures did not meet inclusion criteria
Ampil F, Caldito G, Thibodeaux J, Sangster G, Baluna R. Radiotherapy for cervical spine metastases in breast cancer patients. <i>Eur J Orthop Surg Traumatol</i> 2010; <b>20</b> :527–31	Outcome measures did not meet inclusion criteria
Ampil FL, Mills GM, Burton GV. A retrospective study of metastatic lung cancer compression of the cauda equina. <i>Chest</i> 2001; <b>120</b> :1754–5	Editorial
Ampil FL, Burton GV, Mills GM, Jawahar A, Pelsler R, Nanda A. Cauda equina compression in breast cancer—incidence and treatment outcome. <i>Eur J Gynaecol Oncol</i> 2001; <b>22</b> :257–9	Outcome measures did not meet inclusion criteria
Ampil FL, Nanda A, Willis BK. Metastatic gastrointestinal cancer compressing the spinal cord or cauda equina. <i>Am J Gastroenterol</i> 2000; <b>95</b> :848–9	Editorial
Ampil FL, Abreo F. Radiotherapeutic palliation of spinal epidural compression in small-cell lung-cancer. <i>Southern Med J</i> 1992; <b>85</b> :266–9	Outcome measures did not meet inclusion criteria
An HS, Andreshak TG, Nguyen C, Williams A, Daniels D. Can we distinguish between benign versus malignant compression fractures of the spine by magnetic resonance imaging? <i>Spine</i> 1995; <b>20</b> :1776–82	Outcome measures did not meet inclusion criteria
Appelgren L, Nordborg C, Sjoberg M, Karlsson PA, Nitescu P, Curelaru I. Spinal epidural metastasis: implications for spinal analgesia to treat 'refractory' cancer pain. <i>J Pain Symptom Manage</i> 1997; <b>13</b> :25–42	Outcome measures did not meet inclusion criteria
Apuzzo ML, Weiss MH, Minassian HV. Epidural spinal metastases: factors related to selection of cases for decompressive laminectomy. <i>Bull Los Angeles Neurol Soc</i> 1977; <b>42</b> :63–70	Outcome measures did not meet inclusion criteria

continued

TABLE 36 Excluded studies (continued)

Reference	Reason for exclusion
Arguello F, Baggs RB, Duerst RE, Johnstone L, Mcqueen K, Frantz CN. Pathogenesis of vertebral metastasis and epidural spinal-cord compression. <i>Cancer</i> 1990; <b>65</b> :98–106	Animal study
Bach F, Agerlin N, Sorensen JB, Rasmussen TB, Dombrowsky P, Sorensen PS, <i>et al.</i> Metastatic spinal cord compression secondary to lung cancer. <i>J Clin Oncol</i> 1992; <b>10</b> :1781–7	Outcome measures did not meet inclusion criteria
Baker LL, Goodman SB, Perkash I, Lane B, Enzmann DR. Benign versus pathologic compression fractures of vertebral bodies: assessment with conventional spin-echo, chemical-shift, and STIR MR imaging. <i>Radiology</i> 1990; <b>174</b> :495–502	Outcome measures did not meet inclusion criteria
Baldini M, Tonnarelli GP, Princi L, Vivenza C, Nizzoli V. Neurological results in spinal cord metastases. <i>Neurochirurgia</i> 1979; <b>22</b> :159–65	Outcome measures did not meet inclusion criteria
Barr JD, Barr MS, Lemley TJ, McCann RM. Percutaneous vertebroplasty for pain relief and spinal stabilization. <i>Spine</i> 2000; <b>25</b> :923–8	Outcome measures did not meet inclusion criteria
Bartels RH, Feuth T, Rades D, Hedlund R, Villas C, van der Linden Y, <i>et al.</i> External validation of a model to predict the survival of patients presenting with a spinal epidural metastasis. <i>Cancer Metast Rev</i> 2011; <b>30</b> :153–9	Outcome measures did not meet inclusion criteria
Bartels RHMA, Feuth T, van der Maazen R, Verbeek ALM, Kappelle AC, Grotenhuis JA, <i>et al.</i> Development of a model with which to predict the life expectancy of patients with spinal epidural metastasis. <i>Cancer</i> 2007; <b>110</b> :2042–9	Outcome measures did not meet inclusion criteria
Bauer HC. Posterior decompression and stabilization for spinal metastases. Analysis of sixty-seven consecutive patients. <i>J Bone Joint Surg Am</i> 1997; <b>79</b> :514–22	Outcome measures did not meet inclusion criteria
Bhalla SK. Metastatic disease of the spine. <i>Clin Orthop Relat Res</i> 1970; <b>73</b> :52–60	Case report
Bhugaloo AA, Abdullah BJJ, Siow YS, Ng KH. Diffusion weighted MR imaging in acute vertebral compression fractures: Differentiation between malignant and benign causes. <i>Biomed Imaging Intervent J</i> 2006; <b>2</b> :e12	Outcome measures did not meet inclusion criteria
Bilsky MH, Shannon FJ, Sheppard S, Prabhu V, Boland PJ. Diagnosis and management of a metastatic tumor in the atlantoaxial spine. <i>Spine</i> 2002; <b>27</b> :1062–9	Outcome measures did not meet inclusion criteria
Bilsky MH, Sonntag VKH, Musleh W, Baig MN, Mendel E, Fehlings MG. Predictors of ambulatory function after decompressive surgery for metastatic epidural spinal cord compression. <i>Neurosurgery</i> 2008; <b>62</b> :691–2	Outcome measures did not meet inclusion criteria
Bilsky MH, Laufer I, Fourney DR, Groff M, Schmidt MH, Varga PP, <i>et al.</i> Reliability analysis of the epidural spinal cord compression scale clinical article. <i>J Neurosurg Spine</i> 2010; <b>13</b> :324–8	Outcome measures did not meet inclusion criteria
Bilsky MH, Boland P, Lis E, Raizer JJ, Healey JH. Single-stage posterolateral transpedicle approach for spondylectomy, epidural decompression, and circumferential fusion of spinal metastases. <i>Spine</i> 2000; <b>25</b> :2240–9	Outcome measures did not meet inclusion criteria
Body JJ. Effectiveness and cost of bisphosphonate therapy in tumor bone disease. <i>Cancer</i> 2003; <b>97</b> :859–65	Review
Bono B, Cazzaniga P, Pini V, Zurrida SM, Spagnolo R, Torelli L, <i>et al.</i> Palliative surgery of metastatic bone-disease – a review of 83 cases. <i>Eur J Cancer</i> 1991; <b>27</b> :556–8	Outcome measures did not meet inclusion criteria
Boogerd W, Vandersande JJ. Diagnosis and treatment of spinal-cord compression in malignant disease. <i>Cancer Treat Rev</i> 1993; <b>19</b> :129–50	Review
Boogerd W, Vandersande JJ, Kroger R. Early diagnosis and treatment of spinal epidural metastasis in breast cancer – a prospective study. <i>J Neurol Neurosurg Psychiatry</i> 1992; <b>55</b> :1188–93	Outcome measures did not meet inclusion criteria
Bouza C, Lopez-Cuadrado T, Cediell P, Saz-Parkinson Z, Amate JM. Balloon kyphoplasty in malignant spinal fractures: a systematic review and meta-analysis. <i>BMC Palliat Care</i> 2009; <b>8</b> :12	Review
Brennan RP, Altstadt TJ, Rodgers RB, Horn EM. Multi-level corpectomies and reconstruction via a single posterolateral approach. <i>J Clin Neuroscience</i> 2010; <b>17</b> :1399–404	Outcome measures did not meet inclusion criteria
Brodner RA, Berman AJ, Wisniewski M, Nakagawa H. Thyroid carcinoma presenting as epidural metastasis with spinal cord compression. <i>Mount Sinai J Med</i> 1975; <b>42</b> :207–15	Outcome measures did not meet inclusion criteria

TABLE 36 Excluded studies (continued)

Reference	Reason for exclusion
Brown PD, Stafford SL, Schild SE, Martenson JA, Schiff D. Metastatic spinal cord compression in patients with colorectal cancer. <i>J Neurooncol</i> 1999; <b>44</b> :175–80	Outcome measures did not meet inclusion criteria
Byrne MJ, Scheinberg MA, Mavligit G, Dawkins RL. Hepatocellular carcinoma: presentation with vertebral metastases and radicular compression. <i>Cancer</i> 1972; <b>30</b> :202–5	Outcome measures did not meet inclusion criteria
Byrne TN, Borges LF, Loeffler JS. Metastatic epidural spinal cord compression: Update on management. <i>Semin Oncol</i> 2006; <b>33</b> : 307–11	Review
Byrne, TN. Spinal cord compression from epidural metastases. <i>New Engl J Med</i> 1992; <b>327</b> :614–19	Review
Carmody RF, Yang PJ, Seeley GW, Seeger JF, Unger EC, Johnson JE. Spinal cord compression due to metastatic disease: diagnosis with MR imaging versus myelography. <i>Radiology</i> 1989; <b>173</b> :225–9	Outcome measures did not meet inclusion criteria
Carteni G, Bordonaro R, Giotta F, Lorusso V, Scalone S, Vinaccia V, <i>et al.</i> Efficacy and safety of zoledronic acid in patients with breast cancer metastatic to bone: a multicenter clinical trial. <i>Oncologist</i> 2006; <b>11</b> :841–8	Outcome measures did not meet inclusion criteria
Chadwick DJ, Gingell JC, Gillatt DA, Mukerjee A, Penry JB. Magnetic resonance imaging of spinal metastases. <i>J R Soc Med</i> 1991; <b>84</b> :196–200	Outcome measures did not meet inclusion criteria
Chaichana KL, Pendleton C, Sciubba DM, Wolinsky JP, Gokaslan ZL. Outcome following decompressive surgery for different histological types of metastatic tumors causing epidural spinal cord compression. Clinical article. <i>J Neurosurg Spine</i> 2009; <b>11</b> :56–63	Outcome measures did not meet inclusion criteria
Chaichana KL, Woodworth GF, Sciubba DM, McGirt MJ, Witham TJ, Bydon A, <i>et al.</i> Predictors of ambulatory function after decompressive surgery for metastatic epidural spinal cord compression. <i>Neurosurgery</i> 2008; <b>62</b> :683–92	Outcome measures did not meet inclusion criteria
Chamberlain MC, Sloan A, Vrionis F. Systematic review of the diagnosis and management of malignant extradural spine cord compression: the cancer care Ontario practice guidelines initiative's neuro-oncology disease site group. <i>J Clin Oncol</i> 2005; <b>23</b> :7750–1	Editorial
Chataigner H, Onimus M. Surgery in spinal metastasis without spinal cord compression: indications and strategy related to the risk of recurrence. <i>Eur Spine J</i> 2000; <b>9</b> :523–7	Outcome measures did not meet inclusion criteria
Chen WT, Shih TT, Chen RC, Lo HY, Chou CT, Lee JM, <i>et al.</i> Blood perfusion of vertebral lesions evaluated with gadolinium-enhanced dynamic MRI: in comparison with compression fracture and metastasis. <i>J Magn Reson Imaging</i> 2002; <b>15</b> :308–14	Outcome measures did not meet inclusion criteria
Chi JH, Gokaslan Z, McCormick P, Tibbs PA, Kryscio RJ, Patchell RA. Selecting treatment for patients with malignant epidural spinal cord compression – does age matter?: results from a randomized clinical trial. <i>Spine</i> 2009; <b>34</b> :431–5	Outcome measures did not meet inclusion criteria
Chiewwit P, Danchaivijitr N, Sirivitmaitrie K, Chiewwit S, Thephamongkhol K. Does magnetic resonance imaging give value-added than bone scintigraphy in the detection of vertebral metastasis? <i>J Med Assoc Thai</i> 2009; <b>92</b> :818–29	Outcome measures did not meet inclusion criteria
Cho WI, Chang UK. Comparison of MR imaging and FDG-PET/CT in the differential diagnosis of benign and malignant vertebral compression fractures Clinical article. <i>J Neurosurg Spine</i> 2011; <b>14</b> :177–83	Outcome measures did not meet inclusion criteria
Cohen JI. Clinical conferences at the Johns Hopkins Hospital. Clinical – pathologic conference. <i>Johns Hopkins Med J</i> 1979; <b>144</b> :138–44	Case reports
Colletti PM, Dang HT, Deseran MW, Kerr RM, Boswell WD, Ralls PW. Spinal MR imaging in suspected metastases: correlation with skeletal scintigraphy. <i>Magn Reson Imaging</i> 1991; <b>9</b> :349–55	Outcome measures did not meet inclusion criteria
Colletti PM, Siegel HJ, Woo MY, Young HY, Terk MR. The impact on treatment planning of MRI of the spine in patients suspected of vertebral metastasis: an efficacy study. <i>Comput Med Imaging Graph</i> 1996; <b>20</b> :159–62	Outcome measures did not meet inclusion criteria
de Medicis E, de Leon-Casasola OA. Reversible paraplegia associated with lumbar epidural analgesia and thoracic vertebral metastasis. <i>Anesth Analg</i> 2001; <b>92</b> :1316–18	Case reports

continued

TABLE 36 Excluded studies (continued)

Reference	Reason for exclusion
Deb HK, Sengupta P. Spinal cord compression by metastatic testicular embryonal carcinoma. <i>J Indian Med Assoc</i> 1983; <b>81</b> :168–70	Case reports
Delichtenberg MH, Kvist E, Hjortberg P, Karle A. Adenocarcinoma of the prostate and metastatic medullary compression – a retrospective study of 22 patients. <i>Scand J Urol Nephrol</i> 1992; <b>26</b> :25–8	Outcome measures did not meet inclusion criteria
Denaro V, Di Martino A, Papalia R, Denaro L. Patients with cervical metastasis and neoplastic pachymeningitis are less likely to improve neurologically after surgery. <i>Clin Orthop Relat Res</i> 2011; <b>469</b> :708–14	Outcome measures did not meet inclusion criteria
Dewald RL, Bridwell KH, Prodromas C, Rodts MF. Reconstructive spinal surgery as palliation for metastatic malignancies of the spine. <i>Spine</i> 1985; <b>10</b> :21–6	Outcome measures did not meet inclusion criteria
Di Martino A, Vincenzi B, Denaro L, Barnaba SA, Papalia R, Santini D, et al. 'Internal bracing' surgery in the management of solid tumor metastases of the thoracic and lumbar spine. <i>Oncol Rep</i> 2009; <b>21</b> :431–5	Outcome measures did not meet inclusion criteria
Donato V, Bonfili P, Bulzonetti N, Santarelli M, Osti MF, Tombolini V, et al. Radiation therapy for oncological emergencies. <i>Anticancer Res</i> 2001; <b>21</b> :2219–24	Outcome measures did not meet inclusion criteria
Eriks IE, Angenot EL, Lankhorst GJ. Epidural metastatic spinal cord compression: functional outcome and survival after inpatient rehabilitation. <i>Spinal Cord</i> 2004; <b>42</b> :235–9	Outcome measures did not meet inclusion criteria
Ernstberger T, Kogel M, Konig F, Schultz W. Expandable vertebral body replacement in patients with thoracolumbar spine tumors. <i>Arch Orthop Trauma Surg</i> 2005; <b>125</b> :660–9	Outcome measures did not meet inclusion criteria
Fager CA. Management of malignant intraspinal disease. <i>Surg Clin North Am</i> 1967; <b>47</b> :743–50	Review
Fattal C, Fabbro M, Rouays-Mabit H, Verollet C, Bauchet L. Metastatic paraplegia and functional outcomes: perspectives and limitations for rehabilitation care. Part 2. <i>Arch Phys Med Rehabil</i> 2011; <b>92</b> :134–45	Review
Fattal C, Fabbro M, Gelis A, Bauchet L. Metastatic paraplegia and vital prognosis: perspectives and limitations for rehabilitation care. Part 1. <i>Arch Phys Med Rehabil</i> 2011; <b>92</b> :125–33	Review
Findlay GF. The role of vertebral body collapse in the management of malignant spinal cord compression. <i>J Neurol Neurosurg Psychiatry</i> 1987; <b>50</b> :151–4	Outcome measures did not meet inclusion criteria
Findlay GFG, Sandeman DR, Buxton P. The role of needle biopsy in the management of malignant spinal compression. <i>Br J Neurosurg</i> 1988; <b>2</b> :479–84	Outcome measures did not meet inclusion criteria
Flors L, Lonjedo E, Leiva-Salinas C, Marti-Bonmati L, Martinez-Rodrigo JJ, Lopez-Perez E, et al. Vesselplasty: a new technical approach to treat symptomatic vertebral compression fractures. <i>AJR</i> 2009; <b>193</b> :218–26	Outcome measures did not meet inclusion criteria
Flynn DF, Shipley WU. Management of spinal-cord compression secondary to metastatic prostatic-carcinoma. <i>Urol Clin North Am</i> 1991; <b>18</b> :145–52	Review
Fontana M, Pompili A, Cattani F, Mastrostefano R. Metastatic spinal cord compression. Follow-up study. <i>J Neurosurg Sci</i> 1980; <b>24</b> :141–6	Outcome measures did not meet inclusion criteria
Francken AB, Hong AM, Fulham MJ, Millward MJ, McCarthy WH, Thompson JF. Detection of unsuspected spinal cord compression in melanoma patients by 18F-fluorodeoxyglucose-positron emission tomography. <i>Eu J Surg Oncol</i> 2005; <b>31</b> :197–204	Outcome measures did not meet inclusion criteria
Freundt K, Meyners T, Bajrovic A, Basic H, Karstens JH, Adamietz IA, et al. Radiotherapy for oligometastatic disease in patients with spinal cord compression (MSCC) from relatively radioresistant tumors. <i>Strahlenther Onkol</i> 2010; <b>186</b> :218–23	Outcome measures did not meet inclusion criteria
Fu T-S, Chen L-H, Liao J-C, Lai P-L, Niu C-C, Chen W-J. Magnetic resonance imaging characteristics of benign and malignant vertebral fractures. <i>Chang Gung Med J</i> 2004; <b>27</b> :808–15	Outcome measures did not meet inclusion criteria
Fujii M, Abe K, Hayashi K, Kosuda S, Yano F, Watanabe S, et al. Honda sign and variants in patients suspected of having a sacral insufficiency fracture. <i>Clin Nuclear Med</i> 2005; <b>30</b> :165–9	Outcome measures did not meet inclusion criteria

TABLE 36 Excluded studies (continued)

Reference	Reason for exclusion
Fujii Y, Higashi Y, Owada F, Okuno T, Mizuno H, Mizuno H. Magnetic-resonance-imaging for the diagnosis of prostate-cancer metastatic to bone. <i>Br J Urol</i> 1995; <b>75</b> :54–8	Outcome measures did not meet inclusion criteria
Fukushige T, Sano T, Yamada S, Kaneko S, Ooish Y, Kano T. Spinal paralysis due to spinal metastasis or cancerous invasion. Proceedings of the 12th International Pain Clinic: World Society of Pain Clinicians 2006:131–3	Outcome measures did not meet inclusion criteria
Furstenberg CH, Wiedenhofer B, Gerner HJ, Putz C. The effect of early surgical treatment on recovery in patients with metastatic compression of the spinal cord. <i>J Bone Joint Surg Br</i> 2009; <b>91</b> :240–4	Outcome measures did not meet inclusion criteria
Gaitanis IN, Hadjipavlou AG, Katonis PG, Tzermiadianos MN, Pasku DS, Patwardhan AG. Balloon kyphoplasty for the treatment of pathological vertebral compressive fractures. <i>Eur Spine J</i> 2005; <b>14</b> :250–60	Outcome measures did not meet inclusion criteria
Galasko CSB. Spinal instability secondary to metastatic cancer. <i>J Bone Joint Surg Br</i> 1991; <b>73</b> :104–8	Outcome measures did not meet inclusion criteria
Garcia-Picazo A, Capilla RP, Pulido RP, Garcia de SR. Utility of surgery in the treatment of epidural vertebral metastases. <i>Acta Neurochir</i> 1990; <b>103</b> :131–8	Outcome measures did not meet inclusion criteria
Gasbarrini A, Li HM, Cappuccio M, Mirabile L, Paderni S, Terzi S, et al. Efficacy evaluation of a new treatment algorithm for spinal metastases. <i>Spine</i> 2010; <b>35</b> :1466–70	Outcome measures did not meet inclusion criteria
George R, Jeba J, Ramkumar G, Chacko AG, Leng M, Tharyan P. Interventions for the treatment of metastatic extradural spinal cord compression in adults. <i>Cochrane Database Syst Rev</i> 2008; <b>4</b> :CD006716	Review
Georgy BA, Wong W. Plasma-mediated radiofrequency ablation assisted percutaneous cement injection for treating advanced malignant vertebral compression fractures. <i>AJNR Am J Neuroradiol</i> 2007; <b>28</b> :700–5	Outcome measures did not meet inclusion criteria
Gerszten PC, Mendel E, Yamada Y. Radiotherapy and radiosurgery for metastatic spine disease: what are the options, indications, and outcomes? <i>Spine</i> 2009; <b>34</b> :S78–92	Review
Ghelman B, Lospinuso MF, Levine DB, O'leary PF, Burke SW. Percutaneous computed-tomography-guided biopsy of the thoracic and lumbar spine. <i>Spine</i> 1991; <b>16</b> :736–9	Outcome measures did not meet inclusion criteria
Gibbs IC, Kamnerdsupaphon P, Ryu MR, Dodd R, Kiernan M, Change SD, et al. Image-guided robotic radiosurgery for spinal metastases. <i>Radiother Oncol</i> 2007; <b>82</b> :185–90	Outcome measures did not meet inclusion criteria
Gilbert R, Posner JB. Extradural spinal-cord compression from metastatic cancer – diagnosis and treatment. <i>Neurology</i> 1977; <b>27</b> :366	Abstract
Gilbert RW, Kim JH, Posner JB. Epidural spinal cord compression from metastatic tumor: diagnosis and treatment. <i>Ann Neurol</i> 1978; <b>3</b> :40–51	Outcome measures did not meet inclusion criteria
Godersky JC, Smoker WR, Knutson R. Use of magnetic resonance imaging in the evaluation of metastatic spinal disease. <i>Neurosurgery</i> 1987; <b>21</b> :676–80	Outcome measures did not meet inclusion criteria
Gonzalez-Barcena D, Vadillo-Buenfil M, Cortez-Morales A, Fuentes-Garcia M, Cardenas-Cornejo I, Comaru-Schally AM, et al. Luteinizing hormone-releasing hormone antagonist cetorelix as primary single therapy in patients with advanced prostatic cancer and paraplegia due to metastatic invasion of spinal cord. <i>Urology</i> 1995; <b>45</b> :275–81	Outcome measures did not meet inclusion criteria
Gorter K. Results of laminectomy in spinal cord compression due to tumours. <i>Acta Neurochir</i> 1978; <b>42</b> :177–87	Outcome measures did not meet inclusion criteria
Grant R, Papadopoulos SM, Greenberg HS. Metastatic epidural spinal-cord compression. <i>Neurol Clin</i> 1991; <b>9</b> :825–41	Review
Greenberger JS. The pathophysiology and management of spine metastasis from lung-cancer. <i>J Neurooncol</i> 1995; <b>23</b> :109–20	Review
Grem JL, Burgess J, Trump DL. Clinical features and natural history of intramedullary spinal cord metastasis. <i>Cancer</i> 1985; <b>56</b> :2305–14	Outcome measures did not meet inclusion criteria

continued

TABLE 36 Excluded studies (continued)

Reference	Reason for exclusion
Grommes C, Bosl GJ, DeAngelis LM. Treatment of epidural spinal cord involvement from germ cell tumors with chemotherapy. <i>Cancer</i> 2011; <b>117</b> :1911–16	Outcome measures did not meet inclusion criteria
Grosh W, Greco FA. Spinal cord compression: comparison of extradural and intramedullary metastases. <i>Tenn Med</i> 1981; <b>74</b> :821–4	Outcome measures did not meet inclusion criteria
Guo Y, Palmer JL, Bianty J, Konzen B, Shin K, Bruera E. Advance directives and do-not-resuscitate orders in patients with cancer with metastatic spinal cord compression: advanced care planning implications. <i>J Palliat Med</i> 2010; <b>13</b> :513–17	Outcome measures did not meet inclusion criteria
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. <i>Am J Phys Med Rehabil</i> 2003; <b>82</b> :665–8	Outcome measures did not meet inclusion criteria
Ha'Eri GB, Amirpour V. Surgical treatment of spinal metastases. <i>J Orthop Surg Tech</i> 1987; <b>3</b> :175–81	Outcome measures did not meet inclusion criteria
Haerer AF, Smith RR. Neoplasms involving the spinal cord: an analysis of 85 consecutive cases. <i>Southern Med J</i> 1968; <b>61</b> :801–7	Outcome measures did not meet inclusion criteria
Hall AJ, Mackay NN. The results of laminectomy for compression of the cord or cauda equina by extradural malignant tumour. <i>J Bone Joint Surg Br</i> 1973; <b>55</b> :497–505	Outcome measures did not meet inclusion criteria
Hamamoto Y, Kataoka M, Senba T, Uwatsu K, Sugawara Y, Inoue T, et al. Vertebral metastases with high risk of symptomatic malignant spinal cord compression. <i>Jpn J Clin Oncol</i> 2009; <b>39</b> :431–4	Outcome measures did not meet inclusion criteria
Harrington KD. The use of methylmethacrylate for vertebral-body replacement and anterior stabilization of pathological fracture-dislocations of the spine due to metastatic malignant disease. <i>J Bone Joint Surg Am</i> 1981; <b>63</b> :36–46	Outcome measures did not meet inclusion criteria
Harrington KD. Vertebral compression fractures: differentiation between benign and malignant causes. <i>Iowa Orthop J</i> 1993; <b>13</b> :85–96	Outcome measures did not meet inclusion criteria
Hatrack NC, Lucas JD, Timothy AR, Smith MA. The surgical treatment of metastatic disease of the spine. <i>Radiother Oncol</i> 2000; <b>56</b> :335–9	Outcome measures did not meet inclusion criteria
Helweg-Larsen S, Laursen H. Clinical and autopsy findings in spinal cord compression due to metastatic disease. <i>Eur J Neurol</i> 1998; <b>5</b> :587–92	Outcome measures did not meet inclusion criteria
Helweg-Larsen S. Clinical outcome in metastatic spinal cord compression. A prospective study of 153 patients. <i>Acta Neurol Scand</i> 1996; <b>94</b> :269–75	Outcome measures did not meet inclusion criteria
Helweg-Larsen S, Wagner A, Kjaer L, Johnsen A, Boesen J, Palner T, et al. Comparison of myelography combined with postmyelographic spinal CT and MRI in suspected metastatic disease of the spinal canal. <i>J Neurooncol</i> 1992; <b>13</b> :231–7	Outcome measures did not meet inclusion criteria
Helweg-Larsen S, Johnsen A, Boesen J, Sorensen PS. Radiologic features compared to clinical findings in a prospective study of 153 patients with metastatic spinal cord compression treated by radiotherapy. <i>Acta Neurochirur</i> 1997; <b>139</b> :105–11	Outcome measures did not meet inclusion criteria
Helweg-Larsen S, Sorensen PS. Symptoms and signs in metastatic spinal cord compression: a study of progression from first symptom until diagnosis in 153 patients. <i>Eur J Cancer</i> 1994; <b>30</b> :396–8	Outcome measures did not meet inclusion criteria
Helyar V, Mohan HK, Barwick T, Livieratos L, Gnanasegaran G, Clarke SE, et al. The added value of multislice SPECT/CT in patients with equivocal bony metastasis from carcinoma of the prostate. <i>Eur J Nucl Med Mol Imaging</i> 2010; <b>37</b> :706–13	Outcome measures did not meet inclusion criteria
Herneth AM, Philipp MO, Naude J, Funovics M, Beichel RR, Bammer R, et al. Vertebral metastases: assessment with apparent diffusion coefficient. <i>Radiology</i> 2002; <b>225</b> :889–94	Outcome measures did not meet inclusion criteria
Hessler C, Vettorazzi E, Madert J, Bokemeyer C, Panse J. Actual and predicted survival time of patients with spinal metastases of lung cancer evaluation of the robustness of the Tokuhashi Score. <i>Spine</i> 2011; <b>36</b> :983–9	Outcome measures did not meet inclusion criteria
Hessler C, Vettorazzi E, Madert J, Bokemeyer C, Panse J. Dynamics of neurological deficit after surgical decompression of symptomatic vertebral metastases. <i>Spine</i> 2009; <b>34</b> :566–71	Outcome measures did not meet inclusion criteria

TABLE 36 Excluded studies (continued)

Reference	Reason for exclusion
Hill ME, Richards MA, Gregory WM, Smith P, Rubens RD. Spinal cord compression in breast cancer: a review of 70 cases. <i>Br J Cancer</i> 1993; <b>68</b> :969–73	Outcome measures did not meet inclusion criteria
Hirabayashi H, Ebara S, Kinoshita T, Yuzawa Y, Nakamura I, Takahashi J, <i>et al.</i> Clinical outcome and survival after palliative surgery for spinal metastases – palliative surgery in spinal metastases. <i>Cancer</i> 2003; <b>97</b> :476–84	Outcome measures did not meet inclusion criteria
Hitchins RN, Philip PA, Wignall B, Newlands ES, Begent RH, Rustin GJ, <i>et al.</i> Bone disease in testicular and extragonadal germ cell tumours. <i>Br J Cancer</i> 1988; <b>58</b> :793–6	Outcome measures did not meet inclusion criteria
Hodler J, Peck D, Gilula LA. Midterm outcome after vertebroplasty: predictive value of technical and patient-related factors. <i>Radiology</i> 2003; <b>227</b> :662–8	Outcome measures did not meet inclusion criteria
Holodny AI, Vaicys C, Hinrichs CR. Masking of metastases to the spine by gadolinium enhancement. <i>J Emerg Med</i> 2002; <b>23</b> :279–81	Outcome measures did not meet inclusion criteria
Holove P, Libnoch J, Cox J, Kun L, Byhardt R, Almagro U, <i>et al.</i> Spinal cord metastasis in small cell carcinoma of the lung. <i>Int J Radiat Oncol Biol Phys</i> 1984; <b>10</b> :349–56	Outcome measures did not meet inclusion criteria
Hoskin PJ, Grover A, Bhana R. Metastatic spinal cord compression: radiotherapy outcome and dose fractionation. <i>Radiother Oncol</i> 2003; <b>68</b> :175–80	Outcome measures did not meet inclusion criteria
Hosono N, Ueda T, Tamura D, Aoki Y, Yoshikawa H. Prognostic relevance of clinical symptoms in patients with spinal metastases. <i>Clin Orthop Relat Res</i> 2005; <b>436</b> :196–201	Outcome measures did not meet inclusion criteria
Jame JM, Chen CN, Chen KY. Importance of early diagnosis and radiotherapy in spinal cord compression by metastatic neoplasms. <i>Taiwan i Hsueh Hui Tsa Chih – J Formosan Med Assoc</i> 1981; <b>80</b> :1178–85	Outcome measures did not meet inclusion criteria
Jang JS, Lee SH. Efficacy of percutaneous vertebroplasty combined with radiotherapy in osteolytic metastatic spinal tumors. <i>J Neurosurg Spine</i> 2005; <b>2</b> :243–8	Outcome measures did not meet inclusion criteria
Jankowski R, Nowak S, Zukiel R, Blok T, Paprzycki W, Szymas J. Application of internal stabilisation in the surgical treatment of spinal metastases. <i>Neurol Neurochirurg Polska</i> 2008; <b>42</b> :323–31	Outcome measures did not meet inclusion criteria
Jansson KA, Bauer HC. Survival, complications and outcome in 282 patients operated for neurological deficit due to thoracic or lumbar spinal metastases. <i>Eur Spine J</i> 2006; <b>15</b> :196–202	Outcome measures did not meet inclusion criteria
Jawahar A, Ampil F, Reddy PK, Hartman GH, Sathyanarayana S, Nanda A. Analysis of outcome and prognostic factors in metastatic cauda equina compression: A 20-year single institution experience. <i>Neurosurg Q</i> 2002; <b>12</b> :108–13	Outcome measures did not meet inclusion criteria
Jensen AO, Jacobsen JB, Norgaard M, Yong M, Fryzek JP, Sorensen HT. Incidence of bone metastases and skeletal-related events in breast cancer patients: a population-based cohort study in Denmark. <i>BMC Cancer</i> 2011; <b>11</b> .	Outcome measures did not meet inclusion criteria
Jha RM, Hirsch AE, Yoo AJ, Ozonoff A, Growney M, Hirsch JA. Palliation of compression fractures in cancer patients by vertebral augmentation: a retrospective analysis. <i>J Neurointerventional Surg</i> 2010; <b>2</b> :221–8	Outcome measures did not meet inclusion criteria
Johnson AJ, Ying J, El GT, Timmerman RD, Kim RY, Littenberg B. Which MR imaging sequences are necessary in determining the need for radiation therapy for cord compression? A prospective study. <i>AJNR</i> 2007; <b>28</b> :32–7	Outcome measures did not meet inclusion criteria
Jordan E, Choe D, Miller T, Chamarthy M, Brook A, Freeman LM. Utility of bone scintigraphy to determine the appropriate vertebral augmentation levels. <i>Clin Nucl Med</i> 2010; <b>35</b> :687–91	Outcome measures did not meet inclusion criteria
Jung HS, Jee WH, McCauley TR, Ha KY, Choi KH. Discrimination of metastatic from acute osteoporotic compression spinal fractures with MR imaging. <i>Radiographics</i> 2003; <b>23</b> :179–87	Outcome measures did not meet inclusion criteria
Kakulas BA, Harper CG, Shibasaki K, Bedbrook GM. Vertebral metastases and spinal cord compression. <i>Clin Exp Neurol</i> 1978; <b>15</b> :98–113	Outcome measures did not meet inclusion criteria
Kamholtz R, Sze G. Current imaging in spinal metastatic disease. <i>Semin Oncol</i> 1991; <b>18</b> :158–69	Review

continued

TABLE 36 Excluded studies (continued)

Reference	Reason for exclusion
Kaminski HJ, Diwan VG, Ruff RL. 2nd occurrence of spinal epidural metastases. <i>Neurology</i> 1991; <b>41</b> :744–6	Outcome measures did not meet inclusion criteria
Kanis JA, McCloskey E V, Powles T, Paterson A H G, Ashley S, Spector T. A high incidence of vertebral fracture in women with breast cancer. <i>Br J Cancer</i> 1999; <b>79</b> :1179–81	Outcome measures did not meet inclusion criteria
Karchevsky M, Babb JS, Schweitzer ME. Can diffusion-weighted imaging be used to differentiate benign from pathologic fractures? A meta-analysis. <i>Skeletal Radiol</i> 2008; <b>37</b> :791–5	Review
Karikari IO, Powers CJ, Isaacs RE. Simple method for determining the need for sternotomy/manubriotomy with the anterior approach to the cervicothoracic junction. <i>Neurosurgery</i> 2009; <b>65</b> (Suppl. 1):E165–6	Outcome measures did not meet inclusion criteria
Kasai Y, Kawakita E, Uchida A. Clinical profile of long-term survivors of breast or thyroid cancer with metastatic spinal tumours. <i>Int Orthop</i> 2007; <b>31</b> :171–5	Outcome measures did not meet inclusion criteria
Katagiri H, Takahashi M, Inagaki J, Kobayashi H, Sugiura H, Yamamura S, et al. Clinical results of nonsurgical treatment for spinal metastases. <i>Int J Radiat Oncol Biol Phys</i> 1998; <b>42</b> :1127–32	Outcome measures did not meet inclusion criteria
Khaw FM, Worthy SA, Gibson MJ, Gholkar A. The appearance on MRI of vertebrae in acute compression of the spinal cord due to metastases. <i>J Bone Joint Surg Br</i> 1999; <b>81</b> :830–4	Outcome measures did not meet inclusion criteria
Kienstra GE, Terwee CB, Dekker FW, Canta LR, Borstlap AC, Tijssen CC, et al. Prediction of spinal epidural metastases. <i>Arch Neurol</i> 2000; <b>57</b> :690–5	Outcome measures did not meet inclusion criteria
Kim CH, Chung CK, Jahng TA, Kim HJ. Surgical outcome of spinal hepatocellular carcinoma metastases. <i>Neurosurgery</i> 2011; <b>68</b> :888–96	Outcome measures did not meet inclusion criteria
Kim DS, Hong SH, Choi JY, Paeng JC, Kim NR, Jun WS, et al. Magnetic resonance imaging diagnoses of bone scan abnormalities in breast cancer patients. <i>Nucl Med Comm</i> 2009; <b>30</b> :736–41	Outcome measures did not meet inclusion criteria
Kim HJ, Kim YJ, Seo MD, Yi HG, Lee SH, Lee SM, et al. Patterns of palliative procedures and clinical outcomes in patients with advanced non-small cell lung cancer. <i>Lung Cancer</i> 2009; <b>65</b> :242–6	Outcome measures did not meet inclusion criteria
Kim HJ, Ryu KN, Choi WS, Choi BK, Choi JM, Yoon Y. Spinal involvement of hematopoietic malignancies and metastasis: differentiation using MR imaging. <i>Clin Imaging</i> 1999; <b>23</b> :125–33	Outcome measures did not meet inclusion criteria
Kim JK, Learch TJ, Colletti PM, Lee JW, Tran SD, Terk MR. Diagnosis of vertebral metastasis, epidural metastasis, and malignant spinal cord compression: are T(1)-weighted sagittal images sufficient? <i>Magn Reson Imaging</i> 2000; <b>18</b> :819–24	Outcome measures did not meet inclusion criteria
Kim MK, Lee KH, Hyun MS, Bae SH, Ryoo HM. Metastatic spinal cord compression in patients with hepatocellular carcinoma. <i>J Clin Oncol</i> 2005; <b>23</b> :3675	Abstract
Kim RY. Extradural spinal cord compression from metastatic tumor. <i>Alabama Med</i> 1990; <b>60</b> :10–15	Outcome measures did not meet inclusion criteria
Kim RY, Spencer SA, Meredith RF, Weppelmann B, Lee JY, Smith JW, et al. Extradural spinal cord compression: analysis of factors determining functional prognosis – prospective study. <i>Radiology</i> 1990; <b>176</b> :279–82	Outcome measures did not meet inclusion criteria
King GJ, Kostuik JP, McBroom RJ, Richardson W. Surgical management of metastatic renal carcinoma of the spine. <i>Spine</i> 1991; <b>16</b> :265–71	Outcome measures did not meet inclusion criteria
Kocialkowski A, Webb JK. Metastatic spinal tumours: survival after surgery. <i>Eur Spine J</i> 1992; <b>1</b> :43–8	Outcome measures did not meet inclusion criteria
Kondo T, Hozumi T, Goto T, Seichi A, Nakamura K. Intraoperative radiotherapy combined with posterior decompression and stabilization for non-ambulant paralytic patients due to spinal metastasis. <i>Spine</i> 2008; <b>33</b> :1898–904	Outcome measures did not meet inclusion criteria
Kovner F, Spigel S, Rider I, Otremsky I, Ron I, Shohat E, et al. Radiation therapy of metastatic spinal cord compression. Multidisciplinary team diagnosis and treatment. <i>J Neurooncol</i> 1999; <b>42</b> :85–92	Outcome measures did not meet inclusion criteria

TABLE 36 Excluded studies (continued)

Reference	Reason for exclusion
Kraiwattanapong C, Buranapanitkit B, Kiriratnikom T. Results of radiotherapy in non round cell spinal metastasis. <i>J Med Assoc Thai</i> 2004; <b>87</b> :239–45	Outcome measures did not meet inclusion criteria
Kubota T, Yamada K, Ito H, Kizu O, Nishimura T. High-resolution imaging of the spine using multidetector-row computed tomography: differentiation between benign and malignant vertebral compression fractures. <i>J Comput Assist Tomogr</i> 2005; <b>29</b> :712–19	Outcome measures did not meet inclusion criteria
Kwon YM, Kim KS, Kuh SU, Chin DK, Jin BH, Cho YE. Survival rate and neurological outcome after operation for advanced spinal metastasis (Tomita's classification $\geq$ Type 4). <i>Yonsei Med J</i> 2009; <b>50</b> :689–96	Outcome measures did not meet inclusion criteria
Lafforgue PF, Chagnaud CJ, Daver LMH, Daumenlegre VMS, Peragut JC, Kasbarian MJ, <i>et al.</i> Intervertebral-disk vacuum phenomenon secondary to vertebral collapse – prevalence and significance. <i>Radiology</i> 1994; <b>193</b> :853–8	Outcome measures did not meet inclusion criteria
Laredo JD, Lakhdari K, Bellaiche L, Hamze B, Jankiewicz P, Tubiana JM. Acute vertebral collapse: CT findings in benign and malignant nontraumatic cases. <i>Radiology</i> 1995; <b>194</b> :41–8	Outcome measures did not meet inclusion criteria
Latini P, Maranzano E, Ricci S, Aristei C, Checchaglini F, Panizza BM, <i>et al.</i> Role of radiotherapy in metastatic spinal cord compression: preliminary results from a prospective trial. <i>Radiother Oncol</i> 1989; <b>15</b> :227–33	Outcome measures did not meet inclusion criteria
Laufer I, Rose P, Lis E, Bilsky MH, Yamada Y. An analysis of risk factors for vertebral body fracture following high-dose single-fraction image guided intensity modulated radiotherapy (IG IMRT) of spine metastases. <i>Int J Radiat Oncol Biol Phys</i> 2008; <b>72</b> :S52	Abstract
Lavdas E, Vlychou M, Arikidis N, Kapsalaki E, Roka V, Fezoulidis IV. Comparison of T1-weighted fast spin-echo and T1-weighted fluid-attenuated inversion recovery images of the lumbar spine at 3.0 Tesla. <i>Acta Radiol</i> 2010; <b>51</b> :290–5	Outcome measures did not meet inclusion criteria
Leithner A, Radl R, Gruber G, Hohegger M, Leithner K, Welkerling H, <i>et al.</i> Predictive value of seven preoperative prognostic scoring systems for spinal metastases. <i>Eur Spine J</i> 2008; <b>17</b> :1488–95	Outcome measures did not meet inclusion criteria
Levirov M, Dale J, Stein M, Ben-Shahar M, Ben-Arush M, Milstein D, <i>et al.</i> The management of metastatic spinal cord compression: a radiotherapeutic success ceiling. <i>Int J Radiat Oncol Biol Phys</i> 1993; <b>27</b> :231–4	Outcome measures did not meet inclusion criteria
Li MH, Holtas S, Larsson EM. MR-imaging of spinal lymphoma. <i>Acta Radiol</i> 1992; <b>33</b> :338–42	Outcome measures did not meet inclusion criteria
Li MH, Holtas S, Larsson EM. MRI of extradural spinal tumours at 0.3 T. <i>Neuroradiology</i> 1993; <b>35</b> :370–4	Outcome measures did not meet inclusion criteria
Liao S-H, Yang Z-X, Tang Z. Factors affecting the recovery of spinal functions in patients with spinal metastatic carcinoma. <i>Chinese J Clin Rehab</i> 2006; <b>10</b> :66–167	Outcome measures did not meet inclusion criteria
Liau W, Segelov E, Lih A, Dunleavy R, Links M, Ward R. Off-trial evaluation of bisphosphonates in patients with metastatic breast cancer. <i>BMC Cancer</i> 2005; <b>5</b> :89	Outcome measures did not meet inclusion criteria
Liaw CC, Leung W, Ng KT, Shih LY, Chen MS, Tang SG, <i>et al.</i> Malignant lesions causing spinal compression: review of 139 cases. <i>Taiwan yi xue hui za zhi. J Formosan Med Assoc</i> 1988; <b>87</b> :310–16	Outcome measures did not meet inclusion criteria
Lien HH, Blomlie V, Heimdal K. Magnetic resonance imaging of malignant extradural tumors with acute spinal cord compression. <i>Acta Radiol</i> 1990; <b>31</b> :187–90	Outcome measures did not meet inclusion criteria
Lin F, Lei Y, Li YB. Influence of lesion ratio on diagnostic performance of in-phase/opposed-phase imaging and apparent diffusion coefficient for differentiating acute benign vertebral fractures and metastases. <i>Chinese Med J</i> 2009; <b>122</b> :1293–9	Outcome measures did not meet inclusion criteria
Liskow A, Chang CH, DeSanctis P, Benson M, Fetell M, Housepian E. Epidural cord compression in association with genitourinary neoplasms. <i>Cancer</i> 1986; <b>58</b> :949–54	Outcome measures did not meet inclusion criteria
Loughrey GJ, Collins CD, Todd SM, Brown NM, Johnson RJ. Magnetic resonance imaging in the management of suspected spinal canal disease in patients with known malignancy. <i>Clin Radiol</i> 2000; <b>55</b> :849–55	Outcome measures did not meet inclusion criteria

continued

TABLE 36 Excluded studies (continued)

Reference	Reason for exclusion
Lovelock DM, Zhang ZG, Jackson A, Keam J, Bekelman J, Bilsky M, <i>et al.</i> Correlation of local failure with measures of dose insufficiency in the high-dose single-fraction treatment of bony metastases. <i>Int J Radiat Oncol Biol Phys</i> 2010; <b>77</b> :1282–7	Outcome measures did not meet inclusion criteria
Maeda M, Sakuma H, Maier SE, Takeda K. Quantitative assessment of diffusion abnormalities in benign and malignant vertebral compression fractures by line scan diffusion-weighted imaging. <i>AJR Am J Roentgenol</i> 2003; <b>181</b> :1203–9	Outcome measures did not meet inclusion criteria
Maranzano E, Latini P, Beneventi S, Marafioti L, Piro F, Perrucci E, <i>et al.</i> Comparison of two different radiotherapy schedules for spinal cord compression in prostate cancer. <i>Tumori</i> 1998; <b>84</b> :472–7	Outcome measures did not meet inclusion criteria
Maranzano E, Latini P. Effectiveness of radiation therapy without surgery in metastatic spinal cord compression: final results from a prospective trial. <i>Int J Radiat Oncol Biol Phys</i> 1995; <b>32</b> :959–67	Outcome measures did not meet inclusion criteria
Maranzano E, Latini P, Checcaglini F, Ricci S, Panizza BM, Aristei C, <i>et al.</i> Radiation therapy in metastatic spinal cord compression. A prospective analysis of 105 consecutive patients. <i>Cancer</i> 1991; <b>67</b> :1311–17	Outcome measures did not meet inclusion criteria
Maranzano E, Trippa F, Casale M, Anselmo P, Rossi R. Reirradiation of metastatic spinal cord compression: definitive results of two randomized trials. <i>Radiother Oncol</i> 2011; <b>98</b> :234–7	Outcome measures did not meet inclusion criteria
Maranzano E, Latini P, Perrucci E, Beneventi S, Lupattelli M, Corgna E. Short-course radiotherapy (8 Gy x 2) in metastatic spinal cord compression: an effective and feasible treatment. <i>Int J Radiat Oncol Biol Phys</i> 1997; <b>38</b> :1037–44	Review
Marquardt G, Setzer M, Seifert V. Protein S-100b as serum marker for prediction of functional outcome in metastatic spinal cord compression. <i>Acta Neurochir</i> 2004; <b>146</b> :449–52	Outcome measures did not meet inclusion criteria
Masala S, Mastrangeli R, Petrella MC, Massari F, Ursone A, Simonetti G. Percutaneous vertebroplasty in 1,253 levels: results and long-term effectiveness in a single centre. <i>Eur Radiol</i> 2009; <b>19</b> :165–71	Outcome measures did not meet inclusion criteria
Mavrogenis AF, Pneumaticos S, Sapkas GS, Papagelopoulos PJ. Metastatic epidural spinal cord compression. <i>Orthopedics</i> 2009; <b>32</b> :431–9	Review
Mazurkiewicz T, Godlewski P, Mazurkiewicz M. Radiological assessment of indications for surgical treatment of spinal metastases. <i>Ortoped Traumatol Rehab</i> 2003; <b>5</b> :167–71	Abstract
Metsger U, Lerman H, Blank A, Lievshitz G, Bokstein F, Even-Sapir E. Malignant involvement of the spine: assessment by 18F-FDG PET/CT. <i>J Nucl Med</i> 2004; <b>45</b> :279–84	Outcome measures did not meet inclusion criteria
Mikami Y, Numaguchi Y, Kobayashi N, Fuwa S, Hoshikawa Y, Saida Y. Therapeutic effects of percutaneous vertebroplasty for vertebral metastases. <i>Jpn J Radiol</i> 2011; <b>29</b> :202–6	Outcome measures did not meet inclusion criteria
Milross CG, Davies MA, Fisher R, Mameghan J, Mameghan H. The efficacy of treatment for malignant epidural spinal cord compression. <i>Australas Radiol</i> 1997; <b>41</b> :137–42	Outcome measures did not meet inclusion criteria
Minart D, Vallee JN, Cormier E, Chiras J. Percutaneous coaxial transpedicular biopsy of vertebral body lesions during vertebroplasty. <i>Neuroradiology</i> 2001; <b>43</b> :409–12	Outcome measures did not meet inclusion criteria
Mizumoto M, Harada H, Asakura H, Hashimoto T, Furutani K, Hashii H, <i>et al.</i> Prognostic Factors and a Scoring System for Survival After Radiotherapy for Metastases to the Spinal Column A Review of 544 Patients at Shizuoka Cancer Center Hospital. <i>Cancer</i> 2008; <b>113</b> :2816–22	Outcome measures did not meet inclusion criteria
Mizumoto M, Harada H, Asakura H, Hashimoto T, Furutani K, Hashii H, <i>et al.</i> Radiotherapy for patients with metastases to the spinal column: a review of 603 patients at shizuoka cancer center hospital. <i>Int J Radiat Oncol Biol Phys</i> 2011; <b>79</b> :208–13	Outcome measures did not meet inclusion criteria
Moulding HD, Elder JB, Lis E, Lovelock DM, Zhang Z, Yamada Y, <i>et al.</i> Local disease control after decompressive surgery and adjuvant high-dose single-fraction radiosurgery for spine metastases. <i>J Neurosurg Spine</i> 2010; <b>13</b> :87–93	Outcome measures did not meet inclusion criteria
Mulkern RV, Schwartz RB. In re: Characterization of benign and metastatic vertebral compression fractures with quantitative diffusion MR imaging. <i>Am J Neuroradiol</i> 2003; <b>24</b> :1489–90	Letter

TABLE 36 Excluded studies (continued)

Reference	Reason for exclusion
Murakami H, Kawahara N, Demura S, Kato S, Yoshioka K, Tomita K. Total en bloc spondylectomy for lung cancer metastasis to the spine. <i>J Neurosurg Spine</i> 2010; <b>13</b> :414–17	Outcome measures did not meet inclusion criteria
Muresan MM, Olivier P, Leclere J, Sirveaux F, Brunaud L, Klein M, <i>et al.</i> Bone metastases from differentiated thyroid carcinoma. <i>Endocr Relat Cancer</i> 2008; <b>15</b> :37–49	Review
Nagata M, Ueda T, Komiya A, Suzuki H, Akakura K, Ishihara M, <i>et al.</i> Treatment and prognosis of patients with paraplegia or quadriplegia because of metastatic spinal cord compression in prostate cancer. <i>Prostate Cancer Prostatic Dis</i> 2003; <b>6</b> :169–73	Outcome measures did not meet inclusion criteria
Nanassis K, AlexiadouRudolf C, Rudolf J, Frowein RA. Surgical indications and prognosis in spinal metastases. <i>Neurosurg Rev</i> 1997; <b>20</b> :99–103	Outcome measures did not meet inclusion criteria
Nieder C, Haukland E, Pawinski A, Dalhaug A. Pathologic fracture and metastatic spinal cord compression in patients with prostate cancer and bone metastases. <i>BMC Urol</i> 2010; <b>10</b> :23	Outcome measures did not meet inclusion criteria
Nieder C, Haukland E, Pawinski A, Dalhaug A. Validation of new prognostic and predictive scores by sequential testing approach. <i>Strahlenther Onkol</i> 2010; <b>186</b> :169–73	Outcome measures did not meet inclusion criteria
North RB, LaRocca VR, Schwartz J, North CA, Zahurak M, Davis RF, <i>et al.</i> Surgical management of spinal metastases: analysis of prognostic factors during a 10-year experience. <i>J Neurosurg Spine</i> 2005; <b>2</b> :564–73	Outcome measures did not meet inclusion criteria
Ogihara S, Seichi A, Hozumi T, Oka H, Ieki R, Nakamura K, <i>et al.</i> Prognostic factors for patients with spinal metastases from lung cancer. <i>Spine</i> 2006; <b>31</b> :1585–90	Outcome measures did not meet inclusion criteria
Oztekin O, Ozan E, Hilal AZ, Unal G, Abali Y. SSH-EPI diffusion-weighted MR imaging of the spine with low b values: is it useful in differentiating malignant metastatic tumor infiltration from benign fracture edema? <i>Skeletal Radiol</i> 2009; <b>38</b> :651–8	Outcome measures did not meet inclusion criteria
Papagelopoulos PJ, Mavrogenis AF, Kelekis AD, Katonis P, Galanis EC, Wenger DE, <i>et al.</i> Percutaneous osteoplasty for pelvic and spine metastases. <i>Orthopedics</i> 2006; <b>29</b> :316–23	Review
Parizel PM, Baleriaux D, Rodesch G, Segebarth C, Lalmand B, Christophe C, <i>et al.</i> Gd-DTPA-enhanced MR imaging of spinal tumors. <i>Am J Neuroradiol</i> 1989; <b>10</b> :249–58	Outcome measures did not meet inclusion criteria
Park SW, Lee JH, Ehara S, Park YB, Sung SO, Choi JA, <i>et al.</i> Single shot fast spin echo diffusion-weighted MR imaging of the spine; Is it useful in differentiating malignant metastatic tumor infiltration from benign fracture edema? <i>Clin Imaging</i> 2004; <b>28</b> :102–8	Outcome measures did not meet inclusion criteria
Petren-Mallmin M. Clinical and experimental imaging of breast cancer metastases in the spine. <i>Acta Radiol Suppl</i> 1994; <b>391</b> :1–23	Outcome measures did not meet inclusion criteria
Piggott KH, Baddeley H, Maher EJ. Pattern of disease in spinal cord compression on MRI scan and implications for treatment. <i>Clin Oncol</i> 1994; <b>6</b> :7–10	Outcome measures did not meet inclusion criteria
Piper KJ, Buscull KL. MRI reporting by radiographers: the construction of an objective structured examination. <i>Radiography</i> 2008; <b>14</b> :78–89	Outcome measures did not meet inclusion criteria
Plank C, Koller A, Mueller-Mang C, Bammer R, Thurnher MM. Diffusion-weighted MR imaging (DWI) in the evaluation of epidural spinal lesions. <i>Neuroradiology</i> 2007; <b>49</b> :977–85	Outcome measures did not meet inclusion criteria
Pneumaticos SG, Chatziioannou SN, Sawidou C, Pilichou A, Rontogianni D, Korres DS. Routine needle biopsy during vertebral augmentation procedures. Is it necessary? <i>Eur Spine J</i> 2010; <b>19</b> :1894–8	Outcome measures did not meet inclusion criteria
Podd TJ, Carpenter DS, Baughan CA, Percival D, Dyson P. Spinal cord compression: prognosis and implications for treatment fractionation. <i>Clin Oncol</i> 1992; <b>4</b> :341–4	Outcome measures did not meet inclusion criteria
Pointillart V, Vital JM, Salmi R, Diallo A, Quan GM. Survival prognostic factors and clinical outcomes in patients with spinal metastases. <i>J Cancer Res Clin Oncol</i> 2011; <b>137</b> :849–56	Outcome measures did not meet inclusion criteria
Pollono D, Tomarchia S, Drut R, Ibanez O, Ferreyra M, Cedol J. Spinal cord compression: a review of 70 pediatric patients. <i>Pediatr Hematol Oncol</i> 2003; <b>20</b> :457–66	Outcome measures did not meet inclusion criteria

continued

TABLE 36 Excluded studies (continued)

Reference	Reason for exclusion
Pongpornsup S, Wajanawichakorn P, Danchaivijitr N. Benign versus malignant compression fracture: a diagnostic accuracy of magnetic resonance imaging. <i>J Med Assoc Thai</i> 2009; <b>92</b> :64–72	Outcome measures did not meet inclusion criteria
Portenoy RK, Galer BS, Salamon O, Freilich M, Finkel JE, Milstein D, <i>et al.</i> Identification of epidural neoplasm. Radiography and bone scintigraphy in the symptomatic and asymptomatic spine. <i>Cancer</i> 1989; <b>64</b> :2207–13	Outcome measures did not meet inclusion criteria
Preciado DA, Sebring LA, Adams GL. Treatment of patients with spinal metastases from head and neck neoplasms. <i>Arch Otolaryngol Head Neck Surg</i> 2002; <b>128</b> :539–43	Outcome measures did not meet inclusion criteria
Prentice WB, Kieffer SA, Gold LH, Bjornson RG. Myelographic characteristics of metastasis to the spinal cord and cauda equina. <i>Am J Roentgenol Radium Ther Nucl Med</i> 1973; <b>118</b> :682–9	Outcome measures did not meet inclusion criteria
Puisto V, Rissanen H, Heliovaara M, Knekt P, Helenius I. Mortality in the presence of a vertebral fracture, scoliosis, or Scheuermann's disease in the thoracic spine. <i>Ann Epidemiol</i> 2008; <b>18</b> :595–601	Outcome measures did not meet inclusion criteria
Putz C, van Middendorp JJ, Pouw MH, Moradi B, Rupp R, Weidner N, <i>et al.</i> Malignant cord compression: a critical appraisal of prognostic factors predicting functional outcome after surgical treatment. <i>J Craniovert Junct Spine</i> 2010; <b>1</b> :67–73	Outcome measures did not meet inclusion criteria
Putz C, Wiedenhofer B, Gerner HJ, Furstenberg CH. Tokuhashi prognosis score: an important tool in prediction of the neurological outcome in metastatic spinal cord compression: a retrospective clinical study. <i>Spine</i> 2008; <b>33</b> :2669–74	Outcome measures did not meet inclusion criteria
Rades D, Karstens JH. A comparison of two different radiation schedules for metastatic spinal cord compression considering a new prognostic factor. <i>Strahlenther Onkol</i> 2002; <b>178</b> :556–61	Outcome measures did not meet inclusion criteria
Rades D, Fehlauer F, Stalpers LJ, Wildfang I, Zschenker O, Schild SE, <i>et al.</i> 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. <i>Cancer</i> 2004; <b>101</b> :2687–92	Outcome measures did not meet inclusion criteria
Rades D, Rudat V, Veninga T, Stalpers LJA, Basic H, Karstens JH, <i>et al.</i> A score predicting posttreatment ambulatory status in patients irradiated for metastatic spinal cord compression. <i>Int J Radiat Oncol Biol Phys</i> 2008; <b>72</b> :905–8	Outcome measures did not meet inclusion criteria
Rades D, Stalpers LJ, Hulshof MC, Borgmann K, Karstens JH, Koning CC, <i>et al.</i> Comparison of 1 × 8 Gy and 10 × 3 Gy for functional outcome in patients with metastatic spinal cord compression. <i>Int J Radiat Oncol Biol Phys</i> 2005; <b>62</b> :514–18	Outcome measures did not meet inclusion criteria
Rades D, Stalpers LJ, Schulte R, Veninga T, Basic H, Engenhardt-Cabilic R, <i>et al.</i> Defining the appropriate radiotherapy regimen for metastatic spinal cord compression in non-small cell lung cancer patients. <i>Eur J Cancer</i> 2006; <b>42</b> :1052–6	Outcome measures did not meet inclusion criteria
Rades D, Walz J, Schild SE, Veninga T, Dunst J. Do bladder cancer patients with metastatic spinal cord compression benefit from radiotherapy alone? <i>Urology</i> 2007; <b>69</b> :1081–5	Outcome measures did not meet inclusion criteria
Rades D, Stalpers LJ, Veninga T, Schulte R, Hoskin PJ, Obralic N, <i>et al.</i> Evaluation of five radiation schedules and prognostic factors for metastatic spinal cord compression. <i>J Clin Oncol</i> 2005; <b>23</b> :3366–75	Outcome measures did not meet inclusion criteria
Rades D, Stalpers LJ, Veninga T, Rudat V, Schulte R, Hoskin PJ. Evaluation of functional outcome and local control after radiotherapy for metastatic spinal cord compression in patients with prostate cancer. <i>J Urol</i> 2006; <b>175</b> :552–6	Outcome measures did not meet inclusion criteria
Rades D, Lange M, Veninga T, Stalpers LJ, Bajrovic A, Adamietz IA, <i>et al.</i> Final results of a prospective study comparing the local control of short-course and long-course radiotherapy for metastatic spinal cord compression. <i>Int J Radiat Oncol Biol Phys</i> 2011; <b>79</b> :524–30	Outcome measures did not meet inclusion criteria
Rades D, Heidenreich F, Karstens JH. Final results of a prospective study of the prognostic value of the time to develop motor deficits before irradiation in metastatic spinal cord compression. <i>Int J Radiat Oncol Biol Phys</i> 2002; <b>53</b> :975–9	Outcome measures did not meet inclusion criteria
Rades D, Fehlauer F, Veninga T, Stalpers LJ, Basic H, Hoskin PJ, <i>et al.</i> Functional outcome and survival after radiotherapy of metastatic spinal cord compression in patients with cancer of unknown primary. <i>Int J Radiat Oncol Biol Phys</i> 2007; <b>67</b> :532–7	Outcome measures did not meet inclusion criteria

TABLE 36 Excluded studies (continued)

Reference	Reason for exclusion
Rades D, Veninga T, Stalpers LJ, Basic H, Hoskin PJ, Karstens JH, <i>et al.</i> Improved posttreatment functional outcome is associated with better survival in patients irradiated for metastatic spinal cord compression. <i>Int J Radiat Oncol Biol Phys</i> 2007; <b>67</b> :1506–9	Outcome measures did not meet inclusion criteria
Rades D, Huttenlocher S, Dunst J, Bajrovic A, Karstens JH, Rudat V, <i>et al.</i> Matched pair analysis comparing surgery followed by radiotherapy and radiotherapy alone for metastatic spinal cord compression. <i>J Clin Oncol</i> 2010; <b>28</b> :3597–604	Outcome measures did not meet inclusion criteria
Rades D, Blach M, Nerreter V, Bremer M, Karstens JH. Metastatic spinal cord compression. Influence of time between onset of motoric deficits and start of irradiation on therapeutic effect. <i>Strahlenther Onkol</i> 1999; <b>175</b> :378–81	Outcome measures did not meet inclusion criteria
Rades D, Lange M, Veninga T, Rudat V, Bajrovic A, Stalpers LJ, <i>et al.</i> Preliminary results of spinal cord compression recurrence evaluation (score-1) study comparing short-course versus long-course radiotherapy for local control of malignant epidural spinal cord compression. <i>Int J Radiat Oncol Biol Phys</i> 2009; <b>73</b> :228–34	Outcome measures did not meet inclusion criteria
Rades D, Rudat V, Veninga T, Stalpers LJ, Hoskin PJ, Schild SE. Prognostic factors for functional outcome and survival after reirradiation for in-field recurrences of metastatic spinal cord compression. <i>Cancer</i> 2008; <b>113</b> :1090–6	Outcome measures did not meet inclusion criteria
Rades D, Fehlauer F, Schulte R, Veninga T, Stalpers LJ, Basic H, <i>et al.</i> Prognostic factors for local control and survival after radiotherapy of metastatic spinal cord compression. <i>J Clin Oncol</i> 2006; <b>24</b> :3388–93	Outcome measures did not meet inclusion criteria
Rades D, Veninga T, Stalpers LJ, Schulte R, Hoskin PJ, Poortmans P, <i>et al.</i> Prognostic factors predicting functional outcomes, recurrence-free survival, and overall survival after radiotherapy for metastatic spinal cord compression in breast cancer patients. <i>Int J Radiat Oncol Biol Phys</i> 2006; <b>64</b> :182–8	Outcome measures did not meet inclusion criteria
Rades D, Blach M, Bremer M, Wildfang I, Karstens JH, 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. <i>Int J Radiat Oncol Biol Phys</i> 2000; <b>48</b> :1403–8	Outcome measures did not meet inclusion criteria
Rades D, Hoskin PJ, Karstens JH, Rudat V, Veninga T, Stalpers LJ, <i>et al.</i> Radiotherapy of metastatic spinal cord compression in very elderly patients. <i>Int J Radiat Oncol Biol Phys</i> 2007; <b>67</b> :256–63	Outcome measures did not meet inclusion criteria
Rades D, Fehlauer F, Hartmann A, Wildfang I, Karstens JH, Alberti W. Reducing the overall treatment time for radiotherapy of metastatic spinal cord compression (MSCC): 3-year results of a prospective observational multi-center study. <i>J Neurooncol</i> 2004; <b>70</b> :77–82	Outcome measures did not meet inclusion criteria
Rades D, Stalpers LJ, Veninga T, Hoskin PJ. Spinal reirradiation after short-course RT for metastatic spinal cord compression. <i>Int J Radiat Oncol Biol Phys</i> 2005; <b>63</b> :872–5	Outcome measures did not meet inclusion criteria
Rades D, Bremer M, Goehde S, Joergensen M, Karstens JH. Spondylodiscitis in patients with spinal cord compression: a possible pitfall in radiation oncology. <i>Radiother Oncol</i> 2001; <b>59</b> :307–9	Outcome measures did not meet inclusion criteria
Rades D, Dunst J, Schild SE. The first score predicting overall survival in patients with metastatic spinal cord compression. <i>Cancer</i> 2008; <b>112</b> :157–61	Outcome measures did not meet inclusion criteria
Rades D, Heidenreich F, Bremer M, Karstens JH. Time of developing motor deficits before radiotherapy as a new and relevant prognostic factor in metastatic spinal cord compression: final results of a retrospective analysis. <i>Eur Neurol</i> 2001; <b>45</b> :266–9	Outcome measures did not meet inclusion criteria
Rades D, Douglas S, Veninga T, Stalpers LJA, Hoskin PJ, Bajrovic A, <i>et al.</i> Validation and simplification of a score predicting survival in patients irradiated for metastatic spinal cord compression. <i>Cancer</i> 2010; <b>116</b> :3670–3	Outcome measures did not meet inclusion criteria
Rades D, Douglas S, Huttenlocher S, Rudat V, Veninga T, Stalpers LJA, <i>et al.</i> Validation of a score predicting post-treatment ambulatory status after radiotherapy for metastatic spinal cord compression. <i>Int J Radiat Oncol Biol Phys</i> 2011; <b>79</b> :1503–6	Outcome measures did not meet inclusion criteria

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TABLE 36 Excluded studies (continued)

Reference	Reason for exclusion
Rao SB, Dinakar I. Spinal compression. (Analysis of 200 cases.) <i>J Assoc Physicians Ind</i> 1970; <b>18</b> :1009–13	Outcome measures did not meet inclusion criteria
Rodriguez M, Dinapoli RP. Spinal-cord compression with special reference to metastatic epidural tumors. <i>Mayo Clin Proc</i> 1980; <b>55</b> :442–8	Review
Rogers CL, Theodore N, Dickman CA, Sonntag VKH, Thomas T, Lam S, et al. Surgery and permanent I-125 seed paraspinal brachytherapy for malignant tumors with spinal cord compression. <i>Int J Radiat Oncol Biol Phys</i> 2002; <b>54</b> :505–13	Outcome measures did not meet inclusion criteria
Sahin M, Basoglu T, Bernay I, Yapici O, Canbaz F, Yalin T. Evaluation of metastatic bone disease with pentavalent Tc-99(m)-dimercaptosuccinic acid: a comparison with whole-body scanning and 4/24 hour quantitation of vertebral lesions. <i>Nucl Med Commun</i> 2000; <b>21</b> :251–8	Outcome measures did not meet inclusion criteria
Sakaura H, Hosono N, Mukai Y, Fujii R, Iwasaki M, Yoshikawa H. Persistent local pain after posterior spine surgery for thoracic lesions. <i>J Spinal Dis Tech</i> 2007; <b>20</b> :226–8	Outcome measures did not meet inclusion criteria
Sanguinetti C, Aulisa L, Valassina A, D'Arienzo M. The surgical treatment of spinal cord compression caused by tumorous metastases. A review of 91 cases. <i>Chir Organi Mov</i> 1998; <b>83</b> :113–25	Outcome measures did not meet inclusion criteria
Schiff D, O'Neill BP, Wang CH, O'Fallon JR. Neuroimaging and treatment implications of patients with multiple epidural spinal metastases. <i>Cancer</i> 1998; <b>83</b> :1593–601	Outcome measures did not meet inclusion criteria
Schiff D, O'Neill BP, Suman VJ. Spinal epidural metastasis as the initial manifestation of malignancy: Clinical features and diagnostic approach. <i>Neurology</i> 1997; <b>49</b> :452–6	Outcome measures did not meet inclusion criteria
Schoenfeld AJ, Dinicola NJ, Ehrlar DM, Koerber A, Paxos M, Shorten SD, et al. Retrospective review of biopsy results following percutaneous fixation of vertebral compression fractures. <i>Injury</i> 2008; <b>39</b> :327–33	Outcome measures did not meet inclusion criteria
Schwab JH, Boland PJ, Antonescu C, Bilsky MH, Healey JH. Spinal metastases from myxoid liposarcoma warrant screening with magnetic resonance imaging. <i>Cancer</i> 2007; <b>110</b> :1815–22	Outcome measures did not meet inclusion criteria
Sciubba DM, Gokaslan ZL. Diagnosis and management of metastatic spine disease. <i>Surg Oncol</i> 2006; <b>15</b> :141–51	Review
Sciubba DM, Gokaslan ZL, Suk I, Suki D, Maldaun MVC, McCutcheon IE, et al. Positive and negative prognostic variables for patients undergoing spine surgery for metastatic breast disease. <i>Eur Spine J</i> 2007; <b>16</b> :1659–67	Outcome measures did not meet inclusion criteria
Shaheen H, Abubakar S, Malik I, Altafullah I, Alam F, Khan A. Epidural spinal cord compression from metastatic cancer: clinical features and management. <i>J Pak Med Assoc</i> 1991; <b>41</b> :60–2	Outcome measures did not meet inclusion criteria
Sharr MM. Diagnosis of Spinal-Cord and Cauda-Equina Metastases. <i>Prog Exp Tumor Res</i> 1985; <b>29</b> :93–104	Outcome measures did not meet inclusion criteria
Shaw MD, Rose JE, Paterson A. Metastatic extradural malignancy of the spine. <i>Acta Neurochirur</i> 1980; <b>52</b> :113–20	Outcome measures did not meet inclusion criteria
Shih TTF, Huang K-M, Li Y-W. Solitary vertebral collapse: distinction between benign and malignant causes using MR patterns. <i>J Magn Reson Imaging</i> 1999; <b>9</b> :635–42	Outcome measures did not meet inclusion criteria
Sioutos PJ, Arbit E, Meshulam CF, Galicich JH. Spinal metastases from solid tumors. Analysis of factors affecting survival. <i>Cancer</i> 1995; <b>76</b> :1453–59.	Outcome measures did not meet inclusion criteria
Smith EM, Hampel N, Ruff RL, Bodner DR, Resnick MI. Spinal cord compression secondary to prostate carcinoma: treatment and prognosis. <i>J Urol</i> 1993; <b>149</b> :330–3	Outcome measures did not meet inclusion criteria
Smoker WR, Godersky JC, Knutzon RK, Keyes WD, Norman D, Bergman W. The role of MR imaging in evaluating metastatic spinal disease. <i>AJR Am J Roentgenol</i> 1987; <b>149</b> :1241–8	Outcome measures did not meet inclusion criteria
Soderlund V. Radiological diagnosis of skeletal metastases. <i>Eur Radiol</i> 1996; <b>6</b> :587–95	Outcome measures did not meet inclusion criteria

TABLE 36 Excluded studies (continued)

Reference	Reason for exclusion
Soerdjbalie-Maikoe V, Pelger RC, Nijeholt GA, Arndt JW, Zwinderman AH, Papapoulos SE, et al. Strontium-89 (Metastron) and the bisphosphonate olpadronate reduce the incidence of spinal cord compression in patients with hormone-refractory prostate cancer metastatic to the skeleton. <i>Eur J Nucl Med Mol Imaging</i> 2002; <b>29</b> :494–8	Outcome measures did not meet inclusion criteria
Solberg A, Bremnes RM. Metastatic spinal cord compression: diagnostic delay, treatment, and outcome. <i>Anticancer Res</i> 1999; <b>19</b> :677–84	Outcome measures did not meet inclusion criteria
Souchon R, Wenz F, Sedlmayer F, Budach W, Dunst J, Feyer P, et al. DEGRO practice guidelines for palliative radiotherapy of metastatic breast cancer bne metastases and metastatic spinal cord compression (MSCC). <i>Strahlenther Onkol</i> 2009; <b>185</b> :417–24	Outcome measures did not meet inclusion criteria
Souchon R, Wenz F, Sedlmayer F, Budach W, Dunst J, Feyer P, et al. Risk of skeletal-related events in patients with advanced prostate cancer treated with pamidronate or zoledronic acid. <i>Ann Pharmacother</i> 2010; <b>44</b> :1384–8	Outcome measures did not meet inclusion criteria
Sucher E, Margulies JY, Floman Y, Robin GC. Prognostic factors in anterior decompression for metastatic cord compression. An analysis of results. <i>Eur Spine J</i> 1994; <b>3</b> :70–5	Outcome measures did not meet inclusion criteria
Sundaresan N, Rothman A, Manhart K, Kelliher K. Surgery for solitary metastases of the spine: rationale and results of treatment. <i>Spine</i> 2002; <b>27</b> :1802–6	Outcome measures did not meet inclusion criteria
Sundaresan N, Rothman A, Manhart K, Kelliher K. Differentiation of malignant vertebral collapse from osteoporotic and other benign causes using magnetic resonance imaging. <i>Ann Acad Med Singapore</i> 2002; <b>31</b> :8–14	Outcome measures did not meet inclusion criteria
Tan SB, Kozak JA, Mawad ME. The limitations of magnetic resonance imaging in the diagnosis of pathologic vertebral fractures. <i>Spine</i> 1991; <b>16</b> :919–23	Outcome measures did not meet inclusion criteria
Tang SG, Byfield JE, Sharp TR, Utey JF, Quinol L, Seagren SL. Prognostic factors in the management of metastatic epidural spinal cord compression. <i>J Neurooncol</i> 1983; <b>1</b> :21–8	Outcome measures did not meet inclusion criteria
Tang V, Harvey D, Park DJ, Jiang S, Rathbone MP. Prognostic indicators in metastatic spinal cord compression: using functional independence measure and Tokuhashi scale to optimize rehabilitation planning. <i>Spinal Cord</i> 2007; <b>45</b> :671–7	Outcome measures did not meet inclusion criteria
Tazi H, Manunta A, Rodriguez A, Patard JJ, Lobel B, Guille F. Spinal cord compression in metastatic prostate cancer. <i>Euro Urol</i> 2003; <b>44</b> :527–32	Outcome measures did not meet inclusion criteria
Thariat J, Toubreau M, Ornetti P, Coudert B, Berrielo-Riedinger A, Fargeot P, et al. Sensitivity and specificity of thallium-201 scintigraphy for the diagnosis of malignant vertebral fractures. <i>Eur J Radiol</i> 2004; <b>51</b> :274–8	Outcome measures did not meet inclusion criteria
Tohtz SW, Rogalla P, Taupitz M, Perka C, Winkler T, Putzier M. Inter- and intraobserver variability in the postoperative evaluation of transpedicular stabilization: computed tomography versus magnetic resonance imaging. <i>Spine J</i> 2010; <b>10</b> :285–90	Outcome measures did not meet inclusion criteria
Tokuda O, Harada Y, Ueda T, Ohishi Y, Matsunaga N. Malignant versus benign vertebral compression fractures: can we use bone SPECT as a substitute for MR imaging? <i>Nucl Med Commun</i> 2011; <b>32</b> :192–8	Outcome measures did not meet inclusion criteria
Tokuhashi Y, Ajiro Y, Umezawa N. Outcome of treatment for spinal metastases using scoring system for preoperative evaluation of prognosis. <i>Spine</i> 2009; <b>34</b> :69–73	Outcome measures did not meet inclusion criteria
Tomita K, Kawahara N, Kobayashi T, Yoshida A, Murakami H, Akamaru T. Surgical strategy for spinal metastases. <i>Spine</i> 2001; <b>26</b> :298–306	Outcome measures did not meet inclusion criteria
Trail ZC, Talbot D, Golding S, Gleeson FV. Magnetic resonance imaging versus radionuclide scintigraphy in screening for bone metastases. <i>Clin Radiol</i> 1999; <b>54</b> :448–51	Outcome measures did not meet inclusion criteria
Tschirhart CE, Nagpurkar A, Whyne CM. Effects of tumor location, shape and surface serration on burst fracture risk in the metastatic spine. <i>J Biomechanics</i> 2004; <b>37</b> :653–60	Outcome measures did not meet inclusion criteria
Turgut M, Gul B, Girgin O, Taskin Y. Role of surgical treatment in 70 patients with vertebral metastasis causing cord or root compression. <i>Arch Orthop Trauma Surg</i> 1997; <b>116</b> :415–19	Outcome measures did not meet inclusion criteria

continued

TABLE 36 Excluded studies (continued)

Reference	Reason for exclusion
Ulmar B, Reichel H, Catalkaya S, Naumann U, Schmidt R, Gerstner S, <i>et al.</i> Evaluation and modification of the tomita score in 217 patients with vertebral metastases. <i>Onkologie</i> 2007; <b>30</b> :414–18	Outcome measures did not meet inclusion criteria
Ulmar B, Naumann U, Catalkaya S, Muche R, Cakir B, Schmidt R, <i>et al.</i> Prognosis scores of Tokuhashi and Tomita for patients with spinal metastases of renal cancer. <i>Ann Surg Oncol</i> 2007; <b>14</b> :998–1004	Outcome measures did not meet inclusion criteria
Ulmar B, Richter M, Cakir B, Muche R, Puhl W, Huch K. The Tokuhashi score: Significant predictive value for the life expectancy of patients with breast cancer with spinal metastases. <i>Spine</i> 2005; <b>30</b> :2222–6	Outcome measures did not meet inclusion criteria
van der Linden YM, Dijkstra SP, Vonk EJ, Marijnen CA, Leer JW, Dutch Bone Metastasis Study Group. Prediction of survival in patients with metastases in the spinal column: results based on a randomized trial of radiotherapy. <i>Cancer</i> 2005; <b>103</b> :320–8	Outcome measures did not meet inclusion criteria
Weber MH, Burch S, Buckley J, Schmidt MH, Fehlings MG, Vrionis FD, <i>et al.</i> Instability and impending instability of the thoracolumbar spine in patients with spinal metastases: a systematic review. <i>Int J Oncol</i> 2011; <b>38</b> :5–12	Outcome measures did not meet inclusion criteria
Weiss RJ, Wedin R. Surgery for skeletal metastases in lung cancer. <i>Acta Orthopaed</i> 2011; <b>82</b> :96–101	Outcome measures did not meet inclusion criteria
Williams BJ, Fox BD, Sciubba DM, Suki D, Tu SM, Kuban D, <i>et al.</i> Surgical management of prostate cancer metastatic to the spine. <i>J Neurosurg Spine</i> 2009; <b>10</b> :414–22	Outcome measures did not meet inclusion criteria
Williams MP, Cherryman GR, Husband JE. Magnetic resonance imaging in suspected metastatic spinal cord compression. <i>Clin Radiol</i> 1989; <b>40</b> :286–90	Outcome measures did not meet inclusion criteria
Wong CS, Chu YC, Ma KF, Cheng LF. An appraisal of timely magnetic resonance imaging in diagnosing spinal cord compression. <i>Singapore Med J</i> 2009; <b>50</b> :894–6	Outcome measures did not meet inclusion criteria
Yamashita T, Siemionow KB, Mroz TE, Podichetty V, Lieberman IH. A prospective analysis of prognostic factors in patients with spinal metastases: use of the revised Tokuhashi score. <i>Spine</i> 2011; <b>36</b> :910–17	Abstract
Yamashita T, Aota Y, Kushida K, Murayama H, Hiruma T, Takeyama M, <i>et al.</i> Changes in physical function after palliative surgery for metastatic spinal tumor: Association of the revised tokuhashi score with neurologic recovery. <i>Spine</i> 2008; <b>33</b> :2341–6	Outcome measures did not meet inclusion criteria
Yao WW, Li MH, Yang SX, Zhu LL. Use of diffusion-weighted magnetic resonance imaging to differentiate between acute benign and pathological vertebral fractures: prospective study. <i>J Hong Kong Coll Radiol</i> 2005; <b>8</b> :4–8	Outcome measures did not meet inclusion criteria
Yilmazlar S, Dogan S, Caner B, Turkkan A, Bekar A, Korfali E. Comparison of prognostic scores and surgical approaches to treat spinal metastatic tumors: a review of 57 cases. <i>J Orthop Surg Res</i> 2008; <b>3</b> :37	Outcome measures did not meet inclusion criteria
Zajick DC, Morrison WB, Schweitzer ME, Parellada JA, Carrino JA. Benign and malignant processes: Normal values and differentiation with chemical shift MR imaging in vertebral marrow. <i>Radiology</i> 2005; <b>237</b> :590–6	Outcome measures did not meet inclusion criteria
Zevallos M, Chan PYM, Munoz L, Wagner J, Kagan AR. Epidural spinal-cord compression from metastatic tumor. <i>Int J Radiat Oncol Biol Phys</i> 1987; <b>13</b> :875–8	Outcome measures did not meet inclusion criteria
Zhou XJ, Leeds NE, McKinnon GC, Kumar AJ. Characterization of benign and metastatic vertebral compression fractures with quantitative diffusion MR imaging. <i>AJNR Am J Neuroradiol</i> 2002; <b>23</b> :165–70	Outcome measures did not meet inclusion criteria

## Appendix 6 Quality assessment forms: extracted data for each study

First author: Bayley

Year: 2001

ID: 107

Reviewer(s): PS/MC – Agreed

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]		✓			
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]	✓				
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results		✓			
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up	✓				
	Statement as to the possible effect on the results from missing data					✓
	Loss to follow-up is not associated with key characteristics	✓				
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)	✓				
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>				✓	
	Blinding: were estimators of risk factor status and of outcomes blinded?			✓		
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias		✓			
Outcome	Is the outcome clearly defined?	✓				
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>	✓				
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis	✓				
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results	✓				
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)		4	2	0	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: Bernat**  
**Reviewer(s): PS/MC – Agreed**

**Year: 1983**

**ID: 108**

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/ sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]	✓				
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]	✓				
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results	✓				
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up			✓		
	Statement as to the possible effect on the results from missing data					✓
	Loss to follow-up is not associated with key characteristics	✓				
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)	✓				
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>				✓	
	Blinding: were estimators of risk factor status and of outcomes blinded?			✓		
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias	✓				
Outcome	Is the outcome clearly defined?	✓				
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>			✓		
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis	✓				
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results	✓				
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)		2	3	1	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: Chaichana**  
**Reviewer(s): PS/MC – Agreed**

**Year: 2009**

**ID: 109**

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/ sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]	✓				
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]			✓		
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results		✓			
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables			✓		
	Loss to follow-up			✓		
	Statement as to the possible effect on the results from missing data			✓		
	Loss to follow-up is not associated with key characteristics			✓		
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)		✓			
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>		✓			
	Blinding: were estimators of risk factor status and of outcomes blinded?			✓		
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias		✓			
Outcome	Is the outcome clearly defined?		✓			
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>	✓				
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis	✓				
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results	✓				
	TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)	2	3	1	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: Fisher**  
**Reviewer(s): PS/MC – Agreed**

**Year: 2010**

**ID: 110**

Potential bias	Items to be considered for assessment of potential opportunity for bias					
		Yes	Partly	No	Unsure	NA
Study population/ sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]			✓		
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]			✓		
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results			✓		
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables			✓		
	Loss to follow-up			✓		
	Statement as to the possible effect on the results from missing data			✓		
	Loss to follow-up is not associated with key characteristics			✓		
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)		✓			
	Specified instrument and personnel for measurement of predictive factors		✓			
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>		✓			
	Blinding: were estimators of risk factor status and of outcomes blinded?			✓		
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias		✓			
Outcome	Is the outcome clearly defined?		✓			
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>			✓		
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis		✓			
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results		✓			
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)		0	3	3	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

First author: Goldman

Year: 1989

ID: 111

Reviewer(s): PS/MC – Agreed

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/ sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]		✓			
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]		✓			
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results		✓			
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up	✓				
	Statement as to the possible effect on the results from missing data					✓
	Loss to follow-up is not associated with key characteristics	✓				
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)		✓			
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>					✓
	Blinding: were estimators of risk factor status and of outcomes blinded?			✓		
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias		✓			
Outcome	Is the outcome clearly defined?		✓			
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>			✓		
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis		✓			
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results				✓	
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)		1	3	2	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: Harrison**  
**Reviewer(s): PS/MC – Agreed**

**Year: 1985**

**ID: 112**

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/ sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]	✓				
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]		✓			
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results		✓			
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up	✓				
	Statement as to the possible effect on the results from missing data					✓
	Loss to follow-up is not associated with key characteristics	✓				
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)	✓				
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>					✓
	Blinding: were estimators of risk factor status and of outcomes blinded?			✓		
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias		✓			
Outcome	Is the outcome clearly defined?	✓				
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>			✓		
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis	✓				
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results	✓				
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)		3	2	1	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: Helweg-Larsen Year: 2000**  
**Reviewer(s): PS/MC – Agreed**

**ID: 113**

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/ sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]	✓				
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]		✓			
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results		✓			
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up	✓				
	Statement as to the possible effect on the results from missing data					✓
	Loss to follow-up is not associated with key characteristics	✓				
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)		✓			
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>					✓
	Blinding: were estimators of risk factor status and of outcomes blinded?			✓		
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias		✓			
Outcome	Is the outcome clearly defined?		✓			
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>			✓		
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis		✓			
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results	✓				
	TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)	2	3	1	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

First author: Helweg-Larsen Year: 1995  
 Reviewer(s): PS/MC – Agreed

ID: 114

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/ sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]	✓				
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]		✓			
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results		✓			
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up	✓				
	Statement as to the possible effect on the results from missing data					✓
	Loss to follow-up is not associated with key characteristics	✓				
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)		✓			
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>					✓
	Blinding: were estimators of risk factor status and of outcomes blinded?			✓		
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias		✓			
Outcome	Is the outcome clearly defined?		✓			
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>			✓		
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis		✓			
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results		✓			
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)		1	4	1	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: Huddart**  
**Reviewer(s): PS/MC – Agreed**

**Year: 1997**

**ID: 115**

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/ sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]	✓				
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]	✓				
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results	✓				
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up	✓				
	Statement as to the possible effect on the results from missing data					✓
	Loss to follow-up is not associated with key characteristics	✓				
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement and timing described)		✓			
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>		✓			
	Blinding: were estimators of risk factor status and of outcomes blinded?				✓	
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias		✓			
Outcome	Is the outcome clearly defined?		✓			
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>		✓			
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis	✓				
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results	✓				
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)		3	3	0	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: Husband**  
**Reviewer(s): PS/MC – Agreed**

**Year: 2001**

**ID: 116**

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/ sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]	✓				
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]	✓				
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results	✓				
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up	✓				
	Statement as to the possible effect on the results from missing data					✓
	Loss to follow-up is not associated with key characteristics	✓				
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)	✓				
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>					✓
	Blinding: were estimators of risk factor status and of outcomes blinded?			✓		
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias		✓			
Outcome	Is the outcome clearly defined?	✓				
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>			✓		
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis	✓				
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results		✓			
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)		3	2	1	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: Klekamp**  
**Reviewer(s): PS/MC – Agreed**

**Year: 1998**

**ID: 117**

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/ sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]	✓				
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]	✓				
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results	✓				
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up					✓
	Statement as to the possible effect on the results from missing data					✓
	Loss to follow-up is not associated with key characteristics	✓				
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)		✓			
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>		✓			
	Blinding: were estimators of risk factor status and of outcomes blinded?				✓	
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias		✓			
Outcome	Is the outcome clearly defined?		✓			
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>		✓			
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis	✓				
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results	✓				
	TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)	2	4	0	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: Kuban**  
**Reviewer(s): PS/MC – Agreed**

**Year: 1986**

**ID: 118**

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/ sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]		✓			
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]			✓		
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results		✓			
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up					✓
	Statement as to the possible effect on the results from missing data					✓
	Loss to follow-up is not associated with key characteristics	✓				
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)	✓				
	Specified instrument and personnel for measurement of predictive factors		✓			
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>			✓		
	Blinding: were estimators of risk factor status and of outcomes blinded?			✓		
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias		✓			
Outcome	Is the outcome clearly defined?	✓				
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>			✓		
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis		✓			
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results			✓		
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)		2	2	2	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: Levack**  
**Reviewer(s): PS/MC – Agreed**

**Year: 2002**

**ID: 119**

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/ sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]		✓			
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]	✓				
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results		✓			
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up	✓				
	Statement as to the possible effect on the results from missing data					✓
	Loss to follow-up is not associated with key characteristics	✓				
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)	✓				
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>				✓	
	Blinding: were estimators of risk factor status and of outcomes blinded?				✓	
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias		✓			
Outcome	Is the outcome clearly defined?		✓			
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>				✓	
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis	✓				
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results				✓	
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)		1	3	1	1	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: Loblaw**  
**Reviewer(s): PS/MC – Agreed**

**Year: 2005**

**ID: 62**

Did the review address a clearly focused question?

No—the authors aimed to address a series of questions. (1) What are the clinical symptoms of MSCC? (2) What is the optimal approach for investigating suspected MSCC? (3) Is there a role for systemic corticosteroids in the management of MSCC, and if so, what is the optimal dose? (4) What are the indications for radiotherapy in the management of MSCC? (5) Is there an optimal dose prescription for radiotherapy? (6) What are the treatment options for recurrent MSCC in an area previously irradiated? (7) What are the indications for surgery in the management of MSCC?

Did the authors look for the appropriate sort of papers?

Unclear—all study types were included. Only full publications and abstracts of adult patients with extradural cord compression, but not intramedullary and leptomeningeal cord compression, were included. The authors might have considered limiting inclusion on quality.

Do you think the important, relevant studies were included?

Unclear—however, the authors searched an extensive list of databases. MEDLINE, CANCELIT, and the Cochrane Library databases were searched to January 2004 using terms: spinal cord compression, nerve compression syndromes, spinal cord neoplasms, clinical trial, meta-analysis and systematic review. Also, abstracts published in the Proceedings of the Annual Meetings of the American Society of Clinical Oncology (up to 2003) and the American Society of Therapeutic Radiology and Oncology (1997 to 2003) were searched for ongoing trials. The Canadian Medical Association Infobase and the National Guidelines Clearinghouse were searched for evidence-based practice guidelines.

Did the review's authors do enough to assess the quality of the included studies?

There was no quality assessment of the included studies. This was a substantial weakness of the review. This resulted in all study designs regardless of quality being included.

If the results of the review have been combined, was it reasonable to do so?

The results of the included studies are not clearly displayed to allow a clear comparison of the different studies and to establish whether it was appropriate to pool the studies and to explain the reasons for any variations in results. Furthermore, the authors have attempted to pool different study designs to address the specific questions highlighted, without undertaking a quality assessment of each study.

What are the overall results of the reviews?

Magnetic resonance imaging is the preferred imaging technique and treatment for patients with MSCC should consider pretreatment ambulatory status, comorbidities, technical surgical factors, the presence of bony compression and spinal instability, potential surgical complications, potential radiotherapy reactions and patient preferences. The authors recognised that in summarising the evidence on the diagnosis and management of MSCC, unfortunately, for many questions raised, the current evidence prevents reliable conclusions from being made.

How precise are the results?

Unclear—the authors are conservative in their interpretation of the studies. However, they have attempted to address too many questions. The authors provide percentages and 95% CIs, with limited discussion of the statistical findings from each study.

Can the results be applied to the local population?

No, because the populations in the included studies were poorly defined and probably different from study to study. The limited discussion of the populations in each included study and the lack of quality assessments make it difficult to draw conclusions as to whether these findings can be applied to the local population.

Were all important outcomes considered?

The authors have made a good attempt at addressing different key questions in this area. However, it is difficult to establish whether other outcomes could have been considered as summary tables outlining the measures used in each study are not provided.

Are the benefits worth the harms and costs?

Although the review discussed issues related to adverse events, there was a lack of consideration of the costs of treatment diagnosis and management of malignant extradural spinal cord compression, and the consequential outcomes of false-positive and false-negative predictions or diagnoses.



**First author: Lu**  
**Reviewer(s): PS/MC – Agreed**

**Year: 2005**

**ID: 121**

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]	✓				
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]	✓				
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results	✓				
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up	✓				
	Statement as to the possible effect on the results from missing data		✓			
	Loss to follow-up is not associated with key characteristics	✓				
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)	✓				
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>		✓			
	Blinding: were estimators of risk factor status and of outcomes blinded?			✓		
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias		✓			
Outcome	Is the outcome clearly defined?	✓				
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>			✓		
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis	✓				
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results	✓				
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)		4	1	1	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: McCloskey**  
**Reviewer(s): PS/MC – Agreed**

**Year: 1993**

**ID: 122**

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/ sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]		✓			
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]		✓			
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results		✓			
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up		✓			
	Statement as to the possible effect on the results from missing data				✓	
	Loss to follow-up is not associated with key characteristics		✓			
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)	✓				
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>		✓			
	Blinding: were estimators of risk factor status and of outcomes blinded?				✓	
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias		✓			
Outcome	Is the outcome clearly defined?	✓				
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>				✓	
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis	✓				
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results	✓				
	TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)	2	3	1	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: Oka**  
**Reviewer(s): PS/MC – Agreed**

**Year: 2006**

**ID: 123**

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]	✓				
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]	✓				
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results	✓				
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up	✓				
	Statement as to the possible effect on the results from missing data					✓
	Loss to follow-up is not associated with key characteristics	✓				
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)	✓				
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>		✓			
	Blinding: were estimators of risk factor status and of outcomes blinded?			✓		
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias		✓			
Outcome	Is the outcome clearly defined?	✓				
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>	✓				
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis	✓				
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results	✓				
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)		5	1	0	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: Plunkett**  
**Reviewer(s): PS/MC – Agreed**

**Year: 2000**

**ID: 24**

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/ sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]	✓				
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]		✓			
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results		✓			
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up	✓				
	Statement as to the possible effect on the results from missing data				✓	
Prognostic factor measurement	Loss to follow-up is not associated with key characteristics		✓			
	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)		✓			
	Specified instrument and personnel for measurement of predictive factors		✓			
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>				✓	
	Blinding: were estimators of risk factor status and of outcomes blinded?				✓	
Outcome	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias		✓			
	Is the outcome clearly defined?		✓			
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>				✓	
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis	✓				
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results	✓				
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)		1	4	1	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: Rose**  
**Reviewer(s): PS/MC – Agreed**

**Year: 2009**

**ID: 88**

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]		✓			
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]	✓				
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results		✓			
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up	✓				
	Statement as to the possible effect on the results from missing data					✓
	Loss to follow-up is not associated with key characteristics	✓				
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)	✓				
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>	✓				
	Blinding: were estimators of risk factor status and of outcomes blinded?				✓	
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias	✓				
Outcome	Is the outcome clearly defined?	✓				
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>	✓				
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis	✓				
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results	✓				
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)		5	1	0	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: Roth**  
**Reviewer(s): PS/MC – Agreed**

**Year: 2004**

**ID: 124**

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/ sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]	✓				
	Baseline study sample (i.e. individuals entering the study and their key characteristics [where relevant] and sampling frame are adequately described)		✓			
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results		✓			
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up	✓				
	Statement as to the possible effect on the results from missing data					✓
	Loss to follow-up is not associated with key characteristics	✓				
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)	✓				
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>				✓	
	Blinding: were estimators of risk factor status and of outcomes blinded?				✓	
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias		✓			
Outcome	Is the outcome clearly defined?		✓			
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>			✓		
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis		✓			
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results		✓			
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)		2	3	1	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: Sekine**  
**Reviewer(s): PS/MC – Agreed**

**Year: 2009**

**ID: 125**

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]	✓				
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]	✓				
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results	✓				
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up	✓				
	Statement as to the possible effect on the results from missing data					✓
	Loss to follow-up is not associated with key characteristics	✓				
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)	✓				
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>				✓	
	Blinding: were estimators of risk factor status and of outcomes blinded?			✓		
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias	✓				
Outcome	Is the outcome clearly defined?	✓				
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>		✓			
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis	✓				
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results	✓				
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)		5	1	0	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: Shah**  
**Reviewer(s): PS/MC – Agreed**

**Year: 2003**

**ID: 126**

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/ sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]	✓				
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]	✓				
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results	✓				
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up	✓				
	Statement as to the possible effect on the results from missing data					✓
	Loss to follow-up is not associated with key characteristics	✓				
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)	✓				
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>		✓			
	Blinding: were estimators of risk factor status and of outcomes blinded?			✓		
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias		✓			
Outcome	Is the outcome clearly defined?	✓				
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>			✓		
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis		✓			
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results	✓				
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)		4	1	1	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: Snyder**  
**Reviewer(s): PS/MC – Agreed**

**Year: 2005**

**ID: 127**

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/ sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]			✓		
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]			✓		
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results			✓		
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables				✓	
	Loss to follow-up				✓	
	Statement as to the possible effect on the results from missing data				✓	
	Loss to follow-up is not associated with key characteristics				✓	
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)	✓				
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>				✓	
	Blinding: were estimators of risk factor status and of outcomes blinded?			✓		
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias		✓			
Outcome	Is the outcome clearly defined?	✓				
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>			✓		
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis		✓			
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results	✓				
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)		2	1	2	1	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: Snyder**  
**Reviewer(s): PS/MC – Agreed**

**Year: 2009**

**ID: 128**

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/ sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]		✓			
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]	✓				
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results		✓			
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up				✓	
	Statement as to the possible effect on the results from missing data					✓
	Loss to follow-up is not associated with key characteristics		✓			
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)	✓				
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>				✓	
	Blinding: were estimators of risk factor status and of outcomes blinded?			✓		
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias		✓			
Outcome	Is the outcome clearly defined?	✓				
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>			✓		
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis	✓				
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results	✓				
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)		2	3	1	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: Soerdjbalie-Maikoe**  
**Reviewer(s): PS/MC – Agreed**

**Year: 2004 ID: 129**

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/ sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]		✓			
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]				✓	
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results		✓			
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up	✓				
	Statement as to the possible effect on the results from missing data					✓
	Loss to follow-up is not associated with key characteristics	✓				
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)	✓				
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>	✓				
	Blinding: were estimators of risk factor status and of outcomes blinded?				✓	
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias	✓				
Outcome	Is the outcome clearly defined?	✓				
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>				✓	
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis		✓			
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results		✓			
	TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)	3	2	0	1	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: Sun**  
**Reviewer(s): PS/MC – Agreed**

**Year: 2011**

**ID: 130**

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/ sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]	✓				
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]	✓				
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results	✓				
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up	✓				
	Statement as to the possible effect on the results from missing data					✓
	Loss to follow-up is not associated with key characteristics	✓				
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)	✓				
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>		✓			
	Blinding: were estimators of risk factor status and of outcomes blinded?				✓	
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias		✓			
Outcome	Is the outcome clearly defined?	✓				
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>		✓			
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis		✓			
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results		✓			
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)		3	3	0	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: Talcott**  
**Reviewer(s): PS/MC – Agreed**

**Year: 1999**

**ID: 131**

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]	✓				
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]	✓				
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results	✓				
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up	✓				
	Statement as to the possible effect on the results from missing data		✓			
	Loss to follow-up is not associated with key characteristics	✓				
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)	✓				
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>		✓			
	Blinding: were estimators of risk factor status and of outcomes blinded?				✓	
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias	✓				
Outcome	Is the outcome clearly defined?	✓				
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>		✓			
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis	✓				
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results	✓				
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)		5	1	0	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: Taneichi**  
**Reviewer(s): PS/MC – Agreed**

**Year: 1997**

**ID: 89**

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/ sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]		✓			
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]	✓				
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results		✓			
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up	✓				
	Statement as to the possible effect on the results from missing data					✓
	Loss to follow-up is not associated with key characteristics	✓				
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)	✓				
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>		✓			
	Blinding: were estimators of risk factor status and of outcomes blinded?			✓		
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias		✓			
Outcome	Is the outcome clearly defined?	✓				
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>			✓		
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis		✓			
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results	✓				
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)		3	2	1	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

**First author: Venkitaraman Year: 2007**  
**Reviewer(s): PS/MC – Agreed**

**ID: 132**

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]	✓				
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]	✓				
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results	✓				
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up	✓				
	Statement as to the possible effect on the results from missing data					✓
	Loss to follow-up is not associated with key characteristics	✓				
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)	✓				
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>		✓			
	Blinding: were estimators of risk factor status and of outcomes blinded?			✓		
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias		✓			
Outcome	Is the outcome clearly defined?	✓				
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>			✓		
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis	✓				
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results	✓				
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)		4	1	1	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.

First author: Venkitaraman Year: 2010

ID: 133

Reviewer(s): PS/MC – Agreed

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
Study population/ sample selection <sup>a</sup>	Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]	✓				
	Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]	✓				
	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results	✓				
Study attrition	Statement as to exclusions due to missing data:					
	Baseline variables	✓				
	Loss to follow-up	✓				
	Statement as to the possible effect on the results from missing data					✓
	Loss to follow-up is not associated with key characteristics	✓				
Prognostic factor measurement	Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described)	✓				
	Specified instrument and personnel for measurement of predictive factors	✓				
	Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori <sup>b</sup>		✓			
	Blinding: were estimators of risk factor status and of outcomes blinded?				✓	
	The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias		✓			
Outcome	Is the outcome clearly defined?	✓				
Confounding measurement and account	Do the authors address potential confounders? <sup>c</sup>				✓	
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis	✓				
	The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results	✓				
TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)		4	1	1	0	0

NA, not applicable.

a Is the sampling frame clear (if unclear there is risk of bias), and is the method of sample selection susceptible to bias?

b Cut-off points decided prior to data analysis.

c In particular, if previous treatments were not taken into account in the analyses of potential predictive factors these could confound the validity of other predictive factors that might be identified.



## Appendix 7 Data extraction tables

Author: Bayley 2001<sup>107</sup>

**Country:** Canada

**Source of funding:** Not reported

**Study design:**

*Type of study:* A prospective study

*Aims:* (1) Identify clinical parameters that predict occult SAS compression/SCC, as determined by MRI, in patients with metastatic prostate carcinoma; and (2) define risk groups for occult SAS compression/SCC that can be used to select patients with prostate carcinoma for MRI

*Secondary objectives:* (1) Determine the incidence of occult SAS compression/SCC in patients with metastatic prostate carcinoma; (2) determine the incidence of multiple levels of occult SAS compression/SCC; and (3) determine the risk of developing a clinically evident SCC after a negative screening spinal MRI

*Length of study:* Not reported

*Years of recruitment:* Not reported – recruitment was over an 18-month period

*Inclusion criteria:* Previously documented vertebral bone metastases from prostate carcinoma, no neurological symptoms indicative of SCC, and a normal neurological examination as determined by the physician entering the patient on study

*Exclusion criteria:* Patients with a previous SCC or a contraindication to MRI were excluded

*Study arms (n):* One

**Method:**

*Population characteristics:*

Number of participants selected: 68

Number of participants analysed: 68

Number of participants selected but not followed up: 0

*Sampling frame:* Outpatient radiation oncology clinic

*Method of sample selection:* A cross-sectional sample of newly diagnosed and follow-up patients accrued from the outpatient radiation oncology clinic over 18-month period. Patients approached at discretion of treating physician

*Sex (M/F):* Not reported; 100% male

*Age of patients:*

Mean (SD) – Not reported

Median – 71 years

Range – 50–84 years

*Interval from the time of diagnosis of cancer(s) to study entry:* 2 months to 13.8 years (median 3.6 years)

*Interval from the time of diagnosis of spinal metastases to study entry:* Not reported

*Length of follow-up per patient:*

Mean (SD) – Not reported

Median – 8 months

Range – 1–47 months

*Cancer type(s):* Prostate carcinoma; 64 of 68 receiving hormone therapy at study entry. Of these, 61 were classified as metastatic hormone-resistant prostate cancer on the basis of rising PSA levels or increased number of bone metastases on scintigraphy

continued

Author: Bayley 2001<sup>107</sup>

*Sites of metastasis:* Vertebral metastases were identified by MRI in 65 of 68 patients (96%). Concordance between MRI and bone scan in the diagnosis of vertebral metastases in 64 patients (94%). Two patients were judged to have metastases based on MRI abnormalities alone, and two patients had areas of increased uptake on bone scan without corresponding MRI abnormalities

*Performance/other status scores:* Soloway scale for EOD from bone scintigraphy. Gleason grades  $\leq 5$  ( $n = 3$ ), 6–8 ( $n = 54$ ), 9–10 ( $n = 8$ ), unknown ( $n = 3$ )

*Visceral metastasis:* Unclear, 54% had lymph node or distant metastases

*Duration and rapidity of cord compression:* Unclear

*Spinal level:* 68 patients

Cervical – Three patients with SAS compression/SCC in the cervical area

Thoracic – 20 patients with SAS compression/SCC in the thoracic area

Lumbar – Eight patients with SAS compression/SCC in the lumbar area

Other – Clinically occult SAS compression/SCC was identified in 22 patients (32%). SAS compression alone in 12 patients (17%), and frank compression of the spinal cord or cauda equina in 10 patients (15%). Nine of 22 patients (41%) had SAS compression/SCC at two discontinuous vertebral levels

*Spinal instability:* Not reported

*Medications:* 64/68 on hormone therapy. Twenty-two patients (32%) did not routinely require analgesics, 13 patients (19%) were using acetaminophen or non-steroidal anti-inflammatory medications, and 33 patients (49%) were using narcotic analgesics

#### **Intervention (i.e. screening technologies):**

A bone scan was obtained in all patients within 1 week of study entry (68 patients; 100%). Bone scans showed no evidence of metastatic disease in 3 patients out of 68 patients (4%); X-rays (30 patients, 44%); and MRI of the entire spine (68 patients; 100%) was performed. No further information about trade name, trademark or registered symbol, and the name and location of the manufacturer is provided – we cannot identify this information. A sagittal, T1-weighted, spin-echo sequence was obtained followed by a sagittal, T2-weighted, fast spin-echo sequence

#### **Outcomes:**

*List of potential prognostic factors examined:* Gleason score, alkaline phosphatase, PSA, prostatic acid phosphatase, presence of back pain, bone scan EOD score, duration of hormonal therapy before study entry, haemoglobin concentration. Tested using logistic regression

*List of potential prognostic factors identified as significant:* All above

*Have prognostic factors been validated in another population:* No

#### **Findings:**

Clinically occult SAS compression/SCC was diagnosed in 22 patients (32%) using MRI. Nine patients (13%) had compressions at two discontinuous spinal levels. By univariate analysis: extensive disease on bone scan, duration of continuous hormonal therapy before study entry, and haemoglobin concentration predicted SAS compression/SCC. By multivariate analysis: EOD on bone scan and duration of continuous hormonal therapy were predictors of SAS compression/SCC ( $p = 0.02$  and  $p = 0.04$ , respectively). Risk of occult SAS compression/SCC increased from 32% to 44% in patients with a bone scan that showed  $>20$  bone metastases as duration on hormones increased from 0 to 24 months. Risk in patients with  $\leq 20$  metastases increased from 11% to 17% over same interval. Presence or absence of back pain was not predictive of SAS compression/SCC. Actuarial risk ( $\pm$  standard error) of developing clinical SCC in setting of a previous negative screening MRI was (4/46)  $3.2 \pm 3.2\%$  at 1 year, and  $13.7 \pm 7.6\%$  at 2 years

#### **Author conclusions:**

Patients who are at high risk for occult SAS compression/SCC can be identified using clinical parameters and readily available diagnostic tests. EOD score on bone scan was strongest of two factors that independently predicted occult SAS compression/SCC. Patients with  $>20$  discrete metastases on bone scan had a 44% risk of SAS compression/SCC, whereas patients with fewer metastases had a 19% risk

#### **Reviewer conclusions:**

Patients with a high-risk bone scan may benefit from screening MRI of spine aimed at early detection and treatment of occult SAS compression/SCC. Results are as expected, i.e. the more spinal metastases the greater the chance of clinically occult SCC, and the longer a patient is on hormone therapy then the longer they are at risk of occult SCC. The quantitative estimates of risk probably do not add much value to rather obvious conclusion. What this study does not address is the probability that occult SCC becomes patently symptomatic SCC, and how long after occult SCC is detected this occurs

Author: Bernat 1983<sup>108</sup>**Country:** Canada**Source of funding:** Not reported**Study design:***Type of study:* Retrospective data comparison study*Aims:* (1) To identify a set of clinical findings that would allow a more precise diagnosis at the bedside, thereby separating those patients who need a myelogram from those who do not*Secondary objectives:* (1) Examine characteristics and outcome of patients who were suspected of having cord compression but who do not have a positive myelogram*Length of study:* Unclear*Years of recruitment:* July 1975 to July 1980 (two centres)*Inclusion criteria:* Reviewed data from patients who fulfilled two criteria: (1) a senior staff physician had made a clinical diagnosis of possible epidural compression of the spinal cord or cauda equina by metastatic cancer; and (2) a myelogram had been performed to confirm or exclude the clinical diagnosis*Exclusion criteria:* Not reported*Study arms (n):* One**Method:***Population characteristics:*

Number of participants selected: 133

Number of participants analysed: Unclear

Number of participants selected but not followed up: 0 (figure 1 appears to have missing data for  $n = 18$ )*Sampling frame:* Charts were identified by matching a discharge diagnosis of carcinoma, sarcoma and lymphoma with performance of a myelogram for all patients discharged from Mary Hitchcock Hospital, New Hampshire (1 July 1975 to 1 January 1980) and from Veterans Administration Hospital, Vermont (1 January 1976 to 1 July 1980)*Method of sample selection:* Unclear*Sex (M/F):* 77 male/56 female*Age of patients:*

Mean (SD) – Not reported

Median – 61 years

Range – 7–85 years

*Interval from the time of diagnosis of cancer(s) to study entry:* Not reported*Interval from the time of diagnosis of spinal metastases to study entry:* Not reported*Length of follow-up per patient:*

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

*Cancer type(s):* Lung ( $n = 40$ ); breast ( $n = 27$ ); prostate ( $n = 15$ ); lymphoma ( $n = 12$ ); colon/rectal ( $n = 6$ ); melanoma ( $n = 6$ ); kidney and ureter ( $n = 5$ ); bladder ( $n = 3$ ); other ( $n = 15$ ); unknown ( $n = 6$ ) (Note: some patients did not have metastatic disease to the spine)*Sites of metastasis:* Unclear*Performance status scores:* Not reported*Visceral metastasis:* Unclear

continued

Author: Bernat 1983<sup>108</sup>

*Duration and rapidity of cord compression:* 80% obliteration of SAS considered positive for epidural compression. Of the 133 patients, 62 had myelographic evidence of epidural compression of the spinal cord or cauda equina by metastatic cancer and constitute the 'compression group'. The remaining 71 patients (53%) who did not have myelographic evidence for compression by tumour are the 'non-compression group'. The compression group included 47 patients whose principal lesion was of the spinal cord and 15 patients with primarily cauda equina compression. The thoracic region was the site of compression in 50%, the lumbosacral region in 31% and the cervical region in 19%. Six patients had two separate blocks which were separated by a mean of 12 vertebral segments. A complete myelographic spinal block was seen in 30 patients (64%) and an incomplete block in 17 (36%); a complete block in 3/15 cauda equina and incomplete in 12/15 cauda equina

*Spinal level:*

Cervical – 9% of 47

Thoracic – 50% of 47 (23 or 24)

Lumbar – Sacral 31% of 47

Other – Unclear 15 cauda equina

*Spinal instability:* Unclear

*Medications:* Not reported

**Intervention (i.e. screening technologies):**

CSF examination, X-rays, vertebral radiographs, bone scans and myelograms

**Outcomes:**

*List of potential prognostic factors examined:* Positive vertebral plain films; sensory level or dermatomal loss on examination; history of local pain; older age; history of weakness; history of radicular pain; male sex; paraparesis or radicular weakness on examination

*List of potential prognostic factors identified as significant:* From multiple logistic regression, eight characteristics, in combination, were most effective as an index; *p*-values not reported

*Have prognostic factors been validated in another population:* Unclear

**Findings:**

Multiple logistic regression was used to develop an index of signs and symptoms to identify patients without compression. Eight characteristics, in combination, were most effective as an index, but they were not precise predictors of patients with block. Using multivariate logistic regression equation (not reported) the probability of compression was calculated for all 62 patients with myelographic block and all 71 without block; the frequency of patients (i.e. number of patients) within each of the 10 10%-steps in probability (0–0.09, 0.1–0.19, etc.) was plotted; this showed moderate discrimination of compression and non-compression. Final diagnoses in group without compression were: vertebral metastases 35%, carcinomatous meningitis 24%, plexopathy and/or neuropathy 21%, other 30% (10% had two diagnoses). Note: not all are metastasis to spine. Kaplan–Meier plots of survival postmyelography for positive block and negative block patients were reported; log-rank test result not reported. Sixty-six per cent of patients with compression and 50% without compression died within 6 months, although patients rarely survived much longer

**Author conclusions:**

Attempts to identify symptoms and signs that might increase diagnostic ability were not successful. Logistic regression analysis was used to separate two groups; however, overlap in scores of those with and without compression resulted in difficulty in selecting a useful cut-off point

**Reviewer conclusions:**

Myelographs rarely used now but robust discriminatory factors would have been potentially useful

Author: Chaichana 2009<sup>109</sup>

**Country:** USA

**Source of funding:** Not reported

**Study design:**

*Type of study:* Retrospective review of medical records/reports

*Aims:* (1) Evaluate effects of compression fractures on long-term neurological function, and understand factors that predict development of pathological fractures for patients with metastatic epidural SCC (MESCC) (SCC caused by an EM)

*Length of study:* Unclear

*Years of recruitment:* 1995 to 2007 (one tertiary care centre)

*Inclusion criteria:* Only patients with MESCC;  $\geq 18$  years of age; tissue-proven diagnosis of a primary tumour; and MRI evidence of spinal cord displacement from its normal position in spinal canal by an EM

*Exclusion criteria:* Patients with more than one discrete compressive lesion, concomitant brain metastases, cauda equina or spinal root compression were excluded

*Study arms (n):* Two – compared those MESCC with and without vertebral body compression fractures (confirmed by MRI);  $n = 60$  (in 73 vertebrae) and  $n = 102$ , respectively

**Method:**

*Population characteristics:*

Number of participants selected: 216

Number of participants analysed: 162

Number of participants selected but not followed up: 54

*Sampling frame:* All patients had undergone surgery for MESCC at an academic tertiary care institution between 1995 and 2007

*Method of sample selection:* Unclear

*Sex (M/F):* 95 male/67 female

*Age of patients:*

Mean (SD) – 58 (12) years

Median – Not reported

Range – Not reported

*Interval from the time of diagnosis of cancer(s) to study entry:* Not reported

*Interval from the time of diagnosis of spinal metastases to study entry:* Not reported

*Length of follow-up per patient:*

Mean (SD) – 9.7 (2.6) months

Median – Not reported

Range – Not reported

*Cancer type(s):* Lung ( $n = 26$ , 16%), breast ( $n = 26$ , 16%), prostate ( $n = 20$ , 12%), renal ( $n = 21$ , 13%), haematopoietic ( $n = 28$ , 17%). Other sources included thyroid, gastrointestinal, melanoma and non-renal genitourinary system. One hundred and fifteen patients were examined by CT. Of 162 tumours, 94 (58%) appeared lytic and 13% sclerotic

*Sites of metastasis:* Unclear

*Performance status scores:* Unclear

*Visceral metastasis:* 42% had extracranial/extraspinal metastases ( $n = 68$ )

*Duration and rapidity of cord compression:* Unclear

continued

Author: Chaichana 2009<sup>109</sup>

*Spinal level:*

Cervical –  $n = 35$  patients

Thoracic –  $n = 114$  patients

Lumbar –  $n = 49$  patients

Other: Cervicothoracic –  $n = 22$ ; thoracolumbar –  $n = 24$

*Spinal instability:* Unclear

*Medications:* Not reported

**Intervention (i.e. screening technologies):**

MRI, CT, intraoperative recordings

**Outcomes:**

*List of potential prognostic factors examined:* (factors potentially associated with preoperative compression fracture in patients who receive surgery for MESCC, assessed using logistic regression) Sensory deficits, preoperative chemotherapy, primary breast cancer, thoracic spine involvement, increasing number of spinal levels, number of spinal metastases, anterior cord compression, age, preoperative radiation, pain symptom, motor deficit, lytic-type tumour, blastic-type tumour, extraspinal metastases

*List of potential prognostic factors identified as significant:* (factors associated with preoperative compression fracture in patients who receive surgery for MESCC) Univariate ORs: sensory deficits (OR 0.453;  $p = 0.02$ ), preoperative chemotherapy (OR 2.023;  $p = 0.03$ ), primary breast cancer (OR 2.698;  $p = 0.02$ ), thoracic spine involvement (OR 4.453;  $p < 0.001$ ), increasing number of spinal levels (OR 1.137;  $p = 0.10$ ), number of spinal metastases (OR 1.976;  $p = 0.07$ ) and anterior cord compression (OR 2.726;  $p = 0.005$ ) were associated with preoperative vertebral body compression fractures. Not associated were age, preoperative radiation, pain (tumour, mechanical, radicular), motor deficit, lytic-type tumour, blastic-type tumour, extraspinal metastases

In multivariate regression: preoperative chemotherapy (OR 2.283, 95% CI 1.064 to 4.898;  $p = 0.03$ ), primary breast cancer (OR 4.179, 95% CI 1.457 to 11.983;  $p = 0.008$ ), thoracic spine involvement (OR 3.505, 95% CI 1.343 to 9.143,  $p = 0.01$ ) and anterior cord compression (OR 3.213, 95% CI 1.416 to 7.293;  $p = 0.005$ ) were associated with preoperative vertebral body compression fractures

*Have prognostic factors been validated in another population:* No

**Findings:**

The factors strongly associated with preoperative compression fractures in this study according to multivariate logistic regression were: primary breast cancer (OR 4.179;  $p = 0.008$ ), anterior spine metastases (OR 3.213;  $p = 0.005$ ), thoracic spine involvement (OR 3.505;  $p = 0.01$ ), and preoperative chemotherapy (OR 2.283;  $p = 0.03$ ). Surprisingly, sensory deficits (OR 0.356;  $p = 0.01$ ) had a decreased risk of compression fractures. The presence of preoperative compression fractures was independently associated with decreased postoperative ambulatory status (OR 2.106, 95% CI 1.123 to 4.355;  $p = 0.03$ ). This was independent of age, preoperative ambulatory status, preoperative motor deficit, duration of preoperative symptoms, immediate postoperative motor deficit and lytic tumour appearance

**Author conclusions:**

Findings provide information on the risk stratifying and guidance for surgical management of patients with MESCC. Pathological fracture of the vertebral body may place patients at greater risk of poor neurological outcomes. The factors strongly associated with preoperative compression fractures include lack of sensory deficits, primary breast cancer, anterior spine metastases, thoracic spine involvement, preoperative chemotherapy and possibly preoperative radiation therapy

**Reviewer conclusions:**

A mixed collection of primary cancers so that prognostic factors for compression fracture uncovered may be dominated by the particular make up of tumour types. Selection of patients excluded MESCC patients who did not receive decompressive surgery and the criteria that led to surgery were not defined. Inclusion of all MESCC patients rather than just those that received surgery would better indicate factors associated with compression fracture; however, the main focus of the study appeared to be how compression fracture influenced the postoperative prognosis especially with regard to walking status

Author: Goldman 1989<sup>111</sup>**Country:** UK**Source of funding:** Cancer Research Campaign**Study design:***Type of study:* Analysis of records from patients with SCLC treated in a single randomised trial*Aims:* (1) Perform an analysis of records to define the incidence, clinical features, predictive factors and prognosis of SCC*Length of study:* Not reported*Years of recruitment:* February 1982 to September 1986*Inclusion criteria:* The results of all the bone scans performed during the multicentre trial were obtained and those suggestive of vertebral metastases were selected*Exclusion criteria:* Incorrect diagnosis or second malignancy*Study arms (n):* Two**Method:***Population characteristics:*

Number of participants selected: 616

Number of participants analysed: 610 (24 for risk factors for SCC)

Number of participants selected but not followed up: 6 of RCT did not have SCLC

*Sampling frame:* Participants in a RCT, selection of patients in separate publication. Patients received four or six cycles of three cytotoxic chemotherapies (vincristine, cyclophosphamide and etoposide) and some further chemotherapy with adriamycin and methotrexate*Method of sample selection:* Those patients with SCC at 'presentation' (= entry into trial?) or who developed SCC during follow-up. SCC assessed on clinical grounds of signs and symptoms. Of the 24 with SCC only 11 had myelographs*Sex (M/F):* Unclear – 24 patients (4%) had definite evidence of SCC at some stage of their disease. The sex and age were reported for these patients only. There were 20 males (mean age 56 years, range 30–67 years) and four females (mean age 52 years, range 43–62 years)*Age of patients:*

Mean (SD) – Unclear for non-SCC (see above)

Median – Unclear (see above)

Range – Unclear (see above)

*Interval from the time of diagnosis of cancer(s) to study entry:* Not reported*Interval from the time of diagnosis of spinal metastases to study entry:* Median time for SCC to develop after the diagnosis of SCLC was 27 weeks (range 14–97 weeks)*Length of follow-up per patient:*

Mean (SD) – For 24 SCC followed till death

Median – 6 months

Range – Unclear (all 24 SCC dead by 14 months follow-up)

*Cancer type(s):* SCLC*Sites of metastasis:* The case records of patients presenting with back pain as their major symptom and those with cerebral metastases were examined (for what?). Probably in RCT report*Performance status scores:* Not reported. Probably in RCT report*Visceral metastasis:* Unclear. Probably in RCT report*Duration and rapidity of cord compression:* Unclear

continued

**Author: Goldman 1989<sup>111</sup>**

*Spinal level:* Provide results for the 131 patients with positive bone scans involving the spine at presentation (500 patients were scanned). The numbers account for 121 rather than 131 patients

Cervical – 17 of 131 patients

Thoracic – Thoracic or thoracic and lumbar in 61 patients

Lumbar – Lumbosacral alone in 43 cases

Other – Thoracic or thoracic and lumbar spine in 61 cases and lumbosacral spine alone in 43 cases

*Spinal instability:* Of 24 cases of SCC (table 1), 9 (37.5%) had positive bone scans at presentation with abnormal isotope uptake in spinal column. In all of these abnormalities was located in thoracic spine. Not all were classified as having SCC at presentation

*Medications:* Dexamethasone. At relapse they were again randomised to receive symptomatic treatment only, or further chemotherapy with adriamycin and methotrexate

**Intervention (i.e. screening technologies):**

Treatment of cord compression took the form of laminectomy and decompression of the spinal cord, radiotherapy (30 Gy in 10 fractions) with or without dexamethasone 16 mg daily or symptomatic treatment. Patients were staged at presentation as having local or extensive disease based on clinical examination, chest X-ray, liver function tests, liver ultrasound scan, isotope bone scan and, when clinically indicated, isotope or CT brain scan and bone marrow aspiration

**Outcomes:**

*List of potential prognostic factors examined:* A list of predictive factors for SCC in SCLC. The incidence of cord compression were as follows: 24 of 610 patients (4%) had SCC; bone scans were performed in 22 of 500 patients (4.4%); bone scans were abnormal in 11 of 234 patients (4.7%); bone scan abnormality in the spinal column was found in 9 of 131 patients (7%); 9 of 24 patients (36%) presented with back pain and abnormal bone scan; 4 of 32 patients (12.5%) presented with cerebral metastases; 7 of 87 patients (8%) relapsed with cerebral metastases; all cerebral metastases were found in 11 of 119 patients (9.2%); and cerebral metastases and abnormal bone scan were found in 6 of 24 patients (25%)

*List of potential prognostic factors identified as significant:* Unclear

*Have prognostic factors been validated in another population:* Unclear

**Findings:**

In all, 610 patients with SCLC were reviewed and 24 (4%) cases of SCC were identified. Five hundred patients had bone scans performed at presentation, and in 131 (26%) abnormal isotope uptake in spinal column was recorded; only 7% of these patients developed SCC. Of 24 patients who presented with back pain and had a positive bone scan affecting the spine, 36% (nine) developed SCC. Cerebral metastases occurred at some stage in 19.5% of all patients and in 45% of patients with SCC. Among the 24 that developed SCC there were two distinct forms of clinical presentation. Six patients (group A) presented with SCC; all had back pain and positive bone scans involving the spine, five out of six had sphincter disturbance, and median survival from SCC was 30 weeks. Eighteen patients (group B) developed SCC while on treatment; 28% (five) had positive initial bone scans involving spine or X-ray evidence of vertebral fracture, 11 had negative bone scans, 44% had back pain and 61% had sphincter disturbance, and median survival from cord compression was 4 weeks

**Author conclusions:**

The combination of cerebral metastases and a positive bone scan gave a 25% chance of developing SCC. It may be possible to select patients who should receive radiotherapy to the spine to try to prevent the development of this complication

**Reviewer conclusions:**

An early study with only 24 SCC cases. SCC not confirmed by myelography in all patients and no mention of CT or MRI. No multiple logistic regression was performed; an important potentially influential confounder of risk factors not reported was chemotherapy (some patients received very heavy loads of cytotoxic agents, subsequent studies have indicated that such treatments might affect frequency of SCC. The positive predictive value for the combination + bone scan + cerebral metastases is 25%, but sensitivity is low (25%) and uncertainty large because of small numbers

Author: Helweg-Larsen 2000<sup>113</sup>**Country:** Denmark**Source of funding:** Not reported**Study design:***Type of study:* Prospective study*Aims:* (1) Analyse prognostic significance of various clinical and radiological variables on post-treatment ambulatory function and survival; (2) examine prognostic significance of five variables on gait function and survival time after treatment was analysed*Length of study:* Unclear*Years of recruitment:* Unclear – during a period of 3.5 years*Inclusion criteria:* Diagnosis of spinal cord or nerve root compression due to intraspinal metastases from a known solid malignant tumour*Exclusion criteria:* Patients who underwent laminectomy due to unknown malignant disease or due to earlier radiation therapy in the affected area were excluded*Study arms (n):* One**Method:***Population characteristics:*

Number of participants selected: 153

Number of participants analysed: 153

Number of participants selected but not followed up: Unclear

*Sampling frame:* Unclear*Method of sample selection:* Unclear – consecutive patients with SCC myelography confirmed*Sex (M/F):* 78 male/75 female*Age of patients:*

Mean (SD) – Not reported

Median – Women = 64 years (36–88 years); males = 71 years (26–92 years)

Range – 26–92 years

*Interval from the time of diagnosis of cancer(s) to study entry:* Not reported*Interval from the time of diagnosis of spinal metastases to study entry:* Not reported*Length of follow-up per patient:* to death or a minimum of 11 months

Mean (SD) – Not reported

Median – Not reported

Range – 3 weeks and 3 months after treatment, and then at intervals of 3 months for a minimum period of 11 months or until death

*Cancer type(s):* Breast carcinoma in 56 patients (37%), prostate carcinoma in 43 (28%), NSCLC in 18 (12%), SCLC in 9 (6%), and other solid tumours in the remaining 27 (17%) patients*Sites of metastasis:* Unclear*Performance status scores:* No scale instrument reported; at time of SCC diagnosis: 31/153 patients totally paralysed, 31/153 leg movement positive, 19 walk with assistance, 60 unaided gait*Visceral metastasis:* Unclear

continued

**Author: Helweg-Larsen 2000<sup>113</sup>**

*Duration and rapidity of cord compression:* New events of SCC in another site of spinal cord occurred in 14 (9%) patients 1.0 to 25.4 months (median 4.5 months) after the first episode

*Spinal level:*

- Cervical – 7 (4%) cases
- Thoracic – 102 (67%) cases
- Lumbar – Not reported
- Other – Lumbosacral in 44 (29%) cases

*Spinal instability:* Unclear

*Medications:* Not reported

**Intervention (i.e. screening technologies):**

The diagnosis was supported by myelographic evidence of complete or partial extradural block in all 153 patients (total block in 82, partial block in 71) and in approximately one-third of the patients a supplementary MRI scanning was performed

**Outcomes:**

*List of potential prognostic factors examined:* The prognostic significance of five variables for gait function and survival time after treatment was analysed: tumour type; time from diagnosis of primary tumour until SCC; degree of myelographic blockage; sensory disturbances; and gait function at time of diagnosis for gait function and survival time after treatment for SCC

*List of potential prognostic factors identified as significant:* Time interval from the diagnosis of the primary tumour until the development of SCC

*Have prognostic factors been validated in another population:* Unclear

**Findings:**

Type of primary tumour had a direct influence (1) on interval between diagnosis of primary malignancy and occurrence of SCC ( $p < 0.0005$ ); varies between those primaries in study, with breast slowest to SCC and lung fastest; and (2) also on ambulatory function (total paralysis, paretic, gait with assistance, gait without assistance) at time of SCC diagnosis ( $p = 0.016$ ), breast best and lung worst

Clear correlation between degree of myelographic blockage and gait function ( $p = 0.0001$ ) and between gait function and sensory disturbances ( $p = 0.0001$ ). Final gait was dependent on gait function at time of diagnosis ( $p < 0.0005$ ). Survival time after diagnosis of SCC depended directly on time from primary tumour diagnosis until SCC ( $p = 0.002$ ), on ambulatory function at time of diagnosis ( $p = 0.018$ ) and on ambulatory function after treatment

**Author conclusions:**

There was a significant association ( $p = 0.016$ ) between time interval from diagnosis of primary tumour until development of SCC and type of primary tumour. Pretreatment ambulatory function of SCC patients is main determinant for post-treatment gait function. Survival time is short, especially in non-ambulatory patients, and can only be improved by restoration of gait function in non-ambulatory patients by immediate treatment

**Reviewer conclusions:**

Primary tumour type is important (influences) time to SCC and patient walking status at time of confirmation of SCC. An inference for consideration of other studies with mixed cancer-type populations is that the length of time from primary diagnosis of the patients will influence the results for a mix of patients with different cancer types

Author: Helweg-Larsen 1995<sup>114</sup>**Country:** Denmark**Source of funding:** Danish Cancer Society**Study design:***Type of study:* Prospective study*Aims:* To examine the frequency of initial multiple epidural metastases, the occurrence of secondary cord compression and whether this is influenced by the presence of multiple metastases*Length of study:* Unclear. All patients followed up until death*Years of recruitment:* Unclear – consecutive patients with inclusion criteria during a period of 3.5 years*Inclusion criteria:* All patients had myelography-verified (had imaging of the entire spinal canal) metastatic spinal cord/root compression from a histologically verified solid tumour; some patients (*n* = not reported) also had CT. All were subsequently treated with radiotherapy with 6 MV photon beams*Exclusion criteria:* Not clear*Study arms (n):* One**Method:***Population characteristics:*

Number of participants selected: 107

Number of participants analysed: 107

Number of participants selected but not followed up: 0

*Sampling frame:* Consecutive patients with myelography-verified metastatic spinal cord or root compression from a histologically verified solid tumour*Method of sample selection:**Sex (M/F):* 53 male/54 female*Age of patients:*

Mean (SD) – Not reported

Median – 66 years

Range – 34–91 years

*Interval from the time of diagnosis of cancer(s) to study entry:* Unclear*Interval from the time of diagnosis of spinal metastases to study entry:* Median time between the first and the second occurrence of SCC in the three patients with multiple intraspinal metastases was 5.3 months (range 2.4–6.2 months)*Length of follow-up per patient:*

Mean (SD) – Not reported

Median – Not reported

Range – Followed up till death. Radiation within 24 hours of confirmatory myelography, then followed up at 7 days, 3 weeks, 3 months, and then every 3 months until death

*Cancer type(s):* Primary tumours were carcinoma of the breast 42 cases, adenocarcinoma of the prostate 28, tumour of the lung 21, and other solid tumours in 16*Sites of metastasis:* Multiple spinal epidural metastases were demonstrated in 37 of the 107 patients (35%). In one case four separate lesions, in eight cases three, in 28 two separate lesions*Performance status scores:* Not reported*Visceral metastasis:* Not reported

continued

**Author: Helweg-Larsen 1995<sup>114</sup>**

*Duration and rapidity of cord compression:* In the five patients with a single lesion, the second SCC developed in locations where no malignancy was found on the first myelogram, with a median interval of 3.3 months (range 1.1–10.0 months)

*Spinal level:* Results only for the eight patients who developed a second SCC at a different site to the first SCC

Cervical – Unclear (table 2 summarises the location of initial and second metastases in eight patients)

Thoracic – Unclear (table 2 summarises the location of initial and second metastases in eight patients)

Lumbar – Unclear (table 2 summarises the location of initial and second metastases in eight patients)

Other:

*Spinal instability:* Unclear

*Medications:* Not reported

**Intervention (i.e. screening technologies):**

Myelography alone or myelography combined with postmyelographic CT

**Outcomes:**

*List of potential prognostic factors examined:* Risk of second SCC according to single or multiple spinal metastases at time of confirmatory myelograph

*List of potential prognostic factors identified as significant:* No difference in risk of second SCC between single metastasis at confirmatory myelograph (occurred in 5/70 cases) and multiple metastases at myelography (occurred in 3/37 cases)

*Have prognostic factors been validated in another population:* No

**Findings:**

Multiple metastases were found in 37 patients (35%). Eight (7.5%) patients developed a second occurrence of SCC in another location within spinal canal. Second occurrence of SCC was found with same frequency in patients with single metastases (7.1%) compared with patients with multiple metastases (8.1%). Median survival time after the diagnosis of SCC was 3.4 months, whereas in patients who developed a second occurrence of SCC the median survival time was 9.2 months

**Author conclusions:**

Only symptomatic epidural metastases should be irradiated, and all patients treated should be followed regularly and observed for a second SCC. Patients who developed a second SCC syndrome had a significantly longer survival time, indicating that survival time is a main determining factor for risk of developing a second SCC

**Reviewer conclusions:**

Small study for question of identifying prognostic factors for second SCC ( $n = 8$ ). The number of recurrence events ( $n = 8$ ) was too small to meaningfully investigate prognostic factors predicting recurrence. Unsurprisingly, longer surviving patients were more at risk of recurrence

Author: Huddart 1997<sup>115</sup>**Country:** UK**Source of funding:** Not reported**Study design:***Type of study:* Retrospective analysis of patient records*Aims:* (1) To analyse the outcome of treatment and prognostic factors of cases of prostate cancer with SCC treated at the Royal Marsden Hospital between 1984 and 1992*Length of study:* Unclear*Years of recruitment:* Review of records of patients treated between 1984 and 1992*Inclusion criteria:* Patient records were reviewed and those with cord compression were included*Exclusion criteria:* No cord compression*Study arms (n):* One**Method:***Population characteristics:* Prostate cancer patients with SCC

Number of participants selected: 69

Number of participants analysed: 69

Number of participants selected but not followed up: 0

*Sampling frame:* Unclear (three methods for finding patients, completeness unclear)*Method of sample selection:* Cases were identified from (1) a previous study of hormone-relapsed patients undertaken to identify prognostic factors, (2) patients with prostate cancer having a MRI scan of their spine and (3) a review of radiotherapy records of patients with prostate cancer having spinal irradiation. (Comment: this will not necessarily include patients who did not have MRI or radiotherapy for SCC/vertebral collapse who had not become hormone resistant.) SCC confirmed by MRI/myelography in 63/69 patients with or without MRI/CT; in 3/69 plain X-ray image was unequivocal*Sex (M/F):* Not reported*Age of patients:*

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

*Interval from the time of diagnosis of cancer(s) to study entry:* The median time from first diagnosis to SCC was 84 weeks (range 0–387 weeks); 13 had SCC at presentation. Median time from prostate diagnosis to SCC for 56/69 patients was 586 days*Interval from the time of diagnosis of spinal metastases to study entry:* Not reported*Length of follow-up per patient:* Neurological assessment (motor function) before radiotherapy, and 7 days, 12 weeks, 6 months, 1 year and 2 years after radiotherapy; motor function rated retrospectively on a 5-grade scale after Tomita *et al.*<sup>86</sup>

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

*Cancer type(s):* Prostate cancer*Sites of metastasis:* Most patients had extensive bony metastases at presentation, but only 24 out of 65 (38%) had evidence of vertebral collapse at the site of cord compression

continued

**Author:** Huddart 1997<sup>115</sup>

*Performance status scores:* Based on published instrument by Tomita *et al.*<sup>86</sup> A 5-grade categorisation of neurological/motor function: No impairment; Mild impairment, walking without aids; Moderate, walking with aids; Paraparetic, unable to walk but some power remains, wheelchair bound; Paraplegic, no motor power, wheelchair bound

*Visceral metastasis:* Unclear

*Duration and rapidity of cord compression:* Unclear

*Spinal level:* SCC calculated from percentages given in paper (dorsal taken to be cervical)

Cervical – 5

Thoracic – 57

Lumbar – 20

Other:

*Spinal instability:* Not reported

*Medications:* High dose steroids, hormone therapy if not hormone-resistant prostate cancer, radiotherapy

**Intervention (i.e. screening technologies):**

SCC confirmed by myelography in 63/69 patients with or without MRI/CT; in 3/69 plain X-ray image was unequivocal. Diagnosis established by myelography in 42% of patients (29) and MRI in 47% (32)

**Outcomes:**

*List of potential prognostic factors examined:* Most of this paper is about prognostic factors for survival and for response to treatment. Factors that might be associated with the risk of a second SCC (ambiguous in the paper with neurological relapse) were also mentioned. Second SCC at same site occurred in eight patients and at a new site in five patients. None of the following were associated with second SCC: presenting characteristics, haemoglobin, the number of lesions evident by bone scan, hormonal status or method of diagnosis or radiation dose for first SCC

*List of potential prognostic factors identified as significant:* presenting characteristics, haemoglobin, the number of lesions evident by bone scan, hormonal status or method of diagnosis or radiation dose for first SCC

*Have prognostic factors been validated in another population:* No

**Findings:**

Patients with multiple levels received radiotherapy to a larger field (a median of 18.5- vs. 10-cm field length), had poorer functional status at presentation of SCC and had a poor prognosis (in terms of both functional outcome and survival). On multivariate analysis a single level of compression, no previous hormone therapy and a young age (<65 years) predicted better outcome. Following initial recovery, there was a 45% risk of developing a further episode of cord compression at same or new site by 2 years with a median time to progression of 236 days (range 47–1215 days). 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 haemoglobin >12 g

**Author conclusions:**

Clinical significance of diagnosing multiple levels is difficult to evaluate and confounded by the method of diagnosis with MRI or myelography. No significant factor was identified for risk of future relapse. An early improvement in motor power is a strong predictor of subsequent functional improvement. MRI detects additional sites of asymptomatic SCC which makes it the investigation of choice

**Reviewer conclusions:**

No significant factor was identified for risk of future relapse (i.e. second SCC) but the sample was so small there was little power in the analysis

Author: Husband 2001<sup>116</sup>

**Country:** UK

**Source of funding:** Cancer Research Trust funded the scanner

**Study design:**

*Type of study:* Prospective study

*Aims:* (1) To assess the routine use of whole spine MRI in patients with suspected MSCC; (2) to assess the possibility that a subgroup can be defined in whom spinal cord MRI is not necessary; and (3) to define the distribution and extent of disease to allow definition of appropriate radiation portals in those patients in whom MRI cannot be carried out

*Length of study:* Not reported

*Years of recruitment:* 2 years

*Inclusion criteria:* Suspected MSCC and underwent MRI at the single centre and had been referred for radiotherapy

*Exclusion criteria:* Patients who had undergone MRI at other hospitals before referral, showing MSCC in all cases; these patients were excluded because the number of patients scanned at the other hospitals with negative results was not known, which would have biased the assessment of the diagnostic tests

*Study arms (n):* One

**Method:**

*Population characteristics:*

Number of participants selected: 280 consecutive patients with suspected MSCC

Number of participants analysed: 201 patients had MSCC (186 extradural, 5 intradural extramedullary and 10 intramedullary) and 11 patients had thecal sac compression without evidence of SCC; 79 without MSCC

Number of participants selected but not followed up: 0

*Sampling frame:* 362 consecutive patients with suspected MSCC assessed at a single oncology centre over a 2-year period, 82 were not selected for various reasons

*Method of sample selection:* Unclear. Only included if had been referred for radiotherapy then all were included unless they received MRI at another centre

*Sex (M/F):* 158 male/122 female

*Age of patients:*

Mean (SD) – Not reported

Median – 67 years

Range – 23–89 years

*Interval from the time of diagnosis of cancer(s) to study entry:* Not reported

*Interval from the time of diagnosis of spinal metastases to study entry:* Not reported

*Length of follow-up per patient:*

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

*Cancer type(s):* Breast ( $n = 65$ ), prostate ( $n = 57$ ), bronchus ( $n = 72$ ), haematological ( $n = 23$ ), urinary tract ( $n = 21$ ), gastrointestinal tract ( $n = 13$ ), unknown primary ( $n = 12$ ), other ( $n = 17$ )

*Sites of metastasis:* Malignant disease: thecal sac compression ( $n = 11$ ); spinal root compression ( $n = 6$ ); leptomeningeal metastases ( $n = 13$ ); lumbosacral plexus compression ( $n = 3$ ); vertebral body metastases ( $n = 5$ ). Other: radiation myelopathy ( $n = 3$ ); prolapsed intervertebral disc ( $n = 3$ ); cervical myelopathy ( $n = 7$ ); spinal stenosis ( $n = 7$ ); spinal cord atrophy ( $n = 1$ ); sacral cyst ( $n = 1$ ); no abnormality ( $n = 19$ )

continued

**Author: Husband 2001<sup>116</sup>**

*Performance status scores:* Not reported

*Visceral metastasis:* Not reported

*Duration and rapidity of cord compression:* Not reported

*Spinal level:*  $n$  = number of patients (total 15 + 160 + 71 = 246; i.e. some had SCC at more than one level: 161 patients had SCC in one region, 36 had it in two, and four had it in three regions)

Cervical – 15 (6%)

Thoracic – 160 (65%)

Lumbar/sacra – 71 (29%)

Other:

*Spinal instability:* Unclear

*Medications:* Not reported

**Intervention (i.e. Screening technologies):**

Plain radiographs of the whole spine were taken; for a POSITIVE diagnosis of SCC a consensus on image abnormality with consistent (i.e. compression at that level) neurological signs was required together with not having had radiotherapy to that level = MRI non-mandatory group. A positive X-ray test and previous radiotherapy to that level = MRI non-mandatory because of previous therapy group. A negative X-ray test = MRI mandatory group. MRI was carried out as soon as possible following admission, usually the same or the next day. MRI results scored for: presence of vertebral metastases, collapse, extradural disease, extradural SCC, paraspinal mass, intradural extramedullary SCC, and intramedullary metastases

**Outcomes:**

*List of potential prognostic factors examined:* The diagnostic performance of plain radiographs and neurological examination for the diagnosis of MSCC was compared with MRI (latter taken as gold standard), and specificity, sensitivity and positive and negative predictive values were calculated

*List of potential prognostic factors identified as significant:* Focal radiographic abnormalities with consistent neurological findings

*Have prognostic factors been validated in another population:* No

**Findings:**

The diagnostic performance of plain radiographs and neurological examination for the diagnosis of MSCC was compared with MRI, and specificity, sensitivity, and positive and negative predictive values were calculated. The primary tumour is not helpful in predicting which patients will have more than one site of compression, except that this is uncommon in tumours of haematological origin

**Author conclusions:**

Although focal radiographic abnormalities with consistent neurological findings, when present, accurately predicted the presence and level of MSCC, whole spine MRI is indicated in most patients with suspected MSCC because the additional information may alter the management plan. The primary tumour is not helpful in predicting which patients will have more than one site of compression, although this is uncommon in tumours of haematological origin

**Reviewer conclusions:**

Sensitivity of positive X-ray with consistent neurological finding was only 44%, specificity 98%, positive predictive value 98%, negative predictive value 44%. There appeared to be some numerical errors in this analysis. Note that predictive values are highly dependent on the prevalence of the condition in the population examined; here the prevalence was 69%, which tends to favour high positive predictive values and low negative predictive values

Author: Klekamp 1998<sup>17</sup>**Country:** Germany**Source of funding:** Not reported**Study design:***Type of study:* Observational study*Aims:* (1) Analyse which factors predict local recurrent disease (i.e. of spinal metastases), prolonged survival or a favourable postoperative neurological status in patients who have received surgery for spinal metastases*Secondary objectives:* (1) Provide a decision tree to aid in the treatment planning process for these patients*Length of study:* Not reported*Years of recruitment:* September 1977 to December 1996*Inclusion criteria:* Received surgery for spinal metastases*Exclusion criteria:* Unclear*Study arms (n):* One**Method:***Population characteristics:*

Number of participants selected: 101 patients with 106 spinal metastases that were treated by surgery

Number of participants analysed: 106 spinal metastases

Number of participants selected but not followed up: 0

*Sampling frame:* Nordstadt Hospital, Germany; patients in receipt of spinal tumour treatment ( $n = 740$ ) over specified period between September 1977 and December 1996*Method of sample selection:* 101 patients operated on in the Department of Neurosurgery, representing spinal metastases (106 metastases) during this period. This 106 represented 15% of all spinal tumours treated with surgery*Sex (M/F):* Not reported*Age of patients:*

Mean (SD) – 62 ± 12 years

Median – Not reported

Range – Not reported

*Interval from the time of diagnosis of cancer(s) to study entry:* Not reported*Interval from the time of diagnosis of spinal metastases to study entry:* 4.0 ± 6 months (2 days to 5 years)*Length of follow-up per patient:*

Mean (SD) – Unclear

Median – Unclear

Range – Unclear

*Cancer type(s):* Breast ( $n = 17$ ); prostate ( $n = 15$ ); thyroid ( $n = 9$ ); kidney ( $n = 12$ ); unknown primary tumour ( $n = 25$ ); lung ( $n = 17$ ); colon ( $n = 5$ ); melanoma ( $n = 2$ ); urogenital tract ( $n = 1$ ); pleural mesothelioma ( $n = 1$ ); teratoma ( $n = 1$ ); gallbladder ( $n = 1$ )*Sites of metastasis:* 12 cervical, 62 thoracic, 24 lumbar and 3 sacral metastases. 86.8% of metastases were located anterior to the spinal cord predominantly in the vertebral bodies. 5.7% of metastases were situated laterally and 7.5% posteriorly*Performance status scores:* Clinical course was documented using the Karnofsky score and a score system for symptoms (clinical scoring system, unclear if this was designed a priori or constructed and used post hoc)*Visceral metastasis:* Unclear

continued

**Author:** Klekamp 1998<sup>17</sup>

*Duration and rapidity of cord compression:* Not reported

*Spinal level:*

Cervical – 12

Thoracic – 62

Lumbar – 24

Other: 3 sacral

*Spinal instability:* 56 patients; instability = vertebral collapse/fracture, kyphosis, destruction of intervertebral joints

*Medications:* 'Adjuvant' therapy administered postoperatively to 60% (radiation ± hormone therapy/chemotherapy). All received surgery, various approaches and instrumentations used

**Intervention (i.e. screening technologies):**

*Preoperative:* plain X-rays, CT with bone windows of the affected spinal segment, and a myelogram with postmyelographic CT before MRI became available (MRI with gadolinium then replaced myelography)

**Outcomes:**

*List of potential prognostic factors examined:* Favourable tumour histology, a good general health status, no extraspinal metastases, cervical level, no instability, posterior approach, and male sex favourable, complete resection, low number of affected vertebral bodies, and elective surgery, adjuvant postoperative therapy, age, length of history

*List of potential prognostic factors identified as significant:* Predictors for a long recurrence-free interval were favourable tumour histology, a good general health status, cervical level, complete resection, low number of affected vertebral bodies and elective surgery

For survival, divided patients according to primary tumour type into long and short prognosis (basis for this not reported); found Kaplan–Meier survival much worse for the latter (unclear if classification was designed with investigators blind to survival data). Long postoperative survival was associated with favourable tumour histology, a good general health status, no extraspinal metastases, cervical level, no instability, posterior approach and male sex

*Have prognostic factors been validated in another population:* Unclear

**Findings:**

In all, 57.9% of spinal metastases recurred leading to neurological deterioration within 6 months after surgery (implying SCC), 69.3% within 1 year and 96% within 4 years (Kaplan–Meier method). Multiple regression analyses found long postoperative recurrence-free survival was associated with: favourable tumour histology (that is, tumours in the long survival prognosis group category), cervical level, low number of affected vertebral bodies, good general health status, and elective surgery [as distinct from emergency (70% received emergency surgery), complete resection at surgery]. Adjuvant postoperative therapy, length of history and age did not show a significant influence on local metastatic recurrence rate

**Author conclusions:**

(1) Patients in good health condition and living independently should undergo surgery for spinal metastasis if neurological symptoms are present. Postoperatively, adjuvant therapy should be initiated. (2) Patients with neurological symptoms but in poor condition requiring hospitalisation for their cancerous disease independent of spinal metastasis should not be operated on but should be offered radiotherapy and/or chemotherapy primarily. (3) Patients with spinal instability due to metastatic disease require stabilisation to achieve a satisfactory neurological outcome. However, a surgical procedure has to be tailored according to life expectancy and health status of patient. (4) Patients without neurological symptoms or instability should undergo radiotherapy primarily. (5) Patients who deteriorate after or despite primary radiotherapy may be candidates for surgery, but more complications and higher mortality rates should be expected

**Reviewer conclusions:**

Patient population spans two decades during which imaging and treatment modalities probably changed. Factors were identified that influence reappearance of spinal metastases after surgery; as these were associated with neurological deficit it is possible that these metastases develop to SCC or vertebral collapse, so the factors identified are also likely to be predictive of these

Author: Kuban 1986<sup>118</sup>**Country:** USA**Source of funding:** Not reported**Study design:***Type of study:* case series*Aims:* (1) To determine and analyse, with reference to primary tumour stage and differentiation, the interval between primary diagnosis and SCC, the interval between radiographic evidence of bony metastasis and cord impingement, and the survival period after spinal cord compromise*Length of study:* Not reported*Years of recruitment:* May 1975 to October 1983*Inclusion criteria:* Patients with biopsy-proved adenocarcinoma of the prostate*Exclusion criteria:* Simultaneous lung and bladder primary disease were excluded*Study arms (n):* One**Method:***Population characteristics:*

Number of participants selected: 41 patients with biopsy-proved adenocarcinoma of the prostate seen at the Eastern Virginia Medical School

Number of participants analysed: 41 patients with SCC secondary to adenocarcinoma of the prostate

Number of participants selected but not followed up: 0

*Sampling frame:* 611 patients with prostate cancer seen at the Eastern Virginia Medical School between May 1975 and October 1983*Method of sample selection:* Not clear*Sex (M/F):* 611 male/0 female*Age of patients:*

Mean (SD) – Not reported

Median – 68 years

Range – 50 to 90 years

*Interval from the time of diagnosis of cancer(s) to study entry:* Unclear – 33 patients died 0–27 months after the diagnosis of SCC*Interval from the time of diagnosis of spinal metastases to study entry:* Unclear*Length of follow-up per patient:*

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

*Cancer type(s):* Biopsy-proved adenocarcinoma of the prostate*Sites of metastasis:* Unclear*Performance status scores:* Unclear*Visceral metastasis:* Unclear*Duration and rapidity of cord compression:* Unclear

continued

**Author: Kuban 1986<sup>118</sup>**

*Spinal level:*

Cervical – 2 (4.9%)

Thoracic – 21 (51.2%)

Lumbar – 14 (34.1%)

Other: Cervical and thoracic – 1 (2.4%); cervicothoracic junction – 1 (2.4%); thoracic and lumbar – 2 (4.9%)

*Spinal instability:* Not reported

*Medications:* Not reported

**Intervention (i.e. screening technologies):**

Radioisotopic bone scans, plain films, and myelograms

**Outcomes:**

*List of potential prognostic factors examined:* Tumour stage

*List of potential prognostic factors identified as significant:* None

*Have prognostic factors been validated in another population:* No

**Findings:**

While the prognosis in MSCC, in general, is poor, the length of survival after diagnosis and treatment appears to depend on the tumour type, with prostatic carcinoma carrying an intermediate prognosis

**Author conclusions:**

Overall, tumour stage and differentiation were poor predictors of prognosis once a diagnosis of cord compression was established. MSCC secondary to adenocarcinoma of the prostate most frequently occurs in a thoracic location in patients with poorly differentiated disease at diagnosis. The mechanism of cord involvement appears to begin with osseous vertebral metastasis progressing to extradural compromise in a median interval that is independent of tumour grade. The prognosis following spinal cord involvement remains dismal in the majority of cases

**Reviewer conclusions:**

This paper did not look at predictive factors. Patients who were included had SCC

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Author: Levack 2002<sup>119</sup>**Country:** UK**Source of funding:** CRAG (Clinical Resource and Audit Group of the Scottish Office)**Study design:***Type of study:* Prospective observational study

*Aims:* In abstract – to report details concerning symptoms (especially pain) preceding the development of malignant cord compression; delays between onset/reporting of symptoms and confirmed diagnosis of malignant cord compression; accuracy of investigations carried out. In the background section – to assess the natural history of malignant cord compression from the onset of patient symptoms to the time of diagnosis. Also to document delays in the diagnosis of malignant cord compression, to analyse their duration and where they occurred and to examine the process of diagnosis from the general practitioner, hospital doctor and patient's perspectives

*Length of study:* Not reported*Years of recruitment:* January 1998 to April 1999*Inclusion criteria:* Patients had a definitive diagnosis of malignant cord or cauda equina compression – most often by MRI of the spine*Exclusion criteria:* This study did not include any patients who might have been suspected to have malignant cord compression, but were not referred for any imaging*Study arms (n):* One**Method:***Population characteristics:*

Number of participants selected: 319 (324 episodes of compression)

Number of participants analysed: 319 (324 episodes of compression)

Number of participants selected but not followed up: 0

*Sampling frame:* Three Scottish cancer centres – Edinburgh, Glasgow and Aberdeen*Method of sample selection:* Not reported*Sex (M/F):* 203 male/116 female*Age of patients:*

Mean (SD) – Not reported

Median – 65 years (80% of patients were aged &gt;50 years at diagnosis)

Range – Not reported

*Interval from the time of diagnosis of cancer(s) to study entry:* Not reported*Interval from the time of diagnosis of spinal metastases to study entry:* Not reported*Length of follow-up per patient:*

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

*Cancer type(s):* Primary tumours were lung, prostate and breast, which together accounted for 59% of all cases. Ten per cent (32) of tumours were from the gastrointestinal tract and a further 10% were of haematological origin (myeloma, lymphoma, chronic lymphatic leukaemia). In 23 cases (7%) the site of primary tumour was never identified

*Sites of metastasis:* Not reported*Performance status scores:* Not reported*Visceral metastasis:* Not reported

continued

Author: Levack 2002<sup>119</sup>

*Duration and rapidity of cord compression:* Not reported

*Spinal level:*

Cervical – 7%

Thoracic – 68%

Lumbar – 21%

Other – Sacral 4%; two or more concurrent compressive levels were identified in 55 out of 324 (17%) patients at imaging

*Spinal instability:* Not reported

*Medications:* Patients were taking strong opioids (no more details given)

**Intervention (i.e. screening technologies):**

MRI, plain films, isotope bone scintigraphy

**Outcomes:**

*List of potential prognostic factors examined:* Clinical symptoms such as pain (either spinal nerve root and/or localised back pain), walking, and sensation and urinary and bowel symptoms. Clinical signs such as weakness, sensory abnormalities, type of radiological screening

*List of potential prognostic factors identified as significant:* Weakness or difficulty in walking, altered sensation, urinary and bowel symptoms, neurological abnormalities, MRI

*Have prognostic factors been validated in another population:* No

**Findings:**

Pain was found not to be the predictive factor of malignant cord compression – there was considerable discordance between the level of pain and the structural level of compression. More than half of the patients (54%) with upper thoracic compression (T1–T6) had lumbosacral pain and conversely a similar proportion (54%) with proven lumbosacral compression had thoracic pain. Fewer than one in five patients (18%) were able to walk by the time a diagnosis was made. Patients commonly reported falls, and most patients (210/248; 85%) had noticed weakness or difficulty walking beforehand. The median duration of weakness was 20 days (IQR 7–132 days). There was no association between ability to walk and the patient's self-reported pain level. In particular, patients who reported a pain score of 10/10 were just as likely to walk without help as those with much lower pain scores

The majority of patients (168/248; 68%) had noticed altered sensation before the diagnosis of malignant cord compression, for a median of 12 days (IQR 4–41 days). One hundred and thirty-nine patients (56%) reported at least one problem with passing urine, one-quarter having urinary retention. Other symptoms include urinary incontinence (15%), frequency (6%), urgency (3%) and hesitancy (14%). One hundred and eighty-three (74%) patients reported bowel problems of which by far the commonest was constipation, in 164 patients (66%). Many of these patients were on moderate to strong opioids and the constipation was commonly attributed to medication. Five per cent reported faecal incontinence

The clinical level of sensory abnormality corresponded poorly with the level of cord compression identified on MRI, varying by up to 10 dermatomes below or above the compression level. 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 malignant cord compression, a sensory level was of value in identifying the level of compression in only 16% of the study group

The authors found a number of factors contributing to delays in diagnosis of SCC. Some of them were pain and general practitioner referral. Patients experienced pain (localised back and/or nerve root pain) for approximately 3 months (median = 90 days; IQR 37–205 days) before a definitive diagnosis was established and treatment given. From the point at which the patient reported their first relevant symptom to a health professional, it was approximately 2 months (median = 66 days, IQR 37–205 days;  $n = 152$ ) until a compressive syndrome developed that was recognised, definitively diagnosed and documented. The general practitioner referred approximately 3 weeks after the patient had first told them of their symptoms (median = 18 days; IQR 2–66 days). It was no faster for those patients known to have cancer at the time of telling their GP ( $p = 0.32$ ). A diagnosis of malignant cord compression was made a median time of 15 days after referral (IQR 3–66 days); so in a quarter of patients for whom this time interval was calculable, the diagnosis was made 2 months or more after referral. The rate of diagnosis of malignant cord compression increased through the week and was maximal on a Friday. Few patients were diagnosed and treated at the weekends (fig. 6), presumably reflecting the lack of access to MRI outside the working week

Author: Levack 2002<sup>119</sup>

Using the plain film sign of significant vertebral collapse (50% or more loss of vertebral height) as an indicator of malignant cord compression, 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. Thus in those patients who had plain films, the films obtained correctly predicted the subsequent level of compression in 21%. X-rays were often of an area that subsequently proved not to be the site of compression, but this was understandable considering that the sites of pain and of compression did not correspond. The most common request was for a lumbar spine X-ray, whereas the commonest site of compression was the thoracic spine

Using the site of greatest activity as the most likely level of compression, bone scintigraphy was also a poor predictor of the level of compression. Forty-nine examinations had spinal hot spots suggestive of extensive bone destruction, and in 26 of these the site of greatest activity correctly predicted the level of compression, as identified on MRI. Twenty suggested an incorrect level, and three had no confirmation. Overall scintigraphy correctly predicted the level of cord compression in 26/139 (19%) examinations. 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

**Author conclusions:**

Patients who develop spinal metastases were at risk of irreversible spinal cord damage. Weakness and sensory abnormalities were reported late and identified even later, despite patients having reported pain for a considerable time. Plain films and bone scans 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 was MRI. Certain categories of patients are at risk of malignant cord compression, in particular patients who are already known to have cancer when they first develop pain, are >50 years of age, and those with breast or prostate cancer with known bone metastases

**Reviewer conclusions:**

The paper looked at clinical symptoms, clinical signs and different screening technologies to find out which factors may predict risk of malignant cord compression accurately. Some clinical symptoms and signs were found to predict risk of malignant cord compression accurately. MRI was judged to be the best available technology in predicting risk of malignant cord compression

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**Author:** Loblaw 2005<sup>62</sup>

**Country:** Canada

**Source of funding:** Supported by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care

**Study design:**

*Type of study:* Systematic review

*Aims:* (1) Describes the diagnosis and management of adult patients with a suspected or confirmed diagnosis of extradural malignant SCC

*Objectives:* (1) What are the clinical symptoms of malignant SCC? (2) What is the optimal approach for investigating suspected malignant SCC? (3) Is there a role for systemic corticosteroids in the management of malignant SCC, and if there is, what is the optimal dose? (4) What are the indications for surgery in the management of malignant SCC? (5) What are the indications for radiotherapy in the management of malignant SCC? (6) Is there an optimal dose prescription for radiotherapy? (7) What are the treatment options for recurrent malignant SCC in an area previously irradiated?

**Findings:**

Symptoms for SCC include sensory changes, autonomic dysfunction and back pain; however, back pain was not predictive of SCC. Sensitivity and specificity for MRI ranged from 0.44 to 0.93 and 0.90 to 0.98, respectively, in diagnosis of SCC. Sensitivity and specificity for myelography ranged from 0.71 to 0.97 and 0.88 to 1.00, respectively

Predictive risk models were presented that aimed to define a population of patients at higher risk of developing cord compression; these included:

Loblaw DA, Laperriere NJ, Mackillop WJ. A population-based study of malignant spinal cord compression in Ontario cancer patients. *Clin Oncol (R Coll Radiol)* 2003;**15**:211–17

Bailey A, Milosevic M, Blend R, Logue J, Gospodarowicz M, Boxen I, *et al.* A prospective study of factors predicting clinically occult spinal cord compression in patients with metastatic prostate cancer. *Cancer* 2001;**92**:303–10

Loblaw DA, Laperriere NJ, Mackillop WJ. Who should be screened for malignant spinal cord compression? Defining a high-risk population. *Clin Invest Med* 2000;**23**:S23

Talcott JA, Stomper PC, Drislane FW, Wen PY, Block CC, Humphrey CC, *et al.* Assessing suspected SCC: A multidisciplinary outcomes analysis of 342 episodes. *Support Care Cancer* 1999;**7**:31–8

Talcott *et al.* performed a multivariate analysis of patient, radiographic and neurological factors of 342 CT scans in 258 patients to predict patients at highest risk for SCC. Six predictive risk factors for SCC were found, including increased deep tendon reflexes, inability to walk, compression fractures on radiographs of spine, bone metastases diagnosed more than 1 year earlier, bone metastases present and age <60 years

**Author conclusions:**

Predictive risk models may help define patients at higher risk of developing cord compression, but optimal screening strategy, population and intervention have not been elucidated. Back pain was not predictive of SCC. Treatment for patients with malignant SCC should consider presence of bony compression and spinal instability comorbidities, pretreatment ambulatory status, technical surgical factors, potential RT reactions, patient preferences and potential surgical complications

**Reviewer conclusions:**

Different factors such as 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 <60 years were found to be some of the predictive risk factors for malignant SCC. Back pain was found not to be predictive of malignant SCC

**Author:** Lu 1998<sup>120</sup>**Country:** USA**Source of funding:** National Institute for Health Training Grant**Study design:***Type of study:* Retrospective analysis/study*Aims:* (1) Examine potential clinical risk factors in breast cancer patients with suspected SCC*Length of study:* Not reported*Years of recruitment:* February 1985 to September 1988*Inclusion criteria:* Patients with suspected SCC*Exclusion criteria:* Any patients previously diagnosed with SCC or those not suspected of SCC*Study arms (n):* One**Method:***Population characteristics:*

Number of participants selected: Unclear – 405 episodes were initially identified

Number of participants analysed: 123 episodes of suspected SCC among 93 patients

Number of participants selected but not followed up: Unclear

*Sampling frame:* All patients from a radiology department in Boston*Method of sample selection:* Unclear*Sex (M/F):* 93 females 10 males*Age of patients:*

Mean (SD) – Not reported

Median – 52.9 years

Range – 29.8–77.3 years

*Interval from the time of diagnosis of cancer(s) to study entry:* 3.8 years (range 0.1–17.1 years)*Interval from the time of diagnosis of spinal metastases to study entry:* Not reported*Length of follow-up per patient:*

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

*Cancer type(s):* Breast*Sites of metastasis:* Not clear; 98% and 89% of patients, respectively, had known metastatic and vertebral disease. At the time of diagnosis, 40% of patients had lymph node involvement. The cancer has also metastasised to bone (table 1)*Performance status scores:* Not clear*Visceral metastasis:* Not clear*Duration and rapidity of cord compression:* All patients suspected of SCC – 123 episodes of suspected SCC. Most patients had a single episode of suspected SCC (range 1–4 episodes)

continued

Author: Lu 1998<sup>120</sup>

*Spinal level:*

Cervical – 6%

Thoracic – 67%

Lumbar – 55%

Other: Sacral – 3%

*Spinal instability:* Not clear

*Medications:* Not reported

**Intervention (i.e. screening technologies):**

Spinal CT scans, MRI scans, myelograms and spine radiographs. Please note MRI became available on a limited basis during the study period and was reserved for infrequent cases of uncertainty after CT scanning and for occasional patients with poorly localised signs and symptoms of metastatic epidural SCC

**Outcomes:**

*List of potential prognostic factors examined:* Age >50 years; tumour grade; oestrogen receptor status; prior response to chemotherapy; known bone metastases; known bone metastases  $\geq 3$  months; known bone metastases  $\geq 6$  months; known bone metastases  $\geq 1$  year; known bone metastases  $\geq 2$  years; known vertebral metastases; known vertebral metastases  $\geq 3$  months; known vertebral metastases  $\geq 6$  months; known vertebral metastases  $\geq 1$  year; known vertebral metastases  $\geq 2$  years; known metastases (any site)  $\geq 2$  years; metastatic breast cancer at initial diagnosis; prior spine radiography at suspected site (> 1 year); prior spine radiography at non-suspected site; symptoms – local pain, ambulatory, subjective weakness; signs – objective weakness, increased deep tendon reflexes, abdominal plantar reflex, decreased sphincter tone or distended bladder, objective sensory deficit; radiological features – vertebral compression fracture on spine radiograph; results of prior bone scans – benign or normal

*List of potential prognostic factors identified as significant:* known bone metastases  $\geq 2$  years; metastatic disease at initial diagnosis; objective weakness; vertebral compression fracture on spine radiograph

*Have prognostic factors been validated in another population:* Not clear

**Findings:**

Univariate analysis: assessed potential oncological, neurological and radiological predictors of an index CT scan revealing TSC. The significant predictors among the clinical oncological features were known bone or vertebral metastases  $\geq 1$  year, metastatic breast cancer at initial diagnosis and prior spine radiotherapy. Similarly, the significant predictors among the neurological features were objective weakness, increased deep tendon reflexes and abnormal plantar reflex. It is reported that even the most highly associated neurological feature, objective weakness, had limited positive predictive value (40%) and specificity (67%). Vertebral compression fracture on spine radiograph was significantly associated with TSC whereas the broader category of any abnormalities consistent with metastases was not

Multiple logistic regression analysis: Four independent predictors of TSC were identified and included oncological features [known bone metastases  $\geq 2$  years (OR 3.0, 95% CI 1.2 to 7.6;  $p = 0.02$ ; metastatic disease at initial diagnosis (OR 3.4, 95% CI 1.0 to 11.4;  $p = 0.05$ )] in addition to neurological and radiological features [objective weakness (OR 3.8, 95% CI 1.5 to 9.5;  $p = 0.005$ ), vertebral compression fracture on spine radiograph (OR 2.6, 95% CI 1.0 to 6.5;  $p = 0.05$ )]. These four predictors stratified episodes into subgroups with widely varying risks of TSC, ranging from 12% (0 risk factors) to 85% ( $\geq 3$  risk factors)

**Author conclusions:**

The results suggest that evaluation of breast cancer patients with suspected SCC might include clinical information about disease course in addition to neurological examination and previous imaging studies. If confirmed, these predictors may help clinicians to assess risk in this patient population

**Reviewer conclusions:**

Different neurological and radiographic features can be used to predict or assess risks in patients with breast cancer suspected of SCC

Author: Lu 2005<sup>121</sup>**Country:** USA**Source of funding:** Supported in part by the National Institutes of Health training grant**Study design:***Type of study:* Prospective study*Aims:* (1) To identify independent clinical predictors of SCC in cancer patients through the analysis of potential risk factors based on spine MRI*Length of study:* Unclear*Years of recruitment:* July 1998 to March 1999*Inclusion criteria:* Pathologically confirmed cancer diagnosis (by physician), no metastatic epidural cancer over previous 12 months, age  $\geq 18$  years, consent by the patient to a brief interview within 7 days of the scan, cancer patients with suspected SCC who were evaluated by MRI*Exclusion criteria:* Not given. (Patients not meeting these criteria were excluded)*Study arms (n):* One**Method:***Population characteristics:*

Number of participants selected: 134 patients

Number of participants analysed: 136 episodes of suspected SCC among 134 cancer patients evaluated with spine MRI

Number of participants selected but not followed up: Unclear

*Sampling frame:* Spine MRI scan records from two large hospitals*Method of sample selection:* Unclear*Sex (M/F):* Not reported*Age of patients:*

Mean (SD) – Not reported

Median – 61.5 years

Range – 30.9–84.8 years

*Interval from the time of diagnosis of cancer(s) to study entry:* 1.3 years (range 0–19.4 years)*Interval from the time of diagnosis of spinal metastases to study entry:**Length of follow-up per patient:*

Mean (SD) – Unclear

Median – Unclear

Range – Unclear

*Cancer type(s):* Breast ( $n = 33$ ; 24%), lung ( $n = 33$ ; 24%), prostate ( $n = 21$ ; 15%), non-Hodgkin's lymphoma ( $n = 8$ ; 6%), multiple myeloma ( $n = 6$ ; 4%), others ( $n = 35$ , 26%)*Sites of metastasis:* Bone metastases [all:  $n = 89$  (65%);  $>6$  months:  $n = 40$  (29%);  $>1$  year:  $n = 34$  (25%);  $>2$  years:  $n = 16$  (12%)]; vertebral metastases [all:  $n = 76$  (56%);  $>6$  months:  $n = 28$  (21%);  $>1$  year:  $n = 22$  (16%);  $>2$  years:  $n = 10$  (7%)]*Performance status scores:* Not reported*Visceral metastasis:* Unclear*Duration and rapidity of cord compression:* all participants suspected of SCC

continued

Author: Lu 2005<sup>121</sup>

*Spinal level:*

Cervical – 6%

Thoracic – 64%

Lumbar – 30%

Other: Sacral – 6%

*Spinal instability:* Unclear

*Medications:* Not reported. However, there is information regarding treatment patient received after MRI of the spine. The 50 episodes of TSC received treatment. Forty-four (88%) received subsequent treatment for TSC (spine radiotherapy, 66%; systemic chemotherapy, 14%; surgery, 8%)

**Intervention (i.e. screening technologies):**

MRI of the spine (the scans were interpreted by attending neuroradiologists) – sagittal T1 and/or T2-weighted images of the spine with selected axial images at the discretion of the staff neuroradiologist

**Outcomes:**

*List of potential prognostic factors examined:* Inpatient status, back pain (and seven subtypes of back pain), difficulty walking, bowel or bladder incontinence, abnormal neurological findings, spinal tenderness, weakness, difficulty walking (physician reported), sensory loss, increased deep tendon reflexes, four oncological features)

*List of potential prognostic factors identified as significant:* Four independent predictors of TSC were identified and included information from the neurological examination (abnormal neurological examination), stage IV cancer at initial diagnosis, subject-reported symptoms (middle or upper back pain), and the oncological history (known vertebral metastases and metastatic disease at initial diagnosis)

*Have prognostic factors been validated in another population:* Not clear

**Findings:**

The four 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)

**Author conclusions:**

Results confirmed earlier retrospective studies indicating that evaluation of cancer patients with suspected SCC should be based on clinical information that includes cancer-related history, symptom data and presence of pertinent neurological signs. Predictors may help clinicians to assess risk in this patient population

**Reviewer conclusions:**

The identified risk factors need to be tested in other populations so as to determine their reproducibility and generalisability

Author: McCloskey 1993<sup>122</sup>**Country:** UK**Source of funding:** Breast Cancer Research Trust and by Huhtamaki Oy Leiras**Study design:***Type of study:* Prospective study criteria developed for the presence of vertebral deformity, derived from the controls, were applied to assess the prevalence of vertebral deformity in patients with skeletal metastases from breast cancer*Aims:* (1) To develop a robust radiological method to assess vertebral deformity in women that might be useful for studies investigating the incidence and prevalence of vertebral deformity consequent to osteoporosis*Length of study:* Not reported*Years of recruitment:* Not reported*Inclusion criteria:* Controls: patients with no history of back pain or osteoporotic fracture at vertebral or non-vertebral sites. Cases: patients with skeletal metastases from breast cancer*Exclusion criteria:* None had a history of back pain or osteoporotic fracture at vertebral or non-vertebral sites*Study arms (n):* Two**Method:***Population characteristics:*

Number of participants selected: 100 normal women (controls) and 163 women with skeletal metastases from breast cancer

Number of participants analysed: 100 normal women (controls) and 163 women with skeletal metastases from breast cancer

Number of participants selected but not followed up: 41 (i.e. of the 163 women with skeletal metastases from breast cancer, 122 were studied again 6 months later to assess the incidence of vertebral deformity)

*Sampling frame:* Controls elected randomly from the age–sex register of a general practice population and invited for screening with a response rate of 79%*Method of sample selection:* Patients selected randomly from the register of a general practice population*Sex (M/F):* 100% female*Age of patients:*

Mean (SD) – Controls not reported; cancer group = 59 years

Median – Not reported

Range – Controls = 45–50 years; Cancer group = 30–75 years

*Interval from the time of diagnosis of cancer(s) to study entry:* Not reported*Interval from the time of diagnosis of spinal metastases to study entry:* Not reported*Length of follow-up per patient:*

Mean (SD) – Unclear

Median – Not reported

Range – Not reported

*Cancer type(s):* Breast*Sites of metastasis:* Skeletal metastases; inadequate information*Performance status scores:* Not reported*Visceral metastasis:* No information

continued

**Author: McCloskey 1993<sup>122</sup>**

*Duration and rapidity of cord compression:* Not reported

*Spinal level:*

Cervical – Unclear

Thoracic – Unclear

Lumbar – Unclear

Other – Unclear

*Spinal instability:* Unclear

*Medications:* Not reported

**Intervention (i.e. screening technologies):**

Different vertebral heights and vertebral anatomical shape at different vertebral levels are measured using radiographs. Normal ranges for vertebral shape were obtained from radiographs in 100 women aged 45–50 years. These included ranges for ratios of anterior/posterior, central/posterior and P/PP vertebral heights from T4 to L5. PP was calculated from adjacent vertebrae. Prevalence and incidence of vertebral deformity using different criteria were then compared in a series of women with skeletal metastases from breast cancer in whom radiographs were obtained 6 months apart

**Outcomes:**

*List of potential prognostic factors examined:* Posterior vertebral heights

*List of potential prognostic factors identified as significant:* Posterior vertebral heights

*Have prognostic factors been validated in another population:* Unclear

**Findings:**

Using a cut-off of 3 SDs, prevalence of vertebral deformity in women with breast cancer was 46%. For normal ranges for vertebral height and shape: (1) ratio of actual to predicted posterior height was normally distributed with a mean of 1.00; (2) standard deviations of the P/PP ratio were similar whether PP was derived from one adjacent or from four adjacent vertebrae

**Author conclusions:**

The technique developed for assessment of vertebral deformities is robust and rapid, and has minimal effects on sensitivity while maximising specificity. The method was able to detect minor vertebral deformities which subsequently progress and there is a close relationship between existence of deformities and subsequent rate of deformity in breast cancer

**Reviewer conclusions:**

X-rays coupled with vertebral measurements and the use of the criteria developed by the authors allowed highly specific detection of vertebral deformity in women with breast cancer and skeletal metastases. Such detection before the development of frank neurological involvement could be useful. X-ray of the spine is not now used in the comprehensive way reported in this study and whether the procedures developed could be applied using CT or MRI images is uncertain

Author: Oka 2006<sup>123</sup>**Country:** Japan**Source of funding:** Not reported**Study design:***Type of study:* Retrospective cohort study*Aims:* (1) To provide basic data on the incidence of bone and spinal metastases and SCC in Japanese breast cancer patients treated with endocrine or chemotherapy following primary surgery in a single institution; (2) to calculate the survival rate after breast surgery, bone or spinal metastasis, and paralysis due to cord compression using the Kaplan–Meier method; and (3) to determine the prognostic factors after bone metastases and development of paralysis*Length of study:* It is mentioned that postoperative survival rates up to June 2001 were calculated for these breast cancer patients using the Kaplan–Meier method; maximum follow-up (January 1990 to June 2001) was about 11 years*Years of recruitment:* January 1990 to December 1996*Inclusion criteria:* Patients had undergone radical surgery for breast cancer at Tokyo Metropolitan Komagome Hospital*Exclusion criteria:* Unclear*Study arms (n):* One**Method:***Population characteristics:*

Number of participants selected: 695

Number of participants analysed: 695

Number of participants selected but not followed up: 0

*Sampling frame:* Purposive sample*Method of sample selection:* All patients undergoing radical surgery for breast cancer at Tokyo Metropolitan Komagome Hospital between January 1990 and December 1996*Sex (M/F):* 4 male/691 female*Age of patients:*

Mean (SD) – 53.1 years

Median – Not reported

Range – 24–88 years

*Interval from the time of diagnosis of cancer(s) to study entry:* Not reported*Interval from the time of diagnosis of spinal metastases to study entry:* Not reported*Length of follow-up per patient:*

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

*Cancer type(s):* Breast. Also note that of 39 female patients with bilateral breast cancers, 15 had synchronous cancers, and the remaining 24 had metachronous cancers. Forty-two patients had other concurrent cancer*Sites of metastasis:* Node involvement (N0:  $n = 377$ , N1:  $n = 232$ , N2:  $n = 52$ , N3:  $n = 9$ , N4:  $n = 2$ , unknown:  $n = 23$ ); metastases to axillary lymph nodes (positive:  $n = 295$ , negative:  $n = 377$ , unknown:  $n = 23$ ); metastases to viscera (positive:  $n = 103$ ; negative:  $n = 592$ ); metastases to bone (positive:  $n = 148$ , negative:  $n = 547$ ); metastases to spine (positive:  $n = 121$ , negative:  $n = 574$ )*Performance status scores:* Performance status at baseline of only 17 patients who developed paralysis after treatment is given. The score ranged between 1 and 2, of which majority of them had the latter

continued

Author: Oka 2006<sup>123</sup>

*Visceral metastasis:*  $n = 103$  had visceral metastases at baseline;  $n = 592$  had no visceral metastases

*Duration and rapidity of cord compression:* Unclear

*Spinal level:*

Cervical – Unclear

Thoracic – Unclear

Lumbar – Unclear

Other: metastases to spine (positive:  $n = 121$ , negative:  $n = 574$ )

*Spinal instability:* Unclear

*Medications:* Patients who had both oestrogen receptors and progesterone receptors received endocrine therapy as an initial adjuvant therapy; those without oestrogen and progesterone receptors received chemotherapy; and when metastasis to other organs including bone was identified, patients received chemotherapy

#### **Intervention (i.e. screening technologies):**

Bone scintigraphy, chest radiograph, chest CT, liver ultrasonography, abdominal CT, cranial CT or MRI (or any combination thereof)

#### **Outcomes:**

*List of potential prognostic factors examined:* (1) TNM classification; (2) N stage classification; (3) presence or absence of metastases to lymph nodes; (4) presence or absence of metastases to important organs; (5) complication by other carcinomas; (6) presence or absence of oestrogen receptors; (7) presence or absence of progesterone receptors; (8) presence or absence of bone metastases

*List of potential prognostic factors identified as significant:* Prognostic factors for bone metastases were visceral metastases and progesterone receptor status. Cord compression was observed in 17 of the 148 patients, with the thoracic spine being the most common

*Have prognostic factors been validated in another population:* Not reported

#### **Findings:**

*Frequency of bone metastases:* After surgical treatment of breast cancers, bone metastases developed in 18.1% of the patients over 5 years and in 24.7% of the patients over 10 years

Bone metastases were observed in 148 patients at the end of the observation period (all received chemotherapy, 44 of them had endocrine therapy before the metastases developed)

*Survival rate:* The interval between surgical treatment and the development of bone metastases ranged from 0 to 130 months (median 19 months). After surgery, the 1-, 2-, 3-, 4-, and 5-year survival rates of patients with bone metastases were 96.6%, 78.3%, 68.4%, 53.3% and 45.8%, respectively. In patients without bone metastases, postoperative survival rates were 99.6%, 97.1%, 94.6%, 92.9% and 89.9%, respectively

After the development of the metastases, the 6-month and 1-, 2-, 3-, 4- and 5-year survival rates were 81.6%, 66.3%, 42.3%, 34.2%, 29.5% and 26.1%, respectively

*Multivariate analysis*

*Prognostic factors for breast cancer:* The analysis showed that the prognostic factors for survival (after surgery) were tumour stages evaluated by TNM classification (HR 1.346, 95% CI 1.099 to 1.648;  $p = 0.004$ ), N stage classification (HR 1.524, 95% CI 1.030 to 2.257;  $p = 0.03$ ), the presence or absence of metastases to axillary lymph nodes ( $p = 0.03$ ), presence or absence of metastases to important organs (HR 3.356, 95% CI 2.226 to 5.060;  $p < 0.0001$ ), presence or absence of oestrogen receptors (HR 1.686, 95% CI 1.102 to 2.580;  $p = 0.02$ ), presence or absence of progesterone receptors (HR 1.954, 95% CI 1.274 to 2.997;  $p = 0.002$ ), and the presence or absence of bone metastases (HR 3.704, 95% CI 2.415 to 5.682;  $p < 0.0001$ )

*Prognostic factors for survival after development of bone metastases:* The factors were the presence or absence of metastases to important organs (HR 2.379, 95% CI 1.484 to 3.815;  $p = 0.0003$ ) and the presence or absence of progesterone receptors (HR 2.689, 95% CI 1.553 to 4.657;  $p = 0.0004$ )

*Risk factors for development of bone metastases:* The factors were tumour stages evaluated by TNM classification (HR 1.615, 95% CI 1.322 to 1.973;  $p < 0.0001$ ), N stage classification (HR 2.128, 95% CI 1.381 to 3.279;  $p = 0.0006$ ), the presence or absence of metastases to axillary lymph nodes ( $p = 0.0006$ ), and the presence or absence of metastases to important organs (HR 7.502, 95% CI 5.100 to 11.036;  $p < 0.0001$ )

*Profiles of patients with paralysis due to cord compression:* At the end of the observation period, spinal metastases were observed in 121 of 148 patients with bone metastases; paralysis due to cord compression developed in 17 of these 121. Statistically, there were no factors significantly associated with the prognosis of breast cancer patients with paralysis due to cord compression

Author: Oka 2006<sup>123</sup>

**Author conclusions:**

Reported the incidence and prognostic factors for Japanese breast cancer patients with bone and spinal metastases. To detect a predictive factor of long survival after paralysis and establish indications for surgery, a comparative study among large groups of patients with paralysis and with different backgrounds is needed

**Reviewer conclusions:**

The prognostic factors for development of bone metastases were: tumour stage (TNM classification), N stage classification, metastases to axillary lymph nodes and visceral metastases. Risk factors for survival after development of bone metastases were visceral metastases and presence of progesterone receptors

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**Author:** Plunkett 2000<sup>24</sup>

**Country:** UK

**Source of funding:** Not reported

**Study design:**

*Type of study:* A retrospective analysis/study

*Aims:* (1) To identify factors that predict complications from skeletal disease in patients with bone metastases from advanced breast cancer

*Length of study:* From figure 1, it seems they were followed for up to 10 years. (The figure has been reproduced; see Figure 10)

[‘Survival from diagnosis of bone metastases’ was calculated from the date of diagnosis of bone metastases to the date of death. Patients still alive at the time of analysis were censored at the date they were last known to be alive. ‘Time to fracture’ was calculated from the date of diagnosis of bone metastases to the date of fracture. Patients who were alive without fracture were censored at the date they were last known to be alive. Patients who had died without evidence of fracture were censored at the date of death]

*Years of recruitment:* 1975–91

*Inclusion criteria:* Patient with adequate details of tumour characteristics – number of biological features such as histological grade and steroid receptor status, details of metastatic involvement, response to treatment and survival

*Exclusion criteria:* Patients whose only evidence indicative of bone metastases was an abnormal bone scan without any corroborative radiological changes were excluded

*Study arms (n):* Four – based on the sites of disease at diagnosis of skeletal metastases: (1) bone disease only; (2) bone and soft tissue disease; (3) bone and pleuropulmonary disease; and (4) bone and liver disease

**Method:**

*Population characteristics:*

Number of participants selected: 1437 patients were identified from the database

Number of participants analysed: 859 patients who developed bone metastases from breast cancer

Number of participants selected but not followed up: 578 [460 (32%) were diagnosed elsewhere and 111 (8%) were followed up at other hospitals, so insufficient information was available for inclusion in the analysis. The notes for seven patients (0.5%) could not be found]

*Sampling frame:* All patients attending the Breast Unit at Guy’s Hospital who developed bone metastases between 1975 and 1991 from a database

*Method of sample selection:* Unclear; patients meeting inclusion criteria were selected from the database

*Sex (M/F):* Unclear; presumably all female patients

*Age of patients:*

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

*Interval from the time of diagnosis of cancer(s) to study entry:* Not reported

*Interval from the time of diagnosis of spinal metastases to study entry:* Not reported

*Length of follow-up per patient:*

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

*Cancer type(s):* Breast

*Sites of metastasis:* Patients divided into four groups based on the sites of disease at the time bone metastases were diagnosed (1) bone metastases only ( $n = 243$ , 28%); (2) bone and soft tissue disease only ( $n = 268$ , 31%); (3) bone and pleuropulmonary disease, with or without soft tissue disease ( $n = 237$ , 28%); (4) bone and liver metastases, with or without soft tissue or pleuropulmonary disease ( $n = 111$ , 13%)

Author: Plunkett 2000<sup>24</sup>*Performance status scores:* Not reported

*Visceral metastasis:* Inadequate information; patients have been divided into groups based on the sites of disease at the time bone metastases were diagnosed and one of the groups was 'bone and liver metastases, with or without soft tissue or pleuropulmonary disease'. Thirteen per cent of the patients constitute this group. Therefore there were few patients where the disease had metastasised to liver and lungs

*Duration and rapidity of cord compression:* Not reported*Spinal level:*

Cervical – Unclear

Thoracic – Unclear

Lumbar – Unclear

Other – Unclear

*Spinal instability:* Unclear

*Medications:* Majority received endocrine therapy as the first systemic treatment following the diagnosis of bone metastases. Patients in the other groups may have received systemic treatment for recurrent disease at other sites before the diagnosis of bone metastases. The authors have not mentioned the use of bisphosphonates in the paper. However, in the discussion section, they mentioned that 'the results might be used to select patients for treatment with bisphosphonates and could improve the cost–benefit analysis'

**Intervention (i.e. screening technologies):**

Bone scans, radiographs, histology

**Outcomes:**

*List of potential prognostic factors examined:* Bone scan evidence of metastases, patient groups: bone only ( $n = 243$ ); bone and soft tissue ( $n = 268$ ); bone and pleuropulmonary ( $n = 237$ ); bone and liver ( $n = 111$ )

*List of potential prognostic factors identified as significant:* Bone only

*Have prognostic factors been validated in another population:* Not reported

**Findings:**

Survival from diagnosis of bone metastases was significantly greater for patients with bone disease only at diagnosis of skeletal metastases ( $p < 0.001$ ). The survival from diagnosis of bone metastases was shortest for patients with concomitant liver metastases (median survival: 5.5 months). Survival from the diagnosis of bone metastases did not vary during the study period (data not shown)

The time to vertebral fracture was shortest in the bone only group ( $p < 0.0017$ )

There were no differences between the groups in the time to pathological long bone fractures. However, since patients with bone disease only at diagnosis of skeletal disease lived longest, most fractures occurred in this group. Of a total of 243 such patients, 42 (17%) developed a pathological long bone fracture (i.e. 1 in 5.8 patients), compared with 5 of 111 (5%) patients with bone and liver disease (i.e. 1 in 22.2 patients). The relationship between long bone fracture and bone scan findings was examined. Patients with bone scan evidence of deposits in the femora or humeri at diagnosis of bone metastases were significantly more likely than other patients to fracture these bones ( $p < 0.0001$ ). Patients with bone scan evidence of metastases in the femur or humerus were divided according to the presence of osteolytic disease in these bones on plain radiographs. Patients with bone-only disease developed SCC more rapidly than patients in other groups ( $p = 0.01$ ; data not shown). Thirty-six patients with bone-only disease at diagnosis of bone metastases (15%) developed cord compression compared with 2–6% of patients in the other groups

Bone scan evidence of metastases in the spine did not predict for subsequent development of cord compression (data not shown)

**Author conclusions:**

The results suggest that patients with disease confined to the skeleton at the diagnosis of bone metastases are most likely to develop skeletal-related complications from advanced breast cancer. Such patients may benefit most from treatment with bisphosphonates

**Reviewer conclusions:**

The study does not give detailed information regarding participants – age, time since diagnosis. It is also not clear whether participants used any bisphosphonates (it seems they have not) during the study

Author: Rose 2009<sup>88</sup>**Country:** USA**Source of funding:** Not reported**Study design:***Type of study:* Prospective study*Aims:* (1) Evaluate prospectively obtained MRI/CT imaging studies for post-treatment (single-fraction IG-IMRT) fracture development and tumour recurrence*Primary outcome:* (1) Development of a new fracture or progression of an existing fracture at the site of treatment (fracture progression) obtained from prospectively obtained imaging*Secondary outcomes:* (1) Pain (as measured on a 10-point scale), (2) American Spinal Injury Association (ASIA) impairment scale assessment of neurological function, (3) Karnofsky performance score, (4) narcotic use and (5) tumour recurrence*Length of study:* Not reported*Years of recruitment:* Not reported*Inclusion criteria:* Unclear – cohort of patients prospectively followed after undergoing single-fraction IG-IMRT for solid organ metastases to the spine*Exclusion criteria:* Patients with prior surgery of radiation therapy to the region of interest or high-grade epidural compression were excluded from this analysis*Study arms (n):* One**Method:***Population characteristics:*

Number of participants selected: The study included 71 treated lesions in 62 patients

Number of participants analysed: 62

Number of participants selected but not followed up: 0

*Sampling frame:* Patients undergoing single-fraction IG-IMRT for histologically confirmed solid tumour metastases – although not reported in the study, may be patients attending authors' institution*Method of sample selection:* Not reported*Sex (M/F):* 38 male/24 female*Age of patients:*

Mean (SD) – 62 years

Median – Not reported

Range – Not reported

*Interval from the time of diagnosis of cancer(s) to study entry:* Not reported*Interval from the time of diagnosis of spinal metastases to study entry:* Not reported*Length of follow-up per patient:*

Mean (SD) – Not reported

Median – 13 months; median follow-up time among patients who were alive at the time of analysis was 19 months

Range – Not reported

*Cancer type(s):* Renal cell  $n = 14$ ; melanoma  $n = 9$ ; prostate  $n = 9$ ; sarcoma  $n = 7$ ; colorectal  $n = 6$ ; cholangiocarcinoma  $n = 5$ ; thyroid  $n = 5$ ; NSCLC  $n = 5$ ; breast  $n = 4$ ; other  $n = 7$ *Sites of metastasis:* Spine (cervical, thoracic and lumbosacral region); other sites unclear*Performance status scores:* The median Karnofsky performance score at the time of treatment was 90%

Author: Rose 2009<sup>88</sup>*Visceral metastasis:* Not reported*Duration and rapidity of cord compression:* Not clear*Spinal level:*

Cervical – 6 lesions were located in the cervical spine (9%)

Thoracic – 47 in the thoracic spine (66%)

Lumbar – 18 in the lumbosacral spine (25%)

Other – 46 sites were lytic (65%), 13 were sclerotic (18%) and 12 were mixed (17%)

*Spinal instability:* Twenty-six lesions (37%) occupied 0–20% of the vertebral body, 18 lesions (25%) occupied 21–40%, 10 lesions (14%) occupied 41–60%, seven lesions (10%) occupied 61–80%, and 10 lesions (14%) occupied >80%*Medications:* Twenty-eight of 62 patients received bisphosphonate therapy (not reported which one) within 6 months of vertebral IG-IMRT; 32 of 62 patients were using narcotics for pain control**Intervention (i.e. screening technologies):**

All patients had spinal MRI or CT myelogram before treatment. The patients were examined clinically and radiographically 8 weeks post-treatment and at 3- to 4-month intervals thereafter on an institutional review board-approved treatment protocol until hospice admission or death

**Outcomes:***List of potential prognostic factors examined:* location of the lesion; size of the lesion (tumour occupancy in vertebral body); type of lesion – lytic, sclerotic or mixed; appearance of the lesion in CT; obesity; local kyphosis; bisphosphonate use; IG-IMRT radiation dose; presence of baseline fracture; histology of fracture*List of potential prognostic factors identified as significant:* CT appearance, lesion location and the amount of vertebral body occupied by tumour independently predicted fracture progression. Lesions located between T10 and sacrum and lytic lesions more likely to fracture*Have prognostic factors been validated in another population:* No**Findings:**

Fracture progression was found in 27 vertebral bodies (39%). Multivariate logistic regression analysis showed CT appearance, lesion location and amount of vertebral body occupied by tumour independently predicted fracture progression. Lesions located between T10 and the sacrum were 4.6 times more likely to fracture than were lesions above T10 (95% CI 1.1 to 19.7 times more likely). Lytic lesions were 6.8 times more likely to fracture than were sclerotic and mixed lesions (95% CI 1.4 to 33.3 times more likely). As amount of vertebral body occupied by tumour increased, the odds of fracture increased

Obesity, local kyphosis, bisphosphonate use and IG-IMRT radiation dose were not associated with increased risk. The presence of baseline fracture was not associated with new fracture development or progression. There was no clear correlation between histology and risk of fracture

Median time to fracture was 25 months. The median time to fracture in lytic lesions was 19 months while the median time in sclerotic and mixed lesions was 32 months ( $p < 0.05$ ). By stratifying lesions according to location, median time to fracture changed significantly. The median time to fracture with lesions between T10 and the sacrum was 20 months and it was 35 months for lesions located higher in the spine ( $p < 0.05$ ). Stratification according to the amount of the vertebral body occupied by the lesion also resulted in significantly different fracture probability functions ( $p < 0.02$ ). In the multivariate proportional hazards regression model, only lytic appearance (HR 3.8, 95% CI 1.3 to 11.4) and lesions that occupied 41–60% of the vertebral body (HR 3.9, 95% CI 1.1 to 14.2) were associated with a statistically significant increase in the HRThe Karnofsky performance score at final follow-up was 80%. The median change in Karnofsky performance score among patients with fracture progression was 10% and 0% among patients without fracture progression ( $p < 0.03$ )**Author conclusions:**

The study identifies a high risk of vertebral fracture after single-fraction IG-IMRT to spinal metastases. Lytic disease involving more than 40% of the vertebral body and location at or below T10 confers a high risk of fracture, the presence of which yields significantly poorer clinical outcomes

**Reviewer conclusions:**

The study explores fracture risk after single-fraction IG-IMRT treatment. Therefore not sure if this paper really answers our research question

**Author:** Roth 2004<sup>124</sup>

**Country:** Canada

**Source of funding:** Canadian Breast Cancer Foundation

**Study design:**

*Type of study:* Retrospective study design

*Aims:* (1) To determine the ability of biomechanically based models to accurately predict vertebral stability and yield clear clinical threshold values for burst fracture risk in the metastatically involved spine; (2) To generate simple feasible methods to obtain the required data needed to make valid estimates of burst fracture risk

*Length of study:* Unclear

*Years of recruitment:* September 1998 to November 2001

*Inclusion criteria:* Patients with cancer with lytic spinal metastases confined to the thoracic and lumbar spine as seen on digital CT scans

*Exclusion criteria:* Patients with cancer who did not have lytic spinal metastases confined to the thoracic and lumbar spine

*Study arms (n):* One

**Method:**

*Population characteristics:*

Number of participants selected: 560

Number of participants analysed: 72 (of which a total of 92 vertebrae with osteolytic spinal metastases were examined retrospectively)

Number of participants selected but not followed up: Unclear

*Sampling frame:* Patients attending the authors' institution for spinal metastases

*Method of sample selection:* Unclear

*Sex (M/F):* 34 (46%) male/38 (54%) female

*Age of patients:*

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

*Interval from the time of diagnosis of cancer(s) to study entry:* Not reported

*Interval from the time of diagnosis of spinal metastases to study entry:* Not reported

*Length of follow-up per patient:*

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

*Cancer type(s):* Breast ( $n = 23$ ); lung ( $n = 7$ ); colon ( $n = 3$ ); prostate ( $n = 5$ ); lymphoma ( $n = 6$ ); multiple myeloma ( $n = 5$ ); renal ( $n = 4$ ); other ( $n = 10$ ); unknown ( $n = 9$ )

*Sites of metastasis:* 72 patients had lytic thoracic and lumbar spinal metastases

*Performance status scores:* Not clear

*Visceral metastasis:* Not clear

*Duration and rapidity of cord compression:* Not reported

Author: Roth 2004<sup>124</sup>

*Spinal level:*

- Cervical –
- Thoracic – 48
- Lumbar – 44
- Other –

*Spinal instability:* Fractures were seen in 21 of the 92 vertebrae (23%). Of these 17 were burst fractures and 4 were compression fractures; 71 (77%) were not fractured. Vertebrae were categorised as burst fractured, wedge fractured or intact

*Medications:* Not reported

**Intervention (i.e. screening technologies):**

CT scans. Also the load-bearing capacity parameter (tumour volume, trabecular bone mineral density, disc quality, pedicle involvement) was determined from CT while the load-bearing requirement parameter (pressure load, loading rate) was determined using CT and patient records (retrieved for 37 patients; 52%). The data collected were entered into the biomechanically based predictive models to quantify the risk of burst fracture in each metastatically involved vertebra

**Outcomes:**

*List of potential prognostic factors examined:* Vertebral bulge (maximum radial displacement under load), vertebral axial displacement (maximum axial displacement under load), and a volumetric estimate of tumour size

*List of potential prognostic factors identified as significant:* Vertebral bulge, vertebral axial displacement

*Have prognostic factors been validated in another population:* Unclear

**Findings:**

The most accurate predictor of burst fracture was the vertebral bulge equation using only the spinal load-bearing capacity (constant pressure load). This yielded a specificity and CI of 1 at threshold of 5.04 with a margin of 0.37. Burst fracture prediction using vertebral axial displacement and tumour size were also strong under this configuration with receiver operator curves and Hosmer–Lemeshow test values of 0.992 and 0.985, respectively and 0.988 and 0.752, respectively

Including an estimation of the load-bearing capacity (estimated pressure load) of the vertebrae reduced the sample size of the analysis and performance of the vertebral bulge and vertebral axial displacement models with receiver operator curves and Hosmer–Lemeshow test values of 0.943 and 0.235, respectively, and 0.957 and 0.160, respectively. In this population, tumour size alone was a strong predictor of burst fracture with a sensitivity of 0.917 at 100% specificity (tumour size = 38.2%) and a specificity of 0.914 at 100% sensitivity (tumour size = 24.3%) yielding a Hosmer–Lemeshow test value of 0.996. Inclusion of wedge fractures reduced the sensitivity and specificity of all the predictors

All vertebrae with burst fractures (100%) were in the low density group ( $<0.254 \text{ g/cm}^3$ ), whereas 33 (46%) of the unfractured vertebrae were also classified as low-density bone

**Author conclusions:**

Fracture prediction was optimised using the vertebral bulge model considering only load-bearing capacity with a specificity, sensitivity and CI of 1 to yield a clear threshold for burst fracture risk. Fracture prediction in the other two models, vertebral axial displacement considering only load-bearing capacity and tumour size, also was strong with receiver operator curve values of 0.992 and 0.988, respectively. The predictive power of these models can provide useful clinical information for prophylactic decision-making

**Reviewer conclusions:**

As indicated by the authors, the operator inputs required to undertake the modelling described are considerable and the methods used required relatively sophisticated digital scanning equipment, which may not be widely available. The development of automated systems may be required for the necessary data collection to become routine. Although prediction of burst fractures was impressive the number of samples included was small and the validity of the results needs testing in a larger sample and in different populations

**Author:** Sekine 2009<sup>125</sup>

**Country:** Japan

**Source of funding:** Not reported

**Study design:**

*Type of study:* Retrospective study

*Aims:* (1) To identify the risk factors for SREs in patients with advanced NSCLC

[SREs were defined as (1) pathological fractures, (2) SCC, (3) requirement for radiation therapy, (4) requirement for surgery to the bone, (5) requirement for radiological intervention to the bone and (6) hypercalcaemia of malignancy that was either fatal or required emergency treatment]

*Length of study:* Not reported

*Years of recruitment:* Unclear, possibly December 2000 to June 2006

*Inclusion criteria:* (1) A histological or cytological diagnosis of NSCLC; (2) stage IV disease or postoperative recurrence with distant metastases; (3) no prior chemotherapy; (4) chemotherapy prescribed by the National Cancer Center Hospital between 2000 and 2006

*Exclusion criteria:* Patients with postoperative local recurrence without distant metastases were excluded

*Study arms (n):* One (patients without SREs and patients with SREs were compared)

**Method:**

*Population characteristics:*

Number of participants selected: 642 overall: 524 (81.6%) patients without SREs/118 (18.4%) patients with SREs

Number of participants analysed: 642

Number of participants selected but not followed up: 0

*Sampling frame:* Unclear

*Method of sample selection:* Unclear

*Sex (M/F):* 402 male [patients without SREs 325 (80.8%); patients with SREs 77 (19.2%)]/240 female [patients without SREs 199 (82.9%); patients with SREs 41 (17.1%)]

*Age of patients:*

Mean (SD) – Not reported

Median – Patients without SREs = 61 years; patients with SREs = 59.5 years

Range – Patients without SREs = 24–86 years; patients with SREs = 26–77 years

*Interval from the time of diagnosis of cancer(s) to study entry:* Not reported

*Interval from the time of diagnosis of spinal metastases to study entry:* Not reported

*Length of follow-up per patient:* Unclear

Mean (SD) – Unclear. The overall median survival time was 15.4 (95% CI 14.0 to 16.9) months

Median – Not reported

Range – Not reported

*Cancer type(s):* Advanced NSCLC

*Sites of metastasis:* The initial progression site was the bone in 78 (12.1%) patients, and sites other than the bone in 502 (78.2%) patients

Author: Sekine 2009<sup>125</sup>*Performance status scores:* Method of establishing performance status not stated

Performance status 0 = patients without SREs = 163 (82.7%); patients with SREs = 34 (17.3%)

Performance status 1 = patients without SREs = 335 (81.5%); patients with SREs = 76 (18.5%)

Performance status 2 = patients without SREs = 26 (76.5%); patients with SREs = 8 (23.5%)

*Visceral metastasis:* Unclear, however the study states that in 78.2% of patients the initial progression site was not bone*Duration and rapidity of cord compression:* Not reported*Spinal level:*

Cervical – Not reported

Thoracic – Not reported

Lumbar – Not reported

Other –

*Spinal instability:* Unclear*Medications:* Zoledronic acid (bisphosphonates): In Japan, use of zoledronic acid was approved in January 2005. Please note the recruitment was done between December 2000 and June 2006. This agent was administered before the development of SREs in 26 (4.0%) patients, and after the development of SREs in another 17 (2.6%) patients. The first-line chemotherapy was platinum-based chemotherapy in 469 (73.1%) patients, gefitinib in 117 (18.2%) patients, third-generation monotherapy in 47 (7.3%) patients and non-platinum doublets in 9 (1.4%) patients**Intervention (i.e. screening technologies):**

Unclear

**Outcomes:***List of potential prognostic factors examined:* Sex (female, male); performance status; bone metastases (none, single, multiple); radiotherapy to the bone*List of potential prognostic factors identified as significant:* Male sex, performance status of 2–3, multiple bone metastases, history of radiotherapy before chemotherapy*Have prognostic factors been validated in another population:* No**Findings:**

A total of 118 (18.4%) patients developed SREs during or after initial chemotherapy. Of these, 107 required radiotherapy to bone, 5 developed hypercalcaemia of malignancy, 3 developed compression fracture of vertebrae, 2 required surgical treatment of the bone and 1 underwent radiofrequency ablation therapy to bone. The percentage of patients who developed SREs was not influenced by sex, age, performance status or cancer histology. However, the number of bone metastases at the time of initial diagnosis strongly influenced the rate of occurrence of SREs – a total percentage of 10.3% of patients who had no bone metastasis developed SREs, while 27% of patients with a single bone metastasis and 33% of patients with multiple bone metastases developed SREs during their clinical course ( $p < 0.001$ ). The first SRE occurred within 12 months in 80 (67.8%) of the 107 patients. History of radiotherapy to the bone before chemotherapy was also associated with SREs during and after the chemotherapy – only 103 (17%) of patients who did not require radiotherapy to the bone developed SREs while 15 (38%) of patients who underwent radiotherapy to the bone developed SREs ( $p = 0.001$ )

Results of multivariate analysis revealed that male sex, performance status of 2–3 and multiple bone metastases were risk factors for the first SRE, with HRs to reference of 1.44 (95% CI 0.98 to 2.11), 2.21 (95% CI 0.97 to 5.03) and 4.43 (95% CI 2.91 to 6.76), respectively. SRE-free survival showed a similar trend. HRs of male sex, performance status of 2–3 and multiple bone metastases were 1.64 (95% CI 1.30 to 2.06), 3.72 (95% CI 2.31 to 5.98) and 1.80 (95% CI 1.40 to 2.31), respectively. Many patients with advanced NSCLC live longer after failure of first-line chemotherapy, and they are considered to be at a higher risk of SREs than before

Results of univariate analysis revealed that male sex, performance status of 2–3, multiple bone metastasis and radiotherapy to the bone were risk factors for time to the first SREs. A similar trend was observed for the SRE-free survival

The median SRE-free survival was 23.5 (95% CI 18.6 to 28.5) months in patients with performance status of 0, 13.1 (95% CI 10.4 to 15.8) months in patients with performance status of 1 and 5.2 (95% CI 1.0 to 9.4) months in patients with performance status of 2 or 3 ( $p < 0.001$ )

**Author:** Sekine 2009<sup>125</sup>**Author conclusions:**

The presence of multiple bone metastases was significantly associated with the development of SRE in patients with advanced NSCLC treated by systemic chemotherapy. The factor 'multiple bone metastases' was identified as a risk factor for the development of SREs as assessed by all three parameters, and was, therefore, considered as a definite risk factor for the development of SREs. Male sex and poor performance status may be additional risk factors for the development of SREs in these patients. Male sex and poor performance status were significant risk factors influencing the SRE-free survival, marginally significant in relation to the time to the first SRE, and not significant in relation to the presence of SRE

**Reviewer conclusions:**

The definition of SRE includes number of clinical presentations and so it is difficult to distinguish the number of occurrences related to spines. The study does not report number of spinal metastases. A small proportion of participants used bisphosphonates, drugs that prevent loss of bone mass/delay SREs

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Author: Shah 2003<sup>126</sup>**Country:** USA**Source of funding:** Not reported**Study design:***Type of study:* Retrospective cohort study*Aims:* (1) To identify risk factors for vertebral fracture and epidural impingement in a population of MRI-followed patients at a single centre*Length of study:* Not reported*Years of recruitment:* October 1992 to June 1998 (156.8 person-years)*Inclusion criteria:* Patients included if MRI signs of metastasis were confirmed by biopsy from spinal tissue, primary tumour site or metastatic site other than the spine. When tumoral tissue was not obtained directly from the spine, subjects were included only if three or more non-contiguous levels or more than six contiguous levels were judged to be affected*Exclusion criteria:* (1) The primary tumour was a myeloma, lymphoma or other tumour of haematopoietic origin; (2) MRI was obtained within 30 days of a surgical intervention; and (3) MRI demonstrated a metallic implant*Study arms (n):* One**Method:***Population characteristics:*

Number of participants selected: 120 patients

Number of participants analysed: two random samples – sample one of 53 patients (756 vertebrae); sample two of 67 patients (113 fractured vertebrae). Twenty-two fractures were found to have no metastatic infiltration and were not analysed further, leaving a final sample of 91 fractured vertebrae

Number of participants selected but not followed up: Unclear

*Sampling frame:* T1- and T2-weighted MRI evaluated patients with spinal metastases seen at one university hospital*Method of sample selection:* Patients meeting inclusion criteria during designated time period*Sex (M/F):* Random sample one: 26 male/27 female*Age of patients:*

Mean (SD) – Random sample one: 58 (26) years

Median – Not reported

Range – 20–90 years

*Interval from the time of diagnosis of cancer(s) to study entry:* Not reported*Interval from the time of diagnosis of spinal metastases to study entry:* Not reported*Length of follow-up per patient:*

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

*Cancer type(s):* Random sample one: breast ( $n = 14$ ; 26.4%); lung ( $n = 13$ ; 24.5%); prostate ( $n = 9$ ; 17%); renal ( $n = 7$ ; 13.2%); undifferentiated ( $n = 3$ ; 5.7%); others ( $n = 7$ ; 13.2%)*Sites of metastasis:* Metastatic lesions were found in 253 vertebrae, see spinal level below. Tumours were most commonly located in the medial (66.3%), posterior (54.5%) and superior (53.5%) regions of the vertebral body*Performance status scores:* Unclear*Visceral metastasis:* Unclear

continued

Author: Shah 2003<sup>126</sup>

*Duration and rapidity of cord compression:* Unclear

*Spinal level:* SCC?

Cervical – 6 (3.7%)

Thoracic – 16 (9.8%)

Lumbar – 16 (9.8%)

Other – Sample one: first MRI examinations were of whole spine in 79 examinations (48.2%); of thoracolumbar spine in 39 (23.8%); and of cervicothoracic spine in 8 (4.9%) (giving total of 169 first examinations in 53 patients)

*Spinal instability:* 23% ( $n = 21$ ) of fractured vertebrae presented predominantly anterior compression, 19% ( $n = 17$ ) with lateral compression and 58% ( $n = 53$ ) with symmetric compression. Intervertebral disc implosion into the adjacent vertebral body accompanied end-plate fractures in 71.4% ( $n = 65$ )

*Medications:* Not reported

**Intervention (i.e. screening technologies):**

MRI

**Outcomes:**

*List of potential prognostic factors examined:* Histology, level, fracture pattern, prefracture infiltration and epidural impingement

*List of potential prognostic factors identified as significant:* Upper lumbar, undifferentiated tumours, vertebrae with >80% body infiltration, symmetric fractures with fragments

*Have prognostic factors been validated in another population:* Unclear

**Findings:**

Fracture risk was greatest for upper lumbar (L1–L3) (RR 1.95, 95% CI 1.12 to 3.38;  $p = 0.017$ ) and undifferentiated tumours (RR 7.36, 95% CI 2.69 to 20.12;  $p = 0.001$ ). A fourfold increase in fracture risk was noted in vertebrae with >80% body infiltration (HR 4.5966, 95% CI 1.66 to 12.71). Prostate metastases were associated with the smallest risk of fractures (RR 0.21, 95% CI 0.082 to 0.535;  $p = 0.001$ ). Symmetric fractures with fragments had the greatest risk of epidural impingement ( $p = 0.002$ )

A small correlation was observed between the number of levels affected by metastasis and the number of fractured vertebrae in an individual patient ( $r = 0.325$ ). There was no significant correlation between metastatic involvement of one or both pedicles with fractures ( $p = 0.43$ ). Also the type of fracture was not associated with vertebral level ( $p = 0.45$ )

Four patterns of vertebral fracture were identified: (1) symmetric compression fracture with two sagittal delta fragments, (2) symmetric compression fracture with no delta fragments, (3) lateral compression fracture and (4) anterior compression fracture. The authors identified a vertebral fracture pattern with a marked tendency to progress to migration into the epidural space: symmetric fractures with two delta fractures. The posterior delta fragment of symmetric fractures tended to migrate posteriorly into the canal

Complications of symmetric fractures with no delta fragments and anterior bending fractures included bulging of the posterior wall and direct tumoral extension into the spinal canal

**Author conclusions:**

Fracture risk was greatest for upper lumbar and undifferentiated tumours. Substantial increase in fracture risk among vertebrae with >80% body infiltration and symmetric fractures with fragments had greatest risk of epidural impingement

**Reviewer conclusions:**

The authors selected two random samples from a cohort of patients seen at one university hospital. First sample was used to study the patterns of tumour spread while the second was used to find predictors of fracture and epidural impingement in infiltrated vertebrae with varying tumour histologies using magnetic resonance images. It was found that fracture risk was greatest for upper lumbar and undifferentiated tumours. The risk of fracture increased fourfold in vertebrae with >80% vertebral body infiltration and symmetric fractures with fragments had the greatest risk of epidural impingement

Author: Snyder 2005<sup>127</sup>**Country:** USA**Source of funding:** National Institutes of Health funded research*Aims:* (1) To investigate if prognostic factors identified ex vivo using structural rigidity analysis of transaxial CT image data predicts in vivo vertebral fracture in cancer patients with spinal metastases*Secondary objectives:* (1) To compare the specificity and sensitivity of CT-based structural rigidity analysis against the best available guideline (Taneichi guidelines)**Study design:***Type of study:* Prospective study*Length of study:* 4 months*Years of recruitment:* Not reported*Inclusion criteria:* Unclear; breast cancer patients with spinal metastases*Exclusion criteria:* Not reported*Study arms (n):* One**Method:***Population characteristics*

Number of participants selected: Unclear/not reported

Number of participants analysed: 106 women

Number of participants selected but not followed up: Not reported; appears that all the patients were followed up for 4 months

*Sampling frame:* Not reported*Method of sample selection:* Not reported*Sex (M/F):* All female*Age of patients:*

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

*Interval from the time of diagnosis of cancer(s) to study entry:* Not reported*Interval from the time of diagnosis of spinal metastases to study entry:* Not reported*Length of follow-up per patient:*

Mean (SD) – The patients were followed up for 4 months

Median – The patients were followed up for 4 months

Range – Not reported

*Cancer type(s):* Metastatic breast cancer to the spine*Sites of metastasis:* Spine*Performance status scores:* Not reported*Visceral metastasis:* Unclear/not reported*Duration and rapidity of cord compression:* Unclear

continued

Author: Snyder 2005<sup>127</sup>

*Spinal level:*

Cervical – None

Thoracic – From T8

Lumbar – To L5

Other – None

*Spinal instability:* Not reported

*Medications:* Not reported

**Intervention (i.e. screening technologies):**

Transaxial CT scans performed on all patients to collect the data to calculate the load capacity (failure load) of the vertebrae. The FRI was calculated for each vertebra between T8 and L5 using two different load scenarios for each patient: (1) lifting a 10-kg mass and (2) arising from a chair. FRI > 1 implies that fracture would occur during the applied load condition. The accuracy of FRI was compared with the best available clinical and radiographic criteria (Taneichi guidelines) for predicting metastatic spine fracture to test the hypothesis that structural rigidity assessed by algorithms based on CT measurements predicted the failure load of a vertebra containing a defect better than current radiographic methods

The observation period was 4 months. An independent observer, blinded to the patient, unaware of the fracture risk predictions of the subjects reviewed all plain radiographs and MRI scans

(Taneichi guidelines: Four factors combined to assess fracture risk: percentage of tumour occupancy in the vertebral body, destruction of the pedicle, destruction of the posterior elements except the pedicle and destruction of the costovertebral joint. Fracture risk was defined as predicted probability > 0.5)

**Outcomes:**

*List of potential prognostic factors examined:* See above

*List of potential prognostic factors identified as significant:* See below

*Have prognostic factors been validated in another population:* Compared with cohort of children with benign tumours of the appendicular skeleton where the predicted fracture risk using CT-based structural analysis was 100% sensitive and 94% specific

**Findings:**

Over the 4-month period, out of 106 patients, 10 patients suffered one or more new vertebral fractures. Both the CT-based structural rigidity analysis and the Taneichi criteria predicted that these 10 patients were at increased fracture risk (sensitivity = 100% for either method). However, the CT rigidity analysis was better at predicting which patients would not fracture an affected vertebra (specificity = 49% when FRI > 1 for lifting a 10-kg mass) compared with the Taneichi CT criteria (specificity = 20%). Instead of calculating the FRI for lifting a 10-kg mass, if the load-carrying capacity of the vertebra was normalised by the patient's BMI (kg/m<sup>2</sup>) and the threshold for predicting vertebral fracture was set to achieve 100% sensitivity, the specificity for predicting no vertebral fracture was improved to 69%

The estimated RR for fracture based on FRI > 1 was RR = 4.2 (95% CI 1.4 to 12.8;  $p < 0.001$ ). When controlling for BMI (kg/m<sup>2</sup>), the adjusted RR for fracture based on FRI > 1 was RR = 7.9 (95% CI 1.8 to 34.5;  $p < 0.001$ )

**Author conclusions:**

CT-based structural rigidity analysis was as sensitive as but significantly more specific than the best radiographic guidelines for estimating metastatic cancer vertebral fracture risk

**Reviewer conclusions:**

The paper has inadequate information in terms of patient population and predictive factors. The study compares sensitivity and specificity of CT-based structural rigidity analysis against the best available guideline (Taneichi guidelines)

Author: Snyder 2009<sup>128</sup>**Country:** USA**Source of funding:** National Institutes of Health grant and Charity**Study design:***Type of study:* Prospective observational (before-and-after) study. (Comment: doubtful if this study is truly prospective even though the authors state it is)*Aims:* (1) According to the Abstract: Comparison of CT-based structural rigidity analysis (CTRA) with current standard care for prediction of spinal fracture in women with breast cancer with spinal metastases. Current standard care implied to be plain radiographs used with guidelines. According to Methods: to compare CTRA with an empirically derived logistic regression analysis based on size and location of vertebral metastases observed by axial CT scanning (Taneichi's algorithm)*Secondary objectives:* (1) 'Prospectively' compare sensitivities and specificities of CTRA and standard care for prediction of vertebral fracture to test hypothesis that CTRA is as sensitive as, and more specific than, currently used empirically derived risk prediction based on size and location of lesion. Gold standard: fracture according to commonly used criteria for osteoporotic fracture; radiologists assessing fracture were blinded to results of CT analyses. Unclear if CT analysts were blinded to radiological findings (CT scans were carried out before fracture detection, but there may be a delay between scan and results of the biomechanical calculations becoming available by which time the fracture status may have been known)*Length of study:* 4-months follow-up after CT assessment*Years of recruitment:* Not reported; examined records for 1024 patients to identify those meeting inclusion criteria*Inclusion criteria:* Not stated; Implicitly: patients without an exclusion criterion*Exclusion criteria:* (1) Neural compromise (due to metastases in brain or spinal cord); (2) withdrawal, relocation; (3) previous fracture at metastatic or adjacent site; (4) surgical treatment for impending fracture; and (5) fractured bones due to significant trauma*Study arms (n):* One**Method:***Population characteristics*

Number of participants selected: 94 women (from routine screening for lung and liver metastases)

Number of participants analysed: Presumed 94; 247 vertebrae examined

Number of participants selected but not followed up: Unclear

*Sampling frame:* Unclear (medical records of 1024 women at Dana-Faber Cancer Institute)*Method of sample selection:* Unclear*Sex (M/F):* All female*Age of patients:*

Mean (SD) – 55 (not reported)

Median – Not reported

Range – Not reported; 54% were postmenopausal

*Interval from the time of diagnosis of cancer(s) to study entry:* Unclear*Interval from the time of diagnosis of spinal metastases to study entry:* Unclear*Length of follow-up per patient:*

Mean (SD) – Implicitly 4 months

Median – Implicitly 4 months

Range – Implicitly 4 months

continued

**Author:** Snyder 2009<sup>128</sup>

*Cancer type(s):* Breast

*Sites of metastasis:* At least T8 to L5; visceral

*Performance status scores:* Not reported

*Visceral metastasis:* Not reported

*Duration and rapidity of cord compression:* Not reported

*Spinal level:*

Cervical – None

Thoracic – At least from T8 to L5

Lumbar – At least from T8 to L5

Other –

*Spinal instability:* Not clear

*Medications:* Treatments were continued; treatments not specified

**Intervention (i.e. screening technologies):**

Axial CT scan. Used to estimate rigidity, a product of bone tissue modulus and geometry. It had been previously established (in an ex vivo study) that the force needed to fracture vertebrae was proportional to the weakest cross-section through the affected bone; therefore the scans were used to identify the cross-sectional structural rigidity with weakest resistance to EA, or EI (that is, the minimal EA and EI rigidities for each vertebra). From this the LBC of the vertebra in combined axial compression and forward bending was also estimated using 'beam theory'. The LBC was standardised on BMI (kg/m<sup>2</sup>) (LBC/BMI). The rate of fractures over the next 4 months was recorded (by independent investigators)

**Outcomes:**

*List of potential prognostic factors examined:* EA, EI, LBC, LBC/BMI

*List of potential prognostic factors identified as significant:* LBC/BMI

*Have prognostic factors been validated in another population:* No

**Findings:**

The value for each of the four parameters (EI, EA, LBC, LBC/BMI) in each of the 247 vertebrae was estimated. There were 11 fractures over the 4 months (236 vertebrae did not fracture). The value for each of the four parameters in each of the 11 observed fractured vertebrae was calculated. From these 11 values for each parameter the maximum value was selected as diagnostic threshold for that parameter. For example, for LBC/BMI the maximum value was 46.5; since all other fractured vertebrae had values <46.5, using this as the threshold meant that all fractures would be detected, so the sensitivity was 100%. Of the 236 unfractured vertebrae, 74 also had a LBC/BMI of <46.5 so specificity was  $(236 - 74) / 236 = 68.6\%$  (reported as 70%)

Using the same procedure for LBC, EI and EA, the specificities were 44%, 53% and 55% (all sensitivities at 100%)

Using Taneichi's algorithm specificity was only 20% and sensitivity was 100% (i.e. very many false-positives)

Authors provided a ROC curve for LBC/BMI showing how sensitivity and specificity were affected by changing (reducing) the value of the cut-off. So as cut-off became <46.5, <100% of the fractures were detected, but there were fewer false-positives and so specificity improved. The area under the ROC curves (AUC) was estimated using a binomial semi-parametric model. The results were: Taneichi 0.6; LBC 0.82; EI 0.80; EA 0.68; LBC/BMI 0.84. Corresponding *p*-values for the comparison with chance [tossing a coin; area under the curve (AUC) = 0.5] were 0.25, 0.001, 0.001, 0.002 and <0.001, respectively

**Author conclusions:**

Computerised tomography-based structural rigidity analysis has been seen to be as sensitive and significantly more specific than current radiographic criteria for predicting vertebral fracture in breast cancer

**Reviewer conclusions:**

Patient selection not described; it is possible that sensitivities and specificities could vary depending on stage of vertebral invasion by metastases, therefore selection of participants is important. From at least T8 to L5 for 94 women provides at least 658 potential vertebrae examined; 247 were used for parameter calculations, not reported if this was all those identified with metastases or a proportion. The validity of the comparison with Taneichi's procedure may be questionable because of the post hoc selection of threshold for CTRA but possibly not for Taneichi

Author: Soerdjbalie-Maikoe 2004<sup>129</sup>

**Country:** Netherlands

**Source of funding:** Not reported

**Study design:**

*Type of study:* Observational retrospective (based on discussion stating their method needs to be tested in a prospective analysis)

*Aims:* (1) To find whether high-resolution bone scintigraphy at the time of diagnosis of hormone refractory metastatic prostate cancer has added prognostic value compared with prevailing PSA concentrations and tumour staging (Gleason grading) for survival and for SCC-free survival; (alternative wording in Abstract: whether a new method of evaluating bone scintigraphy would offer better predictive value than is achieved with currently available grading methods)

*Length of study:* Not stated

*Years of recruitment:* Not stated

*Inclusion criteria:* Unstated, implicitly: patients with metastatic prostate cancer who had progressed after hormone therapy

*Exclusion criteria:* None stated

*Study arms (n):* One

**Method:**

*Population characteristics*

Number of participants selected: 84

Number of participants analysed: 84

Number of participants selected but not followed up: 0

*Sampling frame:* Unclear

*Method of sample selection:* Unclear

*Sex (M/F):* 100% male

*Age of patients:*

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

*Interval from the time of diagnosis of cancer(s) to study entry:* Not reported

*Interval from the time of diagnosis of spinal metastases to study entry:* Not reported

*Length of follow-up per patient:* Not reported

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

*Cancer type(s):* Prostate

*Sites of metastasis:* Skeleton (visceral not reported)

*Performance status scores:* Not reported

*Visceral metastasis:* Not reported

*Duration and rapidity of cord compression:* The SCC developed in 20/84 patients 3 days to 10 months after scintigraphy (provided data for time from treatment to SCC for some patients but the time at which treatment was started was not reported)

continued

Author: Soerdjbalie-Maikoe 2004<sup>129</sup>

*Spinal level:* SCC occurred in 20 patients

Cervical –

Thoracic – 14/20 (in four patients also another site: in two patients cervical and in two patients lumbar)

Lumbar – 6/20

Other –

*Spinal instability:* Not reported

*Medications:* At diagnosis of metastatic hormone-resistant prostate cancer in 84 patients, 23 stopped hormone therapy and 8 stopped estramustine (Estracyt<sup>®</sup>, Pharmacia). Majority received palliative treatments: radiotherapy ( $n = 4$ ), <sup>89</sup>Sr ( $n = 33$ ), olpadronate ( $n = 41$ ), conventional analgesic only ( $n = 6$ )

#### **Intervention (i.e. screening technologies):**

<sup>99</sup>Tc<sup>m</sup>-labelled methylenediphosphonate bone scintigraphy at progression to metastatic hormone-resistant prostate cancer (high resolution multi-head gamma cameras, anterior and posterior imaging); progression on clinical grounds, criteria not defined further than: rising PSA and alkaline phosphatase, worse bone pain, appearance or reappearance of bone metastases on bone scintigraphy

Scintigraphy images of vertebrae were classified as involving part (partial) or all (total) of the vertebra (criteria not further defined). Skeletal involvement classified according to Soloway system (grades: 0, 1, 2, 3, 4). CT or MRI was used to establish presence of SCC

#### **Outcomes:**

Overall survival and SCC-free survival

*List of potential prognostic factors examined:* Serum PSA (log-transformed); serum alkaline phosphatase (log-transformed); age; Gleason score  $<7$  or  $\geq 7$ ; Soloway grade (scintigraphy at progression); total vertebral involvement (according to scintigraphy at progression)

*List of potential prognostic factors identified as significant:* For SCC expressed as RR from Cox regression: Soloway grade 4; log-transformed PSA; total involvement of vertebrae

*Have prognostic factors been validated in another population:* No

#### **Findings:**

Used Kaplan–Meier analysis of overall survival and of SCC-free survival with Cox regression to investigate relation between the RR of SCC and: PSA, alkaline phosphatase, Soloway grade, age, Gleason score; 20 patients experienced SCC according to MRI/CT

Mean Gleason score was 7.5. When Gleason score was dichotomised to  $\geq 7$  or  $<7$  the former had significantly shorter SCC-free survival and overall survival. Median SCC-free survival for Gleason  $\geq 7$  vs.  $<7$  was 6.1 vs. 12.3 months ( $p < 0.05$ ); medians for overall survival were Gleason  $\geq 7$ , 6.8 months and Gleason  $<7$ , 12 months ( $p < 0.03$ ). RRs of the Gleason score were RR 1.89 (95% CI 1.02 to 3.53) for mortality and RR 1.76 (95% CI 0.95 to 3.28) for SCC. RRs of the Gleason score remained significant after adjusting for confounders: RR 2.33 ( $p = 0.013$ ) for mortality and RR 2.37 ( $p = 0.003$ ) for SCC

The unadjusted RR for SCC was significantly associated with Soloway grade, i.e. the greater the metastatic skeletal load the more likely SCC will occur ( $p = 0.03$ ); however, after adjustment (PSA, alkaline phosphatase and age) statistical significance disappeared ( $p = 0.35$ ). The unadjusted RR for SCC among grade 4 patients was significantly greater than that for grade 1 patients (this also applied for overall survival). Log-transformed PSA was significantly predictive of increased risk of SCC (Cox regression RR 1.21, 95% CI 1.07 to 1.36). For the 'new method' of assessing total or partial vertebral involvement at progression, the sensitivity and specificity were 0.9 and 0.94, respectively (based on  $2 \times 2$  table values of table 2 of paper)

#### **Author conclusions:**

Data demonstrate that bone scintigraphy performed at the time of development of refractoriness to hormone therapy is of high predictive value for inherent risk of subsequent SCC

#### **Reviewer conclusions:**

There was no indication of how the 84 patients were selected; different patients received various treatments likely to influence the probability of SCC (e.g. bisphosphonates?). It is not clear if these were accounted for in Cox regression analyses. Although the 'total involvement of vertebra' according to scintigraphy appeared to be highly sensitive and specific for subsequent SCC, the study lacks sufficient rigour to be confident of this result; in particular, participant selection was unclear, progression criteria were not defined precisely and no details were given of the method of discriminating total from partial vertebral involvement except that two independent assessors were involved. However, disagreements were not mentioned and it is not clear whether the assessment was conducted before or after SCC was determined to have occurred, and if scintigraphy assessors and MRI/CT assessors were reciprocally blind to each other's results

**Author:** Sun 2011<sup>130</sup>**Country:** Republic of Korea**Source of funding:** Not mentioned**Study design:***Type of study:* Retrospective observational before-and-after study*Aims:* (1) To identify clinical factors that can predict SREs in patients with advanced NSCLC*Length of study:* Data from medical records from diagnosis of advanced NSCLC; earliest January 2006 to October 2009. Median follow-up 11 months (range 0.7–46.0 months)*Years of recruitment:* Patients diagnosed January 2006 to March 2009*Inclusion criteria:* Patients with bone metastases secondary to NSCLC; bone metastases identified by imaging including scintigraphy, PET, biopsy*Exclusion criteria:* None reported*Study arms (n):* One**Method:***Population characteristics*

Number of participants selected: 1166 screened (advanced NSCLC), 273 selected with bone metastases

Number of participants analysed: 273; 171 had at least one SRE during follow up, 46 had multiple SREs; the total SREs was 229

Number of participants selected but not followed up: None (implicit)

*Sampling frame:* Samsung Medical Centre patients with diagnosis of advanced NSCLC January 2006 to March 2009*Method of sample selection:* All from 1166 patients with diagnosis of bone metastases*Sex (M/F):* 60.1% male*Age of patients:*

Mean (SD) – Not reported

Median – Not reported

Range – Of 273 patients: 71.5% &gt;50 years, 28.2% &lt;50 years

*Interval from the time of diagnosis of cancer(s) to study entry:* 0 (NB diagnosis of advanced NSCLC, not NSCLC)*Interval from the time of diagnosis of spinal metastases to study entry:* 242 of 273 patients had bone metastases at study entry (i.e. at diagnosis of advanced NSCLC)*Length of follow-up per patient:*

Mean (SD) – Not reported

Median – 11 months

Range – 0.7–46.0 months

*Cancer type(s):* NSCLC*Sites of metastasis:* Bone. At 528 locations among 273 patients. Two hundred and forty-two of 273 (88.6%) had metastasis at time of diagnosis (of advanced NSCLC)*Performance status scores:* ECOG 0/1 = 76.6% of 273; ECOG 2/3 = 23.4% of 273*Visceral metastasis:* No mention of visceral metastases*Duration and rapidity of cord compression:* Not mentioned. Fourteen out of 273 had compression and fracture, 14/273 had compression without 'definite' fracture. Thirty out of 273 had pathological fracture (not necessarily vertebral). Most common SREs occurred in spine (55.2%)

continued

Author: Sun 2011<sup>130</sup>

*Spinal level:* Paper considers bone metastases at: spine, pelvis, skull, ribs, extremities

Cervical – Not reported

Thoracic – Not reported

Lumbar – Not reported

Other – Not reported

*Spinal instability:* Kyphosis/lordosis not mentioned

*Medications:* Bisphosphonates: 57/273 patients; pamidronate 42, zoledronic acid 9. EGFR TKI [e.g. gefitinib, erlotinib (Tarceva®, Roche)] 192/273 (70.3%) patients, 891 cycles of treatment; cytotoxic agents 259/273 (95%) patients, 1719 cycles administered

**Intervention (i.e. screening technologies):**

Not reported (other than at diagnosis)

**Outcomes:**

*List of potential prognostic factors examined:* Sex, ever a smoker, adenocarcinoma/non-adenocarcinoma, no history of EGFR TKI treatment, ECOG status, BMI (kg/m<sup>2</sup>), age

*List of potential prognostic factors identified as significant:* Sex; ever a smoker; adenocarcinoma/non-adenocarcinoma; no history of therapy with a EGFR TKI such as gefitinib; ECOG status; BMI (kg/m<sup>2</sup>); age

*Have prognostic factors been validated in another population:* No

**Findings:**

In all, 171/273 patients experienced at least one SRE, and 46 had multiple SREs. A total of 229 SREs developed of which 65 occurred before any systemic treatment was received. The most frequent site of SREs was the spine (55.2% of patients)

For first SRE: in multivariate analysis only 'ever smoked' was associated with significantly higher risk (OR 2.8, CI 1.32 to 6.00) (same result if bisphosphonate-receiving patients are left out of the calculation)

The median time from diagnosis of bone metastasis to first SRE was 8.9 months in all patients with a SRE. For median time to first SRE in multivariate analysis: no history of EGFR TKI therapy, ever smoked and histology of non-adenocarcinoma were significantly associated with shorter median time to first SRE

For risk of multiple events (separated by at least 21 days) the same three factors and also ECOG status 2/3 were significantly associated with increased risk

Also: significantly more SRE per cycle of treatment occurred during cytotoxic therapy than during EGFR TKI therapy. Note: authors state potential pitfall in that systemic therapies did not necessarily precede SRE in all cases

**Author conclusions:**

Study suggests that patient with characteristics such as ever smoking, no history of EGFR TKI therapy, poor ECOG status and non-adenocarcinoma are more likely to suffer SREs

**Reviewer conclusions:**

SREs appear to have been classified as: pathological fracture, SCC with or without vertebral fracture, need for radiation or surgery to bone, hypercalcaemia of malignancy. The risk factors identified may well apply equally to SCC and/or vertebral fracture alone but this would need to be investigated using the appropriate narrower definition of an event. This is one of the few studies that considered the risk of repeated events

Author: Talcott 1999<sup>131</sup>**Country:** USA**Source of funding:** National Cancer Institute grant (in part)**Study design:***Type of study:* Retrospective study*Aims:* To examine potential clinical neurological and oncological risk factors for CT-established SCC in metastatic cancer patients with suspected SCC*Length of study:* Between 1 February 1985 and 30 September 1988*Years of recruitment:* Screened CT scan records from 1 February 1985 to 30 September 1988*Inclusion criteria:* CT scan for clinically suspected SCC (SCC = SCC or cauda equina syndrome) = index scan*Exclusion criteria:* CT scans without suspected SCC, scans of previously diagnosed SCC*Study arms (n):* One**Method:***Population characteristics*

Number of participants selected: 258 (342 index scans, of 405 index scans identified from records)

Number of participants analysed: Of the 405 index scans the following were excluded: five had &lt;3 months follow-up, nine scans were unavailable, 49 were excluded because of prior radiotherapy at or near to the site of suspected SCC or a prior CT diagnosis of thecal compression within 1 year before index CT. This left 342 scans in 258 patients who were analysed

Number of participants selected but not followed up: 63 scans (of 405), the number of participants with the 63 scans not reported

*Sampling frame:* CT scans at Dana Faber Cancer Institute during 1 February 1985 to 30 September 1988*Method of sample selection:* CT scan for suspected SCC, according to medical records*Sex (M/F):* 61% female of 258*Age of patients:*

Mean (SD) – Not reported

Median – 56.5 years (age at first study episode)

Range – 18–83 years

*Interval from the time of diagnosis of cancer(s) to study entry:* Median of 'approximately 2 years (762 days)', i.e. 2.086 years*Interval from the time of diagnosis of spinal metastases to study entry:* Not reported*Length of follow-up per patient:* Not clear

Mean (SD) – Not clear

Median – Not clear

Range – Not clear

*Cancer type(s):* Breast 42% of patients NSCLC 14%, prostate 9%, sarcoma 5%, other 30%*Sites of metastasis:* At diagnosis 24% localised, 30% metastatic. Sites not reported but all presumably had spinal metastases*Performance status scores:* Not clear*Visceral metastasis:* Unclear*Duration and rapidity of cord compression:* Not reported, patient population with suspected SCC

continued

**Author:** Talcott 1999<sup>131</sup>

*Spinal level:* Index scan sites

Cervical – Unclear

Thoracic – T12: 30% of 342 index scans

Lumbar – L3 and L4: 43% of 342 index scans

Other – Incomplete reporting of sites for TSC + SCD-positive scans ( $n = 72$ ): most common site T4 + L3, next most common L2, L1, T12

*Spinal instability:* Kyphosis and lordosis not reported

*Medications:* Palliative radiotherapy; prior hormonal and chemotherapies were common

**Intervention (i.e. screening technologies):**

CT scan for suspected SCC, details of imaging procedure and machine provided. Uncertain scans (<5%) were followed up by myelography or MRI

Most received imaging before index CT, mostly to document metastases to bone, especially spine. Plain film radiographs immediately preceded 250 of the 342 index scans; vertebral lesions seen in 68% of the plain films: lytic 29%, blastic 16%, mixed 20%, compression fractures 30%

**Outcomes:**

Predictive variables, survival to 90 days and 1 year after index scan, proportion of positive index scans

*List of potential prognostic factors examined:* Performed for several definitions of SCC: TSC, SCD, TSC + SCD, EM, SCD + TCD + EM. A list of 22 variables examined in univariate logistic regression

*List of potential prognostic factors identified as significant:* In multivariate analysis for TSC: six variables significantly predictive as follows: vertebral body fracture on most recent plain radiograph ( $p < 0.0005$ ), bone metastases previously diagnosed ( $p = 0.05$ ), complaint of inability to walk ( $p = 0.02$ ), increased deep tendon reflexes ( $p = 0.02$ ), bone metastases diagnosed > 1 year before ( $p = 0.04$ ), aged < 60 years ( $p = 0.05$ ). Comment: most of these, though unsurprising, were identified by logistic regression; however,  $p$ -values may indicate most important. Some variables significant in univariate analysis are correlated; this is relevant for validity

*Have prognostic factors been validated in another population:* No

**Findings:**

Positive diagnosis at scan depends on definition of SCC used. For TSC 29/342 index scans positive, for SCD 43/342, for EM only 52/342, for TSC + SCD 72/342, for TSC + SCD + EM 124/342, for TSC + SCD at index or within 90 days follow-up 80/342. If consider local radiation (at site of suspected SCC within 90 days) of CT-negative patient as indication of SCC, then 169/342 (49%) index scans positive

**Author conclusions:**

Clinical history of patients' cancer contributes independently to risk assessment. Prevalence of SCC depends on definition used and whether short-term clinical follow-up is included

**Reviewer conclusions:**

A high number of positive CT index scans not surprising because patients were selected for suspected SCC. The risk factors identified were mostly not a surprise, namely: vertebral fracture on most recent radiograph (note 250 of the 342 index scans were immediately preceded by plain radiograph), bone metastasis previously diagnosed (not going to get SCC without a bone metastasis), complaint of inability to walk (a well-known symptom of SCC), increased deep tendon reflex, bone metastasis diagnosed > 1 year prior (= long time for SCC to develop), age < 60 years

**Author:** Taneichi 1997<sup>89</sup>**Country:** Japan**Source of funding:** Grant-in-aid for Encouragement of Young Scientists from the Ministry of Education, Culture, and Science of Japan**Study design:***Type of study:* Unclear*Aims:* (1) To determine risk factors for vertebral collapse, (2) to estimate the predicted probability of collapse under various states of metastatic vertebral involvement and (3) to establish the criteria of impending collapse*Secondary objectives:* None*Length of study:* Not reported*Years of recruitment:* Not reported*Inclusion criteria:* Patients with metastatic tumours; with or without vertebral collapse; with or without neurological deficit. The vertebrae were selected if they satisfied the following conditions: (1) purely or predominantly osteolytic metastatic lesions, (2) no end-plate fracture in adjacent vertebrae, (3) tomograms (sagittal and coronal plane) and CT performed within 1 week of the initial plain X-ray (anteroposterior and lateral view) examination and qualified for detailed analysis, (4) all radiographic examinations in the study performed before biopsy, radiation therapy or surgical treatment (e.g. laminectomy)*Exclusion criteria:* Not reported*Study arms (n):* All vertebrae were divided into two groups: (1) the thoracic group (Group T), containing the T1 to T10 vertebrae included in the rib cage; (2) the thoracolumbar and lumbar group (Group L), including the T11 and T12 vertebrae with free-ended ribs and all lumbar vertebrae. There were 50 vertebrae in each group**Method:***Population characteristics:*

Number of participants selected: 53

Number of participants analysed: 53 (100 vertebrae)

Number of participants selected but not followed up: Not reported

*Sampling frame:* Presumably patients attending authors' clinic were selected – no details given but the paper states that some of the patients with a collapse and back pain with or without paralysis had visited the authors' clinic for radiological examinations*Method of sample selection:* Not reported*Sex (M/F):* Unclear*Age of patients:*

Mean (SD) – 59.7 (8.8) years

Median – Not reported

Range – 43–80 years

*Interval from the time of diagnosis of cancer(s) to study entry:* Not reported*Interval from the time of diagnosis of spinal metastases to study entry:* Not reported*Length of follow-up per patient:*

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

continued

**Author:** Taneichi 1997<sup>89</sup>

*Cancer type(s):* Cancers were located in various sites

*Sites of metastasis:* Spine; unclear if it had metastasised to other sites

*Performance status scores:* Not reported

*Visceral metastasis:* Unclear if it had metastasised to other organs

*Duration and rapidity of cord compression:* Not reported

*Spinal level:*

Cervical – 0

Thoracic – T1 to T10 (50 vertebrae involved)

Lumbar – T11 to L5 (50 vertebrae involved)

Other – 0

*Spinal instability:* Not reported

*Medications:* Not reported

**Intervention (i.e. Screening technologies):**

CT of the spine

**Outcomes:**

*List of potential prognostic factors examined:* The four potential risk factors of collapse were: (1) %TO in the vertebral body (indicative of the size of the osteolytic metastatic lesion). This was obtained by the following method: the most extensive cross-sectional area of osteolytic lesion (A) within the affected vertebral body was measured on CT; the original cross-sectional area of the same vertebral body (B) was estimated by calculating the average whole body area at the corresponding plane of the adjacent uninvolved vertebra above and below the metastasis. When an area of the osteolytic lesion could not be measured accurately because of a large cortical defect or a concomitant collapse, only the area of the intact portion (C) was measured; the area of osteolytic lesion was obtained indirectly by means of the following formula:  $A = B - C$ . The %TO was calculated as  $A/B \times 100$  (%). The measurements of the cross-sectional area were performed with computer software. The second (2), third (3), and fourth [(4)–in group T only] factors are, respectively, destruction of the pedicle; the posterior elements, not including the pedicle; and the costovertebral joint. Destruction of the pedicle (2) was defined as fracture or circumferential cortical defect of one or both pedicles. The authors limit the definition of the costovertebral joint destruction (4) to involvement of the vertebral body including the articulation of the rib head, independent of costotransverse joint involvement. The second, third and fourth risk factors were judged using CTs and tomograms

A multivariate logistic regression model was used to determine the associations between the occurrence of vertebral collapse and the four risk factors that indicated the size or location of the metastatic lesions in the vertebra. Further, the predicted probability of vertebral body collapse in various states of metastatic vertebral involvement was estimated by the same model. Finally, a set of criteria for 'impending vertebral body collapse' was made

*List of potential prognostic factors identified as significant:* Costovertebral joint destruction and tumour size in the thoracic region, tumour size and pedicle destruction in the thoracolumbar and lumbar spine (T10–L5)

*Have prognostic factors been validated in another population:* Uncertain

**Findings:**

%TO: No significant difference between Group T (40.8%, SD 24.8%,  $n = 50$ ) and Group L (40.3%, SD 24.1%,  $n = 50$ )

Multivariate logistic regression model in Group T: The strongest correlation was between costovertebral joint destruction and vertebral collapse (OR 10.17;  $p = 0.021$ ). The tumour size (%TO) was associated with the risk of vertebral collapse (OR of every 10% increment in %TO 2.44;  $p = 0.032$ ). However, destruction of the pedicle and other posterior elements was not associated with the risk of vertebral collapse [OR (pedicle) 1.73;  $p = 0.703$ ; OR (posterior elements) 1.17;  $p = 0.886$ ]

Multivariate logistic regression model in Group L: The two most important risk factors for vertebral body collapse were %TO (OR of every 10% increment in %TO = 4.35;  $p = 0.002$ ) and pedicle destruction (OR 297.08;  $p = 0.009$ ). Destruction of the posterior elements was inversely correlated with the risk of collapse (OR 0.03;  $p = 0.027$ )

Author: Taneichi 1997<sup>89</sup>

The probability of vertebral body collapse could be estimated from the equations shown below:

Probability of T collapse =  $(\exp(\text{odds of collapse})) / (1 + \exp(\text{odds of collapse}))$

Odds of T collapse =  $(0.089 \times [1] + 0.646 \times [2] + 0.161 \times [3] + 2.319 \times [4] - 4.597)$

where [1], [2], [3] and [4] refer to risk factors

Probability of L collapse =  $(\exp(\text{odds of collapse})) / (1 + \exp(\text{odds of collapse}))$

Odds of L collapse =  $(0.147 \times [1] + 5.694 \times [2] - 3.609 \times [3] - 5.492)$

where [1], [2] and [3] refer to risk factors

The criteria of impending collapse were defined in group T as: (1) 50–60% (%TO) involvement of the vertebral body with no destruction of the other structures; and (2) 25–30% (%TO) involvement of the vertebral body with costovertebral joint destruction. In group L the criteria were defined as: (1) 35–40% (%TO) involvement of the vertebral body with no destruction of the other structures; and (2) 20–25% (%TO) involvement of the vertebral body with destruction of the posterior elements including the pedicle

#### Author conclusions:

With respect to the timing and occurrence of vertebral collapse, there is a distinct discrepancy between the thoracic and thoracolumbar or lumbar spine. When a prophylactic treatment is required, the optimum timing and method of treatment should be selected according to the level and extent of the metastatic vertebral involvement

#### Reviewer conclusions:

Even though published in 1997 this study remains more complete than many in that it develops empirical equations for the prediction of fracture. The study selected only intraspinal tumour-related factors as risk factors for collapse and extraspinal factors such as age and sex were not considered. Any effect exerted from different primary types was not explored. Intraspinal factors such as costovertebral joint destruction and tumour size in the thoracic region were found to be significant risk factors. Factors such as tumour size and pedicle destruction were found to be significant risk factors in the thoracolumbar and lumbar spine. The equations developed need testing prospectively in different populations with spinal metastases

Author: Venkitaraman 2007<sup>132</sup>

**Country:** UK

**Source of funding:** The work was undertaken at The Royal Marsden NHS Trust, which received a proportion of its funding from the NHS executive. The work was also supported by the Institute of Cancer Research, the Cancer Research UK Section of Radiotherapy grant number C46/A2131 and the National Cancer Research Institute (NCRI) South of England Prostate Cancer Collaborative

**Study design:**

*Type of study:* Retrospective study (retrospective analysis of the clinical data)

*Aims:* (1) To determine the role of MRI of the spine in detecting overt or occult SCC in patients with metastatic prostate cancer with no functional neurological deficit; (2) to identify clinical factors that predict a high risk for SCC

*Secondary objectives:* None

*Length of study:* Not reported

*Years of recruitment:* Consecutive patients with prostate cancer who had MRI of the spine between January 2001 and May 2005, from the institution database of The Royal Marsden Hospital, UK

*Inclusion criteria:* Patients with skeletal metastasis who had MRI of the spine detecting clinically occult SCC

*Exclusion criteria:* Functional neurological deficit on clinical examination or any previous SCC

*Study arms (n):* One

**Method:**

*Population characteristics:*

Number of participants selected: 150 (570 screened)

Number of participants analysed: 150

Number of participants selected but not followed up: 0

*Sampling frame:* 570 consecutive patients with prostate cancer who had MRI of the spine between January 2001 and May 2005, from the institution database of The Royal Marsden Hospital, UK

*Method of sample selection:* Not reported

*Sex (M/F):* All male patients

*Age of patients:*

Mean (SD) – Not reported

Median – 69 years

Range – 50–88 years

*Interval from the time of diagnosis of cancer(s) to study entry:* Median 41.3 months (range 3.13–213 months)

*Interval from the time of diagnosis of spinal metastases to study entry:* Not reported

*Length of follow-up per patient:* Not reported

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

*Cancer type(s):* Prostate cancer

*Sites of metastasis:* Spine; the paper states that none of the patients had clinical symptoms of bladder or bowel involvement from metastatic spinal disease

*Performance status scores:* All patients had performance status 0–1

Author: Venkitaraman 2007<sup>132</sup>

*Visceral metastasis:* The paper states that none of the patients had clinical symptoms of bladder or bowel involvement from metastatic spinal disease

*Duration and rapidity of cord compression:*

*Spinal level:*

Cervical – Not reported

Thoracic – 20 patients

Lumbar – 21 patients at lumbosacral

Other –

*Spinal instability:* Not reported

*Medications:* Not reported

#### **Intervention (i.e. screening technologies):**

MRI of the spine. The findings were classified as (1) 'overt SCC', defined as involvement or compression of either the spinal cord or the cauda equina by an epidural or an intramedullary mass lesion or (2) 'occult SCC', defined as metastatic disease causing impingement, indentation or loss of definition of the thecal sac and (3) no SCC (the two categories, i.e. occult and overt SCC were considered together as rSCC)

#### **Outcomes:**

*List of potential prognostic factors examined:* Age, T stage, N stage, M stage at diagnosis, primary Gleason grade  $\geq 4$ , composite Gleason score  $\geq 8$ , serum PSA at diagnosis, time from diagnosis, hormone refractory status, time from starting hormonal treatment, extensive skeletal metastasis (six or less bone sites involved/Soloway extent of disease score 2, 3 or 4), serum PSA at MRI, levels of haemoglobin, serum calcium, alkaline phosphatase, lactate dehydrogenase and back pain

*List of potential prognostic factors identified as significant:* Bone metastasis and back pain

*Have prognostic factors been validated in another population:* No

#### **Findings:**

Out of the 150 patients who had MRI of the spine, 41 (27.33%) had rSCC—24 (16%) overt rSCC and 17 (11.3%) occult rSCC. Seven had rSCC at multiple non-contiguous sites; 20 had compression in the thoracic spinal level and 21 in the lumbosacral region

On univariate analysis, significant determinants of rSCC were found to be bone metastasis ( $p = 0.005$ ) and back pain ( $p = 0.002$ ), whereas 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 ( $p = 0.855$ ) did not predict rSCC

On multivariate analysis, back pain (OR 5.1, 95% CI 1.44 to 18.25;  $p = 0.012$ ) and extensive bone metastasis (OR 2.9, 95% CI 1.012 to 8.35,  $p = 0.047$ ) were significant independent predictors of rSCC. One variable, PSA at the time of MRI (median PSA 402 vs. 98 ng/ml), was significantly different in the patients who had overt SCC and those who had occult SCC (HR 1.005, 95% CI 1.001 to 1.009)

#### **Author conclusions:**

A significant proportion (27.3%) of patients with metastatic prostate cancer may harbour overt or occult SCC in the absence of functional neurological deficit. MRI of the spine for the early diagnosis of SCC may be considered useful in patients with extensive skeletal metastasis and back pain

#### **Reviewer conclusions:**

MRI of the spine in patients with extensive skeletal metastasis and back pain may lead to early diagnosis of SCC

Author: Venkitaraman 2010<sup>133</sup>**Country:** UK

**Source of funding:** The work was undertaken in The Royal Marsden NHS Trust, which received a proportion of its funding from the NHS executive. The work was also supported by the Institute of Cancer Research, the Bob Champion Cancer Trust and the Cancer Research UK Section of Radiotherapy grant number C46/A2131 and the NCRI South of England Prostate Cancer Collaborative. The authors also acknowledged NHS funding to the National Institute for Health Research Biomedical Research Centre

**Study design:**

*Type of study:* Retrospective study (retrospective analysis of the clinical data)

*Aims:* (1) To determine the incidence of neurological deficit in metastatic prostate cancer patients; and (2) to determine the optimal frequency of screening MRI spine required to detect clinically occult rSCC (rSCC was defined as involvement or compression of either the spinal cord or the cauda equina by an epidural or an intramedullary mass lesion or metastatic disease causing impingement, indentation or loss of definition of the thecal sac)

*Secondary objectives:* None

*Length of study:* Patients were censored either at the time of death or at the time of last follow-up for surviving patients who had not developed neurological deficit

*Years of recruitment:* Patients with prostate cancer who had MRI of spine between January 2001 and May 2005, from the institution database of The Royal Marsden Hospital, UK

*Inclusion criteria:* Patients with castration-resistant prostate cancer and skeletal metastasis, who had MRI of spine for detecting clinically occult SCC

*Exclusion criteria:* Neurological deficit on clinical examination or any previous SCC

*Study arms (n):* One

**Method:***Population characteristics*

Number of participants selected: 130 (500 reviewed)

Number of participants analysed: 130

Number of participants selected but not followed up: Not applicable

*Sampling frame:* Patients with prostate cancer who had MRI of spine between January 2001 and May 2005, from the institution database of The Royal Marsden Hospital, UK

*Method of sample selection:* Not reported

*Sex (M/F):* All male patients

*Age of patients:*

Mean (SD) – Not reported

Median – 70 years

Range – 50–88 years

*Interval from the time of diagnosis of cancer(s) to study entry:* 1355 days (median); range 219–6412 days

*Interval from the time of diagnosis of spinal metastases to study entry:* Not reported

*Length of follow-up per patient:*

Mean (SD) – Not reported

Median – 11 months (follow-up after MRI)

Range – 1–50 months (follow-up after MRI)

*Cancer type(s):* Castration-resistant prostate cancer

*Sites of metastasis:* Spine

Author: Venkitaraman 2010<sup>133</sup>

Performance status scores: Not reported

Visceral metastasis: Unclear

Duration and rapidity of cord compression: Not reported

Spinal level:

Cervical – Unclear

Thoracic – Unclear

Lumbar – Unclear

Other – Spinal cord or cauda equina

Spinal instability: Not reported

Medications: Not reported

**Intervention (i.e. screening technologies):**

MRI. MRI findings were classified as (1) rSCC and (2) no rSCC

**Outcomes:**

List of potential prognostic factors examined: rSCC during first MRI; PSA level at the time of initial MRI; PSA doubling time; radiotherapy; back pain

List of potential prognostic factors identified as significant: High PSA level at the time of initial MRI; short PSA doubling time <3 months

Have prognostic factors been validated in another population: No

**Findings:**

Thirty-seven (28.4%) of the 130 patients had rSCC during initial MRI. Median overall survival was 416 days (95% CI 23 to 987 days)

Those who had rSCC during initial MRI ( $n = 37$ ): 10 patients (27%) developed a repeat rSCC on MRI during follow-up. The median time to a second rSCC from the initial MRI was 161 days (95% CI 63 to 259 days). In 6 out of the 10 patients, recurrences occurred at the same site of initial rSCC and radiotherapy

Proportion of patients with neurological deficit due to SCC at the same site of radiotherapy in the spine was 7.5% at 6 months and 15.4% at 1 year and 18.8% at 2 years (unclear what N is or if it differs between time points)

Six of 37 patients (16.2%) developed irreversible paraparesis on follow-up

Those who had no rSCC during initial MRI ( $n = 93$ ): 20 patients (21.5%) developed SCC during repeat MRI. The median time to development of an rSCC for patients with no rSCC on initial MRI was 283 days (95% CI 229 to 337 days). Eight patients (8.6%) developed paraparesis on follow-up

High PSA level at the time of initial MRI (HR 2.04, 95% CI 1.05 to 3.96;  $p = 0.035$ ) and short PSA doubling time <3 months (HR 0.397, 95% CI 0.19 to 0.79;  $p = 0.009$ ) were found to significantly predict for adverse neurological deficit survival on univariate analysis

rSCC on initial MRI ( $p = 0.11$ ) or radiotherapy ( $p = 0.1$ ) were not predictive. Back pain ( $p = 0.059$ ) although an important predictive factor did not attain statistical significance

On multivariate analysis, only a rapid PSA doubling time (<3 months) independently predicted for future neurological deficit ( $p = 0.042$ )

**Author conclusions:**

Magnetic resonance imaging of the spine can be used to detect asymptomatic rSCC in patients with castration-resistant prostate cancer and serial estimations are required to maintain a low incidence of clinical SCC. If serial screening MRI of spine is used to detect rSCC in 90% of patients before the development of neurological signs, the optimum frequency depends on the subset of patients studied

**Reviewer conclusions:**

The study findings are consistent with the notion that in castration-resistant prostate cancer patients lacking neurological deficit but with an MRI scan suggestive of occult SCC (i.e. with rSCC), neurological deficit will develop sooner than in those patients whose MRI scan is negative for occult SCC. Only 37 (28%) patients had occult SCC and so the study lacked power. Rapid escalation of serum PSA was found to be associated with increased risk of neurological deficit



## Appendix 8 Quality assessment results

TABLE 37 Quality assessment results

Subheadings and questions of quality assessment																
A	B			C						D	E	F				
First author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16
Bayley 2001 <sup>107</sup>	P	Y	P	Y	Y	NA	Y	Y	Y	UN	N	P	Y	Y	Y	Y
Bernat 1983 <sup>108</sup>	P	Y	P	Y	N	NA	P	Y	Y	UN	N	P	Y	N	Y	Y
Chaichana 2009 <sup>109</sup>	Y	N	P	N	N	N	N	P	Y	P	N	P	P	Y	Y	Y
Fisher 2010 <sup>110</sup>	N	N	N	N	N	N	N	P	P	P	N	P	P	N	P	P
Goldman 1989 <sup>111</sup>	P	P	P	Y	Y	NA	Y	P	Y	NA	N	P	P	N	P	N
Harrison 1985 <sup>112</sup>	Y	P	P	Y	Y	NA	Y	Y	Y	NA	N	P	Y	N	Y	Y
Helweg-Larsen 2000 <sup>113</sup>	Y	P	P	Y	Y	NA	Y	P	Y	NA	N	P	P	N	P	Y
Helweg-Larsen 1995 <sup>114</sup>	Y	P	P	Y	Y	NA	Y	P	Y	NA	N	P	P	N	P	P
Huddart 1997 <sup>115</sup>	Y	Y	Y	Y	Y	NA	Y	P	Y	P	N	P	P	P	Y	Y
Husband 2001 <sup>116</sup>	Y	Y	Y	Y	Y	NA	Y	Y	Y	NA	N	P	Y	N	Y	P
Klekamp 1998 <sup>117</sup>	P	P	P	Y	NA	NA	Y	P	Y	P	N	P	P	P	Y	Y
Kuban 1986 <sup>118</sup>	P	N	P	Y	NA	NA	Y	Y	P	N	N	P	Y	N	P	N
Levack 2002 <sup>119</sup>	P	Y	P	Y	Y	NA	Y	Y	Y	N	N	P	P	UN	Y	N
Lu 1998 <sup>120</sup>	Y	Y	Y	Y	Y	P	Y	Y	Y	P	N	Y	Y	P	Y	Y
Lu 2005 <sup>121</sup>	Y	Y	Y	Y	Y	P	Y	Y	Y	P	N	P	Y	N	Y	Y
McCloskey 1993 <sup>122</sup>	P	P	P	Y	P	N	P	Y	Y	P	N	P	Y	N	Y	Y
Oka 2006 <sup>123</sup>	Y	Y	Y	Y	Y	NA	Y	Y	Y	P	N	P	Y	Y	Y	Y
Plunkett 2000 <sup>24</sup>	Y	P	P	Y	Y	N	P	P	P	N	N	P	P	N	Y	Y
Rose 2009 <sup>88</sup>	P	Y	P	Y	Y	NA	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
Roth 2004 <sup>124</sup>	Y	P	P	Y	Y	NA	Y	Y	Y	UN	UN	P	P	N	P	Y
Sekine 2009 <sup>125</sup>	Y	Y	Y	Y	Y	NA	Y	Y	Y	UN	N	Y	Y	P	Y	Y
Shah 2003 <sup>126</sup>	Y	Y	Y	Y	Y	NA	Y	Y	Y	P	N	P	Y	N	P	Y
Snyder 2005 <sup>127</sup>	N	N	N	UN	UN	UN	UN	Y	Y	UN	N	P	Y	N	P	Y
Snyder 2009 <sup>128</sup>	P	Y	P	Y	UN	NA	P	Y	Y	UN	N	P	Y	N	Y	Y

continued

TABLE 37 Quality assessment results (continued)

Subheadings and questions of quality assessment																	
A	B			C						D		E	F				
First author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	
Soerdjbalie-Maikoe 2004 <sup>129</sup>	P	N	P	Y	Y	NA	Y	Y	Y	Y	N	Y	Y	UN	P	P	
Sun 2011 <sup>130</sup>	Y	Y	Y	Y	Y	NA	Y	Y	Y	P	N	P	Y	P	P	P	
Talcott 1999 <sup>131</sup>	Y	Y	Y	Y	Y	P	Y	Y	Y	P	N	Y	Y	P	Y	Y	
Taneichi 1997 <sup>89</sup>	P	Y	P	Y	Y	NA	Y	Y	Y	P	N	P	Y	N	P	Y	
Venkitaraman 2007 <sup>132</sup>	Y	Y	Y	Y	Y	NA	Y	Y	Y	P	N	P	Y	N	Y	Y	
Venkitaraman 2010 <sup>133</sup>	Y	Y	Y	Y	Y	NA	Y	Y	Y	P	N	P	Y	N	Y	Y	
<b>Total ratings</b>																	
Y	17	17	11	27	22	0	23	22	27	2	0	5	20	4	19	22	
P	11	8	17	0	1	3	4	8	3	14	0	25	10	6	11	5	
N	2	5	2	2	3	4	2	0	0	3	29	0	0	18	0	3	
UN	0	0	0	1	2	1	1	0	0	6	1	0	0	2	0	0	
NA	0	0	0	0	2	22	0	0	0	5	0	0	0	0	0	0	

N, no; NA, not applicable; P, partly; Q, question; UN, unsure; Y, yes.

**Key: Study population/sample selection:** Q1: Inclusion and exclusion criteria are adequately described [including pretreatment, diagnosis (primary and metastases), start/finish date recruitment]; Q2: Baseline study sample [i.e. individuals entering the study and their key characteristics (where relevant) and sampling frame are adequately described]; Q3: Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results. **Study attrition:** Q4: Statement as to exclusions due to missing data: Baseline variables; Q5: Statement as to exclusions due to missing data: Loss to follow-up; Q6: Statement as to the possible effect on the results from missing data; Q7: Loss to follow-up is not associated with key characteristics. **Prognostic factor measurement:** Q8: Clear definition of the prognostic factors measured is provided (e.g. imaging modality method, measurement, and timing described); Q9: Specified instrument and personnel for measurement of predictive factors; Q10: Continuous variables are reported or appropriate (i.e. not data-dependent) cut-off points are used and specified a priori; Q11: Blinding: were estimators of risk factor status and of outcomes blinded?; Q12: The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias. **Outcome:** Q13: Is the outcome clearly defined? **Confounding measurement and account:** Q14: Do the authors address potential confounders? **Analysis:** Q15: There is sufficient presentation of data to assess the adequacy of the analysis; Q16: The statistical analysis is appropriate for the study design, limiting potential for the presentation of invalid results.

Note: The review by Loblaw (2005)<sup>62</sup> is not listed in this table; please refer to *Appendix 7* for quality assessment of this paper.

## Appendix 9 Cost information relative to the treatment of spinal metastases

Early diagnosis and treatment of SCC is essential for the preservation of neurological function.<sup>107</sup> However, diagnosis is frequently not established until significant neurological deficit is present, by which time functional recovery may be difficult. At this stage treatment may need to be undertaken as an emergency, often with reduced efficiency and at increased cost. Therefore, early diagnosis of SCC before the development of symptoms may allow for treatment to preserve neurological function in some patients who might otherwise be left with significant problems. This may in turn result in more efficient management of diagnostic and therapeutic staff and facilities, and reduce long-term costs of caring for disabled patients. However, none of the identified studies discussed costs or cost-effectiveness.

In the NICE clinical guideline for MSCC,<sup>15</sup> the cost of each MRI scan during normal working hours (i.e. Monday to Friday 0900 to 1700) has been assumed to be £244 on the basis of the national NHS unit cost information. The cost of an MRI scan increases up to £3878 if it is carried out during the extended opening hours (i.e. Monday to Friday between 0800 and 0900 and between 1700 and 2000; and on Saturday and Sunday between 0900 and 1500). These costs should be interpreted with some caution as the guideline had used the NHS reference costs of 2006/7. The guideline also estimated costs of different types of treatment.<sup>15</sup> It has been estimated that radiotherapy per patient, including its administration and treating complications, would cost £1276.50. The costs of vertebroplasty and major surgery were estimated to be £9350 and £13,094, respectively. The guideline also estimated cost of patient care. Those looked after at home would cost £13 or £193 depending on whether the patient was ambulant or non-ambulant. It would cost £81 for those looked after in a nursing home. Please note that these costs were estimated from the NHS reference costs of 2006/7 and therefore should be interpreted carefully.

**TABLE 38** Cost estimation of MRI scan and different treatments

Treatments	Estimated cost per patient (£)
MRI scan during standard working hours	244.00
MRI scan during extended working hours	3878.00
Radiotherapy	12,760.50
Vertebroplasty	9350.00
Major surgery	13,094.00

Source: Adapted from NICE CG75.<sup>15</sup>



# Appendix 10 Short report protocol

## 1. Title of the project:

Natural History of Spinal Metastases

## 2. Name of TAR team and project 'lead'

Produced by:

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Date Completed: 4 May 2011

This project was commissioned by the NIHR HTA Programme as project number 10/91.

The views expressed in this protocol are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

Conflicts of interest: The authors have no conflicts of interest.

### 3. Plain English Summary

When a cancer spreads to a new and different site in the body it very often locates in the bony skeleton. The commonest place for these new cancers in bone is in one or more vertebrae in which case they are called spinal metastases. Sometimes these spinal metastases do not cause symptoms, however they can be a source of severe pain or weakness in the vertebra which may fracture. Spinal metastases may also grow so that the spinal nerve cord that runs through the length of the vertebral column is compressed. When a vertebra fractures it may result in the spine becoming bent or twisted making every day movements more difficult, and there is a danger that vertebral fracture and collapse may also cause compression of the spinal cord. Compression of the spinal cord carries with it the risk of paralysis of body structures below the level of compression. If it were possible to predict which vertebrae were more likely to fracture then early targeted treatment might prevent, reduce or delay such events and the serious unwanted outcomes that might result. The present project aims to look at the scientific evidence about predicting vertebral fracture and spinal compression resulting from spinal metastases so as to find out whether accurate predictions can be made or whether further scientific research is required.

### 4. Decision problem

The objective of this short report is to determine if there is sufficient evidence in the literature deriving from natural history and imaging studies of patients known to have spinal metastases to identify those at high risk of progression to spinal compression and or to spinal collapse. In this context we will look for studies of spinal metastatic disease which identify candidate risk factors that can identify individuals or their vertebrae at risk of these undesirable outcomes. This will be done by systematic review, quality assessment and evidence synthesis of the relevant literature. The remit for this short report stated that the purpose was not to develop a decision rule (e.g. development of a multivariable risk prediction model (1)). However, studies that have developed such models will be included in the review. Ideal studies of this type will have prospectively studied a defined cohort of patients to identify risk factors independently associated with outcome (in this case spinal compression and or spinal collapse) and have prospectively tested the decision rule in a different and appropriate cohort of patients (2).

Other studies may consider patients whose vertebrae collapse without warning (e.g. asymptomatic spinal metastases) and these will be used to map the natural history.

#### 4.1 Background

##### Spinal Metastases

Metastatic cancer is the most common neoplasm involving the skeletal system (3). Prostate, lung and breast cancer all metastasise to bone and are all common accounting for more than 80% of cases of spinal metastatic bone disease (4). Spinal metastases can lead to significant morbidity due to neural compression, pain, and pathologic fracture. Pressure on the periosteum or adjacent neural structures can cause local or radiating pain (5).

The average time from original diagnosis of cancer to development of spinal metastases has been estimated to be ~32 months and the average time from detection of spinal metastases to spinal compression ~27 months (6). Average survival for patients with spinal cord compression has been reported to be 3 to 7 months with a 36% probability of survival to 12 months (6).

##### Epidemiology

Spinal metastasis is common in patients with cancer. Tse (7) reported that 60-70% of patients with systemic cancer develop spinal metastasis and 10% of these patients are symptomatic. Approximately 5 to 10% of cancer patients develop metastatic spinal cord compression (MSCC) during the course of their disease (8). Multiple myeloma (strictly spinal multiple myeloma is not metastatic, it will not be reviewed in

this report) or plasmacytoma, non-Hodgkins lymphoma, and renal cell cancers each account for 5 to 10% of cases (9).

## Treatment

Primary treatment has often relied on radiation therapy (10) with or without systemic chemotherapy or hormonal therapy. More recently systemic treatments with radionuclides (11;12) and bisphosphonates (13;14) have shown positive clinical outcomes. Denosumab has also been used for the prevention of fractures in postmenopausal women with osteoporosis (15) and has been considered for the use with spinal metastases (16). Although the availability of effective treatments has been reported, many studies have documented the lack of adequate pain management for these patients (17).

A large number of prospective trials have investigated the effectiveness of external beam radiation therapy for palliation of pain or control of progression of osseous metastatic disease (18-26). Local radiotherapy plays an important role in the management of bone metastases (27). Agarawal et al., (28) reported results from a meta-analysis of radiotherapy data finding that one month after treatment, over 40% of patients were likely to have 50% reduction in pain but that fewer than 30% were expected to have complete pain relief. Stereotactic single fraction "radio-surgery" has shown promise (29) and such new approaches for the treatment of vertebral metastases using very steep dose gradients from intensity-modulated radiotherapy (IMRT) have been proposed (30).

Radiofrequency ablation (RFA) is an image-guided minimally invasive treatment for solid tumours (4). Patients who are not responding to conventional treatment frequently have a contraindication to initial or repeat radiation, and those who have limited disease, may benefit from palliation with RFA. RFA can safely palliate pain from bone metastases (4). RFA has been used for patients with persistent pain from a solitary focus of metastatic disease who have been treated, or in localized disease where a more local ablative therapy can be performed as an alternative to external beam radiotherapy (31;32).

Percutaneous image-guided procedures for providing local tumour ablative therapy such as ethanol injection (33), vertebroplasty (34;35) and RFA (36;37) have also shown some promise in the treatment of metastatic bone lesions.

A question remains about when treatment should start and whether asymptomatic metastases should be treated prophylactically.

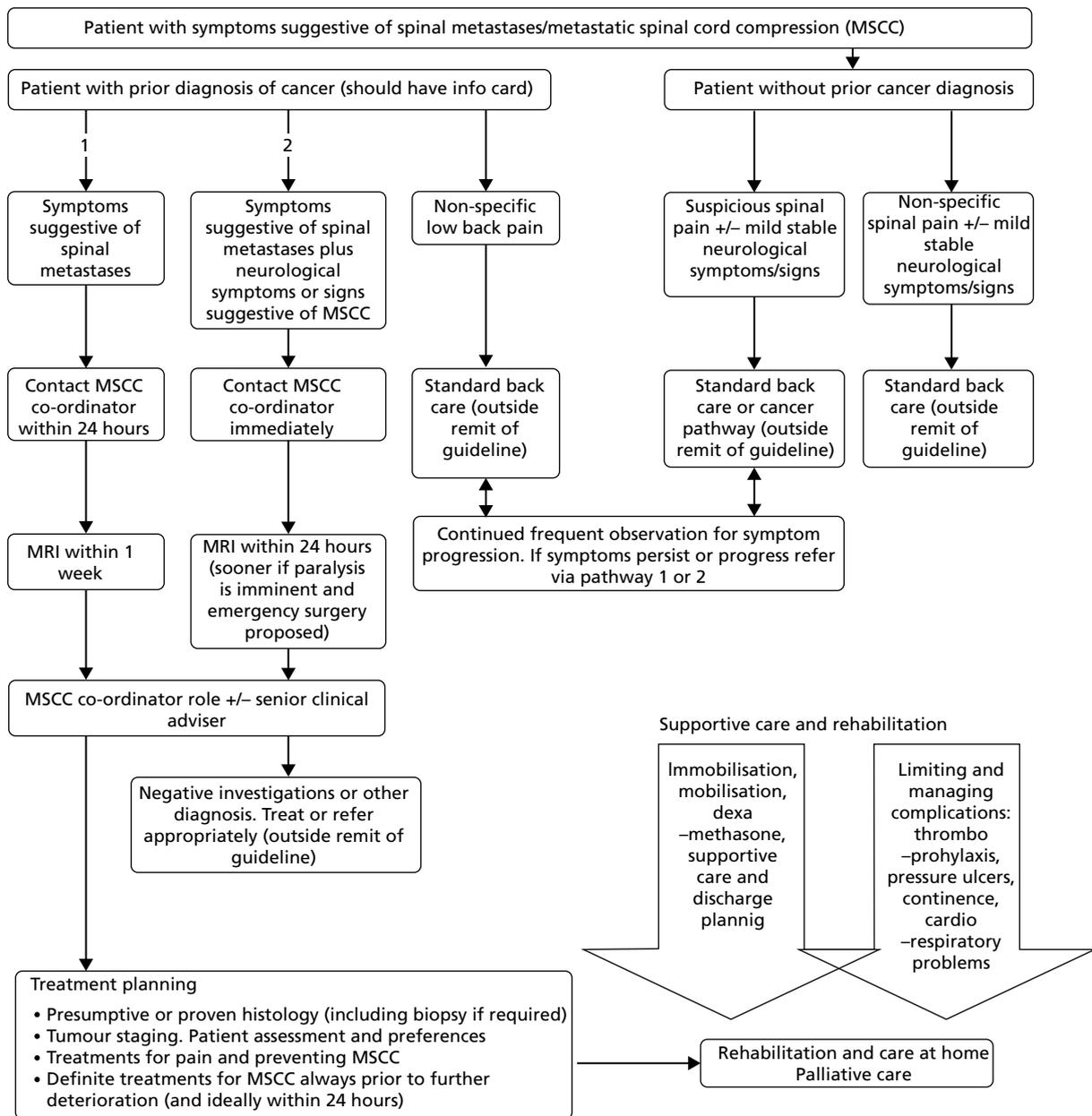
## Spinal cord compression

Spinal cord compression is a critical condition which requires emergency care to prevent loss of neurological function and to reverse established deficits (38). Surgical indication can include bony compression and spinal instability (39). Surgery is often restricted to patients with involvement of one spinal segment with a good performance status and expected life span of >3 months (8).

## Management

In November 2008 NICE issued a clinical guideline for the diagnosis and management of adults at risk of and with metastatic spinal cord compression (40). The guidelines contained treatment algorithms for patients with symptoms suggestive of spinal metastases. The guideline proposed the patient treatment pathways shown in Figure 1.

Radiation therapy and different forms of surgery are the primary methods for treating spinal cord compression. High-dose steroids are administered with radiation treatment and tapered gradually with completion of treatment (38). Surgical interventions include decompression and fixation for the following indications: spinal instability or bony compression, intraspinal bony fragment, impending sphincter dysfunction; single site cord compression, radioresistant tumour; neurological progression during or after radiation treatment or a previously radiated site that has received a maximum cord tolerance dose (9;39).



**FIGURE 1** Patient treatment pathways for diagnosis and management of adults at risk of and with metastatic spinal cord compression. Redrawn from (40)

### Imaging and detection

Spinal metastases may be asymptomatic and detected during routine examination of cancer patients, but suspicious clinical examination or suggestive symptoms such as pain, are more likely to lead to investigation and detection. Detection and localisation of bony metastases is undertaken using various imaging technologies including: radiography, CT scanning, PET with [<sup>18</sup>F] labelled 2 fluoro 2 deoxy-glucose, MRI, and bone scintigraphy using Tc-99m methylene diphosphonate (41-43). There is active discussion in the literature regarding which method or combination of methods (e.g. integrated CT / PET) is most useful and appropriate; nevertheless no method achieves 100% sensitivity or specificity; equivocal images are encountered and methods may yield discordant results. Equivocal diagnoses can be refuted or supported using bone biopsy and or fine needle aspiration, but these procedures are not routinely undertaken. There appear to be no guidelines that recommend specific imaging modalities, however NICE guideline

75 (40) for diagnosis and management of adults at risk of and with metastatic spinal cord compression recommends that MRI imaging should be undertaken very soon after diagnosis or suspected diagnosis.

### *Types of prognostic studies*

In our preliminary scoping searches of the published literature it has become clear it would be impossible to investigate “natural history” without treatment. Although older literature may describe the development of spinal metastases without treatment, the population in these studies are not likely to be representative because imaging modalities will differ from those of today and patients included are likely to be only those with well-developed disease. It has also become clear that the natural history and progression of spinal metastases is likely to be influenced by numerous factors including type of primary tumour (breast, kidney, lung, prostate and myeloma) and current and previous anti-cancer treatments received. A further consideration is whether metastases are osteolytic or osteoblastic. This means that the review team anticipate that there may be several types of progression and each may be associated with different prognostic factors. In other words, progression and risk will have some degree of specificity for the particular primary cancer concerned. Identification of candidate predictors of spinal compression and of spinal collapse will require examination of a wide variety of studies and study designs that are not well indexed in electronic databases and not generally well described within the titles and abstracts of published studies.

Scoping searches have revealed that four main types of prognostic study have been undertaken with regard to metastatic spinal metastases. These comprise:

- Attempts to determine the risk factors which allow the identification of patients most suitable for surgical intervention (e.g. scoring schemes such as Tokuhashi (44;45); Tomita (46) and others). Some of these studies are specific for metastases derived from particular primary tumours (e.g. lung, breast etc);
- Attempts to identify risk factors for survival of patients not considered suitable for radical surgery and who should therefore receive various forms of palliative care (47);
- Attempts to identify risk factors important in determining the survival of patients after surgical interventions for spinal cord compression and or vertebral compression fracture(s) (48;49) (e.g. vertebrectomy and reconstruction, vertebroplasty, kyphoplasty, radiofrequency ablation);
- Assessment of risk factors of clinical or imaging technologies for progression of metastatic spinal metastases to spinal cord compression and or to vertebral compression fracture(s) (50;51). These studies will be the focus of the current short report. As such they might serve several purposes: for example to inform the choice about potential pre-emptive intervention(s) so as to avoid or delay more radical surgical intervention; to bring forward radical interventions before patient health deteriorates to the extent that they are no longer suitable candidates for these interventions; to categorise patients into those more or less suitable for earlier or later radical intervention.

An ideal simple natural history study would be one which follows up patients that have spinal metastases to see how many progress to vertebral collapse or cord compression, especially if factors predictive of these events are recorded.

Scoping searches identified a 2011 systematic review (52) that looked at the evidence about potential predictors of instability and impending instability of the thoracolumbar spine in patients with spinal metastases. The authors included fourteen primary studies which they rated as of good quality and identified the following potential predictors of instability: tumour size, a larger cross sectional area of bone defect, increased force of spinal loading, decreased bone density, posterior location of the tumour within the vertebrae, destruction of the costovertebral joint, pedicle destruction in the thoracolumbar spine, increased axial rigidity, and sagittal spinal deformity. However, much of the work (64%) reported in this review was of biomechanical post mortem studies and the authors were unable to reach definitive conclusions, they commented that this research area required improved research methodology.

## Report methods for synthesis of evidence

The current short report aims to provide an evidence-based perspective on the natural history of metastatic spinal lesions to be able to identify patients at high risk of progression or spinal collapse, either clinically or using imaging investigations.

A systematic review of the evidence for predictive utility of candidate risk factors will be undertaken following the general principles recommended in the PRISMA statement (53;54).

Reviews will also be identified and included in the current report.

### 5.1 Identification and selection of studies

Initial scoping searches have been carried out to assess the volume and type of literature relating to the assessment question. The yield of studies that describe spinal metastases, their progression and the imaging modalities employed in detecting and monitoring disease progression, is numbered in thousands. A narrative synthesis of the evidence on disease progression in relation to all metastases is therefore not feasible within the time constraints of this project, especially since progression of metastases will differ depending on primary tumour.

#### Search strategy

Difficulties can be encountered when literature searching for prognostic studies. There are no widely acknowledged optimal search strategies for searching literature for prognostic studies (55). Strategies for searching Medline and Embase for prognostic studies have been developed and tested, the most sensitive of which range in sensitivity from 82.3% in Medline (56) to 98.7 in Embase (57).

Scoping searches have been undertaken to inform the development of the search strategy. An iterative procedure was used, with input from clinical advisors and previous HTA and systematic reviews (e.g. Cooper et al., 2011 (58), National Collaborating Centre for Cancer 2008, Sutcliffe et al., 2009 (59)). A copy of the search strategy that is likely to be used in the major databases is provided in Appendix 1. This draft search strategy developed for MEDLINE will be adapted as appropriate for other databases. This strategy covers the concepts of metastatic spinal lesions, adults and outcomes (spinal cord compression, vertebral compression, vertebral collapse, or progression of vertebral collapse). The addition of other concepts to this strategy such as natural history, technologies and prediction or prognosis, will be developed as the project progresses. Search filters for prognosis have been identified and assessed.

The search strategy will comprise the following main elements:

- Searching of electronic bibliographic databases
- Contact with experts in the field
- Scrutiny of references of included studies

#### Databases will include

MEDLINE; MEDLINE In-Process & Other Non-Indexed Citations; EMBASE; Cochrane Database of Systematic Reviews; CENTRAL; DARE, NHS EED, HTA databases (NHS-CRD); Science Citation Index and Conference Proceedings (Web of Science); UKCRN Portfolio Database; Current Controlled Trials; Clinical Trials.gov.

The search strategy will not include limits for study design, as all types of study will be screened for potential inclusion.

In addition, the reference lists of relevant articles will be checked and various health services research related resources will be consulted via the Internet. These are likely to include HTA organisations, guideline producing bodies, generic research and trials registers. Citation searches of included studies will be

undertaken using the Web of Science citation search facility. The reference lists of included studies and relevant review articles will also be checked.

### **Inclusion of relevant studies**

Titles and abstracts of retrieved studies will be examined for inclusion by two reviewers independently. Disagreement will be resolved by retrieval of the full publication and consensus agreement. The following inclusion criteria will be used:

#### **Study design**

Prospective or retrospective case series, cohort or case-control studies (case studies will be excluded).

#### **Population**

Adult patients with vertebral metastases at risk of developing (or who have developed) metastatic spinal cord compression, vertebral collapse or progression of vertebral collapse.

#### **Intervention/Technologies**

Diagnostic/prognostic methods, including clinical features and/or imaging technologies (MRI, CT, PET, Technetium-99m scintigraphy, X-rays).

#### **Comparator**

None or another diagnostic/prognostic method.

#### **Outcomes**

Spinal cord compression, vertebral compression, vertebral collapse, or progression of vertebral collapse.

Due to the potential plethora of retrieved studies, the difficulties in identifying prognostic studies (i.e. full texts are often required to be able to confidently evaluate whether a prognostic paper meet the inclusion criteria) and constraints of time in a short report, some modification of the above PICO may be required. If necessary due to time constraints we will focus on breast and prostate cancer.

#### **Exclusion criteria**

- Animal models and post-mortem studies
- Preclinical and biological studies
- Editorials, opinions
- Reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality
- Studies not in English, French and German
- Studies where a majority of patients (>50%) is suffering from multiple myeloma

A record of all papers rejected at full text stage and reasons for exclusion will be documented.

### **Data extraction strategy**

The full data will be extracted independently by one reviewer using a data extraction form informed by the NHS Centre for Reviews and Dissemination (60) and previous HTAs involving prognosis (e.g. Sutcliffe et al., 2009 (59), see Appendix 2). Studies that give rise to uncertainty will be reviewed by a second researcher, and any disagreements will be resolved by discussion. Further discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary. Summary tables will be developed which list all clinical assessments, imaging, and other technologies which may inform prognosis of metastatic spinal lesions reported in the literature, with details of their prognostic value, where adequate information is available. We will not develop a prediction rule or other prognostic tool, but will provide information to assess whether the current evidence base allows such development without further data collection.

Data will be extracted to allow quality assessment of the included studies (see below).

### Quality assessment strategy

The quality of conduct and reporting of prognostic studies has received some criticism (2;61). Surveys indicate that the vast majority of such studies appear to have been undertaken on an ad hoc or opportunistic basis in absence of a defined research question or clear protocol for the design, conduct and analysis of the study. Common weaknesses include lack of information about whether outcomes, populations, and test cut-off were defined before data were collected. Selective reporting of analyses is also a common problem (61).

Due to these anticipated deficiencies the proposed systematic review will put emphasis on assessment of quality of primary studies and will attempt to incorporate quality findings into the evidence synthesis. For example, sensitivity analyses will be undertaken to assess the robustness of any meta-analysis conclusions to the inclusion/exclusion of low quality studies (i.e. those at most risk of bias). Quality assessment of included studies will be informed using the guidelines suggested by Hayden and colleagues as appropriate for prognosis studies (62) (Appendix 3) and modified as necessary according to Sutcliffe et al., (2009) (59) (further details are provided below and in Appendix 4). The risk of bias will be illustrated using the Cochrane Review Manager risk-of-bias tool (63).

There are no widely agreed criteria for quality assessing prognostic studies (Altman, 2001 (55)). Factors which need to be considered in the assessment of prognostic studies include: internal validity, external validity, statistical validity, evaluation of the model, and the clinical usefulness of the model (64-68). As there is an element of subjectivity in quality assessment, as well as a need for attention to detail as reporting methods and formats vary widely, disagreement between reviewers is not uncommon. Two team members will undertake quality assessment. Regular discussion meetings will therefore be arranged to resolve any uncertainty between the two members. A third team member will be asked to attend the meetings when agreement cannot be reached. A statistician will provide additional support in interpreting the statistical models and to validate the quality assessment scores assigned by the two reviewers.

In determining how to approach quality assessment in this short report we identified some systematic reviews of prognostic studies (18;66;67;69;70) to see how the issue had been addressed. The value of an overall quality score, which mixes different issues, has been questioned (71). Common themes in these earlier reviews were internal, external and statistical validity.

Hayden et al., (62) appraised how authors of reviews of prognostic studies had assessed study quality and provided recommendations as to the domains that should be considered, and also the questions which might contribute to the assessment of each domain. Domains proposed by Hayden to assess potential biases in prognostic studies were:

- Study population
- Study attrition
- Prognostic factor measurement
- Outcome measurement
- Confounding measurement and account
- Analysis

Within each of these categories, questions are proposed by Hayden et al., (62) to help assess the extent of possible biases. In line with the previous HTA work undertaken by Sutcliffe et al., (2009) (59) we propose to adapt these to make the questions relevant to the disease area, the types of studies available, and also to clarify the meaning of each question in the context of the short report. The resulting quality assessment tool which we may use is provided in Appendix 4.

In consultation with clinical and statistical advisors, other quality assessment checklists may need to be developed based on the quality assessment instruments used in published systematic reviews and in the literature of prognostic factors. A further example of a prognostic studies quality assessment checklist

is presented in Appendix 5. Validation studies will be assessed using relevant criteria from the quality assessment tool developed by the research team for prognostic models (particularly model evaluation) and the results reported together with the original model.

RCTs and systematic reviews will be quality assessed using an adapted checklist proposed by the NHS Centre for Reviews and Dissemination (60) (see Appendix 6).

### **Methods of analysis/synthesis**

Data will be tabulated and discussed in a narrative review. Each tumour type will be looked at separately.

Meta-analyses of prognostic results will be considered for each risk factor if it is deemed clinically meaningful to synthesise studies. Where meta-analysis is appropriate, for each risk factor of interest, effect estimates will be pooled across trials using a random effects meta-analysis model; this model takes into account between-study heterogeneity in effect estimates, which we believe is likely to occur. Primarily we will seek to synthesise odds ratio estimates (adjusted and unadjusted). But if relative risks are reported, then these will be synthesised if it is appropriate to do so. Heterogeneity across studies will be examined using the  $\chi^2$  test statistic and  $I^2$  statistic (which gives the percentage of the total variability in the data due to between-study heterogeneity) and the tau-squared statistic (which gives an estimate of the between-study variance). Each random-effects analysis will be summarised by reporting the mean prognostic effect estimate and its confidence interval; also we will provide a 95% prediction interval for the prognostic effect in a new study (72), so as to reveal how the effect may vary in different contexts and populations (73). This is important in order to identify the probability that each potential risk factor would actually have prognostic value in practice. If there are sufficient numbers of studies, sub-group analyses and/or meta-regression will be used to explore whether the following pre-specified variables explain any of the heterogeneity: bone density, population parameters, tumour type, imaging modality used, outcome event, length of follow up, and study quality (risk of bias).

It is possible that primary studies have been undertaken and published that have computed hazard ratios that compare populations categorised according to risk factor. Should such studies exist, random-effect meta-analysis using the extracted hazard ratios will be undertaken as above and when judged appropriate. Fitting parametric distributions to the reported Kaplan-Meier plots would be considered in order to illustrate the results from disparate studies should meta-analysis be considered inappropriate.

All the above models and analyses will be undertaken in a frequentist framework using the STATA software (74). Where it is not appropriate to pool data, studies will be tabulated and described separately.

For each meta-analysis containing 10 or more studies, the likelihood of publication bias will be investigated through the construction of contour-enhanced funnel plots (63;75). These help distinguish publication bias from other causes of asymmetry. We recognise that, especially where heterogeneity exists, publication bias may be one of a number of reasons for any small-study effects identified.

### **Report methods for synthesising evidence of cost-effectiveness**

Not applicable for this remit.

### **Expertise in this TAR team**

Warwick Evidence is a newly developed technology assessment group located within Warwick Medical School. Warwick Evidence brings together experts in clinical and cost effectiveness reviewing, medical statistics, health economics and modelling. The team planned for the work includes: Dr Paul Sutcliffe and Dr Martin Connock who are experienced senior systematic reviewers; Ms Rachel Court, information specialist;

Professor Aileen Clarke, professor of health services research; Professor Martin Underwood, professor of primary care and clinical specialist with an interest in back pain; Dr Kandala, principal research fellow in demography and medical statistics; and additional clinical specialists, Professor Charles Hutchinson, Mr Philip Sell and Professor Charles Greenough. Ms Amy Grove will provide project management support.

## Competing interests of authors

None of the authors have any competing interests, although Professor Underwood has been involved in NICE guidelines on back pain.

## Timetable/milestones

The project will be undertaken in phases, including: literature search, study selection, data abstraction and critical appraisal, evidence synthesis, and dissemination of the results. The project is currently planned to be completed in 3 months, once approval of the protocol has been confirmed and after pilot/scoping searches have been completed. Research Team Meetings will be conducted where appropriate via teleconferencing to minimise costs and reduce our carbon footprint. There will be weekly sub-team meetings and monthly expert consultation (via the telephone/email).

Draft protocol finalised TBC

Commissioning decision TBC

Progress report TBC

Draft assessment report TBC

Assessment report 31 October 2011

The proposed draft timelines are shown below:

Project Tasks	Aug 2011	Sept 2011	Oct 2011
Protocol confirmation			
Searching and collecting studies			
Study assessment, data extraction			
Evidence synthesis			
Progress report to NCCHTA			
Writing draft report			
Peer review			
Final report and paper writing			

## 10.1. APPENDICES

### APPENDIX 1 DRAFT SEARCH STRATEGY

#### Medline via Ovid interface, searched on 19/05/2011

Spinal Neoplasms/	9801
((spine or spinal or vertebr* or cervical spine or cervical vertebrae or thoracic or lumbar or sacral or sacrum or coccyx) adj3 (metasta* or lesion* or neoplasm* or neoplasia or tumor* or tumour* or cancer* or carcinoma* or malignan* or adenocarcinoma*)).mp.	33803
1 or 2	33803
metasta*.mp.	297575
exp Neoplasm Metastasis/	134650
4 or 5	302301
3 and 6	7718
limit 7 to (english language and humans and "all adult (19 plus years)")	3980
Fractures, Compression/	697
Spinal Cord Compression/	8636
Polyradiculopathy/	2044
Spinal Fractures/	8239
exp Paralysis/	63791
((spine or spinal or vertebra* or cord) adj5 (collapse* or compression or fractur* or instability)).mp.	27635
compression fracture*.mp.	1924
(cauda equina or polyradicul*).mp.	10451
(paralysis or paraly?ed or plegia or paraplegi* or hemiplegi* or quadriplegi* or tetraplegi*).mp.	83273
(fracture adj3 progression).mp.	35
9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	126217
8 and 19	984

mp. searches the fields: [mp=title, original title, abstract, name of substance word, subject heading word]

## APPENDIX 2 DATA EXTRACTION FORM

### Data extraction tables

Note this table will be piloted and it is anticipated will be used for all included studies whether natural history or prognosis.

#### *Paper ID*

1<sup>st</sup> Author:      Year:      Ref ID:

Reviewer:

#### 1. Study Design

- A.** Cohort = 1                      Case control = 3              Case series = 2      Other = 4  
**B.** Retrospective = 1              Prospective = 2

#### 2. Treatment received by population in study prior to assessment of candidate risk factors

0 = None / not reported	1 = Watchful waiting/ active monitoring
2 = Surgical radical resection (spondectomy)	3 = Surgical reconstruction
4 = Laminectomy	5 = Transpedicular approach
6 = Posterior approach	7 = Costotransversectomy approach
8 = Lateral extracavitary approach	9 = Minimally invasive endoscopic approach
10 = Kyphoplasty	11 = Radiotherapy
12 = Radiation therapy	13 = Robotic radiation therapy
14 = Stereotactic radiation therapy	15 = Intensity-modulated radiation therapy
16 = Spinal stabilization	17 = Medication
18 = Other/mixed	

#### 3. Imaging modalities used to detect metastases and to monitor progression to outcomes of interest

Imaging modalities	No. patients (%)
--------------------	------------------

#### 4. If treatments received according to prediction criteria and relevant outcomes have been reported these details will be extracted and recorded

Treatments received post prediction	Outcomes reported
-------------------------------------	-------------------

## 5. Baseline study characteristics

Paper	Method	Study participation	Outcomes
Author	Aim:	Age:	Endpoints:
Country	<i>Was primary aim of paper to assess prognosis?</i>	Median –	Risk factors:
Journal	<i>Was primary aim of paper to assess natural history</i>	Mean –	Length of follow-up:
	Study design:	Range –	Median –
	Sample size:	Distribution –	Mean –
	<i>Initial:</i>	Sex:	Range –
	<i>In Analysis:</i>	Racial characteristics:	Results reported at X years –
	Inclusion criteria:	Type of primary tumours:	New collapse of vertebrae:
	Start and finish dates:	Non-osseous metastases present (distribution, number, not reported):	Progression of previously collapsed vertebrae:
	Time to event analysis conducted (Cox regression) and/or logistic regression:	Completeness of data:	Compression of spinal cord (proposed causes e.g. bone fragment, growth of metastases):
	Diagnosis of spinal metastases:	Withdrawals and losses to follow up:	Overall survival:
			Quality of life:
			Pain:

## 6. Primary disease and metastases

Primary disease	No. of Vertebrae and location	Primary disease	No. of Vertebrae and location
Myeloma		Breast Cancer	
Renal Cell Carcinoma		Lung cancer	
Malignant lymphoma		Prostate Cancer	

## 7. Potential predictors of instability

Candidate Risk Factor	Yes/no/not reported	Specify
Tumor size		
Larger cross-sectional area of bone defect		
Increased force of spinal loading		
Decreased bone density		
Location of the tumour within the vertebrae		
Destruction of the costovertebral joint		
Pedicle destruction in the thoracolumbar spine		
Increased axial rigidity		
Sagittal spinal deformity		
Magnitude of spinal loading		
Tumour location within the spine / site of involved vertebrae		

continued

Candidate Risk Factor	Yes/no/not reported	Specify
Tumour type		
Blood calcium level		
Lesion type (e.g. lytic / blastic / mixed)		
Other(s)		

Note: Adapted from Weber *et al.*, 2011 (52)

**8. Evaluation of risk factor effect on outcome (univariate analyses)**

Candidate Risk Factor	Mode of analysis (logistic regression/ time event)	Adjusted or unadjusted odds ratio/hazard ratio and 95% CI	P value
General health scale			
No. extraspinal bone metastases foci			
No. metastases in the vertebral bodies			
Metastases to the major internal organs			
Primary site of the cancer			
Spinal cord palsy			
Performance index (Karnovsky score)			
Subluxation			
Other(s) specify.....			
.....			

**Author’s conclusion:**

**Reviewer’s conclusion:**

**9. Evaluation of risk factor effect on outcome (multivariate analyses)**

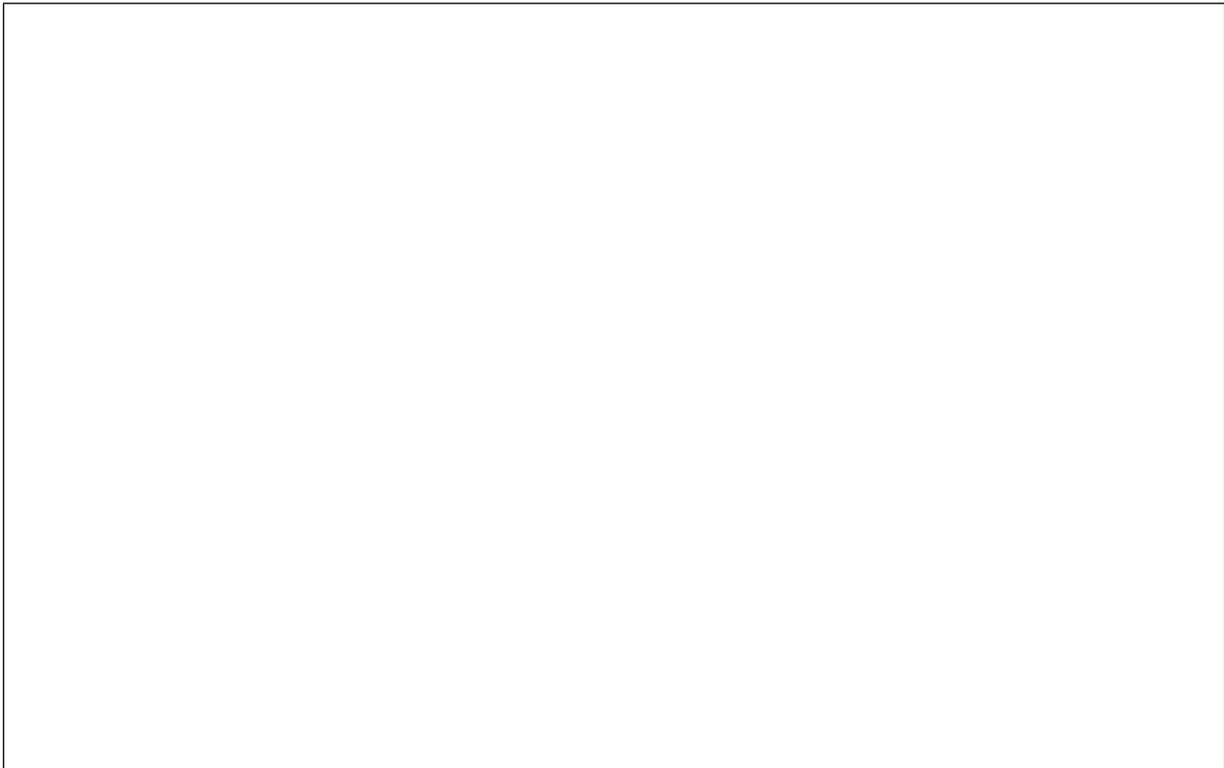
Number of factors (prognostic markers) in final model?

Candidate Risk Factor Risk factors (prognostic markers) in proposed models?	Mode of analysis (logistic regression/ time event)	Adjusted or unadjusted odds ratio/hazard ratio and 95% CI	P value
Specify identity of combined variables (and relative weighting as appropriate) Model 1			
Specify identity of combined variables (and relative weighting as appropriate) Model 2			
Continue as required			

**Author’s conclusion:**

**Reviewer’s conclusion:**

## Summary Conclusions



### APPENDIX 3 ASSESSMENT OF RISK OF BIAS IN PROGNOSTIC STUDIES (HAYDEN ET AL., (62))

Potential Bias	Items To Be Considered for Assessment of Potential Opportunity for Bias
<p>Study participation</p> <p>The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results.</p> <p>Yes</p> <p>Partly</p> <p>No</p> <p>Unsure</p>	<p>The source population or population of interest is adequately described for key characteristics.</p> <p>The sampling frame and recruitment are adequately described, possibly including methods to identify the sample (number and type used, e.g., referral patterns in health care), period of recruitment, and place of recruitment (setting and geographic location)</p> <p>Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or “zero time” description).</p> <p>There is adequate participation in the study by eligible individuals.</p> <p>The baseline study sample (i.e., individuals entering the study) is adequately described for key characteristics.</p>
<p>Study attrition</p> <p>Loss to follow-up (from sample to study) is not associated with key characteristics (i.e., the study data adequately represent the sample), sufficient to limit potential bias.</p> <p>Yes</p> <p>Partly</p> <p>No</p> <p>Unsure</p>	<p>Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.</p> <p>Attempts to collect information on participants who dropped out of the study are described.</p> <p>Reasons for loss to follow-up are provided.</p> <p>Participants lost to follow-up are adequately described for key characteristics.</p> <p>There are no important differences between key characteristics and outcomes in participants who completed the study and those who did not.</p>
<p>Prognostic factor measurement</p> <p>The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias.</p> <p>Yes</p> <p>Partly</p> <p>No</p> <p>Unsure</p>	<p>A clear definition or description of the prognostic factor measured is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).</p> <p>Continuous variables are reported or appropriate (i.e., not data-dependent) cut-points are used.</p> <p>The prognostic factor measure and method are adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).</p> <p>Adequate proportion of the study sample has complete data for prognostic factors.</p> <p>The method and setting of measurement are the same for all study participants.</p> <p>Appropriate methods are used if imputation is used for missing prognostic factor data.</p>
<p>Outcome measurement</p> <p>The outcome of interest is adequately measured in study participants to sufficiently limit bias.</p> <p>Yes</p> <p>Partly</p> <p>No</p> <p>Unsure</p>	<p>A clear definition of the outcome of interest is provided, including duration of follow-up and level and extent of the outcome construct.</p> <p>The outcome measure and method used are adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).</p> <p>The method and setting of measurement are the same for all study participants.</p>

Potential Bias	Items To Be Considered for Assessment of Potential Opportunity for Bias
Confounding measurement and account	All important confounders, including treatments (key variables in conceptual model), are measured.
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest.	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures). Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).
Yes	The method and setting of confounding measurement are the same for all study participants.
Partly	Appropriate methods are used if imputation is used for missing confounder data.
No	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).
Unsure	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis.
The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results.	The strategy for model building (i.e., inclusion of variables) is appropriate and is based on a conceptual framework or model.
Yes	The selected model is adequate for the design of the study.
Partly	There is no selective reporting of results.
No	
Unsure	

## APPENDIX 4 QUALITY ASSESSMENT FORM:

### Assessing quality of prognostic studies on the basis of framework of potential biases (based on Hayden *et al.*, (62); see Appendix 3)

First Author:      Year:      ID:      Reviewer:

Potential bias	Items to be considered for assessment of potential opportunity for bias	Yes	Partly	No	Unsure	NA
<b>Study population</b>	<p>Inclusion and exclusion criteria are adequately described (including pre-treatment, diagnosis (primary and metastases), start/finish date recruitment)</p> <p>Baseline study sample (i.e., individuals entering the study) is adequately described for key characteristics: XX (where relevant)</p> <p>Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results</p>					
<b>Study attrition</b>	<p>Statement as to exclusions due to missing data: – baseline variables</p> <p style="text-align: right;">– loss to follow-up</p> <p>Statement as to the possible effect on the results from missing data</p> <p>Loss to follow-up is not associated with key characteristics</p>					
<b>Prognostic factor measurement</b>	<p>Clear definition of the prognostic factors measured is provided (<i>e.g. imaging modality method, measurement described</i>)</p> <p>Specified instrument and personnel for measurement non-vertebral factors</p> <p>Continuous variables are reported or appropriate (<i>i.e., not data-dependent</i>) cut-points are used</p> <p>Blinding: were estimators of risk factor status and of outcomes blinded?</p> <p>The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias</p>					
<b>Outcome</b>	Is the outcome clearly defined?					
<b>Confounding measurement and account</b>	Do the authors address potential confounders?					
<b>Analysis</b>	<p>There is sufficient presentation of data to assess the adequacy of the analysis</p> <p>The statistical analysis is appropriate for the study design of the study, limiting potential for the presentation of invalid results</p> <p>TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES)</p>					

*Note:* The above table was adapted from: Sutcliffe *et al.*, 2009 (59)

**Overall opinion of study quality =**

## APPENDIX 5 AN EXAMPLE OF QUALITY ASSESSMENT OF PREDICTIVE MODELS

### Quality assessment of predictive models

#### A. External validity

- (i) Was the model generated on a community- or hospital-based population? Patients admitted to hospitals are not representative of all patients with stroke in the community, and different hospitals admit different types of stroke patient. Models generated on hospital-based patients may therefore not be applicable to other stroke patients.
- (ii) Were patients with transient ischaemic attacks and subarachnoid haemorrhages included? (prognostic factors for these may be different from those for stroke)
- (iii) Were there major exclusion criteria (such as age, sex, or type of stroke) that may limit generalisability?
- (iv) Was there a description of the cohort of patients (e.g. age, sex, treatment) on which the models were developed so that clinicians could assess how similar it was to their own patients?

#### B. Internal validity

- (i) Was an inception cohort established? Prognosis should be studied in patients who are at a similar stage in the disease process (an 'inception cohort') since factors that affect prognosis may vary with the time since stroke. Studies in which patients were seen within one week of onset were defined as having the most adequate inception cohort.
- (ii) Were an adequate number of patients in the inception cohort followed up to minimise bias? We arbitrarily defined losses of less than 10% of the original cohort as adequate.
- (iii) Were baseline data collected prospectively? Data collected retrospectively (e.g. from case notes may be less accurate than prospectively collected data).
- (iv) Were references made to the outcomes' validity and reliability?
- (v) Were outcomes assessed at appropriate times? Outcomes should be assessed at a fixed time after stroke onset so that all patients are at a similar stage in the disease process, and long-term outcomes (>30 days) are more meaningful.
- (vi) Were some potentially important predictors not entered into the model? Models that do not include variables known to be important independent predictors are probably less reliable than those that do. It was difficult to define which factors were important in prognosis before completing this systematic review. However, age and stroke severity were likely to be important in prognosis and so we documented whether these variables were entered into the analysis.
- (vii) Were the predictive variables clearly defined, clinically valid, and was reference made to their reliability?

#### C. Statistical validity

- (i) Was the sample size adequate as defined by an EPV of 10 or more? Were interaction terms included for any variables? Was some form of stepwise analysis used and if not was collinearity between the variables assessed? Multiple regression can produce spurious results if all the variables are simply entered into a model and certain highly predictive variables are strongly correlated with each other (collinearity). This is less problematic in stepwise regression.

#### D. Evaluation of the model

- (i) Was the final model validated on the data that were used to generate the model (internal validation)? Models that do not produce accurate predictions on the patients who were used to generate it are clearly unreliable.
- (ii) Was the final model validated on patients who were not used to generate the model (external validation)? Models that predict well on the patients who were used to produce the model may still not provide accurate predictions on other patients. The accuracy must also be tested in an independent cohort of patients, ideally, on several independent cohorts to assess its generalisability.
- (iii) Are the model's predictions better than predictions based on clinical judgement? If prognostic models are to be used in clinical practice, they should be at least as good as clinical judgement.
- (iv) Was the effect of using the model in clinical practice established? If the model's predictions are to be used in clinical practice, their effect on patient outcome should be evaluated. This is best done in randomised trials. The use of a model may harm patients if, for example, patients who are falsely predicted to have a poor outcome are given hazardous treatments or alternatively are left untreated because treatment is judged to be futile.

E. The ease of use (practicality) of the model

(i) Were the data required to make predictions easily available?

Models that include complex variables or those that are not available when the clinician needs to make a prediction are unhelpful. Variables were defined as complex after discussion between the two authors.

(ii) Was the actual model and the coding of variables described so that it could be used?

(iii) Were confidence intervals given for the predictions? Models that only give point estimates for the probability of an outcome can give a false impression of accuracy. Clinicians need to know whether the confidence interval for a prediction is sufficiently narrow to allow a specific prognosis to be given.

*Note:* The above text was based on the Systematic review of prognostic models in patients with acute stroke produced by Counsell et al., 2001 (66)

## APPENDIX 6 QUALITY ASSESSMENT OF RCTS AND REVIEWS

### Quality assessment of RCTs

Questions	Yes/No
Was the method used to assign participants to the treatment groups really random?	
What method of assignment was used?	
Was the allocation of treatment concealed?	
What method was used to conceal treatment allocation?	
Was the number of participants who were randomised stated?	
Were details of baseline comparability presented?	
Was baseline comparability achieved?	
Were the eligibility criteria for study entry specified?	
Were any co-interventions identified that may influence the outcomes for each group?	
Were the outcome assessors blinded to the treatment allocations?	
Were the individuals who administered the intervention blinded to the treatment allocation?	
Were the participants who received the intervention blinded to the treatment allocation?	
Was the success of the blinding procedure assessed?	
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	
Were the reasons for withdrawal stated?	
Was an intention-to-treat analysis included?	

Y – item addressed; N – no; ? – not enough information or not clear; NA – not applicable  
*Note:* The above checklist was taken from the NHS Centre for Reviews and Dissemination (60)

## Quality Assessment of Reviews

Questions	Yes/No
Were the search methods used to find evidence on the primary research question stated?	
Was the search for evidence reasonably comprehensive?	
Were the criteria used for deciding which studies to include reported?	
Was bias in the selection of studies avoided? (e.g., language restrictions not applied, unpublished trials included)	
Were the criteria used for assessing the validity of the included studies reported?	
Was the validity of all studies referred to in the text assessed using appropriate criteria?	
Summary – was review systematic?	
Were the methods used to combine the findings of the relevant studies reported?	
Were the findings of the relevant studies combined appropriately relative to the primary question of the overview? <i>(If no attempt has been made to combine the findings, and no statement is made regarding the inappropriateness of combining them, score “no”. If a summary (general) estimate is given anywhere in the abstract, discussion or summary section of the paper and it is not reported how that estimate was derived, score “no” even if there is a statement regarding the limitations of combining the findings of the studies reviewed. If in doubt, score “?”)</i>	
Were the conclusions made by the author(s) supported by the data and/or analysis reported in the overview?	
Y – item addressed; N – no; P – partially; ? – not enough information or not clear; NA – not applicable	
<i>Note: The above table is adapted from: Oxman and Guyatt’s (1991) index of methodological quality (76) as published by Kelly et al., (77)</i>	

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We acknowledge the importance of our specialist clinical advisors on this piece of work. The aim of the advisory group is to help clarify issues and provide advice on the clinical relevance and scientific quality of the review. It is anticipated that clinical advisors on this panel will be consulted either individually, or as a group at various stages during the review (approximately 2–3 meetings/teleconferences over period of report). In addition, the review team will keep in regular contact with the clinical advisors by email and telephone. The clinical advisors will be contacted when greater clarification of complex studies is required. The clinical advisors will be involved in reading drafts and will be authors on the current review.

## REFERENCE LIST

1. Riley RD, Sauerbrei W, Altman DG. Prognostic markers in cancer: the evolution of evidence from single studies to meta-analysis, and beyond. *Br J Cancer* 2009 Apr 21; **100**(8):1219–29.
2. Hemingway H, Riley RD, Altman DG. Ten steps towards improving prognosis research. *BMJ* 2009; **339**:b4184.
3. Stoll BA, Parbhoo S. *Bone metastases: Monitoring and treatment*. 2 ed. New York: Raven Press; 1983.
4. Dupuy DE, Liu D, Hartfeil D, Hanna L, Blume JD, Ahrar K, *et al*. Percutaneous radiofrequency ablation of painful osseous metastases: a multicenter American College of Radiology Imaging Network trial. *Cancer* 2010 Feb 15; **116**(4):989–97.
5. Twycross RG. Management of pain in skeletal metastases. *Clin Orthop Relat Res* 1995 Mar; **312**:187–96.
6. Boogerd W, van der Sande JJ. Diagnosis and treatment of spinal cord compression in malignant disease. *Cancer Treatment Reviews* 1993; **19**:129–50.
7. Tse V. Spinal Metastases and Metastatic disease to the Spine and Related Structures. 2009. Available from: URL: <http://medicine.medscape.com/article/1157987-overview#a1099> [Accessed april 2011]
8. Rades D, Stalpers LJ, Veninga T, Schulte R, Hoskin PJ, Obralic N, *et al*. Evaluation of five radiation schedules and prognostic factors for metastatic spinal cord compression. *J Clin Oncol* 2005 May 20; **23**(15):3366–75.
9. Prasad D, Schiff D. Malignant spinal-cord compression. *Lancet Oncol* 2005 Jan; **6**(1):15–24.
10. Janjan NA. Radiation for bone metastases: conventional techniques and the role of systemic radiopharmaceuticals. *Cancer* 1997 Oct 15; **80**(8 Suppl):1628–45.
11. Quilty PM, Kirk D, Bolger JJ, Dearnaley DP, Lewington VJ, Mason MD, *et al*. A comparison of the palliative effects of strontium-89 and external beam radiotherapy in metastatic prostate cancer. *Radiother Oncol* 1994 Apr; **31**(1):33–40.

12. Serafini AN, Houston SJ, Resche I, Quick DP, Grund FM, Ell PJ, *et al.* Palliation of pain associated with metastatic bone cancer using samarium-153 leixidronam: a double-blind placebo-controlled clinical trial. *J Clin Oncol* 1998 Apr;**16**(4):1574–81.
13. Hortobagyi GB, Theriault RL, Porter L, Blayney D, Lipton A, Sinoff C. 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* 1999;**12**:1785–91.
14. Conte PF, Latreille J, Mauriac L, Calabresi F, Santos R, Campos D, *et al.* Delay in progression of bone metastases in breast cancer patients treated with intravenous pamidronate: results from a multinational randomized controlled trial. The Aredia Multinational Cooperative Group. *J Clin Oncol* 1996 Sep;**14**(9):2552–9.
15. Cummings SR, San MJ, McClung MR, Siris ES, Eastell R, Reid IR, *et al.* Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009 Aug 20;**361**(8):756–65.
16. Santini D, Fratto ME, Vincenzi B, Napoli N, Galluzzo S, Tantardini M, *et al.* Denosumab: the era of targeted therapies in bone metastatic diseases. [Review] [59 refs]. *Current Cancer Drug Targets* 2009 Nov;**9**(7):834–42.
17. Cleeland CS. The measurement of pain from metastatic bone disease: capturing the patient's experience. *Clin Cancer Res* 2006 Oct 15;**12**(20 Pt 2):6236s–42s.
18. Riley RD, Burchill SA, Abrams KR, Heney D, Sutton AJ, Jones DR, *et al.* A systematic review of molecular and biological markers in tumours of the Ewing's sarcoma family. *Eur J Cancer* 2003 Jan;**39**(1):19–30.
19. Madsen EL. Painful bone metastasis: efficacy of radiotherapy assessed by the patients: a randomized trial comparing 4 Gy X 6 versus 10 Gy X 2. *Int J Radiat Oncol Biol Phys* 1983 Dec;**9**(12):1775–9.
20. Blitzer PH. Reanalysis of then RTOG study of the palliation of symptomatic osseous metastasis. *Cancer* 1984;**55**:1468–72.
21. 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. *Radiother Oncol* 1986 Aug;**6**(4):247–55.
22. Arcangeli G, Micheli A, Arcangeli G, Giannarelli D, La PO, Tollis A, *et al.* The responsiveness of bone metastases to radiotherapy: the effect of site, histology and radiation dose on pain relief. *Radiother Oncol* 1989 Feb;**14**(2):95–101.
23. Cole DJ. A randomized trial of a single treatment versus conventional fractionation in the palliative radiotherapy of painful bone metastases. *Clin Oncol (R Coll Radiol)* 1989 Nov;**1**(2):59–62.
24. Poulter CA, Cosmatos D, Rubin P, Urtasun R, Cooper JS, Kuske RR, *et al.* A report of RTOG 8206: a phase III study of whether the addition of single dose hemibody irradiation to standard fractionated local field irradiation is more effective than local field irradiation alone in the treatment of symptomatic osseous metastases. *Int J Radiat Oncol Biol Phys* 1992;**23**(1):207–14.
25. Arcangeli G, Giovinazzo G, Saracino B, D'Angelo L, Giannarelli D, Arcangeli G, *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 Dec 1;**42**(5):1119–26.
26. Ratanatharathorn V, Powers WE, Moss WT, Perez CA. Bone metastasis: review and critical analysis of random allocation trials of local field treatment. *Int J Radiat Oncol Biol Phys* 1999;**44**:1–18.
27. Bates T. A review of local radiotherapy in the treatment of bone metastases and cord compression. *Int J Radiat Oncol Biol Phys* 1992;**23**(1):217–21.

28. Agarawal JP, Swangsilpa T, van der Linden Y, Rades D, Jeremic B, Hoskin PJ. The role of external beam radiotherapy in the management of bone metastases. *Clin Oncol (R Coll Radiol)* 2006 Dec;**18**(10):747–60.
29. Gerszten PC, Burton SA, Ozhasoglu C, Welch WC. Radiosurgery for spinal metastases: clinical experience in 500 cases from a single institution. *Spine (Phila Pa 1976)* 2007 Jan 15;**32**(2):193–9.
30. Inoue T, Oh RJ, Shiomi H. New approach for treatment of vertebral metastases using intensity-modulated radiotherapy. *Strahlenther Onkol* 2011 Feb;**187**(2):108–13.
31. Callstrom MR, Atwell TD, Charboneau JW, Farrell MA, Goetz MP, Rubin J, *et al*. Painful metastases involving bone: percutaneous image-guided cryoablation--prospective trial interim analysis. *Radiology* 2006 Nov;**241**(2):572–80.
32. Goetz MP, Callstrom MR, Charboneau JW, Farrell MA, Maus TP, Welch TJ, *et al*. Percutaneous image-guided radiofrequency ablation of painful metastases involving bone: a multicenter study. *J Clin Oncol* 2004 Jan 15;**22**(2):300–6.
33. Gangi A, Kastler B, Klinkert A, Dietemann JL. Injection of alcohol into bone metastases under CT guidance. *J Comput Assist Tomogr* 1994 Nov;**18**(6):932–5.
34. Levine SA, Perin LA, Hayes D, Hayes WS. An evidence-based evaluation of percutaneous vertebroplasty. *Manag Care* 2000 Mar;**9**(3):56–60, 63.
35. Taylor RS, Taylor RJ, Fritzell P. Balloon kyphoplasty and vertebroplasty for vertebral compression fractures: a comparative systematic review of efficacy and safety. *Spine (Phila Pa 1976)* 2006 Nov 1;**31**(23):2747–55.
36. Dupuy DE, Hong R, Oliver B, Goldberg SN. Radiofrequency ablation of spinal tumors: temperature distribution in the spinal canal. *AJR Am J Roentgenol* 2000 Nov;**175**(5):1263–6.
37. Rosenthal DI, Hornicek FJ, Wolf MW, Jennings LC, Gebhardt MC, Mankin HJ. Percutaneous radiofrequency coagulation of osteoid osteoma compared with operative treatment. *J Bone Joint Surg Am* 1998;**80**:815–21.
38. Sejpal SV, Bhate A, Small W. Palliative radiation therapy in the management of brain metastases, spinal cord compression, and bone metastases. *Semin Intervent Radiol* 2007 Dec;**24**(4):363–74.
39. 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):2028–37.
40. Metastatic spinal cord compression; diagnosis and management of adults at risk of and with metastatic spinal cord compression. 2008. URL: <http://guidance.nice.org.uk/CG75/Guidance/pdf/English> [Accessed april 2011]
41. Bilsky MH, Lis E, Raizer J, Lee H, Boland P. The diagnosis and treatment of metastatic spinal tumor. *Oncologist* 1999;**4**(6):459–69.
42. Morris PG, Lynch C, Feeney JN, Patil S, Howard J, Larson SM, *et al*. Integrated positron emission tomography/computed tomography may render bone scintigraphy unnecessary to investigate suspected metastatic breast cancer. *J Clin Oncol* 2010 Jul 1;**28**(19):3154–9.
43. Tiwari BP, Jangra S, Nair N, Tongaonkar HB, Basu S. Complimentary role of FDG-PET imaging and skeletal scintigraphy in the evaluation of patients of prostate carcinoma. *Indian J Cancer* 2010 Oct;**47**(4):385–90.
44. Tokuhashi Y, Matsuzaki H, Toriyama S, Kawano H, Ohsaka S. Scoring system for the preoperative evaluation of metastatic spine tumor prognosis. *Spine (Phila Pa 1976)* 1990 Nov;**15**(11):1110–3.
45. Tokuhashi Y, Matsuzaki H, Oda H, Oshima M, Ryu J. A revised scoring system for preoperative evaluation of metastatic spine tumor prognosis. *Spine (Phila Pa 1976)* 2005 Oct 1;**30**(19):2186–91.

46. Tomita K, Kawahara N, Kobayashi T, Yoshida A, Murakami H, Akamaru T. Surgical strategy for spinal metastases. *Spine (Phila Pa 1976)* 2001 Feb 1;**26**(3):298–306.
47. Prognostic factors for patients with spinal metastases from lung cancer. 2011. Available from: URL: [http://www.medscape.com/viewarticle/540597\\_3](http://www.medscape.com/viewarticle/540597_3) [accessed april 2011]
48. Chaichana KL, Pendleton C, Wolinsky JP, Gokaslan ZL, Sciubba DM. Vertebral compression fractures in patients presenting with metastatic epidural spinal cord compression. *Neurosurgery* 2009 Aug;**65**(2):267–74.
49. Sciubba DM, Gokaslan ZL, Suk I, Suki D, Maldaun MV, McCutcheon IE, *et al.* Positive and negative prognostic variables for patients undergoing spine surgery for metastatic breast disease. *Eur Spine J* 2007 Oct;**16**(10):1659–67.
50. Rose PS, Laufer I, Boland P, Hanover A, Bilsky M, Yamada J, *et al.* Risk of fracture after single fraction image-guided intensity modulated radiation therapy to spinal metastases. *J Clin Oncol* 2011;**27**(30):5075–9.
51. Taneichi H, Kaneda K, Takeda N, Abumi K, Satoh S. Risk factors and probability of vertebral body collapse in metastases of the thoracic and lumbar spine. *Spine (Phila Pa 1976)* 1997 Feb 1;**22**(3):239–45.
52. Weber MH, Burch S, Buckley J, Schmidt MH, Fehlings MG, Vrionis FD, *et al.* Instability and impending instability of the thoracolumbar spine in patients with spinal metastases: a systematic review. *Int J Oncol* 2011 Jan;**38**(1):5–12.
53. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009 Oct;**62**(10):1006–12.
54. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;**339**:b2535.
55. Altman DG. Systematic reviews of evaluations of prognostic variables. *BMJ* 2001 Jul 28;**323**(7306):224–8.
56. Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound prognostic studies in MEDLINE: an analytic survey. *BMC Med* 2004 Jun 9;**2**:23.
57. Wilczynski NL, Haynes RB. Optimal search strategies for detecting clinically sound prognostic studies in EMBASE: an analytic survey. *J Am Med Assoc* 2005 Jul;**12**(4):481–5.
58. Cooper K, Meng Y, Harnan S, Ward S, Fitzgerald P. Positron emission tomography (PET) and magnetic resonance imaging (MRI) for the assessment of axillary lymph node metastases in early breast cancer: systematic review and economic evaluation. *Health Technol Assess* 2011;**15**(4).
59. Sutcliffe P, Hummel S, Simpson E, Young T, Rees A, Wilkinson A, *et al.* Use of classical and novel biomarkers as prognostic risk factors for localised prostate cancer: a systematic review. *Health Technol Assess* 2009 Jan;**13**(5).
60. Khan KS, Ter Riet G, Galvin J, Snowdon AJ, Kleijnen J. Undertaking Systematic Reviews of Research on Effectiveness. CRD's Guidance for Carrying Out or Commissioning Reviews. 2nd Edition. (ISBN 1900640201) CRD Report No. 4. York: NHS Centre for Reviews and Dissemination (CRD), University of York. 2001. URL: <http://www.york.ac.uk/inst/crd/report4.htm> [Accessed april 2011].
61. Kyzas PA, Loizou KT, Ioannidis JP. Selective reporting biases in cancer prognostic factor studies. *J Natl Cancer Inst* 2005 Jul 20;**97**(14):1043–55.
62. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med* 2006 Mar 21;**144**(6):427–37.
63. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0. 2011. Available from: URL: <http://www.cochrane-handbook.org/> [Accessed april 2011].

64. Altman DG, Royston P. What do we mean by validating a prognostic model? *Stat Med* 2000 Feb 29;**19**(4):453–73.
65. Braitman LE, Davidoff F. Predicting clinical states in individual patients. *Ann Intern Med* 1996 Sep 1;**125**(5):406–12.
66. Counsell C, Dennis M. Systematic review of prognostic models in patients with acute stroke. *Cerebrovasc Dis* 2001;**12**(3):159–70.
67. Jacob M, Lewsey JD, Sharpin C, Gimson A, Rela M, van der Meulen JH. Systematic review and validation of prognostic models in liver transplantation. *Liver Transpl* 2005 Jul;**11**(7):814–25.
68. Laupacis A, Wells G, Richardson WS, Tugwell P. Users' guides to the medical literature. V. How to use an article about prognosis. Evidence-Based Medicine Working Group. *JAMA* 1994 Jul 20;**272**(3):234–7.
69. Meijer R, Ihnenfeldt DS, de Groot IJ, van LJ, Vermeulen M, de Haan RJ. Prognostic factors for ambulation and activities of daily living in the subacute phase after stroke. A systematic review of the literature. *Clin Rehabil* 2003 Mar;**17**(2):119–29.
70. Martin B, Paesmans M, Mascaux C, Berghmans T, Lothaire P, Meert AP, *et al*. Ki-67 expression and patients survival in lung cancer: systematic review of the literature with meta-analysis. *Br J Cancer* 2004 Dec 13;**91**(12):2018–25.
71. Williams C, Brunskill S, Altman D, Briggs A, Campbell H, Clarke M, *et al*. Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy. *Health Technol Assess* 2006 Sep;**10**(34).
72. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *J R Stat Soc Ser A Stat Soc* 2009 Jan;**172**(1):137–59.
73. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011;**342**:d549.
74. STATA Statistical analysis and software. 2011. URL: <http://www.stata.com/> [accessed April 2011].
75. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol* 2008 Oct;**61**(10):991–6.
76. Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. *J Clin Epidemiol* 1991;**44**(11):1271–8.
77. Kelly KD, Travers A, Dorgan M, Slater L, Rowe BH. Evaluating the quality of systematic reviews in the emergency medicine literature. *Ann Emerg Med* 2001 Nov;**38**(5):518–26.



A decorative graphic consisting of numerous thin, parallel green lines that curve from the left side of the page towards the right, creating a sense of movement and depth.

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HS&DR  
HTA  
PGfAR  
PHR**

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