National Institute for Health and Care Excellence

Draft for consultation

Metastatic spinal cord compression

[N] Invasive interventions

NICE guideline number tbc

Evidence reviews underpinning recommendations 1.10.8, 1.11.1 to 1.11.9 and research recommendation 4 in the NICE guideline

March 2023

Draft for consultation

These evidence reviews were developed by NICE

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Invasive interventions

Review question

What is the effectiveness of invasive interventions, such as vertebroplasty, kyphoplasty, ablation and surgery, in managing spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Introduction

Surgical interventions such as vertebroplasty, kyphoplasty, ablation and surgical stabilisation/ decompression are used to relieve pressure on the spinal cord and to stabilise the spine of people with spinal metastases or direct malignant infiltration. These invasive interventions differ in their technical details but all aim to reduce symptoms and protect neurological and functional status. This evidence review aims to compare the effectiveness of different invasive interventions.

Summary of the protocol

Table 1: Summary of the protocol (PICO table)

Population	• Adults with metastatic spinal disease or direct malignant infiltration of the spine. • Adults with spinal cord or nerve root compression because of metastatic spinal disease or direct malignant infiltration.
Intervention	Surgery: • Vertebroplasty • Kyphoplasty • Ablation • Surgical stabilisation (for example with metalwork) • Surgical decompression
Comparison	• In comparison with each other • No surgery with or without a non-surgical intervention (example external orthosis or chemotherapy)

Outcome	**Critical**
	• Neurological and functional status including:
	  ○ Bowel and bladder function
	  ○ Mobility or ambulatory status
	• Pain
	
	Important
	• Health related Quality of Life
	• Patient satisfaction
	• Treatment related adverse events including:
	  ○ Severe infections
	  ○ Serious adverse events as defined by trials
	  ○ Treatment related mortality
	• Overall survival
	• Spinal stability/deformity

For further details see the review protocol in appendix A.

Methods and process

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

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

Effectiveness evidence

Included studies

Seven studies were included in this review, reporting results from 4 randomised controlled trials (Berenson 2011; Patchell 2005; Korovessis 2014; Orgera 2014) and 3 observational studies (de Almeida 2020; Kumar 2022, Zheng 2021).

One randomised controlled trial compared balloon kyphoplasty to non-surgical management in patients with 1 to 3 painful vertebral compression fractures (Berenson 2011).

One observational study compared spinal laser interstitial thermotherapy to open surgery in patients with MRI confirmed metastatic epidural spinal cord compression (de Almeida 2020).

One randomised controlled trial compared Kiva implant to balloon kyphoplasty in patients with end stage disease with evidence of painful osteolytic vertebral metastases in 1 to 5 vertebral bodies (Korovessis 2014).

One observational study compared minimally invasive spine surgery to open spine surgery (with and without stabilisation) in patients with spinal instability and those with metastatic spinal cord compression (Kumar 2022).

One randomised controlled trial compared vertebroplasty with radiofrequency ablation to vertebroplasty alone in patients with involvement of myeloma in 1 to 3 vertebral bodies of the thoracic and lumbar spine (Orgera 2014).

One randomised controlled trial compared radiotherapy plus direct decompressive surgical resection to radiotherapy alone in patients with metastatic spinal cord compression (Patchell 2005).

One observational study compared hybrid therapy to total en bloc spondylectomy in patients with metastatic spinal cord compression (Zheng 2022).

Two studies were conducted in the United States (de Almeida 2020, Patchell 2005), 1 study was conducted in sites across Australia, Canada, Europe and the United States (Berenson 2011), 1 study was conducted in China (Zheng 2021), 1 in Greece (Korovessis 2014), 1 in Italy (Orgera 2014), and 1 in Singapore (Kumar 2022).See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

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

Summary of included studies

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

Table 2: Summary of included studies.

Study	Population	Intervention	Comparison	Outcomes

Study	Population	Intervention	Comparison	Outcomes
Berenson 2011 Randomised controlled trial Australia, Canada, Europe, and the USA	N=134 cancer patients with 1-3 painful vertebral compression fractures. Age, mean, years (SD): 63.9 (11.1). Sex: female, n=75, male n=59.	Balloon kyphoplasty Balloon kyphoplasty with introducer tools, inflatable bone tamps, and polymethylmethacrylate bone cement and delivery devices, by a percutaneous, bilateral, transpedicular, or extrapedicular method.	Non-surgical management Included walking aids, bed rest, physical therapy, etc. Offered kyphoplasty after 1 month assessment.	• Neurological and functional status • Pain • Health-related quality of life • Spinal stability/deformity
de Almeida, 2020 Observational USA	N=80 patients with metastatic epidural spinal cord compression (MRI confirmed) Age, mean, years (SD): Not reported for sample overall. < 50 years n=13; 51 – 60 years n=31; 61 - 70 years n=25; >71 years n=11. Sex: female n=19, male n=61.	Spinal laser interstitial thermotherapy Laser ablation is performed with real-time intraoperative MRI thermography.	Open surgery Open posterior stabilisation with or without decompression	• Treatment related adverse events • Spinal stability/deformity
Korovessis 2014 Randomised controlled trial Greece	N=47 patients with end stage disease with evidence (history, imaging, biopsy) for painful osteolytic vertebral metastases in 1 to 5 vertebral bodies. Age, mean, years (SD): Kiva group 71 (13), balloon kyphoplasty group 70 (11). Sex: female n=26, male n=21.	Kiva implant with low viscosity PMMA Percutaneous unilateral vertebral augmentation implant - single-use device in which an external delivery handle is used to deploy the Kiva implant over a nitinol coil guidewire	Balloon kyphoplasty with high viscosity PMMA Balex device – similar to traditional balloon kyphoplasty. Wires of 2-mm diameter are inserted through both pedicles of the damaged vertebra). Then, a cannula was inserted into the pedicle with cement filler and pusher	• Neurological and functional status • Pain • Treatment related adverse events
Kumar 2022 Observational Singapore	N=200 patients undergoing surgery for thoracolumbar metastatic spine disease. Age, mean, years (SD): Minimally	Minimally invasive spine surgery Percutaneous pedicle screw fixation or Minimal access separation surgery	Open spine surgery Open posterior stabilisation with or without decompression	• Neurological and functional status • Treatment related adverse events • Overall survival

Study	Population	Intervention	Comparison	Outcomes
	invasive spine surgery median 63 (range 36–83); open spine surgery median 59 (range 22–87). Mean and SD not reported. Sex: female n=100; male, n=100.			
Orgera 2014 Randomised controlled trial Italy	N=36 patients with myeloma with a consistent vertebral involvement of multiple myeloma in 1–3 vertebral bodies of the thoracic and lumbar spine. Age, mean, years (SD): 67.4 (range 51–82). SD not reported. Sex: female n=26, male n=10.	Vertebroplasty with radiofrequency ablation The vertebroplasty needle was advanced with the use of a sterile hammer through the cortical bone in the anterior third of the vertebral lesion. The ablation process lasted between 8 and 10 min.	Vertebroplasty alone	• Neurological and functional status • Pain • Treatment related adverse events
Patchell 2005 Randomised controlled trial United States	N=101 patients with metastatic spinal cord compression. Age, mean, years (SD): surgery + radiotherapy median 60; radiotherapy only median 60. Mean, range, and SD not reported. Sex: female n=31, male n=70.	Surgery plus radiotherapy Direct decompressive surgery within 24 hours of randomisation followed by RT (30 Gy in 10 fractions administered 14 days after surgery).	Radiotherapy only 30 Gy in 10 fractions beginning within 24 hours of randomisation.	• Neurological and functional status • Pain (mean morphine dose) • Treatment related adverse events (30 day mortality) • Overall survival
Zheng 2021 Observational China	N=157 patients with solitary radioresistant high grade epidural spinal cord compression spinal metastases. Age, mean, years (SD): 57.9 (6.6) Sex: female n=36,	Hybrid therapy Combination of separation surgery to provide circumferential decompression of the spinal cord and stereotactic radiosurgery to decrease local recurrence.	Total en bloc spondylectomy Details not reported	• Neurological and functional status • Pain • Health-related quality of life • Treatment related adverse events • Spinal stability/deformity

Study	Population	Intervention	Comparison	Outcomes
	male n=121.			

Gy: Gray; RT: radiotherapy; PMMA: polymethylmethacrylate; SD: standard deviation

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Summary of the evidence

Total hybrid therapy versus en bloc spondylectomy

There was no important difference between hybrid therapy and total en bloc spondylectomy in relation to neurological and functional status, pain, treatment related adverse events, health-related quality of life, or spinal stability/deformity.

No evidence was identified on patient satisfaction, or overall survival for this comparison.

Only 1 study was found relating to this comparison. Outcomes were rated as low to moderate in quality due to serious levels of imprecision in the effect estimates and a serious risk of bias in the evidence contributing to the outcomes.

Kiva novel implant with polymethylmethacrylate (PMMA) versus balloon kyphoplasty with PMMA

There was no important difference between Kiva implant with PMMA and balloon kyphoplasty in relation to neurological and functional status, pain, or treatment related adverse events.

No evidence was identified on health-related quality of life, patient satisfaction, overall survival, or spinal stability/deformity for this comparison.

Only 1 study was found relating to this comparison. The outcomes were rated as low to high quality with some ratings downgraded due to very serious or serious levels of imprecision in the effect estimates.

Balloon kyphoplasty versus non-surgical treatment

Balloon kyphoplasty had important benefits over non-surgical treatment in terms of neurological and functional status (disability), pain, quality of life and spinal stability or deformity (vertebral height restoration).

No evidence was identified in relation patient satisfaction.

Only 1 study was found relating to this comparison. The outcomes were rated as moderate to high quality with some ratings downgraded due to serious levels of imprecision in the effect estimates.

Minimal access separation surgery versus open posterior stabilisation and decompression

There was no important difference between minimal access separation surgery and open posterior stabilisation and decompression in relation to neurological and functional status, treatment related adverse events, or overall survival.

No evidence was identified in relation to pain, health-related quality of life, patient satisfaction, or spinal stability/deformity.

Only 1 study was found relating to this comparison. Outcomes were rated as very low to moderate in quality due to serious or very serious levels of imprecision in the effect estimates and a serious risk of bias in the evidence contributing to the outcomes.

Percutaneous pedicle screw fixation versus open posterior stabilisation

There was no important difference between percutaneous pedicle screw fixation and open posterior stabilisation in relation to neurological and functional status, treatment related adverse events, or overall survival.

No evidence was identified in relation to pain, health-related quality of life, patient satisfaction, or spinal stability/deformity.

Only 1 study was found relating to this comparison. Outcomes were rated as very low to low in quality due to serious or very serious levels of imprecision in the effect estimates and a serious risk of bias in the evidence contributing to the outcomes.

Spinal laser interstitial thermotherapy versus open surgery

Spinal laser interstitial thermotherapy had an important benefit over open posterior stabilisation in relation to treatment related adverse events, but a possible important harm in relation to spinal stability/deformity.

No evidence was identified on neurological and functional status, pain, health-related quality of life, patient satisfaction, or overall survival.

Only 1 study was found relating to this comparison. Outcomes were rated as low to moderate in quality due to a serious risk of bias in the evidence contributing to the outcomes and imprecision in the effect estimates.

Vertebroplasty with radiofrequency ablation versus vertebroplasty alone

There was no important difference between vertebroplasty with radiofrequency ablation did and vertebroplasty alone in relation to neurological and functional status, pain, or treatment related adverse events.

No evidence was identified in relation to health-related quality of life, patient satisfaction, or overall survival, or spinal stability/deformity.

Only 1 study was found relating to this comparison. Outcomes were rated as low to moderate quality due to serious or very serious levels of imprecision in the effect estimates.

Radiotherapy and surgery versus radiotherapy alone

Radiotherapy and surgery had an important benefit over radiotherapy alone in relation to neurological and functional status, and a possible important benefit in treatment related adverse events. There was no important benefit in relation to pain.

No evidence was identified in relation to health-related quality of life, patient satisfaction or spinal stability/deformity.

Only 1 study was found relating to this comparison. Outcomes were rated as low to moderate quality. Outcomes were downgraded in quality due to serious or very serious levels of imprecision in the effect estimates.

See appendix F for full GRADE tables.

Economic evidence

Included studies

Two economic studies were identified which were relevant to this question (Miyazaki 2017, Health Quality Ontario 2016). Both studies compared surgical to non-surgical management.

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

Excluded studies

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

Summary of included economic evidence

Table 3: Economic evidence profile for surgical versus non-surgical management in managing spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectivenss	
Miyazaki (2017) Surgery (removal tumour stabilisation with screw rod system) versus non-surgical management	Potentially serious limitations	Partially applicable	Prospective cohort study over 1 year with costing	US$16,955	0.405 QALYs	US$42,003 per QALY gained	No sensitivity analysis reported
Health Quality Ontario (2016) K)Kyphoplasty V)Vertebroplasty Versus Non-surgical management	Potentially serious limitations	Partially applicable	Markov model with 5 year time horizon. Kyphoplasty and vertebroplasty not directly compared.	K:CA$ 7,247 V:CA$ 3,869	K:0.217 V:0.217	K:CA$ 33,471 V:CA$ 17,870	Results sensitive to HRQoL outcomes
NICE (2023) K)Kyphoplasty V)Vertebroplasty Versus Non-surgical management	Potentially serious limitations	Directly applicable	Retrospective costing and QoL calculations from one randomised controlled trial with 1 and 5 year time horizon. Kyphoplasty and verte-	K:£2,711 V:£2,594	K:0.274 V:0.274	K:£98,935 V:£94,644	Deterministic and probabilistic favour surgical intervention.

Study	Limitations	Applicability	Other	Incremental			Uncertainty
			broplasty not directly compared.				

Economic model

This review updates the economic model comparing kyphoplasty and vertebroplasty for people with myeloma and VCFs created for NICE Guideline NG35 Myeloma: diagnosis and management published in January 2016. The updated model is reported in appendix I.

The economic model compared vertebroplasty and kyphoplasty to best supportive care in people with MSCC. The effectiveness parameters in the model were based on the results of 1 study identified in the evidence review (Berenson 2011) and reported outcomes in terms of cost per QALY adjusted life year. The base-case had a time horizon of 1 year but this was extended to 5 years during sensitivity analysis. The model took an NHS and PSS perspective.

Under the conservative estimates in the base-case, the estimated cost per additional QALY of kyphoplasty and vertebroplasty were greater than values at which NICE usually recommend interventions. However, alternative and less conservative model parameters led to values less than NICE typically recommend interventions and suggested that both interventions could be an efficient use of resources.

A number of weaknesses were identified with the model which likely biased against kyphoplasty and vertebroplasty. The most significant of these were missing costs associated with best supportive care.

Evidence Statements

Miyazaki 2017 was a cost utility analysis which reported outcomes in terms of cost per QALY gained for surgical versus non-surgical management for metastatic spinal disease. The study took a Japanese healthcare payer perspective.

Health Quality Ontario 2016 was a cost utility study which reported outcomes in terms of cost per QALY gained for kyphoplasty and vertebroplasty versus non-surgical management in a mixed population of primary and metastatic cancers causing spinal disease.

NICE 2023 was an update of the cost utility study developed for NICE Guideline NG35 Myeloma: diagnosis and management. This was a cost utility study which reported outcomes in terms of cost per QALY gained for kyphoplasty and vertebroplasty versus non-surgical management in people with MSCC. The study took UK NHS and PSS perspective and reported costs in UK sterling. Health related quality of life outcomes were mapped from SF-36 outcomes to EQ-5D.

Both previously published studies found surgical management to be cost effective at their health care systems willingness to pay threshold. For NICE 2023, surgical management was cost effective a £20,000 per QALY threshold in all but the most conservative base-case estimates. For Health Quality Ontario 2016 and NICE 2023 this conclusion was robust to sensitivity analysis.

Both previous studies were deemed to be partially applicable to the decision problem with serious methodological limitations. NICE 2023 was rated as directly applicable with potentially serious limitations.

See Table 3 for the economic evidence profile of the included studies.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Pain and neurological and functional status were chosen as critical outcomes because untreated malignant spinal disease can cause severe pain and impaired neurological and functional status. Reduction in pain and preservation of neurological and functional status has a beneficial impact on health related quality of life so this was considered an important outcome. Likewise invasive interventions can potentially prolong life, so overall survival was considered an important outcome.

Patient satisfaction and treatment related adverse events were important outcomes, because the different approaches may differ in their acceptability and adverse event rates. For example minimally invasive surgery may allow for quicker recovery and fewer adverse events than open surgery. Finally spinal stability/deformity was an important outcome because interventions can use different techniques to reinforce the spine which may be more or less effective in achieving stability or preventing deformity.

The quality of the evidence

The quality of the evidence was assessed using GRADE and ranged from very low to high. This was mostly due to some outcomes being downgraded for imprecision around the effect estimates and a serious overall risk of bias in the evidence contributing to some of the outcomes.

The committee considered the clinical and economic evidence when drafting recommendations. They noted that the most appropriate type of surgery would depend for example on the level of spinal instability, tumour size or anatomical site so every surgery would need to be tailored to the person's particular condition. The evidence, however, was related to very specific populations and mainly compared different types of surgery making it hard to generalise it to the whole population affected by the condition. The committee therefore also drew on their expertise and experience to draft recommendations.

Benefits and harms

Based on experience, the committee noted that there are many different factors to consider that may impact on the success of surgery. This could relate to overall fitness for surgery, but also prognosis and issues related to primary cancer type and stage. To ensure that all relevant information is taken into account and to make decisions more efficient the committee recommended discussions should take place, before surgery is offered, between people from the appropriate specialties within the multidisciplinary team in the MSCC service. This would usually include the oncologist and spinal surgeon but could also draw on other people's expertise where necessary.

The committee discussed, based on experience, that there are people who present to MSCC services without a known primary cancer type. The committee agreed that establishing this would be important to establish the need for oncological treatment and follow-up and recommended radiologically guided biopsy but only if it could make a difference to the management plan and if an intervention is not needed immediately.

Timing of surgical intervention

There was no evidence about when surgical interventions should be carried out after a person presents with confirmed or suspected MSCC, but the committee agreed that surgery should be carried out as soon as possible, to prevent neurological decline. Given the lack of evidence they could not specify exact timeframes and individual circumstances will differ

when planning the surgical treatment approach. However, they agreed that speed of onset and rate of progression of neurological symptoms and signs would be indicators of urgency.

The committee discussed that some clinicians use time limits to inform treatment plans for people with complete paralysis. For example if the person has been paralysed for a certain length of time then the decision might be made not to offer surgery. They noted that this was not evidence based and that it is not impossible that some paralysis could be reversed even if some time has already passed. To address this, they recommended not to use time cut-offs.

Options for surgical interventions

Interventions to treat spinal metastases or direct malignant infiltration of the spine without MSCC

The committee agreed that plans for surgery depend on whether there is cord compression or not, and there was some evidence relating to interventions for both of these groups.

Most of the evidence did not favour one technique over another for people without cord compression. Whilst they did not show differences in relative terms they achieved improved outcomes from baseline. This was consistent with the committee's experience that clinical judgement is important in surgery and there are many factors that may determine which specific technique would be used (for example, level of spinal instability or tumour size). The committee decided to recommend a choice of potential interventions that may be suitable depending on the characteristics of the person's condition.

The committee acknowledged that there was no evidence related to the prevention of MSCC for people in people with spinal metastases without pain or instability and they decided to make a research recommendation on surgery to prevent MSCC to address this (see appendix K for details).

Interventions to treat spinal metastases or direct malignant infiltration of the spine with MSCC

The evidence on the most effective surgical procedure to treat cord compression was inconclusive. Based on experience, the committee noted that there are only 2 interventions that can be considered. Depending on the person's condition, surgery would focus on decompression or stabilisation of the spine. The committee could not be prescriptive about one or the other because the choice would depend on clinical judgement.

Based on experience, the committee recommended stabilisation surgery when there is cord compression with suspected or proven instability with mechanical pain that is intractable in all circumstances even if there is a severe neurological deficit. This is done because it is an oncological emergency to prevent collapse of the spine.

If surgery cannot be performed because of the prognosis or other factors (which means that surgery is not indicated), the only other possibility of stabilisation is external spinal support to attempt to prevent collapse of the spine. No evidence was identified for this but the committee decided that this would be the only option available to prevent collapse of the spine and should be offered.

Postoperative radiotherapy

The committee discussed the evidence that radiotherapy and surgery had an important benefit over radiotherapy alone in relation to neurological and functional status. Health economic evidence (see evidence review M) also supported the use of radiotherapy with surgery. Based on this the committee recommended that postoperative radiotherapy should be offered.

Cost effectiveness and resource use

The updated economic model concluded that vertebroplasty and kyphoplasty would be a cost effective option for people with MSCC. Although the base-case suggested that the additional cost per QALY may not be an efficient use of NHS resources, probabilistic sensitivity analysis and deterministic sensitivity analysis with less conservative estimates strongly suggested that it would lead to an additional QALY at less than £20,000. Under the one-year time horizon few iterations were cost saving but the majority were cost effective at a willingness to pay of £20,000 per QALY. Whilst vertebroplasty and kyphoplasty would likely lead to an increase in costs this was considered acceptable given the improvements in quality of life. The conclusions of the model were also consistent with the 2 partially applicable economic evaluations (comparing vertebroplasty, kyphoplasty and stabilisation with screw rod system to non-surgical management) identified during the search of previous evidence which both reported increased costs associated with surgery.

As there was no economic evidence identified which directly compared different surgical techniques but there was evidence that surgery was generally cost effective compared to non-surgical management, the committee decided to recommend surgery but provided a list of possible surgical techniques for clinical consideration.

There maybe some additional costs from involving more professionals in treatment plans. Although this should lead to a reduction in surgery where this is inappropriate and the benefits small. This should lead to efficiencies in treatment and improved quality of life.

Guided biopsy is already widely performed where there is a cancer of unknown primary. The recommendation should, where it is not already performed, lead to more appropriate treatment decisions leading to cost savings and quality of life improvements through avoiding inappropriate or less appropriate treatments. It also reiterates the need that urgent treatment is not delayed to undertake a biopsy, improving outcomes and quality of life from surgery.

Offering spinal support for those with spinal instability with mechanical pain not controlled by analgesia and not suitable for surgery was considered the only option for people with these clinical characteristics. This is largely current practice so resource impact is likely to be small. If there are centres which do not currently undertake this, prevention of events such as paraplegia would outweigh any upfront costs.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.10.8, 1.11.1 to 1.11.9 and research recommendation 4 on surgery in the prevention of MSCC for people with spinal metastases without pain or instability.

References – included studies

Effectiveness

Berenson 2011

Berenson J, Pflugmacher R, Jarzem P, et al. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. Lancet: Oncology, 12, 225-35, 2011

de Almeida 2020

de Almeida D, Everson, R, de Oliveira Santos B. et al. A comparison of spinal laser interstitial thermotherapy with open surgery for metastatic thoracic epidural spinal cord compression. Journal of Neurosurgery: Spine, 32, 667-675, 2020

Korovessis 2014

Korovessis P, Vardakastanis K, Vitsas V, et al. Is Kiva implant advantageous to balloon kyphoplasty in treating osteolytic metastasis to the spine? Comparison of 2 percutaneous minimal invasive spine techniques: a prospective randomized controlled short-term study. Spine, 39, e231-9, 2014

Kumar 2022

Kumar, N, Tan J, Thomas A, et al. The Utility of 'Minimal Access and Separation Surgery' in the Management of Metastatic Spine Disease. Global Spine Journal, 21925682211049803, 2022

Orgera 2014

Orgera G, Krokidis, Miltiadis M, Marco, et al. Percutaneous vertebroplasty for pain management in patients with multiple myeloma: is radiofrequency ablation necessary? Cardiovascular and Interventional Radiology 37, 203-10, 2014

Patchell 2005

Patchell R, Tibbs P, Regine W, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet 366, 643-8, 2005

Zheng 2021

Zheng J, Wu L, Shi J, et al. Hybrid Therapy Versus Total en Bloc Spondylectomy in the Treatment of Solitary Radioresistant Spinal Metastases: A Single-center, Retrospective Study. Clinical Spine Surgery, 35, E457-E465, 2021

Economic

Miyazaki 2017

Miyazaki S, Kakutani K, Sakai Y, et al. Quality of life and cost-utility of surgical treatment for patients with spinal metastases: prospective cohort study. International Orthopaedics, 41, 1265-1271, 2017

Health Quality Ontario

Health Quality Ontario. Vertebral Augmentation Involving Vertebroplasty or Kyphoplasty for Cancer-Related Vertebral Compression Fractures: An Economic Analysis. Ontario Health Technology Assessment Series, 16, 1-34, 2016

Appendices

Appendix A Review protocols

Review protocol for review question: What is the effectiveness of invasive interventions, such as vertebroplasty, kyphoplasty, ablation and surgery, in managing spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Table 4: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42021295488
1.	Review title	Invasive interventions in managing spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression
2.	Review question	What is the effectiveness of invasive interventions, such as vertebroplasty, kyphoplasty, ablation and surgery, in managing spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?
3.	Objective	To establish the effectiveness of invasive interventions, such as vertebroplasty, kyphoplasty, ablation and surgery, in managing spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Cumulative Index to Nursing and Allied Health Literature (CINAHL) • Embase • Epistemonikos • International Health Technology Assessment (IHTA) database • MEDLINE & MEDLINE In-Process

ID	Field	Content
		Searches will be restricted by: • Date 1990 onwards • English language studies • Human studies Other searches: Inclusion lists of systematic reviews With the agreement of the guideline committee the searches will be re-run between 6-8 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Invasive interventions in managing spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression
6.	Population	Inclusion: • Adults with metastatic spinal disease or direct malignant infiltration of the spine. • Adults with spinal cord or nerve root compression because of metastatic spinal disease or direct malignant infiltration. Exclusion: • Adults with spinal cord compression because of primary tumours of the spinal cord, meninges or nerve roots. • Adults with spinal cord compression because of non-malignant causes. • Adults with primary bone tumours of the spinal column. • Children and young people under the age of 18.
7.	Intervention	Surgery: • Vertebroplasty • Kyphoplasty • Ablation

ID	Field	Content
		• Surgical stabilization (for example with metalwork) • Surgical decompression
8.	Comparator	• In comparison with each other • No surgery with or without a non-surgical intervention (example external orthosis or chemotherapy)
9.	Types of study to be included	Experimental studies (where the investigator assigned intervention or control) including: • Randomised controlled trials • Non-randomised controlled trials • Comparative observational studies • Systematic reviews/meta-analyses of controlled trials.
10.	Other exclusion criteria	Inclusion: • Full text papers • Observational studies should adjust for baseline differences between patients in different intervention groups in their analyses Exclusion: • Conference abstracts • Articles published before 1990. MRI has made a difference in diagnosis and management since the early 1990s.Surgical techniques have continuously evolved over this time • Papers that do not include methodological details will not be included as they do not provide sufficient information to evaluate risk of bias/study quality. • Non-English language articles
11.	Context	Metastatic spinal cord compression in adults: risk assessment, diagnosis and management (2008) NICE guideline will be updated by this review question

12.	Primary outcomes (critical outcomes)	• Neurological and functional status including:
		  ○ Bowel and bladder function
		  ○ Mobility or ambulatory status
		• Pain

13.	Secondary outcomes (important	• Health related Quality of Life

ID	Field	Content

	outcomes)	• Patient satisfaction
		• Treatment related adverse events including:
		  ○ Severe infections
		  ○ Serious adverse events as defined by trials
		  ○ Treatment related mortality
		• Overall survival
		• Spinal stability/deformity

14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. The full set of records will not be dual screened because the population, interventions and relevant study designs are relatively clear and should be readily identified from titles and abstracts. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Risk of bias of individual studies will be assessed using the preferred checklist as described in Appendix H of Developing NICE guidelines: the manual. ROBIS tool for systematic reviews

ID	Field	Content
		• Cochrane RoB tool v.2 for RCTs and quasi-RCTs • The non-randomised study design appropriate checklist. For example Cochrane ROBINS-I tool for non-randomised controlled trials and cohort studies; the EPOC RoB tool for controlled before and after studies. The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Data Synthesis Where possible, pairwise meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios for dichotomous outcomes. Peto odds ratio will be used for outcomes with zero events Mean differences or standardised mean differences will be calculated for continuous outcomes. Heterogeneity Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. In the case of serious or very serious unexplained heterogeneity (remaining after pre-specified subgroup and stratified analyses) meta-analysis will be done using a random effects model. Minimal important differences (MIDs) Default MIDs will be used for risk ratios and continuous outcomes only, unless the committee pre-specifies published or other MIDs for specific outcomes For risk ratios: 0.8 and 1.25. For continuous outcomes: MID is calculated by ranking the studies in order of SD in the control arms. The MID is calculated as +/- 0.5 times median SD.

ID	Field	Content	
		For studies that have been pooled using SMD (meta-analysed): +0.5 and -0.5 in the SMD scale are used as MID boundaries. Validity The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/	
17.	Analysis of sub-groups	Evidence will be stratified by: • Spinal metastases/infiltration with vs without cord compression Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: • Location of metastasis in spine (cervical, thoracic, lumbar) • Primary cancer type • Subgroups listed in the equality impact assessment form: age, race, sex & socioeconomic status Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery

ID	Field	Content		
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	01/09/21		
22.	Anticipated completion date	23/08/23		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
24.	Named contact	5a. Named contact NICE 5b Named contact e-mail metastaticspinal@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)		
25.	Review team members	NICE Technical Team		
26.	Funding sources/sponsor	This systematic review is being completed by NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's		

ID	Field	Content	
		code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].	
29.	Other registration details		
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=295488	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Invasive interventions; MSCC; vertebroplasty; kyphoplasty; ablation; surgery	
33.	Details of existing review of same topic by same authors		
34.	Current review status	☒	Ongoing
		☒	Completed but not published
		☒	Completed and published
		☒	Completed, published and being updated
		☒	Discontinued
35..	Additional information	N/A	

ID	Field	Content
36.	Details of final publication	www.nice.org.uk

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation
Remove those abbreviations that are not needed and add any that have not yet been explained.

Appendix B Search strategy (clinical/economic)

Literature search strategies for review question: What is the effectiveness of invasive interventions, such as vertebroplasty, kyphoplasty, ablation and surgery, in managing spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Database: Medline – OVID interface

#	Searches
1	Spinal Cord Compression/
2	exp Spinal Cord Neoplasms/ or Spinal Neoplasms/
3	((cauda equina or cervical* or cervicothoracic or cord* or coccyx or duralsac* or dural sac* or intervertebr* or lumbar or lumbosac* or lumbo sac* or medulla* or orthothoracic or sacral or sacrum or spinal or spine* or thecal sac* or thoracic or vertebr* or epidural or extradural or extra dural) adj3 (infiltrat* or invad* or invasion or metast* or oligometast*)).ti,ab.
4	(((cauda equina or cervical* or cervicothoracic or cord* or coccyx or duralsac* or dural sac* or intervertebr* or lumbar or lumbosac* or lumbo sac* or medulla* or orthothoracic or sacral or sacrum or spinal or spine* or thecal sac* or thoracic or vertebr* or epidural or extradural or extra dural or ((axon* or neuron* or nerve*) adj2 root)) adj3 (collaps* or compress* or pinch* or press*)) and (adeno* or cancer* or carcinoma* or chordoma* or intraepithelial* or intra epithelial* or malignan* or metast* or neoplas* or oligometast* or tumo?r*)).ti,ab.
5	(myelopath* or myeloradiculopath* or radiculopath*).ti,ab,hw. or (radicular adj2 (disorder* or syndrome*)).ti,ab.
6	(mescc or mscc).ti,ab.
7	or/1-6
8	exp Cementoplasty/
9	Polymethyl Methacrylate/ or Bone Cements/
10	(kyphoplast* or kyphon or kyphx* or lordoplast* or balloon or BKP).ti,ab.
11	(cementoplast* or vertebroplast* or ((vertebra* or cement* or plastic*) adj3 (augment* or inject*)) or methyl methacrylate or methylmethacrylate or polymethyl methacrylate or pmma).ti,ab.
12	exp Ablation Techniques/
13	(((laser* or microwave* or micro wave* or radiofrequen* or radio frequen* or thermal) adj3 (ablat* or neurotom* or rhizotom*)) or cryotherap* or thermotherap*).ti,ab. or (ablative or ablation).ti.
14	exp Internal Fixators/ or Fracture Fixation/ or exp Fracture Fixation, Internal/
15	(bracing or fixation or instrumentation or metalwork or metal work or osteosynthes* or pinning or plating).ti,ab.
16	((metal* or steel or titanium) adj3 (bar? or bridge? or cage? or clip* or device* or implant* or nail* or plate? or ribbon* or rod? or screw* or stent*)).ti,ab.
17	((bone? or spine or spinal) adj3 (bar? or bridge? or cage? or clip* or device* or implant* or nail* or plate? or ribbon* or rod? or screw* or stent*)).ti,ab.
18	Decompression, Surgical/ or exp Diskectomy/ or Laminectomy/
19	(((surg* or excis* or operat* or resect*) adj3 (decompres* or fix* or insert* or instabilit* or reconstruct* or reinforc* or repair* or stabl* or stabili* or support*)) or corpectom* or dis?ectom* or laminectom* or laminoplast* or vertebrectom*).ti,ab.
20	or/8-19
21	7 and 20
22	letter/ or editorial/ or news/ or exp historical article/ or Anecdotes as Topic/ or comment/ or case report/ or (letter or comment*).ti.
23	randomized controlled trial/ or random*.ti,ab.
24	22 not 23
25	(animals/ not humans/) or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ or (rat or rats or mouse or mice).ti.
26	24 or 25
27	21 not 26
28	limit 27 to english language
29	limit 28 to yr="1990 -Current"
30	meta-analysis/ or meta-analysis as topic/ or "systematic review"/
31	(meta analy* or metanaly* or metaanaly* or ((evidence or systematic*) adj2 (overview* or review*))).ti,ab.
32	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
33	(search strategy or search criteria or systematic search or study selection or data extraction or (search* adj4 literature)).ab.
34	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
35	cochrane.jw.
36	or/30-35
37	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt.
38	drug therapy.fs.
39	(groups or placebo or randomi#ed or randomly or trial).ab.
40	Clinical Trials as Topic/
41	trial.ti.
42	or/37-41
43	Non-Randomized Controlled Trials as Topic/
44	(experimental or nonrandom* or non random*).tw.

#	Searches
45	43 or 44
46	Comparative Studies/ or Follow-Up Studies/ or Time Factors/
47	(chang* or evaluat* or reviewed or prospective* or retrospective* or baseline or cohort or case series).tw.
48	46 or 47
49	36 or 42 or 45 or 48
50	29 and 49

Health economics search

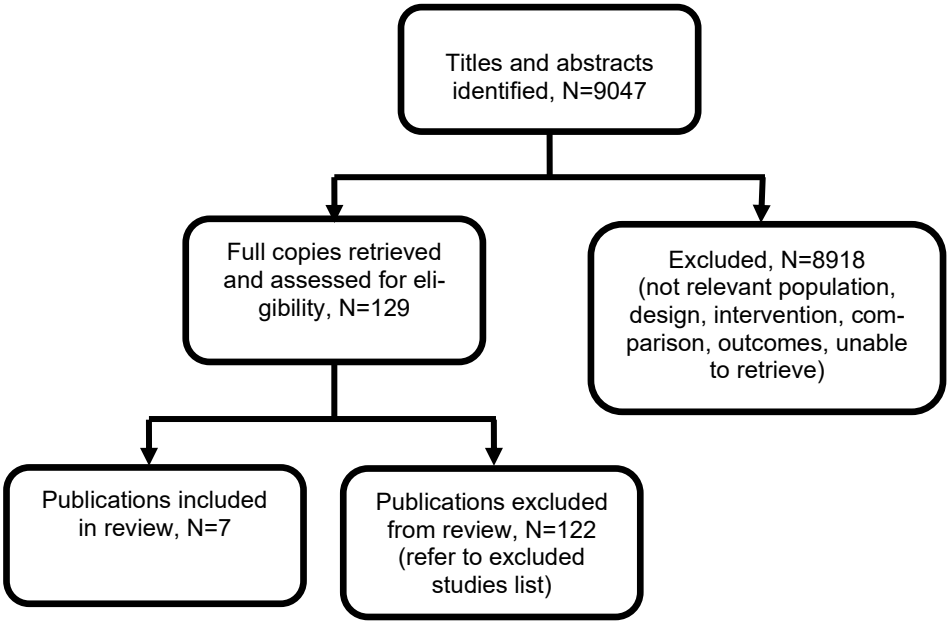
Database: Medline – OVID interface

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

Appendix C Effectiveness evidence study selection

Study selection for: What is the effectiveness of invasive interventions, such as vertebroplasty, kyphoplasty, ablation and surgery, in managing spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What is the effectiveness of invasive interventions, such as vertebroplasty, kyphoplasty, ablation and surgery, in managing spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Berenson, 2011

Berenson, James; Pflugmacher, Robert; Jarzem, Peter; Zonder, Jeffrey; Schechtman, Kenneth; Tillman, John B; Bastian, Leonard; Ashraf, Talat; Vrionis, Frank; Cancer Patient Fracture Evaluation (CAFE), Investigators; Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial.; The Lancet. Oncology; 2011; vol. 12 (no. 3); 225-35

Study details

Country/ies where study was carried out	Australia, Canada, Europe, and the USA (22 sites).
Study type	Randomised controlled trial (RCT). 1:1 ratio, stratified by centre, sex, and cancer type.
Study dates	May 2005 and March 2008.
Inclusion criteria	• ≥21 years • 1-3 painful vertebral compression fractures (T5–L5) clinically diagnosed in conjunction with either plain radiographs or MRI. • Pain numeric rating score ≥4 • Roland-Morris disability questionnaire score ≥10.
Exclusion criteria	• Patients with osteoblastic tumours, primary bone tumours (for example, osteosarcoma), or a plasmacytoma at the index vertebral compression fracture. • Patients enrolled in a concurrent phase 1 investigational anticancer treatment study • Patients with substantial clinical morbidities (aside from vertebral compression fractures and cancer) • Vertebral compression fracture morphology deemed unsuitable for kyphoplasty by the treating physician (for example, vertebra plana, comminuted fractures, fractures that did not have cortical integrity or that had posterior wall involvement, or those with epidural involvement and a tumour noted) • needed additional surgical treatment for the index fracture • needed treatment with high-dose steroids, intravenous pain medication, or nerve blocks to control chronic back pain unrelated to index vertebral compression fractures.
Patient characteristics	• Age, mean, years (SD): 63.9 (11.1). • Sex: female, n=75; male n=59. • Estimated symptomatic fracture age, median, months (IQR): kyphoplasty group 3.4 (2.0–6.4); control group 3.5 (1.1–7.1) • Ethnic origin:

	○ White - kyphoplasty group 62; control group 52 ○ Black - kyphoplasty group 2; control group 7 ○ Asian - kyphoplasty group 1; control group 1 ○ Hispanic - kyphoplasty group 1; control group 0 ○ Other - kyphoplasty group 2; control group 1. • Bisphosphonate use, n: kyphoplasty group 30; control group 33 • Steroid use, n: kyphoplasty group 20; control group 25 • Underlying cause, n: ○ Multiple myeloma - kyphoplasty group 22; control group 27 ○ Breast cancer - kyphoplasty group 16; control group 12 ○ Lung cancer - kyphoplasty group 7; control group 4 ○ Prostate cancer - kyphoplasty group 4; control group 4. • Number of fractures, n: ○ 1 - kyphoplasty group 24; control group 27 ○ 2 - kyphoplasty group 18; control group 20 ○ 3 - kyphoplasty group 26; control group 14 • Treatment for cancer, n: ○ Radiation (all sites) – kyphoplasty group 39; control group 24 ▪ Spine - kyphoplasty group 16; control group 11 (Number of spinal radiation treatments per patient, mean - kyphoplasty group 1.1; control group 1.4) ▪ Bone - kyphoplasty group 7; control group 14 ○ Surgery - kyphoplasty group 34; control group 32 ○ Chemotherapy/hormonal - kyphoplasty group 45; control group 41 ○ Steroids - kyphoplasty group 20; control group 25. • Status of cancer at baseline, n: ○ No evidence – kyphoplasty group 10; control group 10 ○ Remission – kyphoplasty group 4; control group 7 ○ Stable – kyphoplasty group 27; control group 22 ○ Progressive – kyphoplasty group 26; control group 21.
Intervention(s)/control	Intervention: Balloon kyphoplasty with introducer tools, inflatable bone tamps, and polymethylmethacrylate bone cement and delivery devices, by a percutaneous, bilateral, transpedicular, or extra-pedicular method. • All patients could receive analgesics, bed rest, bracing, physiotherapy, rehabilitation programmes, walking aids, radiation treatment, and other antitumour therapy at the discretion of treating physicians. • Patients with concurrent osteoporosis or bone metastasis could also receive treatment with calcium, vitamin D supplements, and antiresorptive or anabolic agents as necessary. Control group: non-surgical management. Patients in the control group were offered kyphoplasty after the 1-month assessment. • Non-surgical treatments for index vertebral compression fractures, n; *p* value at 1 month: • Walking aids – kyphoplasty group – baseline 22, 1 month 16; control group – baseline 22, 1 month 23; $p = 0.028$.

	• Bracing – kyphoplasty group - baseline 9, 1 month 1; control group - baseline 10, 1 month 11; *p* = 0.001 • Wheelchair – kyphoplasty group - baseline - 5, 1 month 1; control group – baseline 3, 1 month 2; *p* = 0.58 • Bed rest – kyphoplasty group – baseline 29, 1 month 15; control group – baseline 32; 1 month 23; *p* = 0.016 • Physical therapy – kyphoplasty group – baseline 11, 1 month 3; control group – baseline 8; 1 month 6; *p* = 0.18 • Any medication – kyphoplasty group - baseline 64, 1 month 34, control group – baseline 51, 1 month 41; *p* = 0.001 • Radiation therapy – kyphoplasty group - baseline 4, 1 month 3; control group 0 – baseline 1, 1 month 4; *p* = 0.70.
Duration of follow-up	1, 3, 6, and 12 months. NB As patients in the control group were offered kyphoplasty after the 1-month assessment data from later timepoints have not been extracted.
Sources of funding	Medtronic Spine LLC.
Sample size	N=134 randomised. Kyphoplasty n=70; non-surgical management n=64. Data available at 1 month follow-up: Kyphoplasty n=65; non-surgical management n=52.
Other information	Patients in the control group were offered kyphoplasty after the 1-month assessment. 38 patients in the control group crossed over to kyphoplasty after the 1-month assessment. No patient in the control group underwent kyphoplasty before 1 month. Mean crossover time was 47 days (SD 45·4) after study entry, and occurred within 1 week of the 1-month visit in 21 of the 38 patients who crossed over. There were no differences between the three groups (kyphoplasty, crossover, or control) in baseline characteristics (data not shown). Of the 104 patients who had kyphoplasty, 84 had general anaesthesia, one had local anaesthesia, and 19 had local anaesthesia with conscious sedation. Roland-Morris disability questionnaire score (0–24) (B) Karnofsky performance status score (0–100); (C) SF-36 physical component summary (PCS) score (0–100; normative score for US general population is 50); (D) SF-36 mental component summary (MCS) score (0–100; normative score for US general population is 50); (E) reduced activity days within the past 2 weeks; (F) bed rest days within the past 2 weeks.

Outcomes

Outcome	**Balloon kyphoplasty, n=70**	**Non-surgical treatment, n=64**
Neurological and functional status – disability — scores (SD) on Roland Morris Questionnaire (follow-up 1 month post-operative, range 0 – 24, lower scores are better)	9.1 (1.68)	18 (0.96)
Pain — scores (SD) on Numeric Rating Scale (follow-up 1 month post-operative, range 0 – 10, lower scores are better)	3.3 (0.63)	6.88 (0.38)
Health related quality of life - quality of life - change from baseline in scores (SD) on Short-Form 36 physical component summary (follow-up 1 month post-operative, range 0 – 100, higher scores are better)	−35 (1.6)	−26 (1)

Outcome	Balloon kyphoplasty, n=70	Non-surgical treatment, n=64
Spinal stability/deformity – improvement in vertebral body height restoration (follow-up 1 month post-operative, mm) –	2.4(0.83)	0.7 (0.58)

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

de Almeida, 2020

de Almeida Bastos, D.C.; Everson, R.G.; de Oliveira Santos, B.F.; Habib, A.; Vega, R.A.; Oro, M.; Rao, G.; Li, J.; Ghia, A.J.; Bishop, A.J.; Yeboa, D.N.; Amini, B.; Rhines, L.D.; Tatsui, C.E.; A comparison of spinal laser interstitial thermotherapy with open surgery for metastatic thoracic epidural spinal cord compression; Journal of Neurosurgery: Spine; 2020; vol. 32 (no. 5); 667-675

Study details

Country/ies where study was carried out	USA.
Study type	Non-randomised controlled trial. Matched group design.
Study dates	January 2010 and December 2016
Inclusion criteria	• Preoperative MRI demonstrating epidural spinal cord compression arising from a tumor located in a vertebral body between T2 and T12, with a Bilsky score of 1c, 2, or 3. • Epidural tumour contained within the boundaries of the posterior longitudinal ligament or periosteum of the dorsal elements. • Deemed suitable for either treatment modality by senior author.
Exclusion criteria	• Severe neurological deficits (Frankel grade A, B, or C)

	• Patients unable to undergo MRI (for example., because of a pacemaker).
Patient characteristics	Age, years, mean (SD): Not reported for sample overall. < 50 years n=13; 51 – 60 years n=31; 61 - 70 years n=25; >71 years n=11. Sex: female n=19 male n=61. Prior treatment, n: o None - spinal laser interstitial thermotherapy 27; open surgery 25. o Conventional external-beam radiation therapy - spinal laser interstitial thermotherapy 8; open surgery 13. o Spinal stereotactic radiosurgery - spinal laser interstitial thermotherapy 2; open surgery 1. o Conventional external-beam radiation therapy and spinal stereotactic radiosurgery - spinal laser interstitial thermotherapy 3; open surgery 1. • Karnofsky Performance Score, n: o 70 - spinal laser interstitial thermotherapy 26; open surgery 30. o < 70 - spinal laser interstitial thermotherapy 14; open surgery 10. • Multiple levels, n: Yes - spinal laser interstitial thermotherapy 25; open surgery 27. • Tumour histology, n: o Renal cell carcinoma - spinal laser interstitial thermotherapy 17; open surgery 11. o Non-small cell lung cancer - spinal laser interstitial thermotherapy 5; open surgery 6. o Hepatocellular carcinoma - spinal laser interstitial thermotherapy 3; open surgery 3. o Colon - spinal laser interstitial thermotherapy 0; open surgery 4. o Breast - spinal laser interstitial thermotherapy 0; open surgery 2. o Melanoma - spinal laser interstitial thermotherapy 3; open surgery 0. o Sarcoma - spinal laser interstitial thermotherapy 3; open surgery 4. o Thyroid - spinal laser interstitial thermotherapy 3; open surgery 4. o Other - spinal laser interstitial thermotherapy 6; open surgery 6.
Intervention(s)/control	**Open Surgery:** All patients underwent circumferential decompression via a standard posterior approach, which included a laminectomy, unilateral or bilateral facetectomies, and circumferential resection of the epidural tumour. Pedicle screw-rod constructs were used in the setting of instability. Vertebral body and additional soft tissue resections were performed depending on the location of the tumour and at the discretion of the surgeon. When necessary, anterior column reconstruction was performed using either polymethylmethacrylate or an expandable cage. **Spinal Laser Interstitial Thermotherapy:** Patient is positioned prone, with arms parallel to the body on the intraoperative MRI (iMRI) transfer table. Fiducial markers are randomly placed in the dorsal region overlying the area of interest, and the patient is transferred to the (iMRI) unit where T2- weighted images of the region of interest are obtained, uploaded to the navigation software and used for surface-matching image guidance registration. Image guidance is used to advance a navigated Jamshidi needle to the final target at a distance of 5–6 mm from the dural edge. Each laser fibre can achieve a 10-mm-diameter sphere of thermal damage; therefore, multiple needles may need to be positioned in tandem to treat larger tumours. A K-wire is used to exchange the Jamshidi needle for a plastic access cannula, which allows placement of the laser catheter. The laser ablation is performed with real-time iMRI thermography under ventilator pause. If stabilisation is required, the patient is removed from the iMRI unit and positioned at a safe distance from the high magnetic field where percutaneous instrumentation can be inserted using either MRI guidance or standard fluoroscopic technique. In

	cases of severe osteoporosis, methylmethacrylate augmentation of the screws is performed to increase the purchase in bone, aiming to achieve a more durable stabilisation. Follow-up imaging is performed generally 6–12 weeks after SLITT.
Duration of follow-up	The median follow-up time was 13 months (95% CI 9 to 16 months) for all patients. All patients underwent postoperative MRI and were evaluated as outpatients approximately every 3–4 months.
Sources of funding	Not reported.
Sample size	N=80: Spinal laser interstitial thermotherapy n=40; open surgery n=40.
Other information	Groups were matched based on variables that could correlate with local recurrence and/or overall survival. The variables selected were 1) Bilsky score, 2) Karnofsky Performance Scale (KPS) score, 3) age, 4) prior radiation treatment, and 5) adjuvant radiation treatment. The degree of spinal cord compression before and after open surgery or SLITT was scored according to the 6-point ESCC scale. Progression-free survival (PFS) was defined as the time between the procedure and local recurrence or last follow-up. Overall survival (OS) was defined as the time interval between the procedure and patient's death or censored. Complications were defined as any adverse event within 30 days related to the procedure. Major complications were defined as medical or surgical complications that required a prolonged hospital stay or new surgical procedure. Results: Treatment related adverse events - complications (any), n: spinal laser interstitial thermotherapy 2/40; open surgery 14/40. Spinal stability/deformity - reduction in epidural spinal cord compression score, n: spinal laser interstitial thermotherapy 29/40; open surgery 36/40.

Outcomes

Outcome	Spinal laser interstitial thermotherapy, n=40	Open surgery, n=40
Treatment related adverse events - complications – any (follow-up: 30 days)	n=2/40	n=14/40
Spinal stability/deformity - reduction in Epidural Spinal Cord Compression score (follow-up: post-operative period)	n=29/40	n=36/40

Korovessis, 2014

Korovessis, Panagiotis; Vardakastanis, Konstantinos; Vitsas, Vasilios; Syrimpeis, Vasilios; Is Kiva implant advantageous to balloon kyphoplasty in treating osteolytic metastasis to the spine? Comparison of 2 percutaneous minimal invasive spine techniques: a prospective randomized controlled short-term study.; Spine; 2014; vol. 39 (no. 4); e231-9

Study details

Country/ies where	Greece.

study was carried out	
Study type	Randomised controlled trial (RCT)
Study dates	March 2010 to March 2012.
Inclusion criteria	Patients with end stage disease with evidence (history, imaging evidences, and biopsy) for painful osteolytic vertebral metastases in 1 to 5 vertebral bodies. In addition to vertebral metastases, all patients showed metastases in the axial skeleton and visceral metastases. Severe back pain refractory or potential of further vertebral deformation and danger for neurological lesion caused by vertebral lesions secondary to osteolytic metastases.
Exclusion criteria	Significant spinal deformity (for example idiopathic, adult scoliosis), previous spinal operation, spinal infection, spinal canal compromise due to epidural disease associated/not with neurological impairment, vertebral osteolysis Tomita grade 12 more than 3 (high potential for cement leakage), radiculopathy, Tomita prognostic score less than 6, and/or uncorrected coagulopathy. Not the erosion of the posterior vertebral body wall, but the simultaneous infiltration of the posterior vertebral body cortex by the tumor with extension into the spinal canal was contraindication or vertebral augmentation. Patients, who were treated combined with vertebral augmentation plus spinal instrumentation for significant angular deformity caused by metastasis (> 75%) were excluded. Thus, patients with significant vertebral wedge deformities due to osteolytic vertebral fractures were not included in this study.
Patient characteristics	N=47 patients with osteolytic vertebral body metastasis. Diagnosis of bone metastasis definitively secured intraoperatively with transpedicular bone biopsy (Balex; Taeyeon Medical Co, Ltd, Incheon, Korea). Age, years, mean (SD): Not reported for sample overall. Kiva group 71 (13), balloon kyphoplasty group 70 (11). Sex: female n=26, male n=21. Primary tumour, n: Lung - Kiva group 6; balloon kyphoplasty group 7. Colon - Kiva group 9; balloon kyphoplasty group 9. Breast - Kiva group 8; balloon kyphoplasty group 8. Tomita prognostic score: Kiva group 6.95 ± 0.88 (range, 6–8); balloon kyphoplasty group 7.04 ± 0.88 (range, 6–8). Neurologically intact at admission, n: Kiva group 23; balloon kyphoplasty group 24.
Intervention(s)/control	The patients were placed in the prone position on a AcroMed frame. Both Kiva and BK augmentations were performed under biplane fluoroscopy and under general anaesthesia and continuous neuromonitoring. Biopsy was routinely obtained from all affected vertebrae, in all patients even when the diagnosis was preoperatively known, prior to augmentation with either balloon kyphoplasty or Kiva. The hospital stay was 24 hours. Patients were mobilized as soon as tolerable with a light body brace. **Kiva Procedure** The Kiva System is a single-use device in which an external delivery handle is used to deploy the Kiva implant over a nitinol coil guidewire. The coil is first advanced through the deployment cannula and into the cancellous portion of the vertebral body using an external handle. The implant is incrementally advanced over the coil to form a nesting, cylindrical column with an in situ outer diameter of 20 mm. The implant should be delivered between anterior and middle third of the vertebral body. Up to 4 loops of the implant may be inserted into the vertebral body for a maximum coil stack height of 12 mm, which re-elevates the endplate, thereby providing the desired vertebral fracture reduction. After the coil is retracted, low viscosity radiopaque PMMA cement is injected through the lumen of the polyether-

	etherketone implant, thereby interlocking the implant to the bone or destructed vertebral body. The manufacturer's instructions are that PMMA should be injected unilaterally close to the anterior two-thirds of the vertebral body through a 1.1-mm thick, 14-cm long delivery needle directly into the PEEK implant. PEEK implant after its implantation, forms a nesting, cylindrical column and through the internal small holes enables low viscosity PMMA to flow into the hollow PEEK cylindrical column and not outside. **Balloon Kyphoplasty Procedure** The Balex (Taeyeon Medical Co, Ltd) device and technique is very similar to the traditional balloon kyphoplasty. K-wires of 2-mm diameter are inserted through both pedicles of the damaged vertebra. Then, a cannula is inserted into the pedicle with cement filler and pusher. The position of the cannula is continuously controlled in both planes. Then, an expander is inserted bilaterally and inflated. After creation of the desired void, PMMA that is a high-viscosity bone cement is slowly injected after removal of the Expander. Inflation of balloons is stopped when 1 of the endpoints of inflation is reached: the pressure reaches over 300 ψ, the balloon contacts the cortical wall of the vertebra, or the maximal inflation volume of the balloon is reached. Mean balloon inflation volume was 4.1 mL (range, 1.3–5.5 mL). All patients in both groups were treated with the same preoperative assessment and postoperative protocol and were mobilized 1 day postoperatively.
Duration of follow-up	1 month
Sources of funding	None reported.
Sample size	N=47. Kiva group n=23. Balloon kyphoplasty group n=24.

Outcomes

Outcome	Kiva novel implant with PMMA, n=23	Balloon kyphoplasty with PMMA, n=24
Neurological and functional status – disability – Oswestry Disability Index (follow-up: 1 month post-operative, range 0 – 100, lower scores are better	38 (8)	37 (9)
Pain — Visual Analogue Scale (follow-up 1 month post-operative, range 0 – 10, lower scores are better)	3.2 (2)	3 (2.5)
Treatment related adverse events – complications (number of patients) - death, neurological, embolic, or cardiovascular (follow-up: 1 month post-operative)	n=0/23	n=0/24
Treatment related adverse events - number of augmented vertebrae in which cement leakage occurred - recorded radiologically - plain X-rays, CT scans (follow-up: 1 month post-operative)	n=0/41	n=4/43

Critical appraisal – Cochrane RoB 2

Section	Question	Answer

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Kumar, 2022
Kumar, Naresh; Tan, Jiong H; Thomas, Andrew C; Tan, Joel Y H; Madhu, Sirisha; Shen, Liang; Lopez, Keith G; Hey, Dennis H W; Liu, Gabriel; Wong, HeeKit; The Utility of 'Minimal Access and Separation Surgery' in the Management of Metastatic Spine Disease.; Global spine journal; 2022; 21925682211049803

Study details

Country/ies where study was carried out	Singapore.
Study type	Retrospective cohort study. Propensity scoring adjustment analysis was used to address heterogenicity of histological tumour subtypes.
Study dates	January 2011 to October 2017.
Inclusion criteria	• aged >21 years who underwent surgery for thoracolumbar metastatic spinal disease • Surgical indications included spinal instability, and MSCC qualified by clinical neurological deficit with evidence of radiological cord compression. • Spinal instability was considered ‘present’ if Spinal Instability Neoplastic Score (SINS) was ≥13 and ‘indeterminate’ if SINS was between 7 and 12. • MSCC was classified as Bilsky grade 2 or 3 epidural spinal cord compression and/or the presence of motor weakness and sensory impairment.
Exclusion criteria	Exclusion criteria included cervical MSD, revision cases, combined anterior and posterior surgery and patients who underwent combined open and MISS techniques. En bloc spondylectomy and vertebroplasty/kyphoplasty were also excluded.
Patient characteristics	N=200 patients undergoing surgery for thoracolumbar metastatic spine disease. Age, years, mean (SD): minimally invasive spine surgery median 63 (range 36–83); open spine surgery median 59 (range 22–87). Mean and SD not reported. Sex: female n=100; male n=100.

Intervention(s)/control	Minimally invasive spine surgery, n=61 Open spine surgery, n=139. n=43 patients with spinal instability. Open posterior stabilisation, n=15 Percutaneous pedicle screw fixation (PPSF), n=28 n=157 patients with metastatic spinal cord compression. Open posterior stabilisation and decompression, n=124 Minimal access separation surgery, n=33
Duration of follow-up	Not reported.
Sources of funding	None reported.
Sample size	N=200
Other information	Patients with extensive visceral metastasis (>3 areas of solid organ involvement) were preferentially done via a minimally invasive approach if permitted. Patients with clinical spinal instability alone guided by SINS (pathological fractures requiring fixation with no clinical and/or radiological compression) were treated with PPSF or open posterior stabilization (OPS) with pedicle screws. Patients with MSCC guided by Bilsky score (clinical and/or radiological cord compression with or without a fracture) were treated with MASS or open posterior stabilization and decompression (OPSD). Standard spinal instrumentation constructs were utilized; no cemented screws were used.

Outcomes

Outcome	**Minimal access separation surgery, n=33**	**Open posterior stabilisation and decompression, n=124**
Neurological and functional status - American Spinal Injury Association Impairment Scale score – improved (follow-up: not reported)	n=23/33	n=75/115
Treatment related adverse events - delayed oncological treatment (follow-up: not reported)	n=6/33	n=22/124
Treatment related adverse events - medical complications (follow-up: not reported)	n=14/28	n=48/124
Treatment related adverse events - surgical complications (follow-up: not reported)	n=5/28	n=22/124
Overall survival - survival > 3 months (follow-up: 3 months)	n=23/28	n=75/115

Outcome	Percutaneous pedicle screw fixation (PPSF), n=28	Open posterior stabilization (OPS), n=15
Neurological and functional status - American Spinal Injury Association Impairment Scale score - no change or improved (follow-up: not reported)	n=28/28	n=13/15
Treatment related adverse events - delayed oncological treatment (follow-up: not reported)	n=2/28	n=3/15
Treatment related adverse events - medical complications (follow-up: not reported)	n=9/28	n=8/15
Treatment related adverse events - surgical complications (follow-up: not reported)	n=1/28	n=4/15
Overall survival - survival > 3 months (follow-up: 3 months)	n=20/28	n=12/15

Critical appraisal – ROBIS

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Orgera, 2014
Orgera, Gianluigi; Krokidis, Miltiadis; Matteoli, Marco; Varano, Gianluca Maria; La Verde, Giacinto; David, Vincenzo; Rossi, Michele; Percutaneous vertebroplasty for pain management in patients with multiple myeloma: is radiofrequency ablation necessary?.; Cardiovascular and interventional radiology; 2014; vol. 37 (no. 1); 203-10

Study details

Country/ies where	Italy.

study was carried out	
Study type	Randomised controlled trial (RCT)
Study dates	January 2008 to August 2012.
Inclusion criteria	• Patients with a consistent vertebral involvement of MM in 1–3 vertebral bodies of the thoracic and lumbar spine. • At least a 3-month history of pain refractory to conservative analgesic therapy, either alone or in combination with chemotherapy and/or radiation therapy. • Karnofsky Performance Score >30. • Absence of neurological symptoms indicating radiculopathy or myelopathy.
Exclusion criteria	• Presence of vertebral involvement in more than 3 levels. • Involvement of the cervical spine • Age younger than 18 years or older than 85 years. • Symptom improvement with analgesic therapy. • Myelopathy in patients with spinal canal compromise due to retropulsion of bone fragments or tumour involvement. • Presence of active local or systemic infections. • Non-correctable coagulopathy. • Known allergy to bone cement or contrast agents. The diagnosis of myeloma was obtained using standardized clinical criteria; however intraprocedural bone biopsy the time of vertebroplasty was performed in all patients. Vertebral body involvement was detected in plain films or cross-sectional imaging, computed tomography (CT), or magnetic resonance imaging (MRI).
Patient characteristics	Age, mean, years (SD): mean age 67.4 (range 51–82). SD not reported. Sex: female n=26; male n=10.
Intervention(s)/control	50 vertebroplasty procedures were included in the study. Twenty-two procedures were performed in group A (8 in the thoracic and 14 in the lumbar spine) and 28 in group B (11 in the thoracic and 17 in the lumbar spine). A 100 % technical success rate was achieved in all patients of both groups. In all but two cases, the procedure was performed under conscious sedation with the use of intravenous midazolam (1–10 mg) and fentanyl (25–200 lg). In the two patients who were unable to tolerate conscious sedation, the procedures was rescheduled and performed under general anaesthesia. Before the procedure, all patients received a prophylactic dose of intravenous antibiotics (750 mg of cefuroxime). All procedures were performed under CT-fluoroscopic guidance; it was based on the operator's choice to use fluoroscopic guidance with a C-arm in some cases in the CT room. The patient was positioned prone. A posterior percutaneous approach at the thoracic and lumbar levels (extrapedicular approach at thoracic levels above T10 and transpedicular approach below T10) was used. The vertebra to be treated was infiltrated with local anaesthetic (lidocaine 1 %) under strict aseptic conditions in the fluoroscopy suite with the use of a 21-gauge spinal needle. A small skin incision was made with a blade and the vertebroplasty needle was advanced with the use of a sterile hammer through the cortical bone in the anterior third of the vertebral lesion. The direction of the needle was adjusted by turning the

	bevelled tip by 90. The needle used in all cases was a 10-gauge vertebroplasty needle (Optimed, Ettlingen, Germany). Through this operative cannula, a biopsy also was performed before procedure in all cases with a sawtooth profile coaxial bone biopsy cannula (Optimed, Ettlingen, Germany). A unipedicular or bipedicular approach was performed according to operator's preference. In the cases where RFA was selected (**group A**) the radiofrequency probe was advanced through the access cannula. The RFA system used in all cases was the Cool-tip (Covidien, Boulder, CO; formerly Tyco Healthcare Valleylab). The generator offers the option of automatic adjustment of energy output according to the tissue impedance. The electrodes used were 17-gauge, straight monopolar 15 or 20 cm with a 2-cm active tip. The electrode was inserted through the cannula until the tip of the electrode reached the anterior third of the vertebral lesion. The working cannula was then retracted to expose the ''active-tip'' of the electrode. The output power was set between 100 and 150 W. The impedance rose up after 3 to 5 min; the final local temperature achieved ranged between 55 and 85 C in all cases. Ablation process lasted between 8 and 10 min. After the completion of ablation, the stylet of the vertebroplasty cannula was inserted and the cannula was advanced again and slow injection of 2–4 ml of polymethylmethacrylate (PMMA) was performed. The PMMAs used were Osteopal 40 and Osteopal V (Biomet Deutschland GmbH, Berlin, Germany). The injection was performed with the use of Optimed Gangi Cemento-Re Gun (Optimed, Ettlingen, Germany). The PMMA was injected slowly under fluoroscopy or intermittent CT fluoroscopy with gradual withdrawing of the needle. In case of suspicion of cement extravasation the injection was immediately stopped and depressurization with the application screw followed. The injection was terminated when at least two thirds of the lytic lesion was filled. Upon termination, the stylet of the needle was inserted again to empty the residual cement into the vertebral body, and both were gradually retracted. Immediate CT scanning was performed after the removal of the needle. In the cases that were randomized for vertebroplasty only (group B), injection of PMMA was performed without previous RFA. Patients were kept on strict bed rest for 2 h and allowed home either the same or the following day. A unipedicular approach was performed in 17 of 22 (77 %) patients of group A and 23 of 28 (82 %) of group B. Median and mean cement volumes injected were 3.5 and 3.38 ml (SD = 0.65, SE = 0.13) for group A and 3.75 and 3.48 ml (SD = 0.55, SE = 0.1) for group B respectively (p = 0.57).
Duration of follow-up	The visual analogue scale was calculated at 24 h postprocedure before patient discharge and 6 weeks after treatment on an outpatient basis. Analgesic consumption and the presence of neurological involvement also were evaluated immediately after the procedure and at 6 weeks. Follow-up with MRI at 1, 3, and 6 months was performed to exclude the involvement of other vertebral levels
Sources of funding	Not reported.
Sample size	N=36. Vertebroplasty with radiofrequency ablation N=18. Vertebroplasty alone n=18.

Outcomes

Outcome	**Vertebroplasty with radiofrequency ablation, n=18**	**Vertebroplasty alone, n=18**
Neurological and functional status - disability — scores on Roland Morris Questionnaire (mean [SD],	9.6 (1.2)	9.5 (1).

Outcome	Vertebroplasty with radiofrequency ablation, n=18	Vertebroplasty alone, n=18
follow-up: 24 hours, range 0 – 24, lower scores are better)		
Neurological and functional status - disability — scores on Roland Morris Questionnaire (mean [SD] follow-up: 6 weeks, range 0 – 24, lower scores are better)	8.2 (1)	8.7 (0.8)
Pain – Visual Analogue Scale (mean [SD] follow-up: 24 hours, range 0 – 10, lower scores are better)	3.4 (1.2)	3 (0.9)
Pain - Visual Analogue Scale (mean [SD] follow-up: 6 weeks, range 0 – 10, lower scores are better)	2 (0.9)	2.3 (0.9)
Treatment related adverse events - cement leakage (follow-up: 6 weeks)	n=2/18	n=2/18

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Patchell, 2005

Patchell, R. A.; Tibbs, P. A.; Regine, W. F.; Payne, R.; Saris, S.; Kryscio, R. J.; Mohiuddin, M.; Young, B.; Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial; Lancet; 2005; vol. 366; 643-8

Study details

Country/ies where study was carried out	United States (7 sites).
Study type	Randomised controlled trial (RCT) Stratified according to treating institution, tumour type, ambulatory status, and relative stability of the spine. Randomisation within strata by permutated blocks was done separately at each institution with a computerised technique, which en-

	sured immediate randomisation at study entry.
Study dates	September 1992 to December 2002.
Inclusion criteria	• At least 18 years old • Tissue-proven diagnosis of cancer (not of central nervous system or spinal column origin) • MRI evidence of MESCC • General medical status good enough to be acceptable surgical candidates • Expected survival of at least 3 months. • At least one neurological sign or symptom of MESCC (including pain). • Not totally paraplegic for longer than 48 hours before study entry. Confirmation of MESCC: MESCC defined radiographically as a true displacement of the spinal cord (by an epidural mass) from its normal position in the spinal canal. MESCC had to be restricted to a single area, which could include several contiguous spinal or vertebral segments. Before randomisation, all patients had imaging of the entire spinal cord. The imaging technique consisted of MRI with whole spine sagittal T1 and T2 imaging and axial T1 imaging. Additional MRI techniques were used as clinically appropriate. There was a central review of all MRI scans for confirmation of MESCC.
Exclusion criteria	• Patients with a mass that compressed only the cauda equina or spinal roots. • Patients with multiple discrete compressive lesions (unless they had one area of compression and multiple non-compressive lesions). • Patients with certain radiosensitive tumours (lymphomas, leukaemia, multiple myeloma, and germ-cell tumours) • Patients with pre-existing or concomitant neurological problems not related directly to their MESCC (eg, brain metastases). • Patients with previous MESCC and those who had received spinal radiation such that they were unable to receive the study dose.
Patient characteristics	Age, mean, years (SD): surgery + radiotherapy median 60; radiotherapy only median 60. Mean, range, and SD not re-ported. Sex: female n=31, male n=70. Primary tumours (n): lung – radiation 13, surgery 13; breast - radiation 6, surgery 7; prostate - radiation 10, surgery 9; other genitourinary - radiation 6, surgery 5; gastrointestinal - radiation 4, surgery 2; melanoma - radiation 3, surgery 3; head and neck – radiation 2, surgery 1; unknown -radiation 3, surgery 5; other radiation 4, surgery 5. Walking at entry (n): Radiation 35; surgery 34. Continent at entry (n): Radiation 32; surgery 30. Median Frankel score at entry: Radiation D; surgery D. D=ambulatory but with neurological symptoms. Median ASIA score at entry: Radiation 90; surgery 89. Spinal level of compression – Cervical - radiation 5, surgery 8; T1-T6 – radiation 18, surgery 20; T7-T12 – radiation 28, surgery 22. Position of spinal tumour - anterior – radiation 33, surgery 28; lateral - radiation 11, surgery 9; posterior – radiation 7, surgery 13. Unstable spine – radiation 18, surgery 20. Median time between diagnosis of primary tumour and development of MESCC, months: radiation 7; surgery 3.

	Median time between development of motor symptoms and treatment of MESCC, days: radiation 12; surgery 10 days.
Intervention(s)/control	**Radiotherapy only:** • 30 Gy (3 x 10 fractions). • Started within 24 hours of randomisation. • Treatments delivered to a port that encompassed one vertebral body above and below the visible lesion. • Protocol compliance monitored through central review of radiotherapy treatment plans. **Direct decompressive surgery followed by radiotherapy:** Operation within 24 hours of randomisation. RT delivered as per intervention group, within 14 days after surgery. Surgical technique: Protocol did not specify operative techniques or fixation devices. However, the aim of surgery was to provide immediate direct circumferential decompression of the spinal cord. The operation was tailored for each patient depending on the level of the spine involved and the patient's circumstances. In general, for anteriorlylocated tumours the approach in the cervical spine was anterior, and in the thoracic and lumbar spine, depending on the tumour location, the approach was through a transversectomy or anterior approach. For laterally-located tumours, a lateral approach was used, and for posteriorly-located tumours, a laminectomy was done and any other posterior elements involved were removed. Stabilisation of tumours in all locations was performed if spinal instability was present; cement (methyl methacrylate), metallic rods, bone grafting, or other fixation devices were used. Within 1 month of treatment operative reports and plans for post-surgery radiotherapy to monitor protocol compliance. Patients were given radiotherapy, as in the radiation group, within 14 days after surgery. Steroids given on same schedule for both groups. When diagnosed, all patients were given 100 mg dexamethasone immediately, then 24 mg every 6 h until the start of radiotherapy or surgery. Corticosteroids were then reduced and continued until completion of radiotherapy. Patients with severe diabetes or other relative contraindications to high-dose corticosteroids were treated with reduced doses when appropriate.
Duration of follow-up	All time dependent endpoints measured from the day of randomisation until death or last follow up. Overall median follow-up times were 102 days (IQR 0–1940) in the surgery + RT group and 93 days (IQR 0–1117 days) in the radiation group (p=0.10). Patients had neurological assessments before treatment, weekly during radiotherapy, and within 1 day after completion of treatment. Patients then had regular study follow-up assessments every 4 weeks until the end of the trial or death. Patients were also reassessed at any time they had symptoms suggestive of neurological progression.
Sources of funding	Grants from - National Cancer Institute (RO1 CA55256), and National Institute for Neurological Disorders and Stroke (K24 NS502180).
Sample size	N=101 randomised. Surgery plus radiotherapy n=50. Radiotherapy alone n=51.
Other information	The trial was stopped early after a comparison of ambulatory rates between the two groups based on ambulatory status. This compari-

	son yielded a p value of 0.001, which fell below the predetermined significance level for early termination of the trial according to the O'Brien Fleming rule ($p < 0.0054$). Because of proven superiority of surgical treatment, the data safety and monitoring committee deemed the trial should be stopped early. Spinal stability was ascertained according to Cybulski's guidelines. Patients with pathological spine fractures or evidence of bone in the spinal canal were also judged to have spinal instability. Protocol violations occurred with five patients. In the surgery group, three patients did not receive postoperative radiotherapy and a fourth patient stopped radiotherapy before receiving the complete course. In the radiation group, one patient was treated with surgery as well as postoperative radiotherapy. Ambulatory status results calculated as follows using 2 methods: • Combined ambulatory rate = Percentage of patients who maintained or regained ability to walk immediately after completion of radiotherapy. • Ambulatory time after treatment to give a measure of long-term success. Patients were deemed ambulatory if they could take at least two steps with each foot unassisted (4 steps total), even if a cane or walker was needed. Corticosteroid use assessed by calculating and comparing mean daily dexamethasone equivalent doses. Pain relief assessed by calculating and comparing mean daily morphine equivalent doses.

Outcomes

Outcome	Radiotherapy + surgery, n=50	Surgery alone, n=51
Neurological and functional status - ambulant after treatment - all patients (follow-up: post-radiotherapy treatment)	n=42/50	n=29/51
Neurological and functional status - ambulant after treatment - patients ambulatory at study entry - all patients (follow-up: post-radiotherapy treatment)	n=32/34	n=26/35
Neurological and functional status - ambulant after treatment - patients non ambulatory at study entry - all patients (follow-up: post-radiotherapy treatment)	n=10/16	n=3/16
Neurological and functional status - maintenance of continence, median, days (follow-up [median]: radiotherapy and surgery 102 days (IQR 0–1940), radiotherapy alone 93 days (IQR 0–1117)	156 days (n=50)	17 days (n=51)
Neurological and functional status - maintenance of muscle strength (ASIA score) median, days (follow-up [median]: radiotherapy and surgery 102 days (IQR 0–1940), radiotherapy alone 93 days (IQR 0–1117)	566 days (n=50)	72 days (n=51)
Neurological and functional status - maintenance of functional ability (Frankel score) median, days (follow-up [median]: radiotherapy and surgery 102 days (IQR 0–1940), radiotherapy alone 93 days (IQR 0–	156 days (n=50)	17 days (n=51)

Outcome	Radiotherapy + surgery, n=50	Surgery alone, n=51
1117)		
Pain - median [IQR] daily equivalent dose of morphine, mg (follow-up [median]: radiotherapy and surgery 102 days (IQR 0–1940), radiotherapy alone 93 days (IQR 0–1117)	0.4 (0 to 60)	4.8 (0 to 200)
Treatment related adverse events - 30 day mortality (follow-up: 30 days)	n=3/50	n=7/51
Overall survival - median overall survival (days)	100 days (n=50)	126 days (n=51)

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Zheng, 2021

Bibliographic Reference Zheng, J.; Wu, L.; Shi, J.; Niu, N.; Yang, Z.; Ding, H.; Hybrid Therapy Versus Total en Bloc Spondyectomy in the Treatment of Solitary Radioresistant Spinal Metastases: A Single-center, Retrospective Study; Clinical Spine Surgery; 2021

Study details

Country/ies where study was carried out	China.
Study type	Non-randomised controlled trial Propensity score matching (1:1 ratio).
Study dates	January 2012 and May 2019.
Inclusion criteria	Solitary spinal metastases involving the thoracic or lumbar spine, high-grade epidural cord compression (grades 2 and 3) according to the Bilsky criteria on MRI, tumour histology resistant to radiotherapy, life expectancy of more than 6 months (Tokuhashi score, 9–11), and good general condition of the patient [Eastern Cooperative Oncology Group Performance Status score ≤3].
Exclusion criteria	Incomplete case data, surgical contraindications, poorly controlled primary tumour, tumour combined with other metastatic lesions, and previous spinal tumour resection.
Patient characteristics	Age, mean, years (SD): 57.9 (6.6) Sex: female n=36, male n=121. *Hybrid therapy group (n=64)* Primary tumour (%): renal cell carcinoma (37%), thyroid (30%), liver (6%), rectal (6%), colon (16%), melanoma (5%) Non-ambulatory (ECOG PS 3 or 4): 33% *Total en bloc spondylectomy (n=93)* Primary tumour (%): renal cell carcinoma (36%), thyroid (24%), liver (9%), rectal (10%), colon (14%), melanoma(7%) Non-ambulatory (ECOG PS 3 or 4): 37%
Intervention(s)/control	• Hybrid therapy (HT): spinal separation surgery followed by stereotactic radiosurgery • Total en bloc spondylectomy (TES)
Duration of follow-up	At least 2 years.
Sources of funding	Ningxia Natural Science Foundation Project (NZ16128, 2019AAC03193)
Sample size	157 (110 included in propensity score matched analysis)

Outcomes

Outcome	Hybrid therapy, n=64	Total en bloc spondylectomy, n=93
Neurological and functional status - American Spinal Injury Association impairment scale - improved or preserved score (follow-up: 6 months)	n=55/55	n=55/55
Pain - Visual Analogue Scale (median [IQR], follow-up: 6 months; range – not reported, lower scores are better)	1 (1 – 2) n=64	1 (1 – 2) n=93
Treatment related adverse events – complications (follow-up: perioperative)	10/55	17/55
Health related quality of life - Spine Oncology Study Group Outcomes score (median [IQR] follow-up: 6 months, range 0 to 80; lower scores are better)	37 (36 - 39) n=64	37 (36–56) n=93
Spinal stability/deformity - Spinal Instability Neoplastic Score (postoperative; range 0 to 18; lower scores are better)	5 (4–5) n=64	5 (4–5) n=93

Critical appraisal – ROBINS-I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(Treatment took place over 7 year period - the hybrid therapy group is more likely to be more recent however the year of treatment is not reported for the 2 groups and not adjusted for in the analysis. Not clear how patients were selected for HT or TES groups - possibly a change in practice over time..)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Low

Section	Question	Answer
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Appendix E Forest plots

Forest plots for review question: What is the effectiveness of invasive interventions, such as vertebroplasty, kyphoplasty, ablation and surgery, in managing spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

No meta-analysis was conducted for this review question and so there are no forest plots.

Appendix F GRADE tables

GRADE tables for review question: What is the effectiveness of invasive interventions, such as vertebroplasty, kyphoplasty, ablation and surgery, in managing spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Table 5: Evidence profile for comparison between hybrid therapy and total en bloc spondylectomy

F							Number of participants		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considera-tions	Hybrid thera-py	Total en bloc spondylectomy	Relative (95% CI)	Absolute (95% CI)		
Neurological and functional status - American Spinal Injury Association impairment scale - improved or preserved score (follow-up: 6 months)												
1 (Zheng 2021)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	55/55	55/55	RR 1.00 (0.97 to 1.04)	0 fewer per 1,000 (from 30 fewer to 40 more)	MODERATE	CRITICAL
Pain - Visual Analogue Scale (follow-up: 6 months; range – not reported, lower scores are better)												
1 (Zheng 2021)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	n=64 (median 1, IQR 1 – 2)	n=93 (median 1, IQR 1 – 2)	not estima-ble	0 points lower with hybrid therapy (p=0.739)	LOW	CRITICAL
Treatment related adverse events – complications (follow-up: perioperative)												

F							Number of participants		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considera-tions	Hybrid thera-py	Total en bloc spondylectomy	Relative (95% CI)	Absolute (95% CI)		
1 (Zheng 2021)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	10/55	17/55	RR 0.59 (0.30 to 1.17)	127 fewer per 1,000 (from 216 fewer to 53 more)	LOW	IMPORTANT
Health related quality of life - Spine Oncology Study Group Outcomes score (follow-up: 6 months, range 0 to 80; lower scores are better)												
1 (Zheng 2021)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	n=64 (median 37, IQR 36 - 39)	n=93 (median 37, IQR 36–56)	not estima-ble	0 points lower with hybrid therapy (p=0.435)	LOW	IMPORTANT
Spinal stability/deformity - Spinal Instability Neoplastic Score (postoperative; range 0 to 18; lower scores are better)												
1 (Zheng 2021)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	n=64 (median 5, IQR 4–5)	n=93 (median 5, IQR 4–5)	not estima-ble	0 points lower with hybrid therapy (p=0.503)	LOW	IMPORTANT

CI: confidence interval; RR: risk ratio

1. Serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I.

2. Sample size < 300

3. 95% CI crosses 1 MID

Table 6: Evidence profile for comparison between Kiva novel implant with polymethylmethacrylate (PMMA) and balloon kyphoplasty with PMMA

Quality assessment							Number of participants		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considera-tions	Kiva novel implant with PMMA	Balloon kyphoplasty with PMMA	Relative (95% CI)	Absolute (95% CI)		
Neurological and functional status – disability – Oswestry Disability Index (follow-up: 1 month post-operative, range 0 – 100, lower scores are better												
1 (Ko-rovessis 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	23	24	not estima-ble	MD 1 higher (3.86 lower to 5.86 higher)	HIGH	CRITICAL
Pain — Visual Analogue Scale (follow-up 1 month post-operative, range 0 – 10, lower scores are better)												
1 (Ko-rovessis 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	23	24	not estima-ble	MD 0.20 higher (1.09 lower to 1.49 higher)	HIGH	CRITICAL
Treatment related adverse events - complications - death, neurological, embolic, or cardiovascular (follow-up: 1 month post-operative)												
1 (Ko-rovessis 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/23	0/24	RD 0.00 (-0.08 to 0.08)	0 fewer (from 80 fewer to 80 more)	LOW	IMPORTANT
Treatment related adverse events - number of augmented vertebrae in which cement leakage occurred - recorded radiologically - plain X-rays, CT scans (follow-up: 1 month post-operative)												
1 (Ko-rovessis 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/41	4/43	RR 0.12 (0.01 to 2.10)	82 fewer per 1,000 (from 92 fewer to 102 more)	LOW	IMPORTANT

CI: confidence interval; MD: mean difference; RR: risk ratio; MD: mean difference

1. Absolute effect range crosses 2 MIDs (10 more per 1000 and 10 fewer per 1000)

2. 95% CI crosses 2 MIDs

Table 7: Evidence profile for comparison between balloon kyphoplasty and non-surgical treatment

Quality assessment							Number of participants		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considera-tions	Balloon kyphoplasty	Non-surgical treatment	Relative (95% CI)	Absolute (95% CI)		
Neurological and functional status – disability — Roland Morris Questionnaire (follow-up 1 month post-operative, range 0 – 24, lower scores are better)												
1 (Beren-son 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	63	50	not estimable	MD 8.90 lower (9.39 lower to 8.41 lower)	MODERATE	CRITICAL
Pain — Numeric Rating Scale (follow-up 1 month post-operative, range 0 – 10, lower scores are better)												
1 (Beren-son 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	64	49	not estimable	MD 3.58 lower (3.77 lower to 3.39 lower)	MODERATE	CRITICAL
Health related quality of life - quality of life - change from baseline in Short-Form 36 physical component summary (follow-up 1 month post-operative, range 0 – 100, higher scores are bet-ter)												
1 (Beren-son 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	58	47	not estimable	MD 8.4 higher (7.7 higher to 9.1 higher	HIGH	IMPORTANT
Health related quality of life - quality of life - change from baseline in Short-Form 36 mental component summary (follow-up 1 month post-operative, range 0 – 100, higher scores are better)												
1 (Beren-son 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	58	47	not estimable	MD 11.1 higher (10.7 high-er to 11.5 higher)	HIGH	IMPORTANT
Spinal stability/deformity – improvement in vertebral body height restoration (follow-up 1 month post-operative, mm)												

Quality assessment							Number of participants		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Balloon kyphoplasty	Non-surgical treatment	Relative (95% CI)	Absolute (95% CI)		
1 (Berenson 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	33	not estimable	MD 3.10 higher (2.74 lower to 3.46 lower)	HIGH	IMPORTANT

CI: confidence interval; MD: standardised mean difference

1. 95% CI crosses 1 MID (0.5x control group SD, for Roland Morris Questionnaire 8.95; for pain – Numeric Rating Scale 3.4).

Table 8: Evidence profile for comparison between minimal access separation surgery and open posterior stabilisation and decompression

Quality assessment							Number of participants		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minimal access separation surgery versus	Open posterior stabilization and decompression	Relative (95% CI)	Absolute (95% CI)		
Neurological and functional status - American Spinal Injury Association Impairment Scale score – improved (follow-up: not reported)												
1 (Kumar 2022)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	23/33	75/115	RR 1.01 (0.92 to 1.12)	9 more per 1,000 (from 74 fewer to 111 more)	MODERATE	CRITICAL
Treatment related adverse events - delayed oncological treatment (follow-up: not reported)												
1 (Kumar 2022)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/33	22/124	RR 1.02 (0.45 to 2.32)	4 more per 1,000 (from 98 fewer to 234 more)	VERY LOW	IMPORTANT

Quality assessment							Number of participants		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minimal access separation surgery versus	Open posterior stabilization and decompression	Relative (95% CI)	Absolute (95% CI)		
Treatment related adverse events - medical complications (follow-up: not reported)												
1 (Kumar 2022)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	14/28	48/124	RR 1.29 (0.84 to 1.99)	112 more per 1,000 (from 62 fewer to 383 more)	LOW	IMPORTANT
Treatment related adverse events - surgical complications (follow-up: not reported)												
1 (Kumar 2022)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/28	22/124	RR 1.01 (0.42 to 2.43)	2 more per 1,000 (from 103 fewer to 253 more)	VERY LOW	IMPORTANT
Overall survival - survival > 3 months (follow-up: 3 months)												
1 (Kumar 2022)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	23/28	75/115	RR 1.07 (0.82 to 1.39)	350 more per 1,000 (from 900 fewer to 1,000 more)	LOW	IMPORTANT

CI: confidence interval; RR: risk ratio

1. Serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I

2. 95% CI crosses 2 MIDs.

3. 95% CI crosses 1 MIDs

Table 9: Evidence profile for comparison between percutaneous pedicle screw fixation (PPSF) and open posterior stabilization (OPS)

Quality assessment	Number of participants	Effect	Quality	Importance

No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Percutaneous pedicle screw fixation (PPSF)	Open posterior stabilization (OPS)	Relative (95% CI)	Absolute (95% CI)		
Neurological and functional status - American Spinal Injury Association Impairment Scale score - no change or improved (follow-up: not reported)												
1 (Kumar 2022)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	28/28	13/15	RR 1.16 (0.94 to 1.45)	139 more per 1,000 (from 52 fewer to 390 more)	LOW	CRITICAL
Treatment related adverse events - delayed oncological treatment (follow-up: not reported)												
1 (Kumar 2022)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/28	3/15	RR 0.36 (0.07 to 1.91)	128 fewer per 1,000 (from 186 fewer to 182 more)	VERY LOW	IMPORTANT
Treatment related adverse events - medical complications (follow-up: not reported)												
1 (Kumar 2022)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	9/28 (32.1%)	8/15	RR 0.60 (0.29 to 1.23)	213 fewer per 1,000 (from 378 fewer to 123 more)	LOW	IMPORTANT
Treatment related adverse events - surgical complications (follow-up: not reported)												
1 (Kumar 2022)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/28	4/15	RR 0.13 (0.02 to 1.09)	232 fewer per 1,000 (from 262 fewer to 24 more)	LOW	IMPORTANT
Overall survival - survival > 3 months (follow-up: 3 months)												

Quality assessment							Number of participants		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Percutaneous pedicle screw fixation (PPSF)	Open posterior stabilization (OPS)	Relative (95% CI)	Absolute (95% CI)		
1 (Kumar 2022)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	20/28	12/15	RR 0.89 (0.63 to 1.26)	88 fewer per 1,000 (from 296 fewer to 208 more)	VERY LOW	IMPORTANT

CI: confidence interval; RR: risk ratio

1. Serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I.

2. 95% CI crosses 1 MIDs

3. 95% CI crosses 2 MIDs

Table 10: Evidence profile for comparison between spinal laser interstitial thermotherapy and open surgery

Quality assessment							Number of participants		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Spinal laser interstitial thermotherapy	Open surgery	Relative (95% CI)	Absolute (95% CI)		
Treatment related adverse events - complications – any (follow-up: 30 days)												
1 (de Almeida 2020)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/40	14/40	RR 0.14 (0.03 to 0.59)	301 fewer per 1,000 (from 339 fewer to 144 fewer)	MODERATE	IMPORTANT
Spinal stability/deformity - reduction in Epidural Spinal Cord Compression score (follow-up: post-operative period)												
1 (de Almeida 2020)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29/40	36/40	RR 0.81 (0.65 to 1.00)	171 fewer per 1,000 (from 315 fewer to 0 fewer)	LOW	IMPORTANT

CI: confidence interval; HR: hazard Ratio; RR: risk ratio

1. Serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I.
2. 95% CI crosses 1 MID.

Table 11: Evidence profile for comparison between vertebroplasty with radiofrequency ablation and vertebroplasty alone

Quality assessment							Number of participants		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vertebroplasty with radiofrequency ablation	Vertebroplasty alone	Relative (95% CI)	Absolute (95% CI)		
Neurological and functional status - disability — Roland Morris Questionnaire (follow-up: 24 hours, range 0 – 24, lower scores are better)												
1 (Orgera 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	18	18	not estimable	MD 0.1 higher (0.62 lower to 0.82 higher)	LOW	CRITICAL
Neurological and functional status - disability — Roland Morris Questionnaire (follow-up: 6 weeks, range 0 – 24, lower scores are better)												
1 (Orgera 2014	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	18	18	not estimable	MD 0.5 lower (1.09 lower to 0.09 higher)	MODERATE	CRITICAL
Pain - Visual Analogue Scale (follow-up: 24 hours, range 0 – 10, lower scores are better)												
1 (Orgera 2014	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	18	18	not estimable	MD 0.4 higher (0.29 lower to 1.09 higher)	MODERATE	CRITICAL
Pain - Visual Analogue Scale (follow-up: 6 weeks, range 0 – 10, lower scores are better)												
1 (Orgera 2014	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	18	18	not estimable	MD 0.3 lower (0.89 lower to 0.29 higher)	MODERATE	CRITICAL
Treatment related adverse events - cement leakage (follow-up: 6 weeks)												

Quality assessment							Number of participants		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vertebroplasty with radiofrequency ablation	Vertebroplasty alone	Relative (95% CI)	Absolute (95% CI)		
1 (Orgera 2014	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	2/18	2/18	RR 1.00 (0.16 to 6.35)	0 fewer per 1,000 (from 93 fewer to 594 more)	LOW	IMPORTANT

CI: confidence interval; MD: mean difference; RR: risk ratio

1. 95% CI crosses 1 MID (0.5x control group SD, for Roland Morris Questionnaire ±0.5).

2. 95% CI crosses 2 MIDs (0.5x control group SD, for Roland Morris Questionnaire ±0.5).

3. 95% CI crosses 2 MIDs

Table 12: Evidence profile for comparison between radiotherapy + surgery and radiotherapy alone

Quality assessment							Number of participants		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy and surgery	Radiotherapy alone	Relative (95% CI)	Absolute		
Neurological and functional status - ambulant after treatment - all patients (follow-up: post-radiotherapy treatment)												
1 (Patchell 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	42/50	29/51	RR 1.48 (1.13 to 1.93)	273 more per 1000 (from 74 more to 529 more)	MODERATE	CRITICAL
Neurological and functional status - ambulant after treatment - Patients ambulatory at study entry - all patients (follow-up: post-radiotherapy treatment)												
1 (Patchell 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	32/34	26/35	RR 1.27 (1.02 to 1.57)	201 more per 1000 (from 15 more to 423 more)	MODRATE	CRITICAL
Neurological and functional status - ambulant after treatment - Patients non ambulatory at study entry - all patients (follow-up: post-radiotherapy treatment)												
1 (Patchell 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	10/16	3/16	RR 3.33 (1.12 to 9.9)	437 more per 1000 (from 23 more to 1000	MODERATE	CRITICAL

Quality assessment							Number of participants		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy and surgery	Radiotherapy alone	Relative (95% CI)	Absolute		
										more)		
Neurological and functional status - maintenance of continence, median, days (follow-up [median]: radiotherapy and surgery 102 days (IQR 0–1940), radiotherapy alone 93 days (IQR 0–1117)												
1 (Patchell 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	156 days (N=50)	17 days (N=51)	2.13 (1.15 to 4.00)	Median 149 days longer	MODERATE	CRITICAL
Neurological and functional status - maintenance of muscle strength (ASIA score) median, days (follow-up [median]: radiotherapy and surgery 102 days (IQR 0–1940), radiotherapy alone 93 days (IQR 0–1117)												
1 (Patchell 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	566 days (N=50)	72 days (N=51)	3.57 (1.64 to 7.69)	Median 494 days longer	MODERATE	CRITICAL
Neurological and functional status - maintenance of functional ability (Frankel score) median, days (follow-up [median]: radiotherapy and surgery 102 days (IQR 0–1940), radiotherapy alone 93 days (IQR 0–1117)												
1 (Patchell 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	156 days (N=50)	17 days (N=51)	4.17 (1.85 to 9.09)	Median 494 days longer	MODERATE	CRITICAL
Pain - median [IQR] daily equivalent dose of morphine, mg (follow-up [median]: radiotherapy and surgery 102 days (IQR 0–1940), radiotherapy alone 93 days (IQR 0–1117)												
1 (Patchell 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	0.4 (0 to 60)	4.8 (0 to 200)	-	Median 4.4 mg lower	MODERATE	CRITICAL
Treatment related adverse events - 30 day mortality (follow-up: 30 days)												
1 (Patchell 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	3/50	7/51	RR 0.44 (0.12 to 1.6)	77 fewer per 1000 (from 121 fewer to 82 more)	LOW	IMPORTANT
Overall survival - median overall survival (days)												
1 (Patchell 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	100 days N=50	126 days N=51	not estimable	26 days longer with surgery + RT (p=0.003)	MODERATE	IMPORTANT

CI: confidence interval; IQR: Interquartile range; mg: milligram; RR: risk ratio; RT: radiotherapy.

1 95% CI crosses 1 MID
2 95% CI crosses 2 MIDs
3 Sample size < 300

Appendix G Economic evidence study selection

Study selection for: What is the effectiveness of invasive interventions, such as vertebroplasty, kyphoplasty, ablation and surgery, in managing spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information

Appendix H Economic evidence tables

Economic evidence tables for review question: What is the effectiveness of invasive interventions, such as vertebroplasty, kyphoplasty, ablation and surgery, in managing spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Table 13: Economic evidence tables

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Author and year: Miyazaki 2017 **Country:** Japan **Type of economic analysis:** Cost utility analysis **Source of funding:** Authors declared that the study received no funding. Conducted at Kobe University Hospital, Japan.	**Intervention**: Surgery. Partial removal of the tumour and stabilisation achieved using the screw-rod system **Comparator:** No surgery. Intensive adjuvant treatment, palliative care services and rehabilitation. People received chemotherapy where clinically indicated.	**Population characteristic**: People with symptomatic spinal metastases with progressive neurological deficits, spinal instability, or intractable pain resistant to conservative care. All of the cohort were eligible for surgical treatment although with decision on the person as to whether to receive spinal surgery or not. **Patient characteristics** Age (Mean±SD) I: 65.1 ± 11.5 C: 64.5 ± 11.0 Sex I: 74% male C: 63% male Health state value Japanese EQ-5D (mean and range): I: 0.036 ± 0.499 (−0.594 to 0.760)	**Survival (mean):** Intervention: 370 days Control: 72 days **Overall survival at 12 months:** Intervention: 54% Control: 25% **Mean cost per participant (±SD)** Intervention: US$25,770 ± 7750 Control: US$8615 ± 12,273 Difference: US$16,955 **Mean outcome per participant (±SD):** Intervention: 0.433 ± 0.327 Control: 0.024 ± 0.028 Difference: 0.405	**ICERs:** US$42,003 per QALY gained No subgroup or sensitivity analyses were undertaken.	**Perspective:** Japanese healthcare payer **Currency**: US Dollars **Cost year:** 2014 **Time horizon:** 1 Year Discounting: N/A **Applicability**: Partly Applicable **Limitations**: Very serious limitations Other comments:

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		C: 0.056 ± 0.442 (range, −0.594 to 0.708) All performance scores (Tokuhashi score, Katagiri score, performance score, Barthel index, Frankel classification) were not statistically significantly different between groups. **Modelling approach:** Costing alongside prospective cohort study **Source of baseline data:** 47 consecutive patients (31 surgery, 16 non-surgery) at Kobe University hospital, Japan. **Source of effectiveness data:** Patient completed Japanese EQ-5D at baseline, 1, 3, 6 and 12 months. **Source of cost data:** Medical remuneration records for all inpatient and outpatient care **Source of unit cost da-**			

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		ta: N/A			
Author and year: Health Quality Ontario 2016 **Country:** Canada **Type of economic analysis:** Cost utility **Source of funding**: Health Quality Ontario	**Intervention in detail :** 1) Kyphoplasty 2) Vertebroplasty **Comparator in detail:** Non-surgical management consisting of some or all of analgesics, bed rest, radiation therapy, use of braces and use of wheelchair	**Population characteristics:** People with primary cancers or metastatic disease (mixed population) leading to vertebral collapse. Mean age: 65 years Outpatient: 90% **Modelling approach**: Markov model **Source of baseline data:** Berenson 2011 RCT as discussed in the clinical evidence review and patient records from 1 hospital in Ontario Canada **Source of effectiveness data:** Survival was estimated from survival analysis from 254 patients after spinal metastases. The patient population was a mix of those receiving surgical and non-surgical interventions. Surgical intervention was as-	**Mean cost per participant:** K: CA$24,320 V: CA$20,942 Control: $17,073 Difference: K:CA$7,247 V:CA$3,869 **Mean outcome per participant:** Intervention: K: 0.414 V: 0.414 Control: 0.197 Difference: 0.217	ICERs (cost per additional QALY): K:CA$33,471 V:CA$17,870 **Subgroup analysis:** Lung and breast cancer only: approximately CA$50,000 per QALY Sensitivity analysis: Results sensitive to changes in HRQoL benefit with ICER increasing to approximately CA$85,000 per QALY. Results were not sensitive to time horizon, using standardised costs or introducing a mortality benefit to surgery. **Probabilistic sensitivity analysis:** Methods suggest this was completed but did not form part of the published results.	**Perspective:** Ontario Ministry of Health and Long-Term Care **Currency**: Canadian dollars **Cost year**: 2015 **Time horizon:** 5 years **Discounting**: 5% both cost and QALYs **Applicability**: Partly applicable **Limitations**: Very serious limitaions **Other comments**: Kyphoplasty and vertebroplasty were not directly compared. Assumptions of the model had effectiveness identical but vertebroplasty was the less costly intervention meaning if such a comparison was appropriate vertebroplasty would be the preferred option.

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		sumed to have no survival benefit. Utility values were derived from Short Form Health Survey (SF-36) survey data from an RCT of patients with cancer related fractures. (n=106) This RCT was the same as that reported by Berenson 2011 **Source of cost data:** All costs of surgical interventions were taken from hospital billing data from 1 hospital in Ontario. **Source of unit cost data:** Cost of professional time was taken from Ontario Schedule of Benefits for Physician Services			
Author and year: NICE 2023 **Country:** UK **Type of economic analysis:** Cost utility **Source of funding**: Department of	**Intervention in detail :** 1) Kyphoplasty 2) Vertebroplasty **Comparator in detail:** Non-surgical management consisting of some or all of	**Population characteristics:** People with primary cancers or metastatic disease (mixed population) leading to vertebral collapse. Mean age: 60	**Mean cost per participant:** K: £3,048 V: £2,930 Control: £337 Difference: K:£2,711 V:£2,594	ICERs (cost per additional QALY): K:£98,935 V:£94,644 **Sensitivity analysis:** Results sensitive to changes in HRQoL, time horizon	**Perspective:** UK NHS+PSS **Currency**: Pound sterling **Cost year**: 2021 **Time horizon:** 1 years and 5 years **Discounting**: 3.5% both cost and

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Health And Social Care For England	analgesics, bed rest, radiation therapy, use of braces and use of wheelchair	years **Modelling approach**: Retrospective costing and QoL calculations from one randomised controlled trial **Source of baseline data:** Berenson 2011 RCT as discussed in the clinical evidence review **Source of effectiveness data:** Survival was estimated from a prospective observational study of 39 patients receiving vertebroplasty in an NHS setting. Utility values were derived from Short Form Health Survey (SF-36) survey data from an RCT of patients with cancer related fractures. (n=106). These were converted to EQ-5D scores using a published algorithm. This RCT was the	**Mean outcome per participant (QALYs):** Intervention: K: 0.4447 V: 0.4447 Control: 0.4173 Difference: 0.0274	and costs around NSM. **Probabilistic sensitivity analysis:** K: One year time horizon was below £20,000 per QALY in 49.7% of iterations increasing to 82.8% for 5 year time horizon. V: One year time horizon was below £20,000 per QALY in 48.1% of iterations increasing to 83.4% for 5 year time horizon.	QALYs **Applicability**: Directly applicable **Limitations**: Very serious limitations **Other comments:** Kyphoplasty and vertebroplasty were not directly compared. Assumptions of the model had effectiveness identical but vertebroplasty was the less costly intervention meaning if such a comparison was appropriate vertebroplasty would be the preferred option.

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		same as that reported by Berenson 2011 **Source of unit cost data:** Unit costs were taken from previous NICE technology appraisals and PSSRU Unit Costs of Health and Social Care			

Appendix I Economic model

Economic model for review question: What is the effectiveness of invasive interventions, such as vertebroplasty, kyphoplasty, ablation and surgery, in managing spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

The Cost effectiveness of balloon kyphoplasty and vertebroplasty compared to non-surgical management for the treatment of vertebral collapse in people with metastatic spinal cord compression.

Background

Metastatic cancer can lead to tumours in or near the spine leading to collapse of one or more vertebrae, which causes very serious consequences including acute severe pain. The core aims of the management of spinal bone disease in metastatic spinal cord compression are decompression, stabilisation and pain control. Non-surgical management (NSM) consists of pain management using drugs (analgesics), radiotherapy, immobilisation and external bracing/orthotics as appropriate. Radiotherapy is effective for pain relief and most patients need one or two fractions; however it may take several weeks for the full effect and some patients experience a pain 'flare' in the early days after treatment.

Faster-acting interventions include procedures such as vertebroplasty (VP) or balloon kyphoplasty (BKP), in which plastic cement is injected into the affected vertebrae (vertebral cement augmentation). These cement techniques can be performed by either surgeons or non-surgeons (typically radiologists) unlike open spinal surgery which are undertaken by either orthopaedic or neurosurgeons. For these reasons cement techniques are referred to as NSM in clinical practise although for clarity are not included in that definition within this report. Side-effects from cement augmentation are usually mild and temporary but may be more serious in a few people. More serious adverse events include neurological deficits and embolic events usually as a result of cement leakage.

There is uncertainty around whether BKP and VP are cost effective when compared to NSM in people with metastatic spinal cord compression (MSCC). Upfront treatment costs will be higher with both BKP and VP although could lead to increased quality of life and reduced resource use post treatment.

This model updates the economic model considering the same question for people with myeloma and vertebral compression fractures created for NICE Guideline NG35 Myeloma: diagnosis and management published in January 2016. The model has been adapted to use evidence more applicable to MSCC and to use contemporaneous values for costs and other model variables where these are available. The clinical and quality of life outcomes in the model remain the same after the evidence review did not identify any better evidence and these remain unchanged between the two models.

Economic Model

Aim of Analysis, population, interventions

The aim of the economic analysis was to assess the cost effectiveness of BKP and VP compared to NSM for the treatment of vertebral compression fractures (VCFs) in people with metastatic spinal cord compression. It was not deemed appropriate to compare BKP directly

to VP as clinical considerations could make one of the treatments clinically inappropriate for some types of VCFs. Therefore, both BKP and VP were compared only to NSM.

Type of Analysis, time horizon, perspective

The analysis measures outcomes in quality-adjusted life years (QALYs). We express the incremental cost-effectiveness ratio (ICER) as a cost per QALY.

Two time horizons were used for the economic evaluation-a one year and five year. The one year analysis covered the duration of Berenson 2011. It was unclear from the accompanying evidence review whether differences in quality of life remained more than 1 year post surgery. The committee considered that the difference was likely to remain after one year and until further VCF or death and that the 1 year time horizon would represent a conservative estimate of any outcomes from cement techniques. Consequently, a 5 year time horizon was also modelled. As no evidence was identified around the effectiveness of BKP or VP after 1 year, 2 different assumptions were investigated. The first assumption was that the difference in quality of life between the groups at 1 year would remain for the entirety of the 5 year time horizon reflecting that increased mobility and reduced pain may continue significantly past 1 year. The second assumption was that in the group with the highest quality of life the difference would taper down at a constant rate until equal to the comparison group at five years. This was to reflect that patients were likely to experience further VCFs over the time horizon which would diminish their quality of life.

The analysis also conservatively assumed that the difference in costs between the two groups would be identical after the first year. A sensitivity analysis was run for this model though that also assumed that the difference in costs not attributable to cement techniques, during the first year, would continue in all years.

A five year time horizon was considered adequate to capture all differences between the two groups as the majority of patients would have either died or had a secondary VCF during this time.

All analyses were conducted from a National Health Service (NHS) and Personal Social Services (PSS) perspective.

Discounting

All costs and QALYs were discounted at 3.5% per annum.

Sensitivity analysis

For the base case analyses a range of deterministic and threshold sensitivity analyses were conducted to test the robustness of the results of the economic analysis to different input parameters. PSA was also conducted around the base case to assess the combined parameter uncertainty in the model. In this analysis, the values that are utilised in the base case are replaced with values drawn from a distribution used to reflect the uncertainty around parameter estimates. The PSA analysis was run for 10,000 iterations for both BKP and VP and for both a 1 year and 5 year time horizon.

Clinical input data

The analysis was an economic evaluation based on outcomes and resource use reported in the 1 RCT identified for vertebral cement augmentation in the accompanying clinical evidence review. (Berenson 2011) The trial compared BKP to NSM for the treatment of painful metastatic VCFs in 134 people.

The trial was conducted over 22 sites in Australia, Canada, Europe and the USA in patients aged at least 21 years who had between one and three VCFs as well as scoring at least 4 on the pain numeric rating score and at least 10 on the Roland-Morris Disability Score. Patients were excluded if they had osteoblastic tumours, primary bone tumours or plasmacytoma in the index VCF all people outside of the scope of this guideline. Patients were also excluded if they were in any phase 1 anticancer trial, had substantial clinical morbidities, were unsuitable for BKP or needed significant additional treatment over the considered interventions of NSM or BKP.

The cohort had an average age of 64 years and was 58% male with an average estimated symptomatic fracture age of 3.5 months. The trial included cancers other than myeloma with 62% of the trial population having another cancer diagnosis.

The study had a large amount of crossover with the study protocol allowing people randomised to NSM to switch to BKP after one month of follow-up. 38 (72%) of the 52 patients randomised to the NSM group crossed over to BKP. Therefore, three groups were presented in the results by the authors: patients randomised to BKP, patients randomised to NSM who ultimately received BKP (crossover) and those who continued with NSM (NSM group). The authors reported no differences in the baseline characteristics of the three groups. Differences at time of crossover were not reported.

All clinical inputs for the model were based on evidence identified in the accompanying evidence review.

For the base case the clinical outcomes were assumed to be identical between the cement augmentation interventions based on the committees clinical opinion although they did hypothesise that it was possible that BKP had improved clinical outcomes and greater quality of life through restoration of lost body height. This potential difference between the two cement techniques was explored during threshold sensitivity analyses.

Patient groups

RCTs are conventionally analysed using an intention to treat (ITT) approach to reduce bias due to non-random loss and crossover of participants. The ITT approach analyses patients by how they were randomised regardless of whether they adhered to the intervention they were randomised to or not. As the Berenson 2011 trial had large crossover the ITT approach may underestimate the true differences between the interventions being considered. The study also did not report the characteristics of the crossover group at the time of crossover and it was unclear as to whether these people differed to those who remained in the NSM groups.

Given the reasons above an ‘as treated’ comparison comparing all patients who ultimately received BKP to those who remained in NSM was chosen as the primary analysis as this would most accurately estimate the difference in effectiveness between the two groups. It would also reflect more closely practice within the NHS where patients are likely to have to wait for cement techniques - by which time most of the people in the NSM arm would have crossed over to BKP. Consequently, for the purpose of this economic evaluation two further groups were created from the trial results - a ‘cement technique received’ group pooling the BKP and crossover groups and an NSM-ITT group pooling the NSM and crossover group (i.e. those randomised to NSM). In the base case ‘as treated’ approach BKP and crossover group (cement technique received group) were compared to the NSM group. A secondary analysis based on ITT principles was also conducted comparing the NSM-ITT group to those randomised to BKP.

Utilisation of non-surgical interventions for VCFs at one month

The study reported the utilisation of seven non-surgical interventions at baseline and one month post randomisation between those randomised to BKP and to NSM. The changes in the use of these interventions are shown in Table 14. Changes in utilisation were statistically significantly lower (p-value<0.05) for the BKP group in all interventions other than wheelchair use, physical therapy and radiation therapy. As no patients crossed over before one month the NSM group was identical for both the 'as treated' and ITT analysis.

Table 14: Percentage change in utilisation of non-surgical interventions between baseline and one month follow-up.

	BKP	NSM
Walking Aids	-9.0%	1.5%
Bracing	-12.7%	-1.4%
Wheelchair	-4.8%	-2.0%
Bed Rest	-22.1%	-12.9%
Physical Therapy	-10.4%	-3.6%
Any Medication	-40.5%	-17.0%
Radiation Therapy	-0.9%	11.3%

For the crossover group, the use of non-surgical interventions was assumed to be equal to BKP for the base case 'as treated' analysis but equal to NSM during the ITT analysis. The difference in utilisation was assumed to be maintained for one year.

Future VCFs

Whilst further VCFs are common in patients receiving both cement techniques and NSM, the accompanying systematic review found no evidence on whether there was a difference in the incidence of future VCFs between the interventions. In lieu of evidence it was assumed that the incidence between the groups was identical. Resultantly, both costs and outcomes of these future events were assumed identical and were not explicitly included as part of this economic analysis.

Adverse Events

Device related adverse events were observed during the trial in the BKP group. Two patients had extravasation, 1 had superficial wound infection and 2 had symptomatic fractures one of which was as a result of cement leakage. Two patients had arrhythmia, attributable to anaesthesia but this was resolved. Adverse events are likely to be rare and the additional costs and quality of life detriment were likely to be significantly outweighed by underestimates of costs and quality of life detriments in the NSM arms. Whilst the costs and quality of life det-

riments of these adverse events were not explicitly considered in the economic evaluation, costs attributable to adverse events of surgery were included (discussed later).

Survival

Survival for the economic analysis was taken from a prospective observational study of outcomes and survival in 39 patients with myeloma receiving VP in an NHS setting. The population had a mean age of 60 years at the time of treatment. The study reported a median survival of 20 months with a 1 year survival of 90% and 5 year survival of 40%. Survival was assumed to be identical for both the cement techniques and NSM groups given the paucity of information to the contrary identified by the systematic review. Survival in this group is likely to be higher than for MSCC although as no difference in survival was assumed between the groups and costs were not accrued in the model beyond 1 year the impact of this will be small. Survival values for each time point are presented in Table 15.

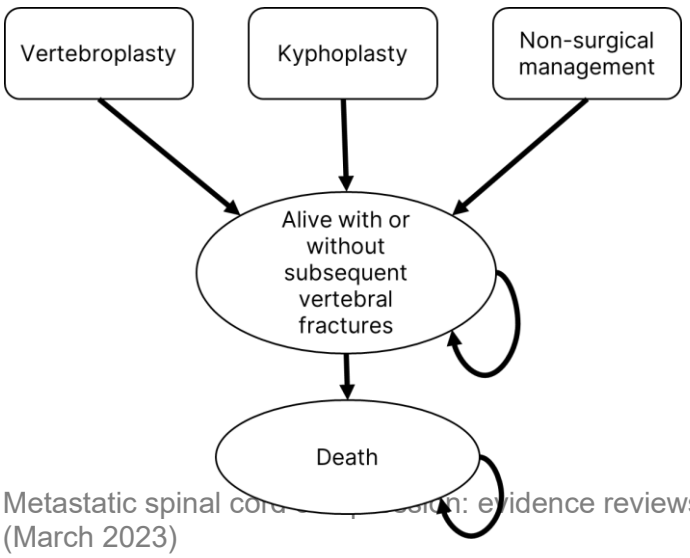
Table 15: Survival after initial treatment

Month	Percent of cohort still alive
1	99.1%
3	97.4%
6	94.8%
12	89.6%
24	70.8%
36	66.0%
48	56.8%
60	40.0%

Model structure

A diagram representing the model structure and how the above parameters are combined in the economic model are presented in Figure 2

Figure 2: Model structure



Quality of Life

The main measure of health-related quality of life (HRQoL) in the trial was the Short Form (36) Health Survey (SF-36) physical component summary score (PCS). The SF-36 is a patient completed generic health survey made up of eight components (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health). These are used to calculate 2 summary scores, a physical component (PCS) and mental component, on a scale of 0 (worse possible health) to 100 (best possible health). The change in SF-36 PCS from baseline for the BKP and NSM group, and from time of treatment for crossover group, is shown in . These were given a normal distribution and varied across their reported range during probabilistic sensitivity analysis (PSA).

Table 16: Change in SF-36 PCS score following treatment.

Follow-up	**1 Month**	**3 Month**	**6 Month**	**12 Month**
BKP	9.2	9.6	8.8	10.6
Crossover	8.8	10.8	10.4	10.6
NSM	-0.2	1.2	-0.8	1.2
Cement Technique Received	9.0	10.1	9.4	10.6
NSM-ITT	5.7	7.5	7.4	8.3

Changes in the SF-36 PCS were converted to UK population preference EQ-5D weights using a mapping algorithm. The EQ-5D UK tariff is NICE's preferred measure of health related quality of life in adults. This was the only algorithm identified for mapping from mean SF-36 component scores to EQ-5D scores. The algorithm showed good predictive value with predicted mean EQ-5D score being correct to within 2 decimal places in both datasets used to build the algorithm and external datasets used in validation. However, the algorithm was not validated in people with MSCC or cancer although it was shown to have good predictive value in a range of health conditions associated with VCF including walking impairment and lower back pain.

Berenson 2011 reported a summary score for the SF-36 PCS whilst the Ara 2008 algorithm needs the mean individual component scores. The proportion of the change in SF-36 scores attributable to each of the four physical components were assumed to be identical to that reported in the Fracture Reduction Evaluation (FREE) trial. The FREE trial was an RCT comparing BKP and NSM in patients with VCFs across 8 European centres. The proportion attributable to each physical component is shown in table 2. Only the physical component contributions were used and all scores were inflated to sum to 100%.

Table 17: Contribution to overall SF-36 score for each physical component

	Contribution(%)

	BKP	NSM
Physical Functioning	34%	34%
Role limitations due to physical health	-13%	-12%
Bodily Pain	55%	56%
General Health Perceptions	24%	22%

Given the changes in the SF-36 score and the contributions to each component in changes in EQ-5D scores were estimated for the group using the Ara & Brazier algorithm (2008). The analysis used reported model 'Model EQ (1)' as this did not require an age variable which was not reported for the NSM group post one month and not reported for the crossover group at all. The use of the age variable increases the predictive precision by less than 1%. The converted EQ-5D scores are reported in.

We assumed that all patients started with a baseline quality of life weight of 0.4392 the pre-treatment mean EQ-5D score based on 11 consecutive patients, receiving VP in an NHS setting. As economic evaluation is primarily an incremental analysis and the choice of baseline quality of life will have no effect on the incremental results this assumption was not tested during sensitivity analysis.

Table 18: Estimated EQ-5D scores following treatment

Follow-up	Baseline	1 Month	3 Month	6 Month	12 Month
BKP	0.4392	0.4667	0.4679	0.4655	0.4709
Crossover	0.4392	0.4657	0.4717	0.4705	0.4709
NSM	0.4392	0.4386	0.4428	0.4368	0.4428
Cement Technique Received	0.4392	0.4662	0.4693	0.4674	0.4709
NSM-ITT	0.4392	0.4563	0.4617	0.4613	0.4643

Berenson 2011 also reported a summary score for the mental component of the SF-36 for 1 month post-randomisation showing a mean difference between the groups of 11.1 points (95% CI 10.7-11.5) between the groups in favour of BKP. As this was only reported at one month and not for the duration of the trial the contribution of the mental component to overall quality of life was not included in the base case analysis. A sensitivity analysis was performed giving an additional quality of life increment to those receiving BKP or VP to capture this non-physical components impact on quality of life. Using the algorithm described above for SF-36 mental component scores a mean difference in terms of the EQ-5D of 0.054 was estimated at one month. Assuming that this difference persists over the time horizon of the

model this equated to an additional 0.054 and 0.270 QALYs for patients surviving the entirety of the 1 year and 5 year time horizons respectively.

Costs

Costs were inflated to 2021 prices, using the hospital & community health services (HCHS) index and converted using the appropriate purchasing power parity where appropriate. All costs are presented in

Treatment Costs

The costs of VP were taken from 11 consecutive patients receiving VP for spinal metastases at 1 NHS hospital. Resource use was collected prospectively using structured questionnaires and costed using NHS reference costs where possible. For items of equipment an estimation of their lifespan, number of uses and maintenance costs to calculate a cost per hour per patient. Staff costs were based on published salaries for consultant radiologist, a registrar in half of cases, two radiographers and four nurses. Costs of complications, inpatient stay and drug costs were all included.

Chew 2013 estimated an average cost of £2213.25 per patient. This consisted of a cost of £744 for the VP kit and other costs of £1469. Chew 2013 considered this was a likely overestimate of the true cost as it was weighted heavily by one patient with widespread metastatic bronchial carcinoma. An alternate non-kit cost of £1,072 was used during sensitivity analysis equal to the average cost if all patients were treated as a day case or overnight stay. Treatment costs other than the kit cost were assumed to be identical for both VP and BKP.

The cost of the BKP kit was taken from NICE TA279 looking at BKP and VP in the treatment of osteoporotic vertebral compression fractures. It noted a list price for a BKP kit including low viscosity cement of £2800 however it noted an average selling price of £2046. Whilst the average selling price was deemed the most appropriate to use in the de novo economic evaluation it was still likely to be an overestimate of the true costs. BKP kit costs are commercially sensitive and likely to differ widely between institutions. This value was therefore given a wide distribution for PSA.

Non-surgical management costs

The annual cost of analgesic medication was taken from a study estimating the costs associated with VCFs from an NHS perspective using Hospital Episode Statistics and Personal Social Services Research Unit data. The study estimated an annual cost of pharmaceutical treatments of £147.

Radiation therapy costs were taken from a cost effectiveness analysis of zoledronic acid in the prevention of skeletal related events for patients with bone metastases secondary to advanced renal cell carcinoma. The study estimated an average cost of radiotherapy of £431 using HRG codes and NHS reference costs and considering a NHS and PSS perspective.

Bracing costs of £556 were estimated using correspondence with 1 NHS trust. Costs of wheelchair and walking aids were taken from PSSRU data. A cost of £103 was used representing the unit cost of the use of self or attendant propelled chair per year. Physical therapy costs were estimated from NHS Reference Costs. Six appointments were assumed equal to a cost of £401.

There was potential resource use that was not covered by the trial. The GDG felt that the most important missed resource use was doctor and nurse time spent fitting, adjusting and advising on bracing and wheelchair use and time spent tailoring pharmaceutical treatment for pain. Previous economic evaluations of spinal interventions found significantly higher re-

source use, post surgery amongst non-surgical arms compared to surgical arms. With a paucity of evidence it was difficult to accurately estimate this cost and therefore it was not included in the base case model. NSM costs estimated in the base case analysis were most likely to be a significant underestimate. Therefore, threshold sensitivity analysis was performed around the non-treatment costs to estimate the additional cost needed in the NSM arm to reduce the cost per QALY to the £20,000, the value at which NICE typically recommend interventions. During PSA a non-specific cost of NSM was added and given a wide uniform distribution ranging from £0 to an upper estimate of £3947 equal to the total annual healthcare related cost of VCFs.

Imaging Costs

Costs of imaging pre-treatment were not included in this de novo economic evaluation as these were assumed to be performed as part of a patient's regular follow-up and would be identical between the two groups.

Table 19: Unit costs included in the economic model

	Value	Source	PSA Distribution
Total Cost BKP	£2918	NHS Supply 2021	Gamma(α=119.7, β=34.0)
Total Cost VP	£2800	NHS Supply 2021	Gamma(α=35.4, β=62.5)
Annual cost pharmaceutical treatment	£147	Puffer 2008	Triangular(£73,£293)
Annual cost radiotherapy	£431	Spencer 2022	Triangular(£216,£863)
Annual cost bracing	£556	NHS Correspondence	Uniform(£278,£1111)
Annual cost wheelchair	£103	PSSRU 2021	Triangular(£52,£206)
Annual cost walking aids	£103	PSSRU 2021	Triangular(£52,£206)
Annual cost physical therapy	£401	NHS Cost Collection 2020	Gamma(α=25.1, β=12.4)

Annual Non-specific NSM costs	£0	GDG Estimate	Uniform(£0,£3947)

Results

Deterministic Base Case Results-one year time horizon

Table 20 and Table 21 show the base case results for BKP and VP respectively. Both cement procedures led to an increase in costs and QALYs. Total QALYs are equal between both cement techniques given the assumptions of the model with BKP having higher incremental costs owing to its increased kit cost. Both incremental cost effectiveness ratios (ICERs) are above the NICE threshold of £20,000 per QALY although as noted earlier they are likely to offer conservative estimates of both incremental QALYs and NSM total costs.

Table 20: Base case deterministic results for balloon kyphoplasty

Outcome	BKP	NSM	Incremental
Total Cost	£3,048	£337	£2,711
Total QALYs	0.4447	0.4173	0.0274
ICER - Cost per QALY gained			£98,935

Table 21: Base case deterministic results for vertebroplasty

Outcome	VP	NSM	Incremental
Total Cost	£2,930	£337	£2,594
Total QALYs	0.4447	0.4173	0.0274
ICER-Cost per QALY gained			£94,644

Deterministic Results five year time horizon

Table 22 and Table 23 show the base case results for BKP and VP respectively when a five year time horizon is assumed with a continuing difference in quality of life. Whilst the ICERs are reduced under the longer time horizon they still both remain above £20,000 per QALY.

Table 22: Five year time horizon deterministic results for balloon kyphoplasty

Outcome	BKP	NSM	Incremental
Total Cost	£3,048	£337	£2,711
Total QALYs	1.5791	1.4767	0.1026
ICER-Cost per QALY gained			£26,438

Table 23: Five year time horizon deterministic results for vertebroplasty

Outcome	VP	NSM	Incremental
Total Cost	£2,930	£337	£2,594
Total QALYs	1.5791	1.4767	0.1026
ICER-Cost per QALY gained			£25,291

Stochastic Base Case Results

Table 24, Table 25, Table 26 and Table 27 show the base case stochastic results calculated from the mean results of the PSA. The stochastic results show an increased cost for NSM whilst the cement technique costs and QALYs for both groups remain consistent compared to the deterministic results. This is as a result of the non-specific NSM costs which is set equal to zero during the deterministic analysis but is always a greater than zero value during PSA. Other than for BKP in the conservative one year time horizon analysis all ICERs are now below the NICE £20,000 threshold. As NSM costs were almost certainly underestimated in the deterministic analysis these results are potentially more reflective of the true cost effectiveness.

Table 24: Base case stochastic results for balloon kyphoplasty one year time horizon

Outcome	BKP	NSM	Incremental
Total Cost	£3,062	£2,440	£622
Total QALYs	0.4447	0.4170	0.0278
ICER-Cost per QALY gained			£22,429

Table 25: Base case stochastic results for vertebroplasty one year time horizon

Outcome	VP	NSM	Incremental
Total Cost	£2,973	£2,377	£170
Total QALYs	0.4447	0.4175	0.0271
ICER-Cost per QALY gained			£21,895

Table 26: Base case stochastic results for balloon kyphoplasty five year time horizon

Outcome	BKP	NSM	Incremental
Total Cost	£3,062	£2,479	£583
Total QALYs	1.5791	1.4784	0.1007
ICER-Cost per QALY gained			£5,794

Table 27: Base case stochastic results for vertebroplasty five year time horizon

Outcome	VP	NSM	Incremental
Total Cost	£2,947	£2,349	£598
Total QALYs	1.5791	1.4784	0.1007
ICER-Cost per QALY gained			£5,736

Deterministic sensitivity analysis

Deterministic sensitivity analysis was carried out to test alternate assumptions and how these influence the results of the economic evaluation (Table 28). The use of a non-kit cost of £1,072, assuming that all patients are treated on an overnight or outpatient reduced the ICER for both cement techniques. The ICER only dropped below £20,000 for the VP under the five year time horizon. The same was true when difference in costs between interventions continued past the first year. The addition of the mental component to the quality of life

scores reduced the ICER below £20,000 for both cement technique options under the five year time horizon. Tapering of quality of life did not result in either ICER dropping below £20,000 per QALY.

Table 28: Deterministic sensitivity analysis results-ICER for alternative assumptions

	BKP-1 Year	BKP-5 year	VP-1 Year	VP-5 Year
Non-kit cost reduced to £1,072	£77,466	£20,700	£73,174	£19,553
Mental component added	£33,274	£7,269	£31,830	£6,954
Difference in costs continue post one year	N/A	£18,374	N/A	£17,227
Tapering quality of life after 1 year	N/A	£27,477	N/A	£25,762

Threshold Analysis

A threshold analysis was performed to see how much extra NSM needed to cost, per patient, before the ICER reduced below £20,000 per QALY (Table 29). All the additional costs were lower than the upper limit of the PSA range.

Table 29: Additional NSM costs required for ICER to be below £20,000 per QALY

	1 Year Time Horizon	5 Year Time Horizon
BKP	£2163	£660
VP	£2045	£543

Threshold analysis also showed that BKP needed to provide an additional 0.001 QALYs over the lifetime of a patient to give the same ICER when compared to VP. Given the assumptions of the model this was irrespective of the time horizon.

Intention to treat analysis

An alternative ITT analysis was carried out against all results and deterministic sensitivity analyses. ITT in all cases significantly increased the cost of the NSM arm (due to the cost of surgery now added to patients who crossed over) as well as increasing the total QALYs. The incremental cost and QALYs between cement techniques and NSM were reduced in all scenarios although the cost per QALY was generally consistent with the 'As Treated' results. The ITT analysis did not alter the results, in terms of being above or below £20,000 per QALY, in any scenario. The results of the ITT analysis are presented in Table 30-Table 33

Table 30: Intention to treat deterministic results for balloon kyphoplasty one year time horizon

Outcome	BKP	NSM	Incremental
Total Cost	£3,048	£2,549	£499
Total QALYs	0.4437	0.4380	0.0057
ICER-Cost per QALY gained			£86,862

Table 31: Intention to treat deterministic results for vertebroplasty one year time horizon

Outcome	VP	NSM	Incremental
Total Cost	£2,930	£2,460	£470
Total QALYs	0.4437	0.4380	0.0057
ICER-Cost per QALY gained			£81,910

Table 32: Intention to treat deterministic results for balloon kyphoplasty five year time horizon

Outcome	BKP	NSM	Incremental
Total Cost	£3,048	£2,549	£499
Total QALYs	1.5779	1.5551	0.0280

ICER-Cost per QALY gained	£26,438

Table 33: Intention to treat deterministic results for vertebroplasty five year time horizon

Outcome	VP	NSM	Incremental
Total Cost	£2,930	£2,460	£598
Total QALYs	1.5779	1.5551	0.0280
ICER-Cost per QALY gained			£20,633

Probabilistic sensitivity analysis

Cost effectiveness plane

Despite the ICER for BKP being above the £20,000 threshold compared to NSM, for both the deterministic and stochastic results, during PSA with a one year time horizon BKP was below the willingness to pay of £20,000 per QALY in 49.7% of iterations. (Figure 3) Under the five year time horizon this figure increased to over 82.8% iterations.(Figure 4) BKP was cost saving and health improving in 35.8% of iterations for both time horizons. VP was cost effective at a £20,000 threshold in 48.1% and 83.4% of iterations for the one year and five year time horizons respectively. (Figure 5 and Figure 6). VP was health improving and cost saving in 35.4% of iterations. For both interventions the majority of iterations were in the North-East quadrant suggesting a more costly yet effective intervention. These results are echoed in the cost effectiveness acceptability curves.(Figure 7-Figure 10)

Figure 3: Cost effectiveness plane for balloon kyphoplasty with a one year time horizon

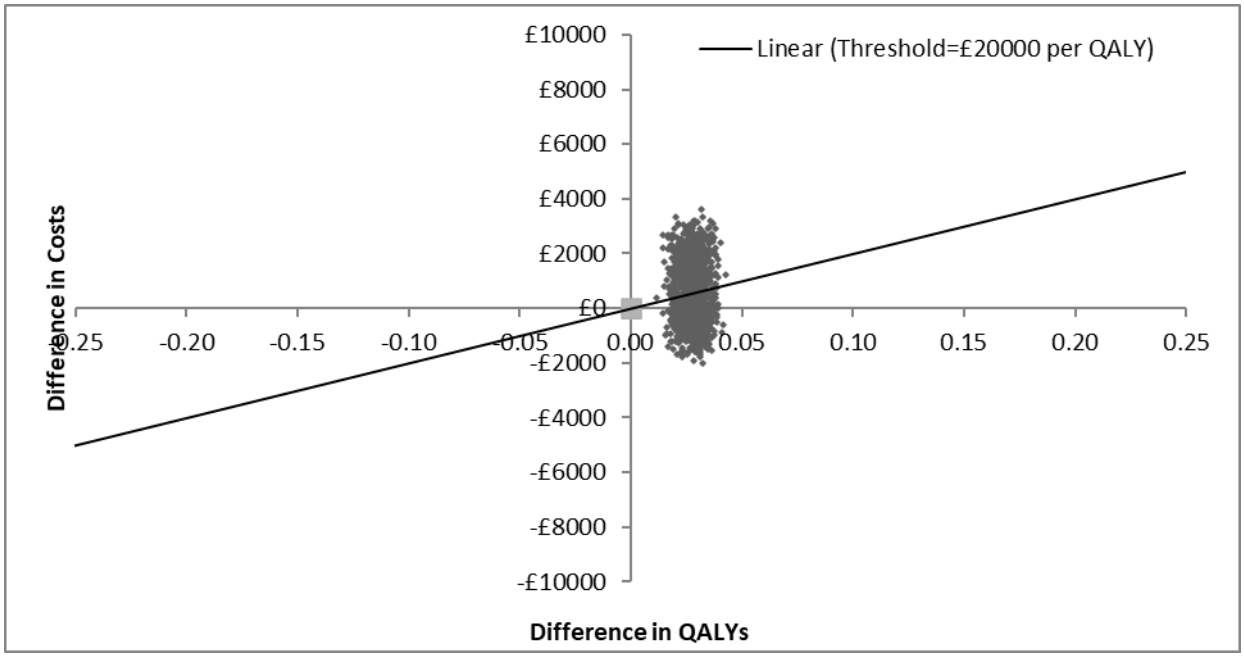


Figure 4: Cost effectiveness plane for balloon kyphoplasty with a five year time horizon

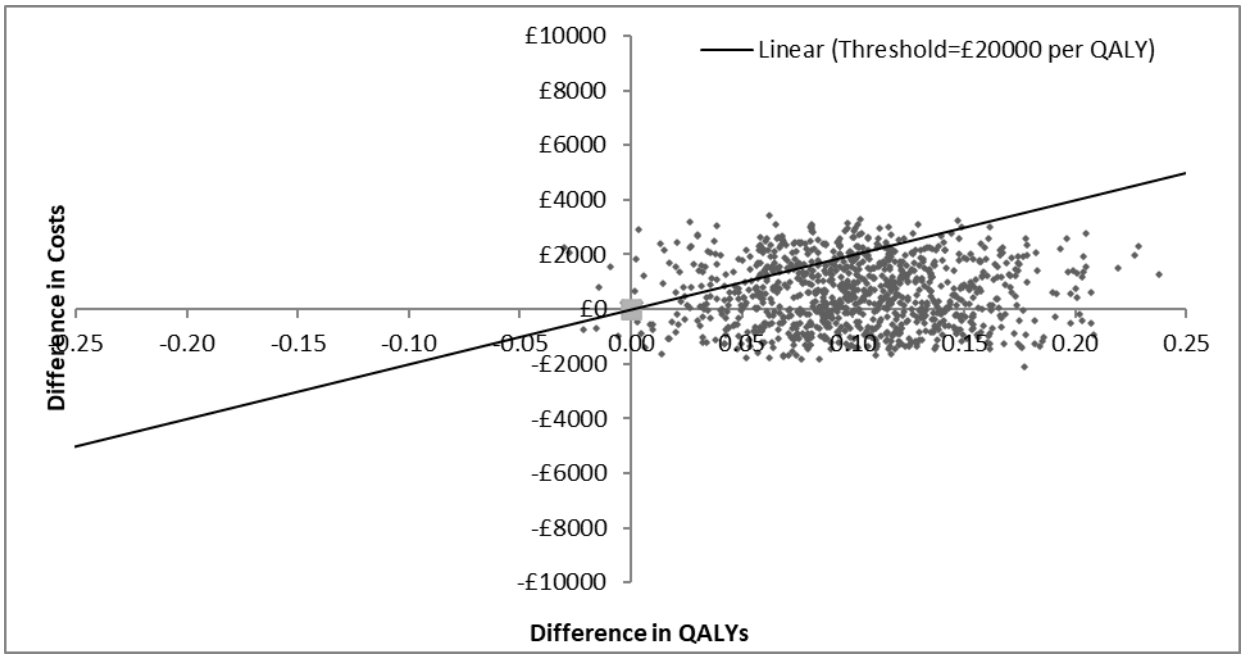


Figure 5: Cost effectiveness plane for vertebroplasty with a one year time horizon

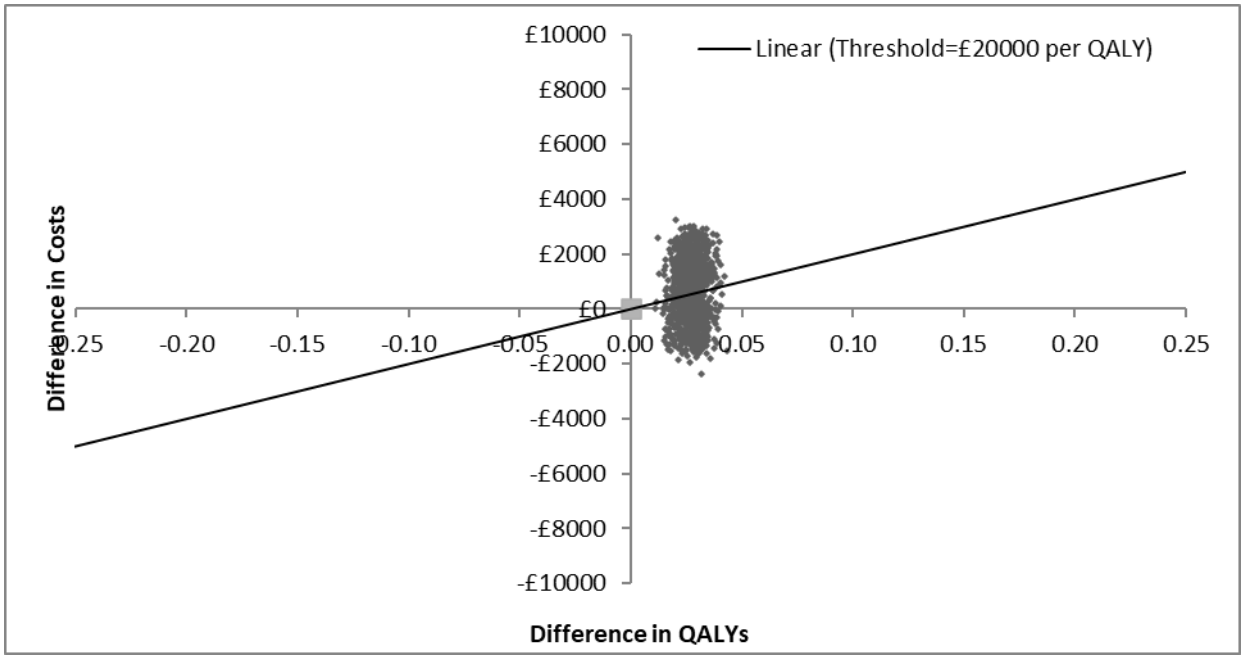


Figure 6: Cost effectiveness plane for vertebroplasty with a five year time horizon

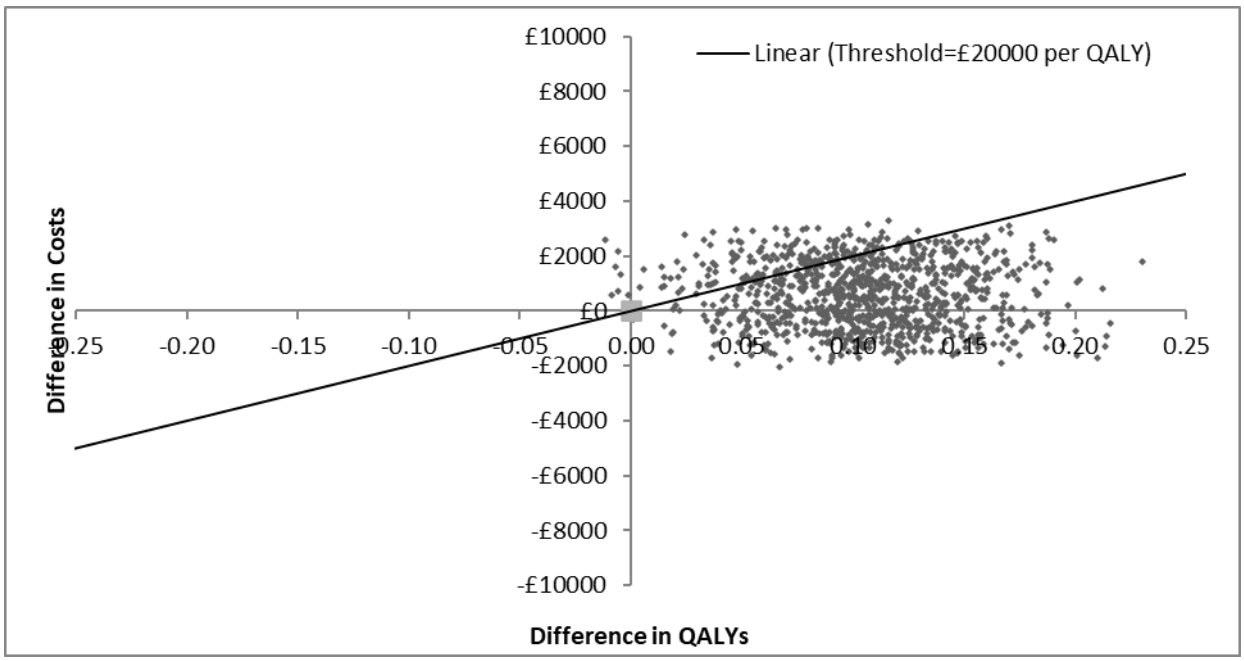


Figure 7: Cost effectiveness acceptability curve for balloon kyphoplasty with a one year time horizon

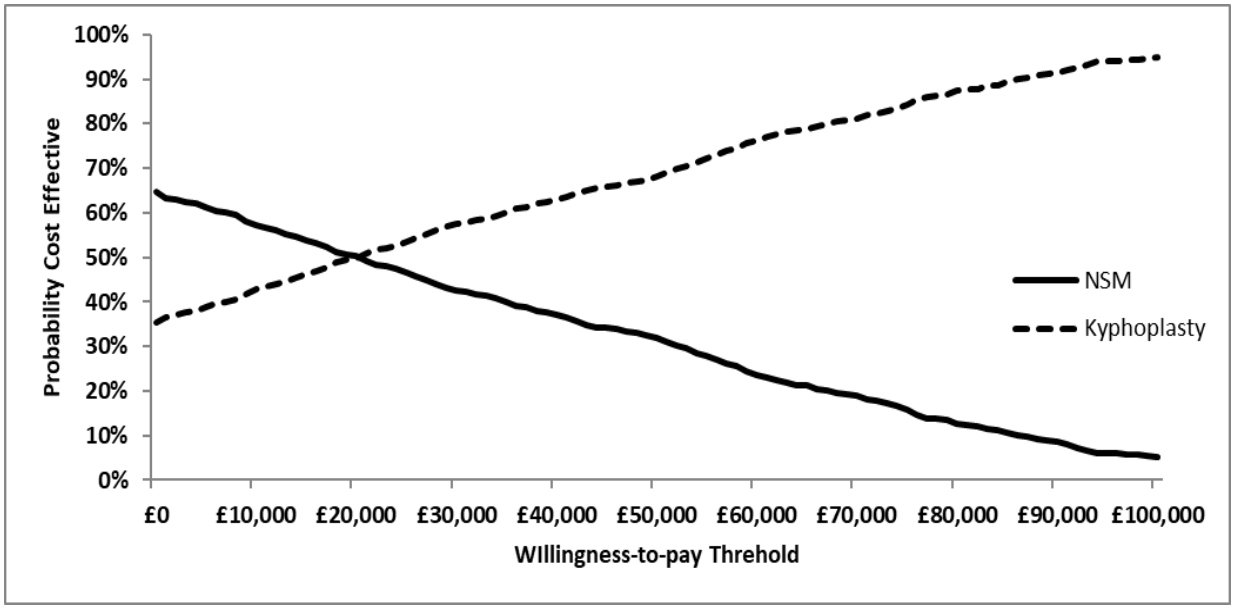


Figure 8: Cost effectiveness acceptability curve for balloon kyphoplasty with a five year time horizon

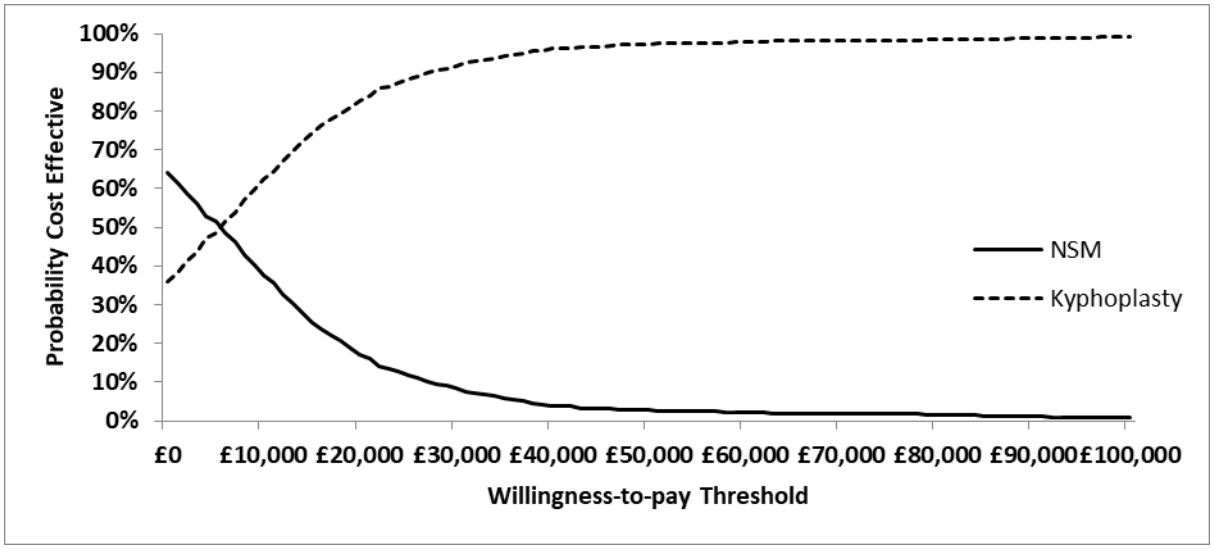


Figure 9: Cost effectiveness acceptability curve for vertebroplasty with a one year time horizon

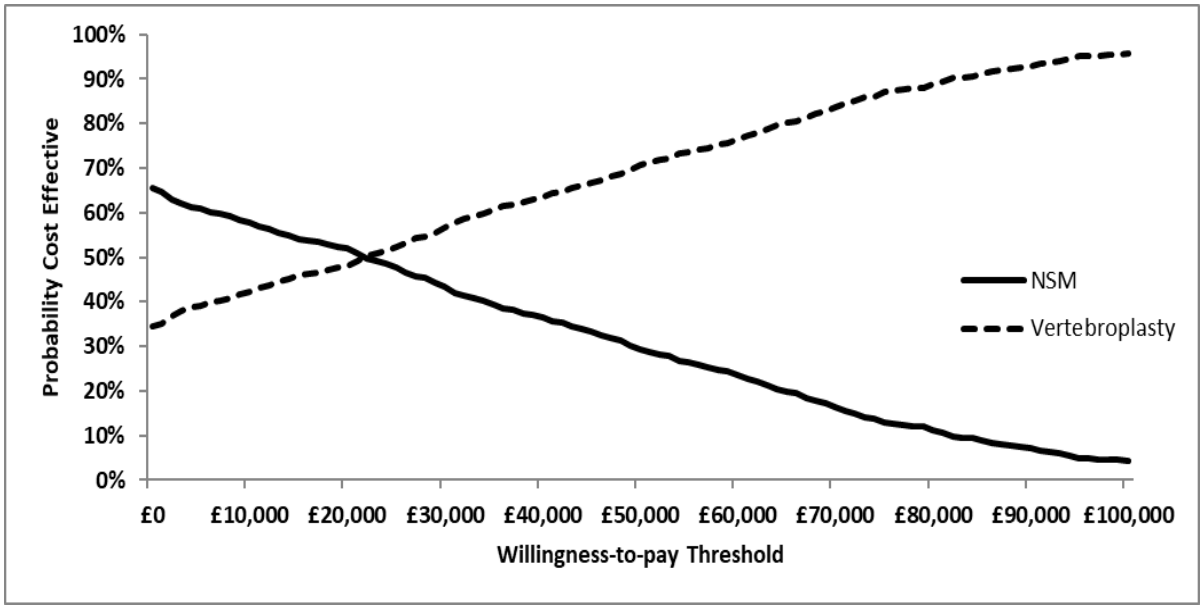
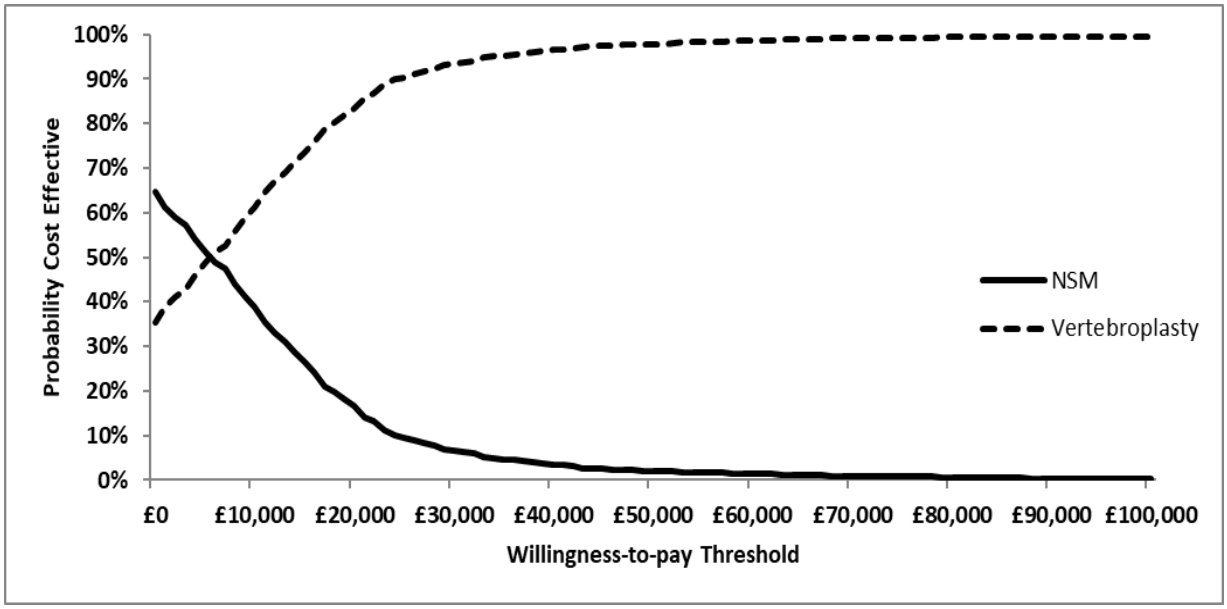


Figure 10: Cost effectiveness acceptability curve for vertebroplasty with a five year time horizon



Conclusions

The results of the base case analysis showed that BKP and VP were not cost effective over a one-year time horizon and only VP was cost effective over a five year time horizon. However, when considering the stochastic results, both cement techniques were shown to be cost effective over a five-year time horizon with VP also cost effective under a one-year time horizon. Furthermore, during PSA and under a five-year time horizon both cement techniques were cost effective in the majority of iterations with VP being cost saving and health improving in 40% of cases.

The results were shown to be particularly sensitive to the costs of NSM. Threshold sensitivity analysis showed that even if our economic analysis only modestly underestimates the true cost of NSM or the effectiveness of cement techniques then both VP and BKP would likely be cost effective.

The main weakness of this economic evaluation was the large amount of crossover in the underlying RCT. There were wide differences in the estimates of costs, outcomes and cost effectiveness between the ‘as treated’ and the ‘ITT’ analysis. It is not clear if crossover activity in the NHS i.e., what proportion of people indicated for NSM would eventually receive surgical intervention. If crossover in the NHS is similar to the trial then the ITT analysis would be most appropriate but if crossover is limited the ‘as treated’ maybe more accurate. It is also highlighted by the committee that it was likely that people who crossed over likely had better clinical indications than those remaining in the NSM group. If this is the case than the difference in QALYs will be overestimated by the model.

The results of this economic evaluation are consistent with the two previous economic evaluations, from perspectives other than the UK NHS and PSS identified by this evidence report, that considered this review question. That is that vertebroplasty and kyphoplasty were likely to be cost effective when wider estimates of the cost of NSM were used.

Appendix J Excluded studies

Excluded studies for review question What is the effectiveness of invasive interventions, such as vertebroplasty, kyphoplasty, ablation and surgery, in managing spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Excluded effectiveness studies

Table 34: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Alshareef, Mohammed Abdul, Klapthor, Gibson, Lowe, Stephen R et al. (2020) Strategies for posterior-only minimally invasive surgery in thoracolumbar metastatic epidural spinal cord compression. Surgical neurology international 11: 462	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Alshareef, Mohammed, Klapthor, Gibson, Alawieh, Ali et al. (2021) Evaluation of open and minimally invasive spinal surgery for the treatment of thoracolumbar metastatic epidural spinal cord compression: a systematic review. European spine journal, 30(10): 2906-2914	Other protocol criteria - not available
Amelot, Aymeric, Moles, Alexis, Cristini, Joseph et al. (2016) Predictors of survival in patients with surgical spine multiple myeloma metastases. Surgical oncology 25(3): 178-83	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Anselmetti, Giovanni Carlo, Manca, Antonio, Montemurro, Filippo et al. (2012) Vertebroplasty using transoral approach in painful malignant involvement of the second cervical vertebra (C2): a single-institution series of 25 patients. Pain physician 15(1): 35-42	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Armstrong, V., Schoen, N., Madhavan, K. et al. (2019) A systematic review of interventions and outcomes in lung cancer metastases to the spine. Journal of Clinical Neuroscience 62: 66-71	Study design – systematic review which included studies without a control group
Astur, Nelson and Avanzi, Osmar (2019) Balloon Kyphoplasty in the Treatment of Neoplastic Spine Lesions: A Systematic Review. Global spine journal 9(3): 348-356	Study design - systematic review which did not provide sufficient detail to allow use of data in this review
Bach, F., Agerlin, N., Sorensen, J.B. et al. (1992) Metastatic spinal cord compression secondary to lung cancer. Journal of Clinical Oncology 10(11): 1781-1787	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Bach, F, Larsen, B H, Rohde, K et al. (1990) Metastatic spinal cord compression. Occurrence, symptoms, clinical presentations and prognosis in 398 patients with spinal cord compression. Acta neurochirurgica 107(12): 37-43	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Bae, Jin Woo, Gwak, Ho-Shin, Kim, Sohee et al. (2016) Percutaneous vertebroplasty for patients	Other protocol criteria – non-randomised study which did not adjust for baseline differences be-

Study	Reason for exclusion
with metastatic compression fractures of the thoracolumbar spine: clinical and radiological factors affecting functional outcomes. The spine journal : official journal of the North American Spine Society 16(3): 355-64	tween patients in different intervention groups
Bakar, Dara, Tanenbaum, Joseph E, Phan, Kevin et al. (2016) Decompression surgery for spinal metastases: a systematic review. Neurosurgical focus 41(2): e2	Study design – systematic review which included studies without a control group
Castaneda Rodriguez, W.R. and Callstrom, M.R. (2011) Effective pain palliation and prevention of fracture for axial-loading skeletal metastases using combined cryoablation and cementoplasty. Techniques in Vascular and Interventional Radiology 14(3): 160-169	Study design - commentary
Cazzato, Roberto Luigi, Garnon, Julien, Caudrelier, Jean et al. (2018) Percutaneous radiofrequency ablation of painful spinal metastasis: a systematic literature assessment of analgesia and safety. International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group 34(8): 1272-1281	Study design – systematic review which included studies without a control group
Chen, X., Meng, C., Zhang, W. et al. (2016) Efficacies of percutaneous vertebral angioplasty, percutaneous kyphoplasty and conventional open operation in the treatment of spinal tumor. International Journal of Clinical and Experimental Medicine 9(2): 3398-3406	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Chew, C, Craig, L, Edwards, R et al. (2011) Safety and efficacy of percutaneous vertebroplasty in malignancy: a systematic review. Clinical radiology 66(1): 63-72	Study design - expert review/narrative
Cho, Jae Hwan, Ha, Jung-Ki, Hwang, Chang Ju et al. (2015) Patterns of Treatment for Metastatic Pathological Fractures of the Spine: The Efficacy of Each Treatment Modality. Clinics in orthopedic surgery 7(4): 476-82	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Colman, M.W., Kirkwood, J.M., Schott, T. et al. (2014) Does metastasectomy improve survival in skeletal melanoma?. Melanoma Research 24(4): 354-359	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Cornelis, Francois H, Joly, Quentin, Nouri-Neuville, Maud et al. (2019) Innovative Spine Implants for Improved Augmentation and Stability in Neoplastic Vertebral Compression Fracture. Medicina (Kaunas, Lithuania) 55(8)	Study design - expert review/narrative
Dakson, Ayoub, Leck, Erika, Brandman, David M et al. (2020) The clinical utility of the Spinal Instability Neoplastic Score (SINS) system in spinal epidural metastases: a retrospective study. Spinal cord 58(8): 892-899	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
de Almeida Bastos, Dhiego Chaves, Everson, Richard George, de Oliveira Santos, Bruno Fer-	Other protocol criteria - duplicate publication

Study	Reason for exclusion
nandes et al. (2020) A comparison of spinal laser interstitial thermotherapy with open surgery for metastatic thoracic epidural spinal cord compression. Journal of neurosurgery. Spine: 1-9	
De la Garza-Ramos, Rafael; Benvenutti-Regato, Mario; Caro-Osorio, Enrique (2016) Vertebroplasty and kyphoplasty for cervical spine metastases: a systematic review and meta-analysis. International journal of spine surgery 10: 7	Study design – systematic review which included studies without a control group
de Oliveira, M.F.; Rotta, J.M.; Botelho, R.V. (2015) Survival analysis in patients with metastatic spinal disease: The influence of surgery, histology, clinical and neurologic status. Arquivos de Neuro-Psiquiatria 73(4): 330-335	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Delpla, Alexandre, Tselikas, Lambros, De Baere, Thierry et al. (2019) Preventive Vertebroplasty for Long-Term Consolidation of Vertebral Metastases. Cardiovascular and interventional radiology 42(12): 1726-1737	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Dhamija, Bhoresh; Batheja, Dheeraj; Balain, Birender Singh (2021) A systematic review of MIS and open decompression surgery for spinal metastases in the last two decades. Journal of clinical orthopaedics and trauma 22: 101596	Study design – systematic review which included studies without a control group
Dim, E.M., Yau, C.H.R., Ho, W.Y.K. et al. (2018) Profile of Surgically-treated Metastatic Extremity Bone Tumours at a University Hospital in Hong Kong. Journal of Orthopaedics, Trauma and Rehabilitation 24: 1-8	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Du, Zhiye, Guo, Wei, Yang, Rongli et al. (2016) What Is the Value of Surgical Intervention for Sacral Metastases?. PloS one 11(12): e0168313	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Echt, Murray, Stock, Ariel, De la Garza Ramos, Rafael et al. (2021) Separation surgery for metastatic epidural spinal cord compression: comparison of a minimally invasive versus open approach. Neurosurgical focus 50(5): e10	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Fan, Wenshuai, Zhou, Tianyao, Li, Jinghuan et al. (2021) Freehand Minimally Invasive Pedicle Screw Fixation and Minimally Invasive Decompression for a Thoracic or Lumbar Vertebral Metastatic Tumor From Hepatocellular Carcinoma. Frontiers in surgery 8: 723943	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Fang, Taolin, Dong, Jian, Zhou, Xiaogang et al. (2012) Comparison of mini-open anterior corpectomy and posterior total en bloc spondylectomy for solitary metastases of the thoracolumbar spine. Journal of neurosurgery. Spine 17(4): 271-9	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Fanous, Sherry Nabil, Saleh, Emad Gerges, Abd Elghafar, Ekramy Mansour et al. (2021) Randomized controlled trials between dorsal root ganglion thermal radiofrequency, pulsed radiofrequency and steroids for the management of intractable	Intervention does not match review protocol - compares methods for nerve block of dorsal root ganglion)

Study	Reason for exclusion
metastatic back pain in thoracic vertebral body. British journal of pain 15(3): 270-281	
Fisher, Carl, Ali, Zakariya, Detsky, Jay et al. (2019) Photodynamic Therapy for the Treatment of Vertebral Metastases: A Phase I Clinical Trial. Clinical cancer research : an official journal of the American Association for Cancer Research 25(19): 5766-5776	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
George, R., Jeba, J., Ramkumar, G. et al. (2015) Interventions for the treatment of metastatic extradural spinal cord compression in adults. Cochrane Database of Systematic Reviews 2015(9): cd006716	Intervention does not match protocol – systematic review that did not report on comparisons of relevance to this review
George, Reena, Jeba, Jenifer, Ramkumar, Govindaraj et al. (2015) Interventions for the treatment of metastatic extradural spinal cord compression in adults. The Cochrane database of systematic reviews: cd006716	Other protocol criteria - duplicate publication
George, Reena, Jeba, Jenifer, Ramkumar, Govindraj et al. (2008) Interventions for the treatment of metastatic extradural spinal cord compression in adults. The Cochrane database of systematic reviews: cd006716	Other protocol criteria - systematic review which has been updated
Gerber, David E and Grossman, Stuart A (2006) Does decompressive surgery improve outcome in patients with metastatic epidural spinal-cord compression? Nature clinical practice. Neurology 2(1): 10-1	Other protocol criteria - not available
Giercksky K, E, Gronbech J, E, Hammelbo, T et al. (2003) Use of palliative surgery in the treatment of cancer patients.	Other protocol criteria - not available
Greif, Dylan N, Ghasem, Alexander, Butler, Alexander et al. (2019) Multidisciplinary Management of Spinal Metastasis and Vertebral Instability: A Systematic Review. World neurosurgery 128: e944-e955	Study design - expert review/narrative
Gu, Yi-Feng, Tian, Qing-Hua, Li, Yong-Dong et al. (2017) Percutaneous vertebroplasty and interventional tumor removal for malignant vertebral compression fractures and/or spinal metastatic tumor with epidural involvement: a prospective pilot study. Journal of pain research 10: 211-218	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Guzik, Grzegorz (2017) Oncological and functional results of the surgical treatment of vertebral metastases in patients with multiple myeloma". BMC surgery 17(1): 92	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Hadjipavlou, A.G., Tzermiadianos, M.N., Katonis, P.G. et al. (2005) Percutaneous vertebroplasty and balloon kyphoplasty for the treatment of osteoporotic vertebral compression fractures and osteolytic tumours. Journal of Bone and Joint Surgery - Series B 87(12): 1595-1604	Study design - expert review/narrative
Hamad, Abdulkader, Vachtsevanos, Leonidas, Cattell, Andrew et al. (2017) Minimally invasive	Other protocol criteria – non-randomised study which did not adjust for baseline differences be-

Study	Reason for exclusion
spinal surgery for the management of symptomatic spinal metastasis. British journal of neurosurgery 31(5): 526-530	tween patients in different intervention groups
Han, Xiuxin, Zhang, Chao, Li, Lili et al. (2021) A Retrospective Evaluation of Operative and Postoperative Outcomes in Patients with Spinal Metastases from a Single Center to Compare Vertebrectomy with Combined Vertebrectomy and Radiofrequency Ablation. Medical science monitor : international medical journal of experimental and clinical research 27: e932995	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Hansen-Algenstaedt, Nils, Kwan, Mun Keong, Algenstaedt, Petra et al. (2017) Comparison Between Minimally Invasive Surgery and Conventional Open Surgery for Patients With Spinal Metastasis: A Prospective Propensity Score-Matched Study. Spine 42(10): 789-797	Other protocol criteria - not available
HAYES and Inc (2016) Kiva VCF treatment system for treatment of vertebral compression fractures.	Other protocol criteria - not available
He, S., Wei, H., Ma, Y. et al. (2017) Outcomes of metastatic spinal cord compression secondary to primary hepatocellular carcinoma with multidisciplinary treatments. Oncotarget 8(26): 43439-43449	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Health Quality, Ontario (2016) Vertebral Augmentation Involving Vertebroplasty or Kyphoplasty for Cancer-Related Vertebral Compression Fractures: A Systematic Review. Ontario health technology assessment series 16(11): 1-202	Study design - expert review/narrative
Hikata, T., Isogai, N., Shiono, Y. et al. (2017) A Retrospective Cohort Study Comparing the Safety and Efficacy of Minimally Invasive Versus Open Surgical Techniques in the Treatment of Spinal Metastases. Clinical Spine Surgery 30(8): e1082-e1087	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Hubertus, Vanessa, Gempt, Jens, Marino, Michelle et al. (2021) Surgical management of spinal metastases involving the cervicothoracic junction: results of a multicenter, European observational study. Neurosurgical focus 50(5): e7	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Hunter, R E and Wigfield, C C (2008) Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomized trial. British journal of neurosurgery 22(5): 713-4	Study design - commentary
Ibrahim, Ahmed, Crockard, Alan, Antonietti, Pierre et al. (2008) Does spinal surgery improve the quality of life for those with extradural (spinal) osseous metastases? An international multicenter prospective observational study of 223 patients. Invited submission from the Joint Section Meeting on Disorders of the Spine and Peripheral Nerves, March 2007. Journal of neurosurgery. Spine 8(3): 271-8	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups

Study	Reason for exclusion
Jain, Sumit, Kinch, Logan, Rana, Maunak et al. (2020) Comparison of post-operative pain scores and opioid use between kyphoplasty and radiofrequency ablation (RFA) systems combined with cement augmentation. Skeletal radiology 49(11): 1789-1794	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Jarzem, P, Berenson, J, Tillman, J et al. (2010) Balloon kyphoplasty improves both Roland Morris Disability Questionnaire scores and bone pain among cancer patients with vertebral compression fractures: interim analysis of results from phase IV randomized trial. Canadian journal of surgery. Journal canadien de chirurgie 53(3suppl): 28	Publication type - conference abstract
Jha, Ruchira M, Yoo, Albert J, Hirsch, Ariel E et al. (2009) Predictors of successful palliation of compression fractures with vertebral augmentation: single-center experience of 525 cases. Journal of vascular and interventional radiology, 20(6): 760-8	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Jiang, W., Cao, X., Liu, Y. et al. (2018) Minimally invasive posterior percutaneous pedicle screw fixation for instability of spinal metastases. International Journal of Clinical and Experimental Medicine 11(5): 5359-5366	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Jung, Jong-Myung, Chung, Chun Kee, Kim, Chi Heon et al. (2019) Minimally Invasive Surgery without Decompression for Hepatocellular Carcinoma Spinal Metastasis with Epidural Spinal Cord Compression Grade 2. Journal of Korean Neurosurgical Society 62(4): 467-475	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Kakutani, K., Sakai, Y., Maeno, K. et al. (2017) Prospective Cohort Study of Performance Status and Activities of Daily Living after Surgery for Spinal Metastasis. Clinical Spine Surgery 30(8): e1026-e1032	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Kasperk, C., Haas, A., Hillengass, J. et al. (2012) Kyphoplasty in patients with multiple myeloma a retrospective comparative pilot study. Journal of Surgical Oncology 105(7): 679-686	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Ke, Zhen-Yong, Wang, Yang, Zhong, Yue-Long et al. (2015) Percutaneous vertebroplasty combined with percutaneous pediculoplasty for lytic vertebral body and pedicle lesions of metastatic tumors. Pain physician 18(3): e347-53	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Knisely, J. and Strugar, J. (2006) Can decompressive surgery improve outcome in patients with metastatic epidural spinal-cord compression?. Nature Clinical Practice Oncology 3(1): 14-15	Study design - commentary
Landmann, C; Hunig, R; Gratzl, O (1992) The role of laminectomy in the combined treatment of metastatic spinal cord compression. International journal of radiation oncology, biology, physics	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups

Study	Reason for exclusion
24(4): 627-31	
Lenschow, M., Lenz, M., von Spreckelsen, N. et al. (2022) Impact of Spinal Instrumentation on Neurological Outcome in Patients with Intermediate Spinal Instability Neoplastic Score (SINS). Cancers 14(9): 2193	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Li, Meiling; Zhang, Yan; Zhang, Xiujuan (2020) Effects of surgery and radiofrequency ablation in the treatment of spinal metastases and analysis of the influencing factors of prognosis. Experimental and therapeutic medicine 19(2): 1072-1078	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Li, Yan, Gu, Yi-Feng, Sun, Zhen-Kui et al. (2013) Comparison of percutaneous vertebroplasty with and without interventional tumour removal for malignant vertebral compression fractures with symptoms of neurological compression. European radiology 23(10): 2754-63	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Li, Zhi, Ni, Caifang, Chen, Long et al. (2014) Kyphoplasty versus vertebroplasty for the treatment of malignant vertebral compression fractures caused by metastases: a retrospective study. Chinese medical journal 127(8): 1493-6	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Lv, Nanning, Geng, Rui, Ling, Feng et al. (2020) Clinical efficacy and safety of bone cement combined with radiofrequency ablation in the treatment of spinal metastases. BMC neurology 20(1): 418	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Masala, S., Guglielmi, G., Petrella, M.C. et al. (2011) Percutaneous ablative treatment of metastatic bone tumours: Visual analogue scale scores in a short-term series. Singapore Medical Journal 52(3): 182-189	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Maseda, Masafumi, Uei, Hiroshi, Nakahashi, Masahiro et al. (2019) Neurological outcome of treatment for patients with impending paralysis due to epidural spinal cord compression by metastatic spinal tumor. Journal of orthopaedic surgery and research 14(1): 291	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Mattie, Ryan, Brar, Nick, Tram, Jennifer T et al. (2021) Vertebral Augmentation of Cancer-Related Spinal Compression Fractures: A Systematic Review and Meta-Analysis. Spine 46(24): 1729-1737	Study design - expert review/narrative
Medical Advisory, Secretariat (2004) Balloon kyphoplasty: an evidence-based analysis. Ontario health technology assessment series 4(12): 1-45	Study design – systematic review which included studies without a control group
Mendoza, Tito R, Koyyalagunta, Dhanalakshmi, Burton, Allen W et al. (2012) Changes in pain and other symptoms in patients with painful multiple myeloma-related vertebral fracture treated with kyphoplasty or vertebroplasty. The journal of pain 13(6): 564-70	Study design - not comparative
Mercadante, Sebastiano, Klepstad, Pal, Kurita, Geana Paula et al. (2016) Minimally invasive pro-	Study design - expert review/narrative

Study	Reason for exclusion
cedures for the management of vertebral bone pain due to cancer: The EAPC recommendations. Acta oncologica (Stockholm, Sweden) 55(2): 129-33	
Miller, Jacob A, Balagamwala, Ehsan H, Berri-ochoa, Camille A et al. (2017) The impact of de-compression with instrumentation on local failure following spine stereotactic radiosurgery. Journal of neurosurgery. Spine 27(4): 436-443	Outcomes do not match protocol
Milross, C.G., Davies, M.A., Fisher, R. et al. (1997) The efficacy of treatment for malignant epidural spinal cord compression. Australasian Radiology 41(2): 137-142	Other protocol criteria – non-randomised study which did not adjust for baseline differences be-tween patients in different intervention groups
Molina, Camilo A; Gokaslan, Ziya L; Sciubba, Daniel M (2011) A systematic review of the cur-rent role of minimally invasive spine surgery in the management of metastatic spine disease. Inter-national journal of surgical oncology 2011: 598148	Study design – systematic review which included studies without a control group
Molina, Camilo, Goodwin, C Rory, Abu-Bonsrah, Nancy et al. (2016) Posterior approaches for symptomatic metastatic spinal cord compression. Neurosurgical focus 41(2): e11	Study design - expert review/narrative
Murali, Navanith, Turmezei, Thomas, Bhatti, Sumbal et al. (2021) What is the effectiveness of radiofrequency ablation in the management of patients with spinal metastases? A systematic review and meta-analysis. Journal of orthopaedic surgery and research 16(1): 659	Study design – systematic review which included studies without a control group
Muto, M, Perrotta, V, Guarnieri, G et al. (2008) Vertebroplasty and kyphoplasty: friends or foes? La Radiologia medica 113(8): 1171-84	Other protocol criteria – non-randomised study which did not adjust for baseline differences be-tween patients in different intervention groups
Nater, Anick, Tetreault, Lindsay A, Kopjar, Branko et al. (2018) Predictive factors of survival in a surgical series of metastatic epidural spinal cord compression and complete external validation of 8 multivariate models of survival in a prospective North American multicenter study. Cancer 124(17): 3536-3550	Other protocol criteria – non-randomised study which did not adjust for baseline differences be-tween patients in different intervention groups
National Institute for Clinical, Excellence (2003) Balloon kyphoplasty for vertebral compression fractures.	Study design does not match protocol - guidance
Noh, S.H., Takahashi, T., Inoue, T. et al. (2022) Postoperative spinal deformity and instability after cervical spinal cord tumor resection in adults: A systematic review and meta-analysis. Journal of Clinical Neuroscience 100: 148-154	Study design - expert review/narrative
Patchell, R.A. (2007) Metastatic epidural spinal cord compression. European Journal of Cancer, Supplement 5(5): 35-40	Study design - commentary
Patchell, R, Tibbs, PA, Regine, F et al. (2003) A randomized trial of direct decompressive surgical resection in the treatment of spinal cord compres-sion caused by metastasis. Journal of clinical on-	Publication type - conference abstract

Study	Reason for exclusion
cology 21: 237s	
Paulino Pereira, N.R., Ogink, P.T., Groot, O.Q. et al. (2019) Complications and reoperations after surgery for 647 patients with spine metastatic disease. Spine Journal 19(1): 144-156	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Pennington, Zach, Pairojboriboon, Sutipat, Chen, Xuguang et al. (2022) Utility of expanded anterior column resection versus decompression-alone for local control in the management of carcinomatous vertebral column metastases undergoing adjuvant stereotactic radiotherapy. The spine journal, 22(5): 835-846	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Peterson, K.A., Zehri, A.H., Lee, K.E. et al. (2021) Current trends in incidence, characteristics, and surgical management of metastatic breast cancer to the spine: A National Inpatient Sample analysis from 2005 to 2014. Journal of Clinical Neuroscience 91: 99-104	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Pichon Riviere, A, Augustovski, F, Ferrante, D et al. (2004) Percutaneous vertebroplasty usefulness for vertebral fracture treatment.	Other protocol criteria - not available
Prezzano, Kavitha M, Prasad, Dheerendra, Hermann, Gregory M et al. (2019) Radiofrequency Ablation and Radiation Therapy Improve Local Control in Spinal Metastases Compared to Radiofrequency Ablation Alone. The American journal of hospice & palliative care 36(5): 417-422	Other protocol criteria - not available
Proschek, Dirk, Kurth, Andreas, Proschek, Petra et al. (2009) Prospective pilot-study of combined bipolar radiofrequency ablation and application of bone cement in bone metastases. Anticancer research 29(7): 2787-92	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Ptashnikov, D., Zaborovskii, N., Kostrickii, S. et al. (2020) Metastasectomy and targeted therapy for patients with spinal metastases of renal cell carcinoma. International Journal of Spine Surgery 14(6): 982-988	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Qi, L., Li, C., Wang, N. et al. (2018) Efficacy of percutaneous vertebroplasty treatment of spinal tumors. Medicine (United States) 97(3): e9575	Other protocol criteria - duplicate publication
Qi, Lei, Li, Chuankun, Wang, Ning et al. (2018) Efficacy of percutaneous vertebroplasty treatment of spinal tumors: A meta-analysis. Medicine 97(3): e9575	Study design – systematic review which included studies without a control group
Rades, D. and Schild, S.E. (2007) Spinal cord compression. European Journal of Cancer, Supplement 5(5): 359-370	Study design - commentary
Rao, G., Ha, C.S., Chakrabarti, I. et al. (2006) Multiple myeloma of the cervical spine: Treatment strategies for pain and spinal instability. Journal of Neurosurgery: Spine 5(2): 140-145	Study design - not comparative
Ravikanth, Reddy (2020) Management of metastatic vertebral lesions by interventional techniques: Systematic review of outcomes. Journal	Study design - systematic review without pooled results/quantitative data, checked for relevant studies

Study	Reason for exclusion
of craniovertebral junction & spine 11(2): 61-70	
Rosian, K and Piso, B (2017) Radiofrequency ablation for metastatic spinal lesions.	Study design - expert review/narrative
Rosian, Katharina; Hawlik, Katharina; Piso, Brigitte (2018) Efficacy Assessment of Radiofrequency Ablation as a Palliative Pain Treatment in Patients with Painful Metastatic Spinal Lesions: A Systematic Review. Pain physician 21(5): e467-e476	Study design – systematic review which included studies without a control group
Sadeghi-Naini, Mohsen, Aarabi, Shahram, Shokraneh, Farhad et al. (2018) Vertebroplasty and Kyphoplasty for Metastatic Spinal Lesions: A Systematic Review. Clinical spine surgery 31(5): 203-210	Other protocol criteria - not available
Sagoo, Navraj S, Haider, Ali S, Ozair, Ahmad et al. (2022) Percutaneous image-guided cryoablation of spinal metastases: A systematic review. Journal of clinical neuroscience, 96: 120-126	Study design – systematic review which included studies without a control group
Sagoo, Navraj S, Haider, Ali S, Rowe, Scott E et al. (2021) Microwave Ablation as a Treatment for Spinal Metastatic Tumors: A Systematic Review. World neurosurgery 148: 15-23	Study design - expert review/narrative
Sagoo, NS, Haider, AS, Rowe, SE et al. (2021) Microwave Ablation as a Treatment for Spinal Metastatic Tumors. World neurosurgery	Study design - expert review/narrative
Schilling, Andrew T, Ehresman, Jeff, Huq, Sakibul et al. (2020) Risk Factors for Wound-Related Complications After Surgery for Primary and Metastatic Spine Tumors: A Systematic Review and Meta-Analysis. World neurosurgery 141: 467-478e3	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Sohn, Seil, Chung, Chun Kee, Han, Kyung Do et al. (2019) A Nationwide Study of Surgery in a Newly Diagnosed Spine Metastasis Population. Journal of Korean Neurosurgical Society 62(1): 46-52	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Sorensen, Simon Thorbjorn, Kirkegaard, Andreas Ole, Carreon, Leah et al. (2019) Vertebroplasty or kyphoplasty as palliative treatment for cancer-related vertebral compression fractures: a systematic review. The spine journal : official journal of the North American Spine Society 19(6): 1067-1075	Study design – systematic review which included studies without a control group
Spencer, Benjamin A, Shim, Jin Joo, Hershman, Dawn L et al. (2014) Metastatic epidural spinal cord compression among elderly patients with advanced prostate cancer. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 22(6): 1549-55	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Spiessberger, Alexander, Arvind, Varun, Gruter, Basil et al. (2020) Thoracolumbar corpectomy/spondylectomy for spinal metastasis: a pooled analysis comparing the outcome of seven different surgical approaches. European spine journal :	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups

Study	Reason for exclusion
official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society 29(2): 248-256	
Street, John, Fisher, Charles, Sparkes, Joseph et al. (2007) Single-stage posterolateral vertebrectomy for the management of metastatic disease of the thoracic and lumbar spine: a prospective study of an evolving surgical technique. Journal of spinal disorders & techniques 20(7): 509-20	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Su, Yan, Sun, Zhong-Zhen, Shen, Long-Xiang et al. (2017) Comparison of percutaneous vertebroplasty with and without interventional tumor removal for spinal metastatic tumor without epidural involvement. Journal of bone oncology 6: 1-7	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Sugita, Shurei, Hozumi, Takahiro, Yamakawa, Kiyofumi et al. (2018) The significance of spinal fixation in palliative surgery for spinal metastases. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia 48: 163-167	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Tabbara, I A; Sibley, D S; Quesenberry, P J (1990) Spinal cord compression due to metastatic neoplasm. Southern medical journal 83(5): 519-23	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Tao, Fenghua, Shi, Zhicai, Tao, Haiying et al. (2020) Comparison of subtotal vertebral resection with reconstruction and percutaneous vertebroplasty for treatment of metastasis in the lumbar spine. British journal of neurosurgery 34(3): 308-312	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Tazi, H, Manunta, A, Rodriguez, A et al. (2003) Spinal cord compression in metastatic prostate cancer. European urology 44(5): 527-32	Other protocol criteria - not available
Telera, Stefano, Caroli, Fabrizio, Raus, Laura et al. (2016) Spine Surgery in Patients with Metastatic Breast Cancer: A Retrospective Analysis. World neurosurgery 90: 133-146	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Tomita, K., Kawahara, N., Kobayashi, T. et al. (2001) Surgical strategy for spinal metastases. Spine 26(3): 298-306	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Trilling, G.M., Cho, H., Ugas, M.A. et al. (2012) Spinal metastasis in head and neck cancer. Head and Neck Oncology 4(1): 36	Study design - expert review/narrative
Uei, H.; Tokuhashi, Y.; Maseda, M. (2018) Treatment outcomes of patients with spinal metastases derived from hepatocellular carcinoma. International Journal of Clinical Oncology 23(5): 886-893	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Uei, Hiroshi and Tokuhashi, Yasuaki (2019) Therapeutic Impact of Percutaneous Pedicle Screw Fixation on Palliative Surgery for Metastatic Spine Tumors. Indian journal of orthopaedics 53(4): 533-541	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Uei, Hiroshi, Tokuhashi, Yasuaki, Maseda, Masa-	Other protocol criteria – non-randomised study

Study	Reason for exclusion
fumi et al. (2018) Comparison between minimally invasive spine stabilization with and without posterior decompression for the management of spinal metastases: a retrospective cohort study. Journal of orthopaedic surgery and research 13(1): 87	which did not adjust for baseline differences between patients in different intervention groups
Vargas, Enrique, Lockney, Dennis T, Mummaneni, Praveen V et al. (2021) An analysis of tumor-related potential spinal column instability (Spine Instability Neoplastic Scores 7-12) eventually requiring surgery with a 1-year follow-up. Neurosurgical focus 50(5): e6	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Xing, D., Dong, Z., Zheng, X. et al. (2019) The protective effects of surgery according to the spinal instability neoplastic score for patients with the EGFR mutation, lung adenocarcinoma, and spinal metastatic instability. International Journal of Clinical and Experimental Medicine 12(11): 12764-12772	Population does not match review protocol – included patients who did not have spinal metastases and treatment effect not reported separately
Yang, Si-Zhen, Tang, Yu, Zhang, Ying et al. (2017) Prognostic Factors and Comparison of Conservative Treatment, Percutaneous Vertebroplasty, and Open Surgery in the Treatment of Spinal Metastases from Lung Cancer. World neurosurgery 108: 163-175	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Yildizhan, Serhat, Boyaci, Mehmet Gazi, Rakip, Usame et al. (2021) Role of radiofrequency ablation and cement injection for pain control in patients with spinal metastasis. BMC musculoskeletal disorders 22(1): 912	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups
Zehri, A.H., Peterson, K.A., Lee, K.E. et al. (2022) National trends in the surgical management of metastatic lung cancer to the spine using the national inpatient sample database from 2005 to 2014. Journal of Clinical Neuroscience 95: 88-93	Other protocol criteria – non-randomised study which did not adjust for baseline differences between patients in different intervention groups

Excluded economic studies

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information

Appendix K Research recommendations – full details

Research recommendations for review question: What is the effectiveness of invasive interventions, such as vertebroplasty, kyphoplasty, ablation and surgery, in managing spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

K.1.1 Research recommendation

What is the effectiveness of surgery in the prevention of MSCC for people with spinal metastases without pain or instability?

K.1.2 Why this is important

Surgery for people with spinal metastases or direct malignant infiltration of the spine is usually reserved for those with symptomatic spinal cord compression, pain and/or spinal instability. Surgery at an earlier stage, before pain or instability develops could conceivably prevent MSCC occurring and lead to better long-term outcomes. The patient may be better able to tolerate pre-emptive surgery because a less invasive procedure could be needed when the extent of disease is smaller. However preventative surgery puts a patient at risk of unnecessary surgical complications if their spinal disease would never have progressed to symptomatic MSCC.

K.1.3 Rationale for research recommendation

Table 35: Research recommendation rationale

Importance to 'patients' or the population	MSCC has an adverse impact on quality of life due to severe pain and adverse neurological and functional status.
Relevance to NICE guidance	Surgery in the prevention of MSCC for people with spinal metastases without pain or instability has been considered in this guideline and there is a lack of data.
Relevance to the NHS	Determining whether surgical prevention of MSCC is effective for people with spinal metastases without pain or instability is relevant to the NHS because it could prevent progression of a condition which could turn into a medical emergency and risks collapse of the spine. This would also prevent extra resources being used to deal with the consequences of MSCC.
National priorities	Improving cancer survival rates is one of the priorities within the NHS long term plan: 'The latest Global Burden of Disease study shows that the top five causes of early death for the people of England are: heart disease and stroke, cancer, respiratory conditions, dementias, and self-harm. It also reveals that the slower improvement since 2010 in years-of-life-lost is "mainly driven by distinct condition-specific trends, predominantly in cardiovascular diseases and some cancers'
Current evidence base	The PROMPTS randomised trial found that pre-emptive radiotherapy for people with impending spinal cord compression did not improve outcomes. However, there is no evidence about surgery in this situation.
Equality considerations	None known
Feasibility	Numbers of people with MSCC are relatively low compared to the

	overall number of people with cancer and recruitment may therefore be difficult. However, otherwise it would be feasible to carry out such research - multicentre or multinational study likely to be needed.

MSCC: metastatic spinal cord compression

K.1.4 Modified PICO table

Table 36: Research recommendation modified PICO table

Population	People with spinal metastases with early radiological signs of impending SCC but without pain, spinal instability or MSCC
Intervention	Immediate surgery (with or without radiotherapy)
Comparator	Radiotherapy (with surgery delayed until the onset of pain or spinal instability)
Outcome	• Neurological and functional status • Pain • Quality of life • Adverse events due to treatment
Study design	Randomised controlled trial or controlled observational study
Timeframe	2 years
Additional information	Observational studies will need to adjust for baseline differences in patient groups such as: site of primary cancer, number of MSCC sites, location of spinal metastases, ambulatory status and performance status

MSCC: metastatic spinal cord compression; SCC: spinal cord compression