National Institute for Health and Care Excellence

Final

Spinal metastases and metastatic spinal cord compression

[F] Evidence reviews for investigations – diagnosis

NICE guideline number NG234

Evidence reviews underpinning recommendations 1.5.1, 1.5.5 to 1.5.9 in the NICE guideline

September 2023

Final

These evidence reviews were developed by NICE

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Investigations - diagnosis

Review question

How effective are radiological imaging techniques in the diagnosis of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Introduction

The diagnosis of metastatic spinal cord compression or spinal metastases typically requires radiological imaging. Clinical signs may be the same for malignant and benign spinal disease in people with known primary cancer. Some people without known primary cancer present with spinal cord compression as their first symptom. MRI has been the method of choice for investigating malignant spinal disease and cord compression, due to its ability to identify metastatic disease within bone, visualise the soft tissue component of lesions and show the degree of any cord compression. Computed tomography (CT) and fluorodeoxyglucose-positron emission tomography-computed tomography (FDG-PET-CT) also potentially provide additional information. This review aimed to summarise the effectiveness of different radiological imaging techniques in the diagnosis of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression.

Summary of the protocol

See Table 1 for a summary of the Population, Index test, Reference standard (or Comparator), Target condition and Outcome (PIRTO) characteristics of this review.

Table 1: Summary of the protocol (PIRTO table)

Population	Adults with suspected or confirmed • metastatic spinal disease • direct malignant infiltration of the spine. Adults with suspected or confirmed spinal cord or nerve root compression because of • metastatic spinal disease • direct malignant infiltration of the spine

Index test	For diagnosis of spinal metastasis / direct infiltration:
	• MRI
	  ○ T1 sequences (with/without contrast)
	  ○ short T1 inversion recovery (STIR) sequences
	  ○ T2 weighted sequences (to show the level and degree of compression of the cord / lesions within cord)
	  ○ Whole spine imaging
	• CT (whole spine or other)
	• Image guided biopsy (for example for solitary metastasis)
	• Plain X-ray
	• FDG-PET-CT

Reference standard (or comparator)	For *test and treat studies* comparisons are: • Routine imaging versus sign/symptom directed • Delayed versus early imaging • Different test sequences in comparison with each other For *diagnostic accuracy studies* reference standard is: • Biopsy result / surgical pathology

	• Clinical and radiological follow up (if no surgery/biopsy done)
Target condition	• Metastatic spinal disease • Direct malignant infiltration of the spine • Spinal cord compression associated with the above
Outcomes	**Critical** For *test and treat* studies: • Overall survival • Disease-related morbidity • Neurological/functional status • Quality of life For *diagnostic accuracy* studies: • Sensitivity, specificity • Likelihood ratios • PPV, NPV **Important** • Pain • Time to treatment • Test-related morbidity, for example: • Consequences of false positives • Morbidity due to biopsy • Test failure (incomplete or cancelled test – for example due to anxiety or claustrophobia during MRI)

CT: computed tomography; FDG-PET-CT: fluorodeoxyglucose-positron emission tomography-computed tomography; MRI: magnetic resonance imaging; NPV: negative predictive value; PPV: positive predictive value.

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.

Diagnostic evidence

Included studies

Twenty studies were included in this evidence review, 1 randomised trial (Dearnaley 2022), 1 observational study (Allan 2009), 3 systematic reviews (Kim 2020, Li 2019, Suh 2018) and 15 diagnostic accuracy studies (Bacher 2021, Husband 2001, Kato 2015, Kim 2000, Laufer 2009, Maeder 2018, Perry 2018, Phadke 2001, Razek 2019, Schmeel 2018, Schmeel 2021, Shi 2017, Spinnato 2018, Taheri 2017, Zafar 2020).

Test and treat studies

One test-and-treat RCT (Dearnaley 2022) compared screening MRI with no screening MRI in men at high risk of malignant spinal cord compression.

One study (Allan 2009) compared a rapid MRI referral hotline for suspected malignant spinal cord compression with usual care.

Diagnostic test accuracy studies

One systematic review (Suh 2018) and 5 additional studies (Maeder 2018, Perry 2018, Schmeel 2021, Shi 2017, Taheri 2017) evaluated chemical shift MRI for the differential diagnosis of malignant and non-malignant bone marrow lesions.

Two systematic reviews (Li 2019, Suh 2018) and 2 additional studies (Bacher 2021, Schmeel 2018) evaluated chemical shift MRI for the differential diagnosis of malignant and non-malignant vertebral compression fractures.

One systematic review (Li 2019) and 3 additional studies (Kato 2015, Razek 2019, Zafar 2020) evaluated conventional MRI sequences, contrast enhanced MRI and diffusion weighted imaging for the differential diagnosis of malignant and non-malignant vertebral compression fractures.

One systematic review (Kim 2020) evaluated FDG-PET-CT or FDG-PET for the differential diagnosis of malignant and non-malignant vertebral compression fractures.

One study (Husband 2001) evaluated plain radiographs and neurology for the diagnosis of malignant spinal cord compression and for the impact of MRI on treatment planning.

One study (Kim 2000) reported the diagnostic accuracy of T1-weighted sagittal images alone for the for the diagnosis of malignant spinal cord compression.

Three studies (Laufer 2009, Phadke 2001, Spinnato 2018) reported the diagnostic yield of CT-guided biopsy of suspected malignant spinal lesions.

The included studies are summarised in Table 2.

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	Index test or intervention	Reference standard or comparison	Target condition	Outcomes
Allan 2009 Retrospective cohort study UK	N=424 • Patients with suspected malignant spinal cord compression referred via hotline • Patients with malignant spinal cord compression (Clinical Re-	• Telephone hotline group (quick access to MRI)	• Control group (diagnosis following usual care)	• MSCC	• Neurological and functional status: ○ Number of patients walking at time of diagnosis • Time to treatment: ○ Time from referral to diagnosis of MSCC

Study	Population	Index test or intervention	Reference standard or comparison	Target condition	Outcomes
	search and Audit group) Age and sex not reported.				
Bacher 2021 Retrospective cohort study Switzerland	N=95 Consecutive patients undergoing spine MRI (at a single institution) prior to cementoplasty for acute vertebral compression fractures. Age, mean, years (SD): 76 (12) for those with benign lesions 63 (12) for those with malignant lesions	• MRI - single sagittal fast spin echo T2-weighted Dixon sequence	• Radiological follow-up (radiographs, CT, MRI, bone scans and PET-CT studies) and biopsy results, follow-up 9 months	• Malignant VCF	Accuracy of the MRI diagnosis: • Sensitivity/ specificity • Likelihood ratios • PPV, NPV
Dearnley 2022 RCT UK	N=410 Patients with metastatic castration resistant prostate cancer with bone involvement. Age: (median, IQR) MRI group: 74.3 (68.0–79.3) Control group: 74.2 (68.5–79.3) Sex: male n=410	• Screening spinal MRI	• No screening MRI	• MSCC	• Overall survival • Neurological and functional status • Quality of life • Pain
Husband 2001 Prospective cohort study UK	N=280 Consecutive patients with suspected spinal cord compression un-	• Plain radiograph and neurological examination	• Radiological follow-up (MRI carried out as soon as possible usually the next day)	• MSCC	Accuracy of the X-ray plus neurological examination diagnosis: • Sensitivity/ specificity

Study	Population	Index test or intervention	Reference standard or comparison	Target condition	Outcomes
	dergoing MRI. Age, median, years (range): 67 (23 – 89) Sex: female n=122; male n=158.				• Likelihood ratios • PPV, NPV
Kato 2015 Retrospective cohort study Japan	N=200 Patients with radiologically apparent collapse of thoracolumbar vertebra due to metastatic vertebral compression fractures or osteoporotic vertebral fractures. Age, mean, years (SD): people with osteoporotic fractures 73 (11) people with metastatic fractures 64 (11) Sex: female n=130; male n=70.	• MRI	• Biopsy result / surgical pathology • Clinical and radiological follow up of 60 days (if no surgery/biopsy done)	• Malignant VCF	Accuracy of the MRI diagnosis: • Sensitivity/ specificity • Likelihood ratios • PPV, NPV
Kim 2000 Retrospective cohort study USA	N=57 Consecutive patients undergoing MRI for clinically suspected malignant spinal cord compression. Age, median, years (range): 49 (22 – 87). Sex: female n=26; male	• MRI - T1-weighted sagittal images only	• MRI – complete imaging studies of spinal column (T1 and T2 weighted sagittal images; and T1 and/or T2 weighted axial images. Based on agreement in diagnosis between 3 radiologists on examination of complete imaging study for each patient.	• MSCC	Accuracy of the MRI diagnosis for different spinal metastases or MSCC divided according to external and internal standard : • Sensitivity/ specificity • Likelihood ratios

Study	Population	Index test or intervention	Reference standard or comparison	Target condition	Outcomes
	n=31.				
Kim 2020 Systematic review of diagnostic accuracy studies	N=274 (in 5 studies) Patients with vertebral compression fractures Age, mean years: range 60 to 72. SD not reported Sex: female n=92; male n=182.	• FDG-PET • FDG-PET/CT	• Composite reference standard of biopsy, clinical follow-up and repeat imaging	• Malignant VCF	Accuracy of the FDG-PET or FDG PET/CT diagnosis: • Sensitivity/ specificity • Likelihood ratios
Laufer 2009 Retrospective cohort study USA	N=82 Patients with a previous diagnosis of cancer undergoing CT-guided biopsy of suspected malignant spinal column lesion. Age, mean, years (SD): 56. SD not reported. Sex: female n=49; male n=41.	• FDG-PET	• CT guided biopsy	• Malignant spinal column lesions	• Test failure/success ○ diagnostic yield of biopsy
Li 2019 Systematic review of diagnostic accuracy studies	N=895 Patients with vertebral fractures Age: mean ranged from 54.6 to 69 years across the studies Sex: female n=486; male n=409.	• MRI chemical shift imaging • MRI conventional sequences plus diffusion weighted imaging • MRI conventional sequences • MRI conventional	• Biopsy result / surgical pathology • Clinical and radiological follow up (if no surgery/biopsy done)	• Malignant VCF	Accuracy of the MRI diagnosis: • Sensitivity/ specificity • Likelihood ratios • PPV, NPV

Study	Population	Index test or intervention	Reference standard or comparison	Target condition	Outcomes
		sequences plus contrast enhanced images			
Maeder 2018 Retrospective cohort study Switzerland	N=121 Consecutive patients undergoing whole spine MRI for suspected vertebral metastases. Age, mean, years (SD): 61.4 (11.8). Sex: female n=58; male n=63.	• MRI – sagittal SE Dixon T2-weighted fat-only and water-only imaging. • MRI – sagittal SE T1-weighted and SE Dixon T2-weighted water-only images.	• Biopsy result / surgical pathology • Clinical and radiological follow up of at least 8 months	• Malignant BML	Accuracy of the MRI diagnosis: • Sensitivity/ specificity • Likelihood ratios • PPV, NPV
Perry 2018 Retrospective cohort study USA	N=101 Patients undergoing opposed-phase MRI of the cervical, thoracic, or lumbar spine. Age, mean, years (SD): 57.7 (14.1). Sex: female n=62; male n=39.	• Opposed phase MRI	• Biopsy result / surgical pathology • Clinical and radiological follow up (if no surgery/biopsy done) up to 2 years	• Malignant BML	Accuracy of the MRI diagnosis: • Sensitivity/ specificity • Likelihood ratios • PPV, NPV
Phadke 2001 Retrospective cohort study USA	N=78 Patients undergoing CT guided fine needle aspiration biopsy for vertebral and intervertebral lesions (included patients without a known malig-	• CT guided fine needle aspiration biopsy	• Cytopathologist's assessment of sample adequacy and diagnosis (if sample was adequate)	• Malignant spinal lesions	• Test failure/success ○ diagnostic yield of biopsy

Study	Population	Index test or intervention	Reference standard or comparison	Target condition	Outcomes
	nancy). Age: not reported. Sex: female n=49; male n=29.				
Razek 2019 Retrospective cohort study Egypt	N=45 Patients with untreated compressed vertebrae undergoing MRI. Age, mean, years (SD): 56.14 (7.9). Sex: female n=22; male n=22.	• MRI – T1 and T2 weighted and DTI	• Biopsy result / surgical pathology	• Malignant VCF	Accuracy of the MRI diagnosis: • Sensitivity/ specificity • Likelihood ratios • PPV, NPV
Schmeel 2018 Retrospective cohort study Germany	N=37 Consecutive patients with a suspected acute vertebral compression fracture or known primary malignancy and suspected pathological vertebral compression fracture. Age, mean, years (SD): 64.8 (16.5). Sex: female n=20; male n=17.	• MRI – T2-weighted.	• Biopsy result / surgical pathology	• Malignant VCF	Accuracy of the MRI diagnosis: • Sensitivity/ specificity • Likelihood ratios • PPV, NPV
Schmeel 2021 Prospective cohort study	N=55 Consecutive patients with untreated vertebral bone marrow lesions	• MRI - sagittal DWI and CSE-based MRI in addition to routine clinical	• Biopsy result / surgical pathology • Clinical and radiological follow up (if no surgery/biopsy	• Malignant BML	Accuracy of the MRI diagnosis: • Sensitivity/ specificity • Likelihood ratios

Study	Population	Index test or intervention	Reference standard or comparison	Target condition	Outcomes
Germany	undergoing MRI. Age, mean, years (SD): 68 (14). Sex: female n=30; male n=25.	spine MRI and chemical shift imaging	done) of at least 6 months		• PPV, NPV
Shi 2017 Retrospective cohort study China	N=53 • Consecutive patients with spinal haemangiomas • Consecutive patients with spinal metastases Age, mean, years (SD): 60.62 (8.23). Sex: female n=11; male n=16.	• MRI – T1-weighted imaging with and without fat suppression, chemical shift imaging, DWI, and enhanced imaging at 3.0 T MRI.	• Biopsy result / surgical pathology • Clinical and radiological follow up (if no surgery/biopsy done) of at least 6 months	• Malignant BML	Accuracy of the MRI diagnosis: • Sensitivity/ specificity • Likelihood ratios • PPV, NPV
Spinnato 2018 Retrospective cohort study Italy	N=32 Patients with 1 or more non-traumatic vertebral fracture of unknown aetiology. Age, mean, years (SD): 57.1 (23.3). Sex: female n=19; male n=13.	• CT guided biopsy	• Histopathologist's assessment of sample adequacy and diagnosis	• Malignant spinal lesions	• Test failure/success ○ diagnostic yield of biopsy
Suh 2018 Systematic review of diagnostic accuracy studies	N=591 Patients with vertebral bone marrow lesions undergoing MRI	• MRI chemical shift imaging	• Biopsy result / surgical pathology • Clinical or radiological follow-up (range 1 to 20 months)	• Malignant BML • malignant VCF	Accuracy of the MRI diagnosis: • Sensitivity/ specificity • Likelihood ratios • PPV, NPV

Study	Population	Index test or intervention	Reference standard or comparison	Target condition	Outcomes
	Age: ranged from 45 to 68 across studies Sex: female n=293; male n=277 (where reported).				
Taheri 2017 Prospective cohort study Iran	N=51 Patients with vertebral focal lesions referred for routine MRI of the spine. Age, mean, years (SD): 52.61 (13.52). Sex: female n=23; male n=28.	• MRI – dual-phase chemical shift imaging	• Biopsy result / surgical pathology • Clinical and radiological follow up (if no surgery/biopsy done)	• Malignant BML	Accuracy of the MRI diagnosis: • Sensitivity/ specificity • Likelihood ratios • PPV, NPV
Zafar 2020 Prospective cohort study Pakistan	N=280 Patients with vertebral fractures on digital x ray of spine showing decreased vertebral body height, reduced disc intervertebral disc space or collapsed vertebra Age, mean, years (SD): 42.61 (11.79). Sex: female n=124; male n=156.	• MRI – Plain and DWI.	• Biopsy result / surgical pathology	• Malignant VCF	Accuracy of the MRI diagnosis: • Sensitivity/ specificity • Likelihood ratios • PPV, NPV

BML: bone marrow lesions; CT: computed tomography; DTI: diffusion-tensor imaging; DWI: diffusion weighted imaging; FDG-PET: fluorodeoxyglucose positron emission tomography; MRI: magnetic resonance imaging; MSCC: metastatic spinal cord compression; NPV: negative predictive value; PPV, positive predictive value; RCT: randomised controlled trial; SD: standard deviation; VCF: vertebral compression fractures

See the full evidence tables in appendix D, the forest plots in appendix E and the study data in appendix L.

Summary of the evidence

Screening MRI verses no screening MRI

Evidence from a randomised trial indicated that screening using spinal MRI for people at high risk of metastatic spinal cord compression made no important difference to overall survival. There was also no evidence of important difference in neurological and functional status, pain or quality of life. The evidence quality ranged from low to high.

MSCC hotline verses usual care

Evidence from an observational study showed a benefit of a telephone hotline compared to usual care because it enabled rapid referral and diagnosis of patients with suspected MSCC. Median time from referral to diagnosis was 2 weeks shorter in the telephone hotline group compared to usual care. Patients referred via the hotline were also more likely to be ambulant at the time of diagnosis. The evidence quality ranged from very low to low.

Chemical shift MRI for the differential diagnosis of malignant and non-malignant vertebral bone marrow lesions

Chemical shift MRI had acceptable (>80%) sensitivity and specificity in the differential diagnosis of malignant and non-malignant vertebral bone marrow lesions (BML). Likelihood ratios indicated that chemical shift MRI is a useful test in this context (positive likelihood ratio [LR+] > 5 and negative likelihood ratio [LR-] < 0.2). The evidence quality for this was moderate to high.

FDG-PET for the differential diagnosis of malignant and non-malignant vertebral compression fractures

FDG-PET or FDG-PET-CT had acceptable (>80%) sensitivity for the differential diagnosis of malignant and non-malignant VCF, but somewhat lower specificity suggesting false positives would be an issue with this imaging modality. Likelihood ratios indicated that FDG-PET or FDG-PET-CT was potentially a useful test (LR+ between 2 and 5, LR- <0.2) again indicating some uncertainty in positive test results. The evidence quality for this was low.

Chemical shift MRI for the differential diagnosis of malignant and non-malignant vertebral compression fractures

Chemical shift MRI had acceptable (>80%) sensitivity and specificity for differential diagnosis of malignant and non-malignant vertebral compression fractures (VCF). Likelihood ratios indicated that chemical shift MRI is a useful test in this context (LR+ > 5, LR- < 0.2). The evidence quality for this was moderate to high.

Conventional MRI sequences(with or without DWI) for the differential diagnosis of malignant and non-malignant vertebral compression fractures

Conventional MRI sequences with or without diffusion weighted imaging or contrast enhancement had acceptable sensitivity and specificity for differential diagnosis of VCF. Likelihood ratios indicated that conventional MRI sequences with diffusion weighted imaging is a useful test in this context (LR+ > 5, LR- < 0.2). The evidence quality for this was moderate. Likelihood ratios indicated that conventional MRI sequences are a useful test in this context (LR+ > 5, LR- < 0.2). The evidence quality for this was very low to moderate.

Tests for diagnosis of metastatic spinal cord compression

Evidence for imaging diagnosis of spinal cord compression was more limited. One study indicated that T1-weighted sagittal MRI images alone had relatively low sensitivity but high specificity for spinal cord compression. Likelihood ratios indicated this was potentially a useful test (LR+ > 5, LR- between 0.2 and 0.5). Another observational study found that plain ra-

diographs plus neurological examination had very low sensitivity but high specificity for spinal cord compression. The likelihood ratios indicated plain radiographs plus neurological examination was unlikely to be a useful test for metastatic spinal cord compression (LR+ > 5, LR- > 0.5). The evidence quality for this was low.

Very low quality evidence suggested that CT-guided biopsies of suspected metastatic spinal lesions do not always provide sufficient material for diagnosis. There was uncertainty, however, about how often this occurs with reported diagnostic yields ranging from 81% to 99% in the included studies.

See appendix F for GRADE and modified GRADE tables.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

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.

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Critical outcomes were overall survival, disease related morbidity, neurological/functional status and quality of life. This was because prompt and accurate diagnosis should lead to appropriate treatment, avoiding the morbidity caused by spinal cord compression and potentially prolonging life. For this reason, diagnostic accuracy was also a critical outcome.

Pain was an important outcome because it is a common symptom of metastatic spinal disease with negative impact on quality of life. Time to treatment was an important outcome because diagnostic uncertainty can delay treatment. Also, referral for specialist tests or dealing with equivocal test results can cause treatment delays. False positive test results can have important consequences in this group, leading to unnecessary treatment or biopsy. Morbidity caused by biopsy was included as an important outcome for this reason. Finally test failure was included as an important outcome, because sometimes diagnostic tests do not produce a clear positive or negative result, leading to uncertainty, repeated tests and diagnostic delays.

The quality of the evidence

The quality of the evidence rated using GRADE ranged from low to high. The main issues that lowered the quality of the outcomes were risk of bias and imprecision.

No evidence was identified relating to CT scans or for the outcomes of disease-related morbidity, pain, consequences of false positives and morbidity due to biopsy.

Benefits and harms

Radiologist involvement

Based on their knowledge and experience the committee noted that carrying out radiological imagining of the spine and interpreting the results is complex (for example, selecting the correct sequencing and, if necessary, supplementary axial imaging) and that the impact of errors may have very serious consequences. In their experience there is also variation in how urgently results are reported, which can affect starting timely treatment. The committee agreed that imaging should be overseen by a radiologist. It was discussed that having a radiologist present at all MRI imaging appointments for MSCC would be difficult because of the urgency in which they would need to be conducted. They noted that it is now possible that scans can be overseen virtually which means that a radiologist would not necessarily need to be there in person but could oversee it remotely. Having a radiologist there also means that they can interpret and report the findings promptly.

The committee discussed the evidence showing an important benefit of a telephone hotline compared to usual care. They noted that it enabled rapid referral and diagnosis of patients with suspected MSCC. They agreed that any pathway to urgent MRI is useful and there are service configurations that work in some areas but not others. However, they decided not to recommend a hotline for MRI because they did not want to be prescriptive about how services organise their MRI lists to provide urgent access. They acknowledged that this is addressed in another part of the guideline that is focused on service configuration to support urgent MRI diagnosis of MSCC (see evidence review A).

MRI assessment

Based on the evidence and their experience the committee agreed that conventional MRI sequences (including T1-weighted imaging, T2-weighted imaging and short TI inversion recovery (STIR) sequences) have acceptable sensitivity and specificity (considerably higher than the committee's decision threshold of 80%) for identifying metastatic disease within bone when the correct sequences are used, and they listed the appropriate sequences in their recommendation. Sagittal T1 and/or STIR sequences of the whole spine would be used identify spinal metastases. Whereas sagittal T2 weighted sequences (with supplementary axial imaging) can also show any soft tissue component of the mass and the degree of spinal cord compression.

The committee discussed the evidence on adding contrast-enhanced MRI, diffusion weighted imaging or chemical shift MRI to conventional sequences which may have a role in differentiating normal versus malignant bone marrow or osteoporotic versus malignant compression fractures. They were not convinced the evidence supported routinely adding these additional sequences to conventional MRI because the main role of MRI in this context is to identify the presence or absence of metastases and involvement of the spinal cord, rather than differentiate benign verses malignant lesions or fractures, however they understood that these additional sequences may be useful in selected cases and that local protocols or guidelines would be typically in place for their use.

They recommended not to perform routine MRI in people without symptoms or signs of cord compression in order to screen for MSCC, because evidence from a randomised trial did not demonstrate any benefit of surveillance MRIs in people who are asymptomatic but are at high risk of MSCC.

Other imaging techniques for diagnosis and management

Although there was no evidence about the use of CT in diagnosis of metastatic spinal disease the committee acknowledged that MRI might be contraindicated in some people (for instance anyone with metal implants). They considered CT was an appropriate alternative

(although less sensitive than modern MRI) for imaging the spine in these cases and widely used for cancer staging. They acknowledged, based on experience that in rare cases there may be an indication for CT myelography, but this would need to be done in a specialist centre because it is an invasive procedure which is associated with some risks.

The committee discussed that many patients presenting with symptoms of spinal metastases or cord compression may have already had plain X-rays as initial investigations, but they agreed based on their experience that plain X-rays were not as sensitive for detecting metastatic bone disease as MRI and recommended they should not be used to diagnose or rule out spinal metastases, direct malignant infiltration (DMI) of the spine or MSCC. There was also evidence that X-rays and neurological examination would detect less than half of the cases of spinal cord compression which can accompany spinal metastases.

The committee noted the evidence showing that CT-guided biopsies of suspected metastatic spinal lesions do not always provide sufficient material for diagnosis. However, they decided that due to the very low quality there was too much uncertainty about this evidence to base a recommendation on.

Cost effectiveness and resource use

No economic evidence was identified for this topic from the systematic search of previously published evidence. The committee considered cost effectiveness based on their own experience and knowledge.

Recommendations for this topic will lead to cost savings with no or limited impact on outcomes for people receiving these healthcare services. Whilst imaging being overseen by a radiologist would take up their time and associated costs the consequences of missing important details would be serious which would accrue larger costs in the long term. Recommendations against routine MRI in people without symptoms or signs of MSCC should reduce the number of MRIs undertaken although only a handful of centres are currently performing MRI in these circumstances. RCT evidence suggests this will have no impact upon outcomes or quality of life for patients.

Recommendations against x-ray, although a less expensive imaging technique should reduce costs as the diagnostic utility of them is very limited and MRI diagnostic imaging would always have to be carried out to get sufficiently detailed information to locate the tumour and plan treatment.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.1 and 1.5.5 to 1.5.9 in the NICE guideline.

References – included studies

Diagnostic

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Spinnato 2018

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Appendices

Appendix A Review protocols

Review protocol for review question: How effective are radiological imaging techniques in the diagnosis of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022303705
1.	Review title	Radiological imaging techniques in the diagnosis of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression
2.	Review question	How effective are radiological imaging techniques in the diagnosis of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?
3.	Objective	To establish effective radiological imaging techniques in the diagnosis of 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) • Cumulative Index to Nursing and Allied Health Literature (CINAHL) • Database of Abstracts of Reviews of Effects (DARE) • Embase • Epistemonikos • International Health Technology Assessment (IHTA) database • MEDLINE & MEDLINE In-Process Searches will be restricted by: • Date: 1990 onwards (see rationale under Section 10)

ID	Field	Content
		• 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	Radiological imaging techniques in the diagnosis of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression

6.	Population	**Inclusion:**
		• Adults with suspected or confirmed
		  ○ metastatic spinal disease
		  ○ direct malignant infiltration of the spine.
		• Adults with suspected or confirmed spinal cord or nerve root compression because of
		  ○ metastatic spinal disease
		  ○ direct malignant infiltration of the spine.
		
		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/test	For diagnosis of spinal metastasis / direct infiltration: • MRI ○ T1 sequences (with/without contrast)

ID	Field	Content
		○ short T1 inversion recovery (STIR) sequences ○ T2 weighted sequences (to show the level and degree of compression of the cord / lesions within cord) ○ Whole spine imaging • CT (whole spine or other) • Image guided biopsy (for example for solitary metastasis) • Plain X-ray • FDG-PET-CT
8.	Comparator/Reference standard	For **test and treat studies** comparisons are: • Routine imaging versus sign/symptom directed • Delayed versus early imaging • Different test sequences in comparison with each other For **diagnostic accuracy studies** reference standard is: • Biopsy result / surgical pathology • Clinical and radiological follow up (if no surgery/biopsy done)
9.	Types of study to be included	For test and treat studies: experimental studies (where the investigator assigned intervention or control) including: • Randomised controlled trials • Non-randomised controlled trials • Systematic reviews/meta-analyses of controlled trials. For diagnostic accuracy studies, the following designs will be included: • Observational studies (where neither control nor intervention were assigned by the investigator) including: ○ Systematic reviews of diagnostic studies. ○ Diagnostic accuracy (cross-sectional) studies
10.	Other exclusion criteria	Inclusion: • Full text papers

ID	Field	Content
		Exclusion: • Conference abstracts • Articles published before 1990. MRI has regularly been used in diagnosis since the early 1990s – patient cohorts from pre-1990 are unlikely to representative of current cohorts. • 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)	For test and treat studies: • Overall survival • Disease-related morbidity • Neurological/functional status • Quality of life For diagnostic accuracy studies: • Sensitivity, specificity • Likelihood ratios • PPV, NPV
13.	Secondary outcomes (important outcomes)	• Pain • Time to treatment • Test-related morbidity, for example: ○ Consequences of false positives ○ Morbidity due to biopsy • Test failure (incomplete or cancelled test – for example, due to anxiety or claustrophobia during MRI)
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclu-

ID	Field	Content
		sion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. 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. 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. PICOTS will be extracted from each study. For prediction models, development stage and validation status will be extracted.
15.	Risk of bias (quality) assessment	Risk of bias of individual studies will be assessed using the preferred checklist as described in Developing NICE guidelines: the manual. • ROBIS tool for systematic reviews • 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. Quality assessment of diagnostic accuracy studies will be performed using the following checklist • QUADAS-2 for diagnostic accuracy studies

ID	Field	Content
		The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.

16.	Strategy for data synthesis	**Test and treat review**
		Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively.
		
		<u>Data Synthesis</u>
		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.
		
		<u>Heterogeneity</u>
		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.
		
		<u>Minimal important differences (MIDs)</u>
		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.
		  ○ For studies that have been pooled using SMD (meta-analysed): +0.5 and -0.5 in the SMD scale are used as MID boundaries.
		
		Diagnostic review:

ID	Field	Content	
		Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where appropriate, meta-analysis of diagnostic test accuracy will be performed using the metandi package in STATA and Cochrane Review Manager software. Sensitivity, specificity, positive and negative likelihood ratios, with 95% CIs will be used as outcomes for diagnostic test accuracy. These diagnostic accuracy parameters will be obtained from the studies or calculated by the technical team using data from the studies. PPV & NPV will be calculated by combining the summary estimates of sensitivity & specificity with prevalence estimates. <u>Validity (for both test & treat and diagnostic accuracy analyses)</u> 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: • Myeloma versus other cancer types • Functional status / fitness for treatment Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: • 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

ID	Field	Content			
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	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 National Institute for Health and Care Excellence (NICE) 5b Named contact e-mail metastaticspinal@nice.org.uk 5e Organisational affiliation of the review			

ID	Field	Content	
		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 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: https://www.nice.org.uk/guidance/CG75	
29.	Other registration details	N/A	
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=303705	
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	spinal metastases; malignant infiltration of the spine; spinal cord compression; cancer; radiology; imaging; diagnosis	
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☐	Ongoing

ID	Field	Content	
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information		
36.	Details of final publication	www.nice.org.uk	
37.	Relevant SRs	N/A	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CT: computed tomography; DARE: Database of Abstracts of Reviews of Effects; FDG-PET-CT: fluorodeoxyglucose-positron emission tomography-computed tomography; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimally important difference; MRI: magnetic resonance imaging; NHS: National health service; NICE: National Institute for Health and Care Excellence; NPV: negative predictive value; PPV: positive predictive value; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation.

Appendix B Search strategy (clinical/economic)

Literature search strategies for review question: How effective are radiological imaging techniques in the diagnosis of 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	(mescc or mscc).ti,ab.
6	or/1-5
7	Diagnostic Imaging/
8	((diagnos* adj (imag* or radiogra* or scan*)) or ((radiogra* or radiolog*) adj (exam* or imag* or investigat* or scan* or test*))).ti,ab.
9	exp Magnetic Resonance Imaging/
10	(magnetic resonance or DWI or FMRI or MRE or MRI or MRS or NMR* or T1W or T2W or zeugmatogra* or ((diffusion or echoplanar or functional or magnet* or MR or nuclear or NM or planar or weight*) adj2 (diagnos* or elastogra* or examin* or imag* or scan* or spectroscop* or tomogra*))).ti,ab.
11	exp Tomography, Emission-Computed/ or exp Tomography, X-Ray Computed/
12	(((CAT or CT or comput* or electron beam or FDG or multidetector or multi detector or multislice or multi slice or PET or positron emission or spiral) adj2 (detect* or diagnos* or exam* or imag* or scan* or tomogra*)) or (FDG adj2 PET) or MDCT or MSCT or SPECT or spiral CT or tomodensitomet*).ti,ab.
13	Myelography/
14	(medullogra* or myelogra*).ti,ab.
15	Diagnostic Techniques, Radioisotope/ or Radionuclide Imaging/
16	(((gamma or radionuclide* or radioisotop*) adj2 (diagnos* or imag* or investigat* or scan* or scintigra* or scintimet* or scintiscan*)) or osteoscintigra*).ti,ab.
17	Absorptiometry, Photon/
18	(DEXA or DPX or DXA or ((dual emission or dual energy or dualenergy or photon) adj3 (absorptiomet* or densitomet* or imag* or photodensitomet* or scan*))).ti,ab.
19	((bone* or BMD or skelet*) adj (imag* or scan* or scintigra* or scintiscan* or survey*)).ti,ab.
20	x rays/
21	(x ray* or xray* or digital radiogra* or discogra* or diskogra* or grenz ray* or plain film* or plain radiogra* or radiodiagnos* or radio diagnos* or radioimag* or radiophoto* or roent* or x radiat* or xradiat*).ti,ab.
22	exp Angiography/ or exp Radionuclide Angiography/
23	(angiogra* or arteriogra*).ti,ab.
24	exp Image-Guided Biopsy/
25	((biops* or sampl*) adj3 ((imag* or scan* or tomogra* or ultraso* or ultra so* or CAT or CT or MR*) adj3 guid*)).ti,ab.
26	(biops* or sampl*).ti,ab. And dg.fs.
27	or/7-26
28	6 and 27
29	letter/ or editorial/ or news/ or exp historical article/ or Anecdotes as Topic/ or comment/ or case report/ or (letter or comment*).ti.
30	randomized controlled trial/ or random*.ti,ab.
31	29 not 30
32	(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.
33	31 or 32
34	28 not 33
35	limit 34 to english language
36	limit 35 to yr="1990 -Current"
37	meta-analysis/ or meta-analysis as topic/ or "systematic review"/
38	(meta analy* or metanaly* or metaanaly* or ((evidence or systematic*) adj2 (overview* or review*))).ti,ab.
39	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
40	(search strategy or search criteria or systematic search or study selection or data extraction or (search* adj4 literature)).ab.
41	(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.
42	cochrane.jw.

#	Searches
43	or/37-42
44	36 and 43
45	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt.
46	drug therapy.fs.
47	(groups or placebo or randomi#ed or randomly or trial).ab.
48	Clinical Trials as Topic/
49	trial.ti.
50	or/45-49
51	36 and 50
52	Non-Randomized Controlled Trials as Topic/
53	(experimental or nonrandom* or non random*).tw.
54	52 or 53
55	36 and 54
56	Comparative Studies/ or Cross-Sectional Studies/ or Follow-Up Studies/ or Time Factors/
57	(chang* or evaluat* or reviewed or prospective* or retrospective* or baseline or cohort or case series or cross section-al).tw.
58	56 or 57
59	36 and 58
60	or/44,51,55,59

Economic literature search strategy

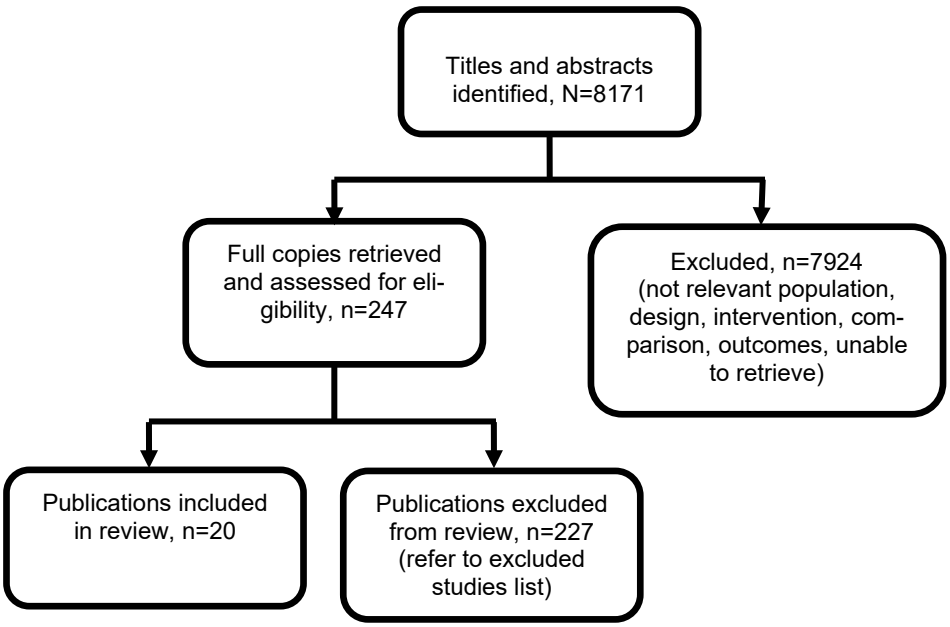
Database: MEDLINE – OVID interface

#	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 com-press* 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 ((ax-on* 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: How effective are radiological imaging techniques in the diagnosis of 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: How effective are radiological imaging techniques in the diagnosis of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Allan 2009
Allan L, Baker L, Dewar J, et al. Suspected malignant cord compression – Improving time to diagnosis via a hotline: A prospective audit. British Journal of Cancer, 100, 1867-1872, 2009

Study details

Country/ies where study was carried out	UK
Study type	Retrospective cohort study
Study dates	MSCC hotline established in 2004
Inclusion criteria	Criteria for the suspected MSCC hotline: patient known to have, or strongly suspected to have, cancer; new severe nerve root pain (unilateral or bilateral) and/or new severe localised vertebral pain, especially thoracic; and any new difficulty in walking. The comparison group came from Clinical Research and Audit Group (CRAG) audit data of people with MSCC from several Scottish centres.
Exclusion criteria	None reported
Patient characteristics	N=424 Patients with suspected malignant spinal cord compression referred via hotline and patients with malignant spinal cord com-pression (Clinical Research and Audit group) Gender [number of male, female]: not reported Age, mean (SD): not reported Myeloma versus other cancer types [percentage with myeloma]: 6% had myeloma in the MSCC hotline group – but not reported in the comparison group. Functional status/fitness for treatment [percentage who were ambulant]: Not reported. Ambulant rates at diagnosis of MSCC were reported – see outcomes below.
Intervention(s)/control	Hotline group: The referring GP or a hospital doctor speaks directly with a senior clinician on a dedicated phone number. After further discussion, usually between the hotline clinician and the patient's oncologist, the hotline clinician decides whether an MRI is required within 24 h, or the hotline clinician or the patient's oncologist may arrange to examine the patient before determining whether an urgent scan is required. An MRI slot was reserved at the end of each day's list for hotline referrals (if not used by mid-day it was re-allocated to an urgent inpatient or an outpatient). Patients with probable MCC presenting after this time were scanned first thing the next morning. An ad hoc on-

	call service was available at weekends and public holidays. Scans were immediately reported on a dedicated proforma by radiologists with a particular interest in MRI. MRI evidence of MCC was considered to be present if there was any extension into the epidural space with impingement, displacement or compression of the cord with or without cord signal change. The results were immediately communicated to the clinical team caring for the patient. Control group: a national Clinical Research and Audit Group (CRAG) prospective audit (324 cases of MCC) whose diagnosis followed usual care.
Duration of follow-up	From symptoms until results of diagnostic MRI.
Sources of funding	Macmillan Cancer Relief
Sample size	Hotline group N=100 (n=44 with MSCC); comparison group N=324 (all with MSCC)

Outcomes

Outcome	Hotline for suspected MSCC, Baseline, n=44	Comparison group (CRAG audit), Baseline, n=324
Time from GP or a hospital doctor referring the patient to diagnosis, days, median (IQR)	1 (0 to 21)	15 (3 to 66)
Number of patients walking (unaided or with assistance) at time of MSCC diagnosis	n=34	n=175

Critical appraisal – ROBINS-I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Serious *(Analysis not controlled for confounders)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Serious *(No information about patients discussed on the hotline but not referred for diagnostic tests)*
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
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Serious *(Unclear how the baseline timepoint was decided for the comparison group)*

Section	Question	Answer
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	Critical. Risk of bias due to confounding, selection of participants, and measurement of outcomes.
Overall bias	Directness	Directly applicable

Bacher 2021
Bacher S, Hajdu S, Maeder Y, et al. Differentiation between benign and malignant vertebral compression fractures using qualitative and quantitative analysis of a single fast spin echo T2-weighted Dixon sequence. European Radiology, 31, 9418-942, 2021

Study details

Country/ies where study was carried out	Switzerland.
Study type	Retrospective cohort study
Study dates	July 2014 – June 2020.
Inclusion criteria	Consecutive patients undergoing spine MRI (at a single institution) prior to cementoplasty for acute vertebral compression fractures.
Exclusion criteria	• No MRI prior to cementoplasty or 1.5T MRI • No T2-weighted Dixon sequence • History of hematologic neoplasia • Benign vertebral compression fractures but history of malignancy; or malignancy detected ≥9-month follow-up; or no follow-up data ≥9 months available.
Patient characteristics	N=95 Consecutive patients undergoing spine MRI (at a single institution) prior to cementoplasty for acute vertebral compression fractures. Age, mean (SD), years: benign 76 (12); malignant 63 (12) Gender [number of male, female]: benign – male n=23; female n=40; malignant – male n=20; female n=12. Myeloma versus other cancer types [number with myeloma]: 0/95 (0%). Patients with a history of haematologic neoplasms were excluded. Functional status/fitness for treatment [percentage who were ambulant]: Not reported.
Index test(s)	MRI – single sagittal fast spin echo (FSE) T2-weighted Dixon sequence.
Reference standard(s)	Best value comparator (including biopsy results). Vertebral compression fractures were categorised as benign or malignant based on a best valuable comparator consisting of a consensus reading performed by three observers after the end of readings of all available medical records, radiographs, CT, MRI, bone scans and PET-CT studies, and biopsy data (biopsy of target vertebra performed during cementoplasty).

	For vertebral compression fractures categorized as benign according to the best valuable comparator, a follow-up of nine months or more was required, in particular to avoid false negative results of biopsy. Vertebral compression fractures were therefore considered benign if fulfilling all of the following criteria: no current or past history of malignancy, no positive biopsy result (biopsy could be absent or negative), no malignancy found at clinical and imaging follow-up of nine months or more. Vertebral compression fractures were considered malignant if the best valuable comparator based on all data available was suggestive of a malignant origin.
Duration of follow-up	Patients diagnosed with benign vertebral compression fractures were only included if they had follow-up data of greater than 9 months.
Sources of funding	None.
Results	See Appendix L

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High – *potential incorporation bias as MRI was part of the composite reference standard*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Dearnaley 2022
Dearnaley D, Hinder V, Hijab A, et al. Observation versus screening spinal MRI and pre-emptive treatment for spinal cord compression in patients with castration-resistant prostate cancer and spinal metastases in the UK (PROMPTS): an open-label, randomised, controlled, phase 3 trial. Lancet: Oncology, 23, 501-513, 2022

Study details

Country/ies where study was carried out	UK
Study type	Randomised controlled trial (RCT)
Study dates	February 2013 to April 2017
Inclusion criteria	Eligible patients were aged 18 years and older, had a confirmed pathological diagnosis of prostate adenocarcinoma or a clinical diagnosis of prostate cancer with osteoblastic bone metastases and a serum prostate specific antigen (PSA) concentration of 100 ng/mL or higher at any time between diagnosis and randomisation. Other inclusion criteria were the presence of asymptomatic spinal metastasis, castration-resistant state (defined as PSA >5 ng/dL and more than 50% increase above the nadir during treatment with a luteinising hormone-releasing hormone analogue or after orchidectomy), PSA concentration of more than 5 ng/mL within 21 days before randomisation, life expectancy of 6 months or longer, and Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.
Exclusion criteria	Presence of any back pain or neurological symptoms from spinal metastases, previous spinal MRI within 12 months from trial entry, previous external beam radiotherapy to the vertebrae or spinal surgery to treat SCC, and any contraindication for MRI.
Patient characteristics	N=410 Patients with metastatic castration resistant prostate cancer with bone involvement. Age at randomisation, years (median, IQR): MRI group: 74.3 (68.0–79.3) Control group: 74.2 (68.5–79.3)
Intervention(s)/control	Intervention: screening spinal MRI (in men with metastatic castration resistant prostate cancer with bone involvement) to detect and treat asymptomatic spinal cord compression Control: No MRI
Duration of follow-up	36 months
Sources of funding	Cancer Research UK
Sample size	Total: 420 Intervention: 210 Control: 210

Outcomes

Outcome	**MRI screening, 24 month, n=210**	**Control, 24 month, n=210**	**Relative effect**
Overall survival (event is death from any cause)	172/210	174/210	Adj HR 0.98

Outcome		MRI screening, 24 month, n=210		Control, 24 month, n=210	Relative effect
					(0.79 to 1.21)[1]
Neurological and functional status – clinical spinal cord compression	19/210	26/210	Adj HR 0.61 (0.35 to 1.08)[1]		
Neurological and functional status – persistent neurological functional deficit (Frankel score A-D)	15/210	23/210	RR 0.73 (0.42 to 1.28)		

1. Adjusted for time since development of castration-resistant prostate cancer, time since start of continuous hormone treatment, ECOG performance status (0, 1, and 2), and natural logarithm of PSA concentration.

Outcome	Mean (95% CI) difference MRI screening – Control (Change from baseline to 12 months)
Quality of life – EQ-5D-5L – health state today (range 0 to 100, higher scores are better)	-1.5 (-5.7 to 2.7)
Pain – Brief Pain Index – severity (range 0 to 10, lower scores are better)	0.4 (-0.2 to 0.9)

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

Husband 2001
Husband D, Grant K, Romaniuk C. MRI in the diagnosis and treatment of suspected malignant spinal cord compression. British Journal of Radiology 74, 15-23, 2001

Study details

Country/ies where study was carried out	UK.
Study type	Prospective cohort study
Study dates	Not reported.
Inclusion criteria	Consecutive patients with suspected malignant spinal cord compression undergoing MRI at a single institution.
Exclusion criteria	Not reported.
Patient characteristics	N=280 patients undergoing MRI for suspected malignant spinal cord compression Age, mean (SD), years: range 23 – 89 (median 67). Mean and SD not reported. Gender [number of male, female]: male n=158; female n=122. Myeloma versus other cancer types [percentage with myeloma]: Not reported. Functional status/fitness for treatment [percentage who were ambulant]: Not reported.
Index test(s)	Plain radiograph and neurological examination
Reference standard(s)	Radiological follow-up (MRI carried out as soon as possible usually the next day)
Duration of follow-up	Not reported.
Sources of funding	Not reported.
Results	Diagnostic accuracy – plain radiograph plus neurological examination (N=280) TP 89, FP 2, FN 112, TN 87 (from which sensitivity, specificity, likelihood ratios as well as PPV and NPV were calculated)

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low

Section	Question	Answer
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High *(composite index test of X-ray & neurological examination)*
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Kato 2015
Kato S, Hozumi T, Yamakawa K, et al. META: an MRI-based scoring system differentiating metastatic from osteoporotic vertebral fractures. Spine Journal, 15, 1563-70, 2015

Study details

Country/ies where study was carried out	Japan.
Study type	Retrospective cohort study
Study dates	April 2004 – September 2011.
Inclusion criteria	• Patients with radiologically apparent collapse of thoracolumbar vertebra due to metastatic vertebral fractures or osteoporotic vertebral fractures. • Evaluated using MRI within 60 days of possible injury. • 100 cases of metastatic vertebral fracture were selected at random from database. Diagnosis confirmed either by positive biopsy results or by malignant radiographic changes (progressive expansion of vertebral signal intensity change or spinal canal invasion) observed for more than 60 days after their first presentation associated with a clinical diagnosis of malignancy at other sites. • 100 cases of osteoporotic vertebral fractures were selected at random from database. Diagnosis confirmed by eventual reduction of vertebral signal intensity change and remission of clinical symptoms observed for more than 60 days.
Exclusion criteria	• Metastatic vertebral fractures associated with haematologic disorders, including multiple myeloma and malignant lymphoma • Previously diagnosed metastatic vertebral fractures that had already received irradiation (due to potential to affect MRI appearance).
Patient characteristics	N=200 Patients with radiologically apparent collapse of thoracolumbar vertebra due to metastatic vertebral compression fractures or osteoporot-

	ic vertebral fractures Age, mean (SD), years: metastatic vertebral fractures 64 (11); osteoporotic vertebral fractures 73 (11). Gender [number of male, female]: metastatic vertebral compression fractures – male n=43; female n=57; osteoporotic vertebral fractures – male n=27; female n=73. Myeloma versus other cancer types [number with myeloma]: 0/200 (0%). Patients with metastatic fractures associated with haematological disorders were excluded. Functional status/fitness for treatment [percentage who were ambulant]: Not reported.
Index test(s)	MRI. All images obtained using: Magnetom Avanto 1.5T; Signa Hde 1.5T; or Intera Achieva 1.5T.
Reference standard(s)	Biopsy result / surgical pathology (or clinical and radiological follow-up if no surgery/biopsy was done)
Duration of follow-up	60 days
Sources of funding	None.
Results	See Appendix L

Critical appraisal – Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(not reported if reference standard results interpreted without knowledge of the results of the index test)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Kim 2000

Kim J, Learch T, Colletti P, et al. Diagnosis of vertebral metastasis, epidural metastasis, and malignant spinal cord compression: are T(1)-weighted sagittal images sufficient? Magnetic Resonance Imaging 18, 819-24, 2000

Study details	
Country/ies where study was carried out	USA
Study type	Retrospective cohort study
Study dates	Not reported.
Inclusion criteria	Consecutive patients undergoing MRI for clinically suspected malignant spinal cord compression at a single institution.
Exclusion criteria	Not reported.
Patient characteristics	N=57 Consecutive patients undergoing MRI for clinically suspected malignant spinal cord compression Age, median (range), years: 49 (22 – 87). Gender [number of male, female]: male n=31; female n=26. Myeloma versus other cancer types [number with myeloma]: n=10 studies in patients with multiple myeloma. Functional status/fitness for treatment [percentage who were ambulant]: Not reported.
Index test(s)	T1-weighted sagittal images alone (a subset of the complete studies – see reference standard information).
Reference standard(s)	Complete magnetic resonance studies of the spinal column (a complete study consisting of T1-weighted sagittal images, T2-weighted sagittal images, and T1- and/or T2-weighted axial images). This was divided into 'external standard' which is the agreement in diagnosis between radiologists on examination of complete imaging study for each patient and 'internal standard' which is the individual radiologist's diagnosis based on complete imaging study for each patient
Duration of follow-up	Not reported.
Sources of funding	Not reported.
Results	Diagnostic findings in cases reviewed (n=94 MRI studies in 57 patients) Vertebral metastasis n=72; epidural metastasis n=28; cord compression n=22. Sensitivity and specificity (ability to detect each diagnostic parameter) of T1-weigted sagittal images alone (in comparison to 'external standard' that is agreement in diagnosis between radiologists on examination of complete imaging study for each patient): Vertebral metastasis – sensitivity 87% (249/288) 95% CI 82 – 90; specificity 83% (73/88) 95% CI 74 – 89. Cord compression – sensitivity 70% (62/88) 95% CI 60 – 79; specificity 97% (278/288) 95% CI 90 – 99. Epidural metastasis – sensitivity 46 (51/112) 95% CI 37 – 55; specificity 89 (236/264) 95% CI 85 – 93. Sensitivity and specificity (ability to detect each diagnostic parameter) of T1-weigted sagittal images alone (in comparison to 'internal standard' that is individual radiologist's diagnosis based on complete imaging study for each patient): Vertebral metastasis – sensitivity 91% (242/265) 95% CI 87 – 94; specificity 80% (89/111) 95% CI 72 – 87. Cord compression – sensitivity 62% (62/100) 95% 52 – 71; specificity 96% (266/276) 95% CI 93 – 98. Epidural metastasis – sensitivity 48 % (49/102) 95% 39 – 58; specificity 89% (244/274) 95% CI 85 – 92.

Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(57 patients but 94 MRI studies, unclear how many studies per patient)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	High. (*Results for 3 radiologists pooled - giving artificially narrow confidence intervals for sensitivity and specificity)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(Risk of incorporation bias of index test in reference standard)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear. *(Some patients had contrast enhanced MRI)*

Kim 2020

Kim S, Lee J. (2020) Diagnostic performance of F-18 FDG PET or PET/CT for differentiation of benign from malignant vertebral compression fractures; A meta-analysis. World Neurosurgery, 137: e626-e633, 2020

Study details

Country/ies where study was carried out	South Korea
Study type	Systematic review of diagnostic accuracy studies
Study dates	Included studies were published between 2008 and 2018
Inclusion criteria	Studies F-18 FDG PET or PET/CT used to differentiate benign and malignant VCFx; sufficient data available to reassess the sensitivity

	and specificity of F-18 FDG PET or PET/CT for the differentiation of malignant VCFxs or the absolute numbers had been provided of the true-positive, true-negative, false-positive, and false-negative data; and no data overlap.
Exclusion criteria	Duplicated studies were excluded, as were review articles, case reports, conference papers, and letters that did not contain the original data.
Patient characteris-tics	5 studies included in review (N=274) Age: mean age across studies ranged from 60 to 72 years Sex Male/female 182/92
Index test(s)	• FDG-PET • FDG-PET-CT Interpretation was based o SUV-max with cut-off ranging from 2 to 4.75 across studies. FDG dose ranged from 370 to 555 MBq.
Reference stand-ard(s)	• Composite reference standard of biopsy, clinical follow-up and repeat imaging
Duration of follow-up	Not reported
Sources of funding	Not reported
Other information	5 studies included and assessed with QUADAS-2. None were at high risk of bias. All were at unclear risk of bias for patient selection and some details of the imaging test were unclear in most of studies. All were at low risk of bias for reference standard and flow & timing.

Outcomes

Outcome	**Pooled results N=274**
Sensitivity (95% CI)	0.96 (0.82 to 0.99)
Specificity (95% CI)	0.77 (0.56 to 0.89)
Positive likelihood ratio (95% CI)	4.1 (2.1 to 8)
Negative likelihood ratio (95% CI)	0.05 (0.01 to 0.23)
Area under the curve (95% CI)	0.94 (0.92 to 0.96)

Critical appraisal - ROBIS checklist

Section	**Question**	**Answer**
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low

Section	Question	Answer
Synthesis and findings	Concerns regarding the synthesis and findings	Low
Overall study ratings	Overall risk of bias	Low
Overall study ratings	Applicability as a source of data	Fully applicable

Laufer 2009
Laufer I, Lis E, Pisinski L, et al. The accuracy of [(18) F] fluorodeoxyglucose positron emission tomography as confirmed by biopsy in the diagnosis of spine metastases in a cancer population. Neurosurgery, 64, 107-4, 2009

Study details

Country/ies where study was carried out	USA.
Study type	Retrospective cohort study
Study dates	1996 - 2005.
Inclusion criteria	• Patients with a previous diagnosis of cancer undergoing CT guided biopsy of suspected malignant spinal column lesion (initially identified via MRI). • Patients who underwent FDG-PET scan within 6 weeks of initial CT guided biopsy.
Exclusion criteria	• Radiotherapy of chemotherapy initiated before biopsy. • Clear radiographic and clinical discitis/ osteomyelitis.
Patient characteristics	N=82 patients with a previous diagnosis of cancer undergoing CT guided biopsy of suspected malignant spinal column lesion Age, mean (SD), years: 56. SD not reported. Gender [number of male, female]: male n=41; female n=49. Myeloma versus other cancer types [number with myeloma]: n=5/82. Functional status/fitness for treatment [percentage who were ambulant]: Not reported.
Index test(s)	FDG-PET.
Reference standard(s)	CT guided biopsy.
Duration of follow-up	Not reported.
Sources of funding	Not reported.
Results	Insufficient detail to extract diagnostic accuracy data for FDG-PET <u>Biopsy results (n=82):</u>

	Positive on biopsy n=74 Negative on biopsy n=8. Biopsy failure rate 1/82 Diagnostic yield: 81/82

Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Li 2019

Li K, Huang L, Lang Z, et al. Reliability and Validity of Different MRI Sequences in Improving the Accuracy of Differential Diagnosis of Benign and Malignant Vertebral Fractures: A Meta-Analysis. American Journal of Roentgenology, 213, 427-436, 2019

Study details

Country/ies where study was carried out	China
Study type	Systematic review of diagnostic accuracy studies
Study dates	Jan 2000 to Sep 2016
Inclusion criteria	Studies related to the differential diagnosis of benign and malignant vertebral fractures by MRI and reference standard (histopathologic diagnosis or clinical follow-up examination)
Exclusion criteria	Abstracts, reviews or conference papers. Studies performed on cadavers or animals, the sample size was less than 20, raw data was not complete, patients were not examined with MRI and reference standard, the trial was not double-blind and repeated studies.
Patient characteristics	N=895 Patients with vertebral fractures Age: mean ranged from 54.6 to 69 years across the studies Sex: female n=486; male n=409.

Index test(s)	• MRI chemical shift imaging • MRI conventional sequences plus diffusion weighted imaging • MRI conventional sequences • MRI conventional sequences plus contrast enhanced images
Reference standard(s)	Histopathologic diagnosis (from surgery or biopsy) or clinical & radiological follow-up
Duration of follow-up	Not reported
Sources of funding	Not reported
Results	See Appendix L
Other information	18 studies included and assessed with QUADAS-2. None were at high risk of bias. Flow and timing was unclear in 8/12 studies and some details of MRI were unclear in 12/18 studies.

Critical appraisal - ROBIS checklist

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Concerns regarding the synthesis and findings	Low
Overall study ratings	Overall risk of bias	Low
Overall study ratings	Applicability as a source of data	Fully applicable

Maeder 2018
Maeder Y, Dunet V, Richard R, et al. Bone Marrow Metastases: T2-weighted Dixon Spin-Echo Fat Images Can Replace T1-weighted Spin-Echo Images. Radiology, 286, 948-959, 2018

Study details

Country/ies where study was carried out	Switzerland.
Study type	Retrospective cohort study
Study dates	September 2014 - April 2016.
Inclusion criteria	Consecutive patients undergoing whole spine MRI for suspected vertebral metastases at a single institution.

Exclusion criteria	• History of haematological neoplasia • Spinal osteosynthesis • MRI performed with 1.5T scanner • Incomplete MRI sequences
Patient characteristics	N=121 consecutive patients undergoing whole spine MRI for suspected vertebral metastases Age, mean (SD), years: 61.4 (11.8). Gender [number of male, female]: male n=63; female n=58. Myeloma versus other cancer types [number with myeloma]: 0/121 (0%). Patients with a history of haematological neoplasia were excluded. Functional status/fitness for treatment [percentage who were ambulant]: Not reported.
Index test(s)	• MRI - sagittal SE Dixon T2-weighted fat-only and water-only imaging. • MRI - sagittal SE T1-weighted and SE Dixon T2-weighted water-only images.
Reference standard(s)	• Best value comparator (including biopsy result where possible). This consisted of consensus reading of all examinations by two musculoskeletal radiologists (performed 1 month after the end of all readings), as well as review of all available medical data. These data included clinical, histologic (spinal bone biopsy data, available for 30 patients), biologic, and imaging data.
Duration of follow-up	≥ 8 months after imaging (mean 15.2 months).
Sources of funding	Not reported.
Other information	All imaging performed with 3-T scanner. A total of three contiguous sagittal stacks with nonenhanced fast. SE T1-weighted and fast SE Dixon T2-weighted sequences of the entire spine from the base of the skull to the last sacral piece were performed for all patients. Four sets of images were routinely reconstructed from the Dixon T2 sequences: in-phase, out-of phase, Dixon T2-weighted water-only, and Dixon T2-weighted fat-only images, of which only the latter two were considered for our study. Additional sequences performed on a case-by case basis whenever indicated were considered only for the best valuable comparator. They included contrast material–enhanced fat-suppressed T1-weighted sequences on the sagittal and axial planes, as well as axial fat suppressed T2-weighted sequences.
Results	See Appendix L

Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low

Section	Question	Answer
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(Potential for incorporation bias)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Perry 2018
Perry M, and Sebro R. Accuracy of Opposed-phase Magnetic Resonance Imaging for the Evaluation of Treated and Untreated Spinal Metastases. Academic Radiology, 25, 877-882, 2018

Study details

Country/ies where study was carried out	USA.
Study type	Retrospective cohort study
Study dates	January 2006 - November 2016.
Inclusion criteria	Patients undergoing opposed-phase MRI of the cervical, thoracic, or lumbar spine.
Exclusion criteria	• Patients whose MRI studies did not include opposed-phase sequences. • Patients whose MRI studies were motion-degraded. • Patients with lesions confirmed as osteomyelitis or spondylodiscitis.
Patient characteristics	N=101 Patients undergoing opposed-phase MRI of the cervical, thoracic, or lumbar spine. Gender [number of male, female]: male n = 39; female n=62. Age, mean (SD), years: 57.7 (14.1) Myeloma versus other cancer types [number with myeloma]: n=13. Functional status/fitness for treatment [percentage who were ambulant]: Not reported. n=136 lesions identified from n=120 opposed phase MRI studies. Benign lesions n=25 Untreated metastases n=25 Treated spinal metastases n=86 (radiation n=19; chemotherapy only n=67).
Index test(s)	Opposed phase MRI.

	All examinations performed on 1.5-T or 3-T systems. Opposed-phase gradient recalled-echo images were performed in the sagittal plane, 1.5-T (repetition time [TR] 140–350 ms, echo time [TE] out-of-phase 2.204–2.54 ms, TE in-phase 4.373–5.04 ms, slice thickness 4 mm, interslice gap 0.4–0.8 mm); 3-T (TR 4.82–173 ms, TE out-of-phase 1.24– 1.28 ms, TE in-phase 2.48–2.56 ms, slice thickness 4 mm, interslice gap 0.4–0.8 mm). All images were reviewed using a GE Centricity Picture Archiving and Communication System (PACS) workstation. Region of interest (ROI) measurements were obtained using the PACS ellipse ROI markup tool. The largest possible ROI was placed over the lesion and the mean SI was recorded on out-of-phase and in-phase sequences. An approximately similar sized ROI (same area) was placed on the out-of-phase and in-phase sequences. Care was taken to avoid vessels and vertebral body cortex when obtaining ROIs. The SIR of out-of-phase SI to the inphase SI was then calculated (SIR = mean lesion SI on out-of-phase MRI sequence/mean lesion SI on in-phase MRI sequence).
Reference standard(s)	• Biopsy result / surgical pathology. • Clinical and Radiological follow up (if no surgery/biopsy done) up to 2 years. Lesions were determined to be spinal metastases if there was histologic confirmation of spinal metastases from percutaneous or surgical biopsies; if there was progression of disease (increase in size of lesion) on subsequent imaging over 2 years; or if there was decrease in size or imaging appearance of the lesion in response to chemotherapy or radiation therapy. Lesions were categorized as benign if there was no evidence of change in size or imaging appearance of the lesion for at least 2 years or if there was histologic confirmation that they were benign and there was no history of malignancy. Lesions confirmed as osteomyelitis or spondylodiscitis were excluded from the study.
Duration of follow-up	≥ 2 years (for benign lesions).
Sources of funding	Not reported.
Results	See Appendix L

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review ques-	Low

Section	Question	Answer
	tion?	
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Phadke 2001
Phadke D, Lucas D, Madan S. Fine-needle aspiration biopsy of vertebral and intervertebral disc lesions: specimen adequacy, diagnostic utility, and pitfalls. Archives of Pathology and Laboratory Medicine, 125, 1463-8, 2001

Study details

Country/ies where study was carried out	USA.
Study dates	January 1994 – February 2000.
Inclusion criteria	Not reported.
Exclusion criteria	Not reported.
Patient characteristics	N=78 Patients undergoing CT guided fine needle aspiration biopsy for vertebral and intervertebral lesions. Included patients with and without a known primary malignancy. Age, mean (SD), years: Not reported. Gender [number of male, female]: male n=29; female n=49. Myeloma versus other cancer types [number with myeloma]: Not reported. Functional status/fitness for treatment [percentage who were ambulant]: Not reported.
Index test(s)	CT guided fine needle aspiration biopsy. N=36 patients with vertebral lesions had a history of malignancy at another site. In these cases, FNAB was performed on radiologically suspected or detected lesions to rule out metastasis. In the other 42 cases of both vertebral and intervertebral lesions, FNAB was performed as a part of the workup in patients presenting with signs and symptoms related to the spine and abnormal radiologic findings.
Reference standard(s)	A cytopathologist classified the biopsy as: Positive for malignancy, Suspicious for malignancy, Normal cellular elements present, with no evidence of malignancy, Unsatisfactory/inadequate for diagnosis or Benign neoplastic lesion.
Duration of follow-up	Not reported.
Sources of funding	Not reported.
Results	Vertebral lesions with a clinical history of malignancy – cytologic diagnosis (n=36) Positive for malignancy: n=24/36.

	Suspicious for malignancy: n=0/36. Normal cellular elements present, with no evidence of malignancy: n=5/36. Unsatisfactory/inadequate for diagnosis: n=4/36. Benign neoplastic lesions: n=2/36. Acute inflammatory process: n=1/36. <u>Vertebral lesions without a clinical history of malignancy – cytologic diagnosis (n=30)</u> Positive for malignancy: n=11/30. Suspicious for malignancy: n=0/30. Normal cellular elements present, with no evidence of malignancy: n=3/30. Unsatisfactory/inadequate for diagnosis: n=11/30. Benign neoplastic lesions: n=5/30. <u>Intervertebral disc lesions – cytologic diagnosis (n=12)</u> Positive for malignancy: n=0/12. Suspicious for malignancy: n=0/12. Normal cellular elements present, with no evidence of malignancy: n=1/12. Unsatisfactory/inadequate for diagnosis: n=6/12. Benign neoplastic lesions: n=0/12. Acute inflammatory process: n=3/12. Degenerative disc disease: n=2/12. <u>Vertebral and intervertebral disc lesions – comparison of radiologic impression with cytologic diagnosis (n=48)</u> Malignant on radiology (n=9) – malignant on cytology n=7; normal cellular elements with no evidence of malignancy n=2. Indeterminate on radiology (n=30) – malignant on cytology n=13; benign n=6; normal cellular elements with no evidence of malignancy n=4; unsatisfactory/inadequate for diagnosis n=6; suspicious for malignancy n=1. Benign on radiology (n=9) – benign on cytology n=4; normal cellular elements with no evidence of malignancy n=1; unsatisfactory/inadequate for diagnosis n=4.

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(no details of inclusion/ exclusion criteria)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low

Section	Question	Answer
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(limited details of diagnostic criteria used by cytopathologist)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Razek 2009
Razek A, Sherif, F. Diagnostic accuracy of diffusion tensor imaging in differentiating malignant from benign compressed vertebrae. Neuroradiology, 61, 1291-1296, 2019

Study details

Country/ies where study was carried out	Egypt.
Study type	Retrospective cohort study
Study dates	Not reported.
Inclusion criteria	Patients with untreated compressed vertebrae undergoing MRI at a single institution.
Exclusion criteria	Patients whose imaging was of a poor quality.
Patient characteristics	N=45 Patients with untreated compressed vertebrae undergoing MRI Age, mean (SD), years: 56.14 (7.9). Gender [number of male, female]: male n=22; female n=22. Myeloma versus other cancer types [number with myeloma]: Not reported. Functional status/fitness for treatment [percentage who were ambulant]: Not reported.
Index test(s)	MRI – All patients were examined using routine T1- and T2-weighted MR imaging and DTI of the spine.All MR images were performed using a 1.5-Tesla scanner. Images were analysed by two neuroradiologists who were blinded to the clinical presentation and final histopathological results..
Reference standard(s)	• Biopsy result / surgical pathology. Final diagnosis done with biopsy, performed 10 – 18 days after MRI.

Duration of follow-up	Not reported.
Sources of funding	None.
Results	See Appendix L

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Schmeel 2018
Schmeel F, Luetkens J, Feist A, et al. Quantitative evaluation of T2* relaxation times for the differentiation of acute benign and malignant vertebral body fractures. European Journal of Radiology, 108, 59-65, 2018

Study details

Country/ies where study was carried out	Germany.
Study type	Retrospective cohort study
Study dates	February 2015 – March 2018.
Inclusion criteria	Consecutive patients with a suspected acute vertebral compression fracture or known primary malignancy and suspected pathologic vertebral compression fracture. • > 18 years • acute onset of back pain (less than 1 month from admission) • presence of an acute benign (osteoporotic and/or post-traumatic) or malignant vertebral compression fracture as determined on routine clinical spine MRI • histopathologic confirmation of vertebral compression fracture obtained from direct bone biopsy.
Exclusion criteria	• Pregnancy

	• Contraindications to MRI (such as non-MR conditional cardiac pacemaker) • Prior bisphosphonate treatment • metallic instrumentation of the spine segment under investigation.
Patient characteristics	N=37 Consecutive patients with a suspected acute vertebral com-pression fracture or known primary malignancy and suspected pathological vertebral compression fracture. Gender [number of male, female]: male n=17; female n=20. Age, mean (SD), years: 64.8 (16.5) Myeloma versus other cancer types [number with myeloma]: n=7. Functional status/fitness for treatment [percentage who were ambulant]: Not reported. Patients were divided into two groups according to underlying pathology. Group 1 (n=19) patients with acute osteoporotic and/or benign vertebral compression fractures. Diagnosis of benign vertebral compression fractures was established on the basis of direct biopsy and histopathologic con-firmation of bone specimens obtained during vertebroplasty or spinal instrumentation. Group 2 (n=18) patients with neoplastic vertebral compression fractures due to hematological malignancies (n=8) or vertebral metastasis (n=17). Diagnosis of malignant vertebral compression fractures was established on the basis of direct bone biopsy and subsequent histopathological confirmation of bone specimens obtained via CT-guidance, surgery and/or spinal instrumentation.
Index test(s)	MRI - T2*-weighted. All imaging was performed on a clinical 3.0-Tesla whole-body MR imager. Routine clinical MRI of the spine included at least a sagittal T1-weighted spin-echo (450–750/6-12 [repetition time ms (TR)/echo time ms (TE)]) and T2-weighted turbo spin-echo sequence (3000-5000/80-120 [TR/TE]) as well as a sagittal T2 spectral-attenuated-inversion-recovery (SPAIR)-weighted turbo spin-echo sequence (3000-5000/80-120 [TR/TE]).
Reference standard(s)	• Biopsy result / surgical pathology
Duration of follow-up	Not reported.
Sources of funding	None.
Results	See Appendix L

Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low

Section	Question	Answer
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Schmeel 2021
Schmeel F, Enkirch S, Luetkens J, et al. Diagnostic Accuracy of Quantitative Imaging Biomarkers in the Differentiation of Benign and Malignant Vertebral Lesions: Combination of Diffusion-Weighted and Proton Density Fat Fraction Spine MRI. Clinical Neuroradiology, 31, 1059-1070, 2021

Study details

Country/ies where study was carried out	Germany.
Study type	Prospective cohort study
Study dates	June 2018 - September 2019
Inclusion criteria	Consecutive patients with untreated vertebral bone marrow lesions (benign and malignant) undergoing MRI. Presence of at least one vertebral bone marrow lesion with ≥1cm in size as determined on routine clinical spine MRI or at least one of the following indications: • clinically suspected acute vertebral fracture and acute onset of back pain (≤1 month from admission) • suspected osseous metastasis or malignant spine disease • and/or persisting localized back pain without typical discogenic radiation for more than 3 months.
Exclusion criteria	• Contraindication for MRI (such as nonconditional cardiac pacemaker) • previous or concurrent chemotherapy (including angiogenesis inhibitors) and/or radiotherapy • bisphosphonate and/or growth colony-stimulating factor treatment • previous surgery and metallic implants in the spine segment under investigation.
Patient characteristics	N=55 Consecutive patients with untreated vertebral bone marrow lesions (benign and malignant) undergoing MR Age, mean (SD), years: 68 (14) Gender [number of male, female]: male n=25; female n=30. Myeloma versus other cancer types [number with myeloma]: Patients with myeloma were included however the number of patients is not reported. Functional status/fitness for treatment [percentage who were ambulant]: Not reported.

Index test(s)	MRI - sagittal DWI (single-shot spin-echo echo-planar with multi-slice short TI inversion recovery fat suppression) and CSE-based MRI (gradient-echo 6-point modified Dixon) in addition to routine clinical spine MRI at 1.5T or 3.0T.
Reference standard(s)	• Biopsy result / surgical pathology • Clinical and radiological follow up (if no surgery/biopsy done)
Duration of follow-up	≥ 6 months.
Sources of funding	Not reported.
Results	See Appendix L

Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Shi 2017

Shi Y, Li X, Zhang X, et al. Differential diagnosis of hemangiomas from spinal osteolytic metastases using 3.0 T MRI: comparison of T1-weighted imaging, chemical-shift imaging, diffusion-weighted and contrast-enhanced imaging. Oncotarget, 8, 71095-71104, 2017

Study details

Country/ies where study was carried out	China.
Study type	Retrospective cohort study
Study dates	October 2013 - November 2015.
Inclusion criteria	• history of primary malignancy confirmed by needle biopsy or pathological examination following surgery • patients with spinal lesions who underwent conventional MRI at 3T as well as DWI with ADC values, chemical-shift imaging, and contrast-enhanced imaging

	• CT scanning on the corresponding vertebrae • ≥ 6 months follow-up with either MR or CT imaging • No radiation and chemotherapy history.
Exclusion criteria	• spinal lesions complicated with fracture • lesions without a complete MRI examination • lesions of osteoblastic metastases.
Patient characteristics	N=53 Consecutive patients with spinal haemangiomas or cancer patients with spinal metastases Spinal haemangioma group (n=27): n=33 lesions Age, mean (SD), years: 60.62 (8.23). Gender [number of male, female]: male n=16; female n=11. Myeloma versus other cancer types [percentage with myeloma]: NA. Functional status/fitness for treatment [percentage who were ambulant]: Not reported. Cancer group (n=26) n=71 lesions Age, mean (SD), years: 54.33 (10.66). Gender [number of male, female]: male n=9; female n=17. Myeloma versus other cancer types [number with myeloma]: 0/26. Functional status/fitness for treatment [percentage who were ambulant]: Not reported.
Index test(s)	MRI - T1-weighted imaging with and without fat suppression, chemical-shift, diffusion-weighted imaging, and enhanced imaging at 3.0 T MRI.
Reference standard(s)	• Biopsy result / surgical pathology • Clinical and radiological follow up (if no surgery/biopsy done) of at least 6 months
Duration of follow-up	6 – 24 months.
Sources of funding	• National Natural Science Foundation of China (Grant No.81471640) • National Natural Science Foundation of China (Grant No. 81371715) • Beijing Health System High Level Health • Technical Personnel Training Plan (No. 2013-3-083).
Results	See Appendix L

Critical appraisal - QUADAS-2

Section	Question	Answer

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low.
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Spinnato 2018
Spinnato P, Bazzocchi A, Facchini G, et al. Vertebral Fractures of Unknown Origin: Role of Computed Tomography-Guided Biopsy. International Journal of Spine Surgery, 12, 673-679, 2018

Study details

Country/ies where study was carried out	Italy.
Study type	Retrospective cohort study
Study dates	Not reported.
Inclusion criteria	Patients with 1 or more non-traumatic vertebral fracture of unknown aetiology.
Exclusion criteria	Not reported.
Patient characteristics	N=32 Patients undergoing CT guided biopsy for vertebral fractures of unknown origin Age, mean (SD), years: 57.1 (23.3). NB included paediatric patients: 5/32 were under 10 years of age. Not reported how many were younger than 16. Gender [number of male, female]: male n=13; female n=19. Myeloma versus other cancer types [number with myeloma]: Not reported. Functional status/fitness for treatment [percentage who were ambulant]: Not reported.
Index test(s)	CT guided biopsy.
Reference standard(s)	Histopathologist’s assessment of sample adequacy and diagnosis.
Duration of follow-up	Not reported.
Sources of funding	Not reported.
Results	Biopsy specimen of diagnostic standard n=26/32 (Osteopenia n=8/26; multiple myeloma lesions n=6/26; oste-

	omyelitis n=4/26; eosinophilic granuloma n=2/26; lung cancer metastases n=2/26; kidney cancer metastasis n=1/26; mastocytosis n=1/26; Paget's disease n=1/26; dysmielopoiesis secondary to a specific systemic disease n=1/26). Need for second biopsy n=4/32. Complication rate n=0/32.

Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High. *Included paediatric patients: 5/32 were under 10 years of age. Not reported how many were younger than 16..*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(No detail on criteria for sample adequacy or histopathology criteria)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Suh 2018
Suh C, Yun S, Jin W, et al. Diagnostic Performance of In-Phase and Opposed-Phase Chemical-Shift Imaging for Differentiating Benign and Malignant Vertebral Marrow Lesions: A Meta-Analysis. American Journal of Roentgenology 211, W1-W10, 2018

Study details

Country/ies where study was carried out	South Korea
Study type	Systematic review of diagnostic accuracy studies
Study dates	October 2017

Inclusion criteria	Studies in patients with vertebral BMLs or VCFs where MRI was used to differentiate between benign and malignant, histo-pathologic result or best-value comparator used as reference standard, an original article and enough data to make a 2x2 table
Exclusion criteria	Case reports or case series; review articles, guidelines, consensus statements, letters, editorials, clinical trials and conference abstracts; studies where opposed-phase images were the index test; studies with insufficient data and studies with overlapping populations
Patient characteristics	N=591 in 12 studies Age, mean, years (SD): ranged from 45 to 68 across studies, SD not reported Sex: female n=293; male n=277 (where reported in 11 studies). Myeloma versus other cancer types [number with myeloma]: Not reported. Functional status/fitness for treatment [percentage who were ambulant]: Not reported.
Index test(s)	MRI chemical shift imaging
Reference standard(s)	Histopathologic result of biopsy or surgery or best-value comparator (for example clinical or radiological follow-up)
Duration of follow-up	Ranged from 1 to 20 months
Sources of funding	Not reported
Results	See Appendix L
Other information	8/12 included studies were prospective, 4/12 retrospective. Risk of bias assessed using QUADAS 2. 2/12 studies were at high risk of bias due to exclusion criteria and pre-designated cut-off value respectively – others at low risk of bias.

Critical appraisal - ROBIS checklist

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Concerns regarding the synthesis and findings	Low
Overall study ratings	Overall risk of bias	Low
Overall study ratings	Applicability as a source of data	Fully applicable

Taheri 2017

Taheri M, Mirzaei H, Shahhamzei S, et al. Comparison of chemical shift MR imaging findings between vertebral benign and metastatic lesions. International Journal of Cancer Management 10, e8661, 2017

Study details	
Country/ies where study was carried out	Iran.
Study type	Prospective cohort study
Study dates	2010 - 2012.
Inclusion criteria	Patients with vertebral focal lesions referred for routine MR imaging of the spine at a single institution (cervical, thoracic, lumbosacral imaging or any combination) • vertebral lesions with abnormal SI on conventional MRI or bone nuclear scan • previous history of malignancy and vertebral lesion • known metastatic vertebral lesions and new onset of acute back pain and tenderness over vertebral column) (less than 20 days).
Exclusion criteria	• Patients who had received radiotherapy. • Patients for whom adequate follow-up or documentation could not be obtained were excluded from the analysis.
Patient characteristics	N=51 Patients with vertebral focal lesions referred for routine MR imaging n=116 vertebral focal lesions Age, mean (SD), years: 52.61 (13.52) Gender [number of male, female]: male n=28; female n=23. Myeloma versus other cancer types [percentage with myeloma]: Not reported. Functional status/fitness for treatment [percentage who were ambulant]: Not reported.
Index test(s)	MRI - dual-phase chemical shift MRI. MR imaging was performed for all patients using a 1.5-Tesla superconducting system. Also a phased array spine coil was used. The following pulse sequences were used for all patients: sagittal T1-weighted spin-echo (400-700/8-16 [repetition time (TR) msec/echo time (TE) msec]), sagittal T2-weighted fast spin-echo (TR/TE 2000-5000/80-100) fast multi-planar spoiled gradient-echo MR imaging. Chemical shift sequences for sagittal IP were obtained at RT/ET 100-165/4.2 and OP 100-165/2.4 with breath holding. The flip angle was 30°. For chemical shift MR imaging, the total imaging time was 40 - 50 seconds for the entire pulse sequence. Sagittal images with a 4-mm section thickness and a 1- mm section gap were obtained for all sequences. The field of view was 20 cm for cervical vertebrae, 34 cm for thoracic vertebrae, and 24 cm for lumbosacral vertebrae. The matrix was 256 - 192.
Reference standard(s)	• Biopsy result / surgical pathology • Clinical and radiological follow up (if no surgery/biopsy done) On the basis of final clinical diagnosis after follow-up, vertebral lesions were classified as either benign focal lesions or malignant lesions. Final diagnosis of malignant lesions was proved by biopsy in 27 lesions, 49 of them had known underlying malignancy and metastatic vertebral lesion and in 11 cases diagnosis was based on clinical basis.
Duration of follow-up	6 - 12 months.
Sources of funding	National Foundation of Iranian Elites, Tehran, Iran No. 15/3012 dated 22/7/1389 (14 October 2010).

Results	See Appendix L.

Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Zafar 2020
Zafar U, Malik A, Shahzad I, et al. Diagnostic accuracy of qualitative diffusion weighted MRI of spine in differentiating between benign and malignant vertebral fractures taking histopathology as gold standard. Pakistan Journal of Medical and Health Sciences 14, 390-392, 2020

Study details

Country/ies where study was carried out	Pakistan.
Study type	Prospective cohort study
Study dates	July 2016 - June 2017.
Inclusion criteria	• Patients with vertebral fractures on digital x ray of spine showing decreased vertebral body height, reduced disc intervertebral disc space or collapsed vertebra (reported by radiologist) • Aged between 16 and 60 years
Exclusion criteria	• Patients with history of caries spine • Patients with claustrophobia • Patients with prosthesis/metal implants.
Patient characteristics	N=280 Patients with vertebral fractures on digital x ray of spine showing decreased vertebral body height, reduced disc intervertebral disc space or collapsed vertebra referred for diffusion weighted magnetic resonance imaging Age, mean (SD), years: 42.61 (11.79). Gender [number of male, female]: male n=156; female n=124.

	Myeloma versus other cancer types [percentage with myeloma]: Not reported. Functional status/fitness for treatment [percentage who were ambulant]: Not reported.
Index test(s)	MRI - Plain and diffusion weighted imaging with a 1.5-T MR unit and a spine-array surface coil. The conventional MR imaging protocols included a sagittal T1- weighted turbo spin-echo sequence, sagittal T2- weighted turbo spin-echo sequences with and without fat suppression, and an axial T2-weighted turbo spin-echo sequence. An axial T1- weighted turbo spin-echo sequence and axial and sagittal fat-suppressed contrast material–enhanced T1-weighted sequences was performed. A single consultant radiologist reported the vertebral fracture as benign or malignant lesion without prior knowledge of biopsy results. Data was collected on structured proforma.
Reference stand-ard(s)	• Biopsy result / surgical pathology
Duration of follow-up	Not reported.
Sources of funding	Not reported.
Results	See Appendix L.

Critical appraisal - QUADAS-2

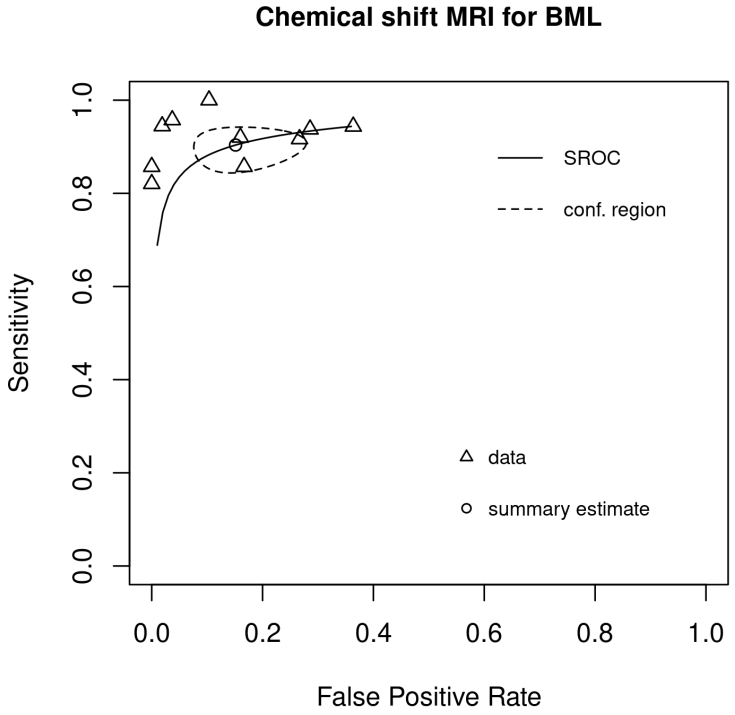
Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Appendix E Forest plots

Forest plots for review question: How effective are radiological imaging techniques in the diagnosis of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

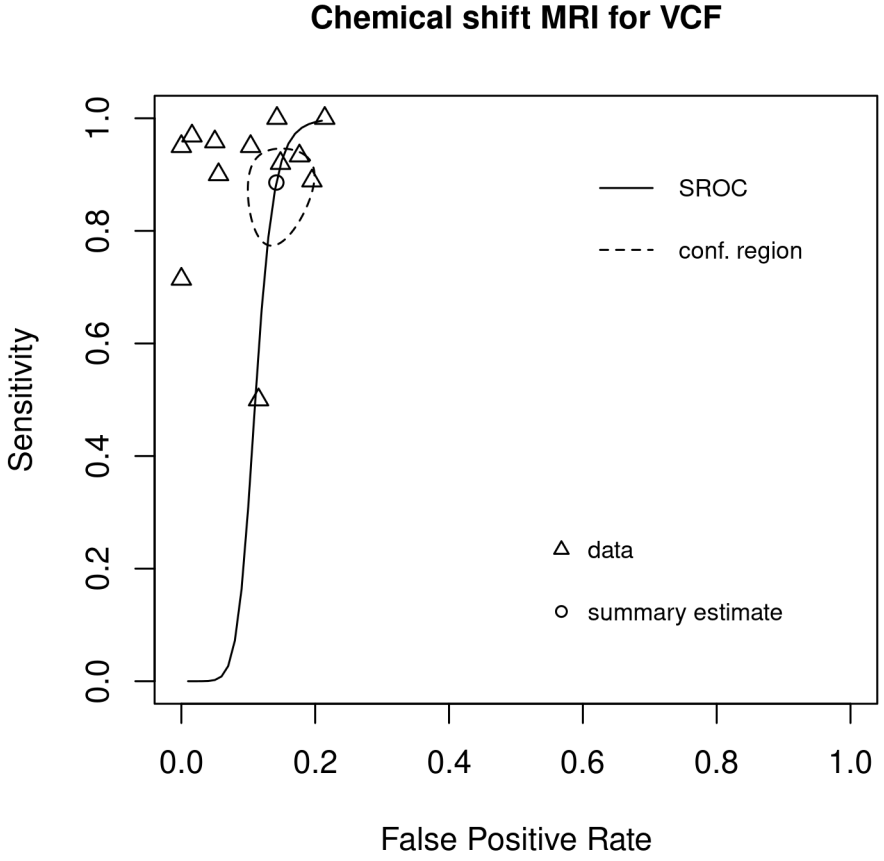
This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Figure 2: Chemical shift MRI for differential diagnosis of malignant and non-malignant vertebral bone marrow lesions



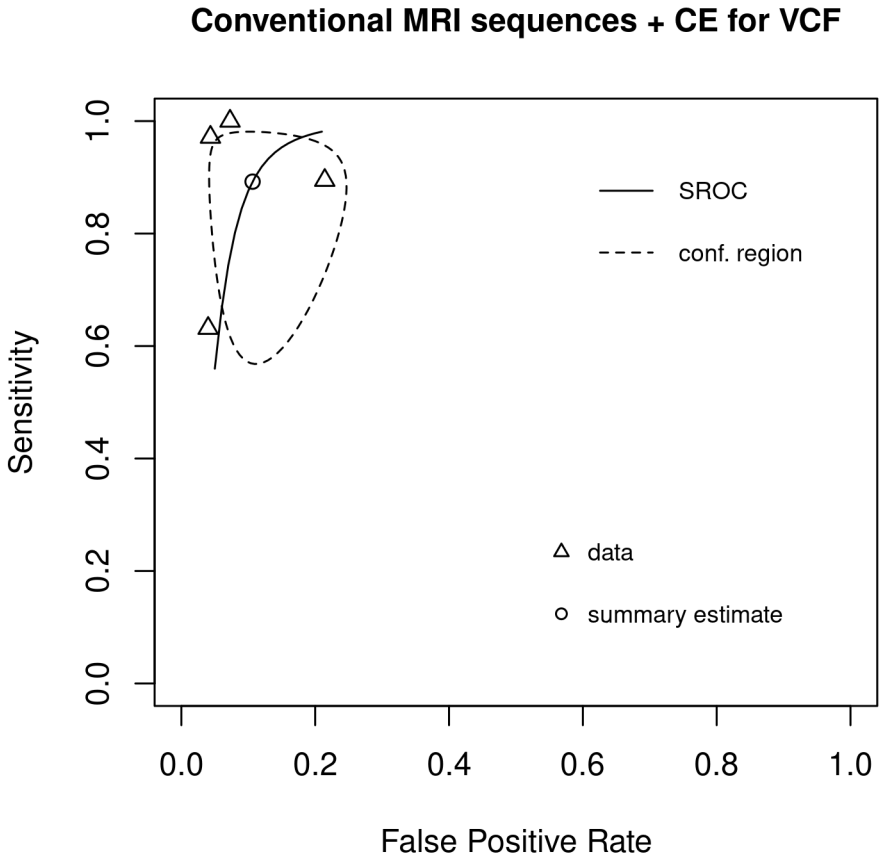
BML: bone marrow lesions; SROC: summary receiver operating characteristic curve

Figure 3: Chemical shift MRI for differential diagnosis of malignant and non-malignant vertebral compression fractures



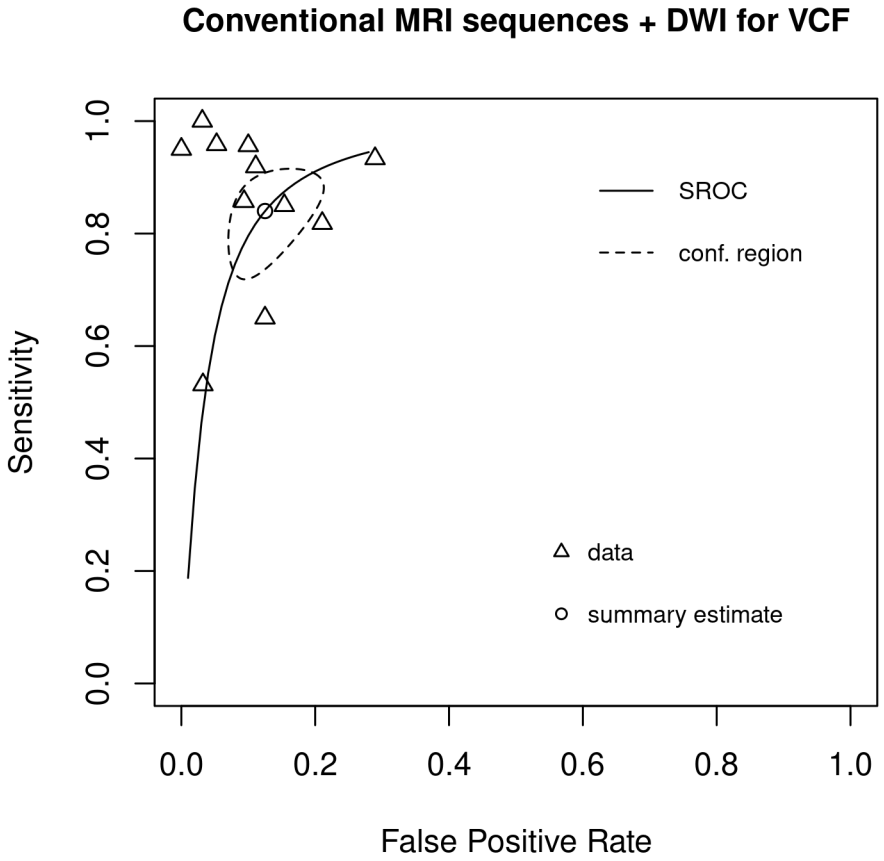
SROC: summary receiver operating characteristic curve; VCF: vertebral compression fractures

Figure 4: Conventional MRI sequences plus contrast enhanced MRI for differential diagnosis of malignant and non-malignant vertebral compression fractures



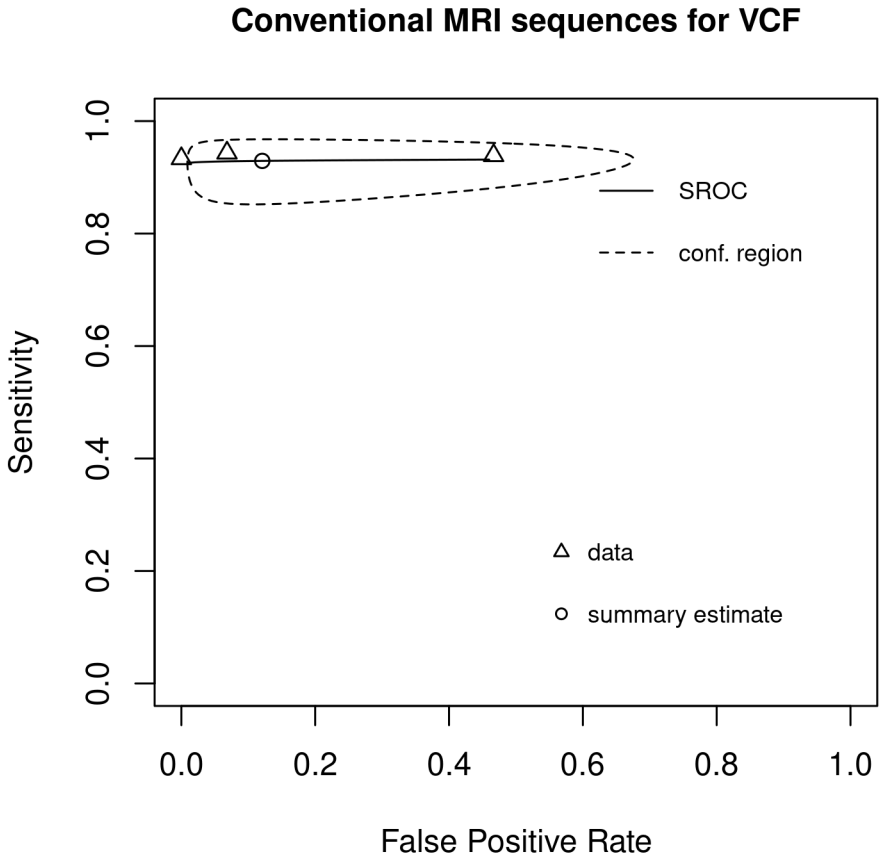
CE: contrast enhanced; SROC: summary receiver operating characteristic curve; VCF: vertebral compression fractures

Figure 5: Conventional MRI sequences plus diffusion weighted imaging for differential diagnosis of malignant and non-malignant vertebral compression fractures



DWI: diffusion weighted imaging; SROC: summary receiver operating characteristic curve; VCF: vertebral compression fractures

Figure 6: Conventional MRI sequences for differential diagnosis of malignant and non-malignant vertebral compression fractures



SROC: summary receiver operating characteristic curve; VCF: vertebral compression fractures

Appendix F GRADE and modified GRADE tables

GRADE tables for review question: How effective are radiological imaging techniques in the diagnosis of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Table 4: Evidence profile for screening spinal MRI in people at high risk of metastatic spinal cord compression

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consid-erations	Screening spinal MRI	Control	Relative (95% CI)	Absolute		
Overall survival (event is death from any cause; maximum follow-up 36 months in survivors)												
Dearnaley 2022	randomised trials	no serious risk of bias	no serious in-consistency	no serious indirectness	serious[1]	none	172/210 (84%)	174/210 (56.9%)	Adj. HR 0.98 (0.79 to 1.21)[3]	not estimable	MODERATE	CRITICAL
Neurological and functional status - clinical spinal cord compression (follow-up 24 months)												
Dearnaley 2022	randomised trials	no serious risk of bias	no serious in-consistency	no serious indirectness	serious[1]	none	19/210 (9.2%)	26/210 (12.6%)	Adj. HR 0.61 (0.35 to 1.08)[3]	not estimable	MODERATE	CRITICAL
Neurological and functional status - persistent neurological functional deficit (Frankel score A-D; follow-up 24 months)												
Dearnaley 2022	randomised trials	no serious risk of bias	no serious in-consistency	no serious indirectness	very serious[2]	none	15/210	23/210	RR 0.73 (0.42 to 1.28)	30 fewer per 1000 (from 64 fewer to 31 more)	LOW	CRITICAL
Quality of life - EQ-5D-5L – health state today (range 0 to 100, higher scores are better; change from baseline to 12 months)												
Dearnaley 2022	randomised trials	no serious risk of bias	no serious in-consistency	no serious indirectness	no serious imprecision	none	112	121	not estimable	-1.5 (-5.7 to 2.7)	HIGH	CRITICAL
Pain - Brief Pain Index – severity (range 0 to 10, lower scores are better; change from baseline to 12 months)												
Dearnaley 2022	randomised trials	no serious risk of bias	no serious in-consistency	no serious indirectness	no serious imprecision	none	107	111	not estimable	0.4 (-0.2 to 0.9)	HIGH	CRITICAL

Adj: adjusted; CI: confidence interval; HR: hazard ratio; RT: radiotherapy.
1 95% CI crosses 1 MID
2 95% CI crosses 2 MIDs
3 Adjusted for time since development of castration-resistant prostate cancer, time since start of continuous hormone treatment, ECOG performance status (0, 1, and 2), and natural logarithm of PSA concentration.

Table 5: Evidence profile for early MRI referral in people with suspected metastatic spinal cord compression

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early MRI referral (MSCC hotline)	Usual care	Relative (95% CI)	Absolute		
Neurological and functional status - ambulant at MSCC diagnosis												
Allan 2009	Cohort study	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	34/44 (77%)	175/324 (54%)	RR 1.43 (1.18 to 1.73)	232 more per 1,000 (from 97 more to 394 more)	VERY LOW	CRITICAL
Time to treatment - time from referral to diagnosis of MSCC, days, median (IQR)												
Allan 2009	Cohort study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	N=44 (median 1 day [0 to 21])	N=324 (median 15 days [3 to 66])	Not estimable	Median 14 fewer days (P<0.002)	LOW	IMPORTANT

CI: confidence interval; MSCC: malignant spinal cord compression; RR: risk ratio
1 Very serious risk of bias as per ROBINS-I
2. 95% CI crosses 1 MID

Table 6: Evidence profile: tests for differential diagnosis of malignant and non-malignant vertebral bone marrow lesions

No. of studies	Study design	Sample size	Prevalence of malignant BML (%)	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratios (95% CI)	Predictive values (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
Diagnostic accuracy of Chemical Shift MRI													
10[1]	Cohort studies	788	Range 21 to 78	0.90 [0.86–0.94]	0.85 [0.75–0.91]	LR+ 6.22 [3.63–10.30]	PPV 90% (78% to 96%)	Not serious	Not serious	Not serious	Serious[2]	MODERATE	CRITICAL
						LR- 0.12 [0.08–0.17]	NPV 89% (83% to 93%)				Not serious	HIGH	

BML: bone marrow lesions; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value
1 Douis 2016, El-Samie 2015, Kim 2014, Maeder 2018, Perry 2018, Rathore 2017, Schmeel 2021, Shi 2017, Tadros 2016, Taheri 2017
2 95% CI of LR+ crosses 1 default MID (2, 5)

Table 7: Evidence profile: tests for differential diagnosis of malignant and non-malignant vertebral compression fractures

No. of studies	Study design	Sample size	Prevalence of malig-nant VCF (%)	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratios (95% CI)	Predictive values (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[9]	Quality	Importance
Diagnostic accuracy – FDG-PET or FDG-PET CT													
5[1]	Cohort studies	274	Range 34 to 71	0.96 [0.82–0.99]	0.77 [0.56–0.89]	LR+ 4.1 [2.1–8.0]	not estimable	Not serious	Serious[2]	Not serious	Serious[3]	LOW	CRITICAL
						LR- 0.05 [0.01–0.23]	not estimable				Serious[4]	LOW	
Diagnostic accuracy – chemical Shift MRI													
12[5]	Cohort studies	690	Range 28 to 55	0.89 [0.80–0.94]	0.86 [0.81–0.89]	LR+ 6.28 [7.83–26.88]	PPV 84% (78% to 88%)	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
						LR- 0.14 [0.07–0.23]	NPV 92% (85% to 95%)				Serious[3]	MODERATE	
Diagnostic accuracy –conventional MRI sequences + contrast enhanced MRI													
4[6]	Cohort studies	231	Range 33 to 60	0.89 [0.66–0.97]	0.89 [0.79–0.95]	LR+ 8.85 [3.9–17.70]	PPV 88% (73% to 95%)	Not serious	Not serious	Not serious	Serious[3]	MODERATE	CRITICAL
						LR- 0.15 [0.03–0.39]	NPV 92% (76% to 98%)				Serious[4]	MODERATE	
Diagnostic accuracy –conventional MRI sequences + diffusion weighted imaging													
11[7]	Cohort studies	782	Range 11 to 70	0.84 [0.75–0.90]	0.88 [0.81–0.92]	LR+ 6.85 [4.49–10.20]	PPV 86% (77% to 91%)	Not serious	Not serious	Not serious	Serious[3]	MODERATE	CRITICAL
						LR- 0.19 [0.11–0.28]	NPV 89% (83% to 94%)				Serious[4]	MODERATE	
Diagnostic accuracy – conventional MRI sequences													
3[7]	Cohort studies	221	Range 50 to 77	0.93 [0.87–0.96]	0.88 [0.45–0.99]	LR+ 13.4 [1.69–60.00]	PPV 92% (82% to 97%)	Not serious	Serious[2]	Not serious	Very serious[8]	VERY LOW	CRITICAL
						LR- 0.09 [0.04–0.19]	NPV 89% (73% to 96%)				Not serious	MODERATE	

CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; VCF: vertebral compression fractures

1 Aggarwal 2013, Bredella 2008, Cho 2011, He 2018, Shin 2008 (reported in Kim 2020 systematic review – the results are taken directly from Kim 2020 and were not updated, so there is no Forest plot)

2 Serious heterogeneity unexplained by subgroup analysis

3 95% CI of LR+ crosses 1 default MID (2, 5)
4 95% CI of LR- crosses 1 default MID (0.2, 0.5)
5 Bacher 2021, Erly 2006, Geith 2012, Kim 2017, Mittal 2016, Ogura 2012, Ovali 2017, Ragab 2009, Schmeel 2018, Zampa 2002, Zidan 2014
6 Arvelo-Perez 2015, Geith 2013, Jung 2003, Pongorsop 2009
7 Bhugaloo 2006, Biffar 2010, Biffar 2011, Geith 2014, Mubarak 2011, Oztekin 2009, Pozzi 2012, Razek 2019, Sung 2014, Wonglaksanapimon 2012, Zafar 2020
7 Kato 2015, Tokuda 2011, Zou 2016
8 95% CI of LR+ crosses 2 default MIDs (2, 5)
9 Precision estimates based separately on LR+ and LR-

Table 8: Evidence profile: tests for diagnosis of metastatic spinal cord compression

No. of studies	Study design	Sample size	Prevalence of MSCC (%)	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratios (95% CI)	Predictive values (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
Diagnostic accuracy – plain radiograph plus neurological examination													
Husband 2001	Cohort study	280	72	0.44 [0.37–0.51]	0.98 [0.91–1.00]	LR+ 19.70 [4.96–78.24]	PPV 98% (92% to 99%)	Not serious	NA	Serious[1]	Serious[2]	LOW	CRITICAL
						LR- 0.57 [0.50–0.66]	NPV 44% (41% to 47%)				Serious[3]	LOW	
Diagnostic accuracy – T1-weighted sagittal MRI images													
Kim 2000	Cohort study	57	23	0.71 [0.59–0.79]	0.97 [0.94–0.98]	LR+ 20.29 [10.87-37.86]	Not esti-mable	Very serious[2]	NA	Not serious	Not serious	LOW	CRITICAL
						LR- 0.31 [0.22–0.42]	Not esti-mable				Not serious	LOW	

CI: confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio; MSCC: metastatic spinal cord compression; NPV, negative predictive value; PPV, positive predictive value
1 Index test is seriously indirect – composite of X-ray and neurological examination
2 95% CI of LR+ crosses 1 default MID (2, 5)
3 95% CI of LR- crosses 1 default MID (0.2, 0.5)
2 Very serious risk of bias per QUADAS-2

Table 9: Evidence profile: CT guided biopsy of suspected malignant spinal lesions

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Diagnostic yield	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
Test failure/success: diagnostic yield of CT-guided biopsy (proportion of biopsies providing sufficient material to make diagnosis)											

3[1]	Cohort stud-ie	150	Not reported	Not reported	Median 89% (range 81% to 99%)	Serious[2]	Very serious[3]	Not serious	Serious[4]	VERY LOW	IMPORTANT

CI: confidence interval; CT: computed tomography
1 Laufer 2009, Phadke 2001, Spinnato 2018
2 Serious risk of bias per QUADAS-2
3 Very serious heterogeneity unexplained by subgroup analysis
4 Sample size < 300

Appendix G Economic evidence study selection

Study selection for: How effective are radiological imaging techniques in the diagnosis of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

No economic evidence was identified which was applicable to this review question.

Appendix H Economic evidence tables

Economic evidence tables for review question: How effective are radiological imaging techniques in the diagnosis of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: How effective are radiological imaging techniques in the diagnosis of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: How effective are radiological imaging techniques in the diagnosis of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Excluded diagnostic studies

Table 10: Excluded studies and reasons for their exclusion

Study	Exclusion reason
Abdel-Wanis, M E; Solyman, Mohamed Tharwat Mahmoud; Hasan, Nahla Mohamed Ali (2011) Sensitivity, specificity and accuracy of magnetic resonance imaging for differentiating vertebral compression fractures caused by malignancy, osteoporosis, and infections. Journal of orthopaedic surgery (Hong Kong) 19(2): 145-50	Outcomes do not match review protocol
Abdullayev, N, Grose Hokamp, N, Lennartz, S et al. (2019) Improvements of diagnostic accuracy and visualization of vertebral metastasis using multi-level virtual non-calcium reconstructions from dual-layer spectral detector computed tomography. European radiology 29(11): 5941-5949	Index test - does not match review protocol
Abedi, S.M.; Mardanshahi, A.; Zeanali, R. (2021) Added diagnostic value of SPECT to evaluate bone metastases in breast cancer patients with normal whole body bone scan. Caspian Journal of Internal Medicine 12(3): 290-293	Population - does not match review protocol
Abikhzer, G., Srour, S., Fried, G. et al. (2016) Prospective comparison of whole-body bone SPECT and sodium 18F-fluoride PET in the detection of bone metastases from breast cancer. Nuclear Medicine Communications 37(11): 1160-1168	Population - does not match review protocol
Abrahm, J.L. (2004) Assessment and treatment of patients with malignant spinal cord compression. Journal of Supportive Oncology 2(5): 377-391	Study design - does not match review protocol
Adamova, Blanka, Bednarik, Josef, Andrasinova, Tereza et al. (2015) Does lumbar spinal stenosis increase the risk of spondylotic cervical spinal cord compression? 24(12): 2946-53	Population - does not match review protocol
Adams, S, Baum, R P, Stuckensen, T et al. (1998) Prospective comparison of 18F-FDG PET with conventional imaging modalities (CT, MRI, US) in lymph node staging of head and neck cancer. European journal of nuclear medicine 25(9): 1255-60	Population - does not match review protocol
Adogwa, Owoicho, Rubio, Daniel R, Buchowski, Jacob M et al. (2022) Spine-specific skeletal related events and mortality in non-small cell lung cancer patients: a single-institution analysis. Journal of neurosurgery. Spine 36(1): 125-132	Index test - does not match review protocol
Aggarwal, Ashish, Salunke, Pravin, Shekhar, Bala Raja et al. (2013) The role of magnetic resonance imaging and positron emission tomography-computed tomography combined in differentiating benign from malignant lesions contributing to vertebral compression fractures. Surgical neurology international 4(suppl5): 323-6	Other protocol criteria - study reported in an included systematic review (Kim 2020)
Ahn, Ji Eun, Lee, Jeong Hyun, Yi, Jong Sook et al. (2008) Diagnostic accuracy of CT and ultrasonography for evaluating metastatic cervical lymph nodes in patients with thyroid cancer. World journal of surgery 32(7): 1552-8	Population - does not match review protocol
Algra, P R, Bloem, J L, Tissing, H et al. (1991) Detection of vertebral metastases: comparison between MR imaging and bone scintigraphy.	Outcomes - do not match review protocol

Study	Exclusion reason
Radiographics: a review publication of the Radiological Society of North America, Inc 11(2): 219-32	
Alkalay, Ron N, Groff, Michael W, Stadelmann, Marc A et al. (2022) Improved estimates of strength and stiffness in pathologic vertebrae with bone metastases using CT-derived bone density compared with radiographic bone lesion quality classification. Journal of neurosurgery. Spine 36(1): 113-124	Population - does not match review protocol
Altehoefer, C, Ghanem, N, Hogerle, S et al. (2001) Comparative detectability of bone metastases and impact on therapy of magnetic resonance imaging and bone scintigraphy in patients with breast cancer. European journal of radiology 40(1): 16-23	Population - does not match review protocol
Ambrosini, Valentina, Nanni, Cristina, Zompatori, Maurizio et al. (2010) (68)Ga-DOTA-NOC PET/CT in comparison with CT for the detection of bone metastasis in patients with neuroendocrine tumours. European journal of nuclear medicine and molecular imaging 37(4): 722-7	Population - does not match review protocol
An, H S, Vaccaro, A R, Dolinskas, C A et al. (1991) Differentiation between spinal tumors and infections with magnetic resonance imaging. Spine 16(8suppl): 334-8	Other protocol criteria - study reported in an included systematic review (Thawait 2012)
Anatol'Evich Byvaltsev, V.; Stepanov, I.A.; Kichigin, A.I. (2019) The role of diffusion-weighted MRI of patients with spine metastases. Coluna/ Columna 18(4): 289-293	Outcomes – do not match review protocol
Andreasson, I, Petren-Mallmin, M, Strang, P et al. (1990) Diagnostic methods in planning palliation of spinal metastases. Anticancer research 10(3): 731-3	Outcomes - do not match review protocol
Anonymous. (2022) Correction to Lancet Oncol 2022; 23: 501-13 (The Lancet Oncology (2022) 23(4) (501-513), (S1470204522000924), (10.1016/S1470-2045(22)00092-4)). The Lancet Oncology 23(4): e161	Study design - does not match review protocol
Arevalo-Perez, Julio, Peck, Kyung K, Lyo, John K et al. (2015) Differentiating benign from malignant vertebral fractures using T1 -weighted dynamic contrast-enhanced MRI. Journal of magnetic resonance imaging : JMRI 42(4): 1039-47	Other protocol criteria - study reported in an included systematic review (Li 2019)
Asa, Sertac, Sonmezoglu, Kerim, Uslu-Besli, Lebriz et al. (2021) Evaluation of F-18 DOPA PET/CT in the detection of recurrent or metastatic medullary thyroid carcinoma: comparison with GA-68 DOTA-TATE PET/CT. Annals of nuclear medicine 35(8): 900-915	Population - does not match review protocol
Asilturk, Murad; Abdallah, Anas; Sofuoglu, Erhan Ozden (2020) Radiologic-Histopathologic Correlation of Adult Spinal Tumors: A Retrospective Study. Asian journal of neurosurgery 15(2): 354-362	Population - does not match review protocol
Baker, L L, Goodman, S B, Perkash, I et al. (1990) Benign versus pathologic compression fractures of vertebral bodies: assessment with conventional spin-echo, chemical-shift, and STIR MR imaging. Radiology 174(2): 495-502	Other protocol criteria - study reported in an included systematic review (Thawait 2012)
Baleriaux, D; Matos, C; De Greef, D (1993) Gadodiamide injection as a contrast medium for MRI of the central nervous system: a comparison with gadolinium-DOTA. Neuroradiology 35(7): 490-4	Comparator - does not match review protocol
Balliu, E, Vilanova, J C, Pelaez, I et al. (2009) Diagnostic value of apparent diffusion coefficients to differentiate benign from malignant vertebral bone marrow lesions. European journal of radiology 69(3): 560-6	Other protocol criteria - study reported in an included systematic review (Thawait 2012)
Balogova, Sona, Zakoun, Joseph Ben, Michaud, Laure et al. (2014) Whole-body 18F-fluorocholine (FCH) PET/CT and MRI of the spine for monitoring patients with castration-resistant prostate cancer metastatic to bone: a pilot study. Clinical nuclear medicine 39(11): 951-9	Outcomes - do not match review protocol
Baur, A, Huber, A, Ertl-Wagner, B et al. (2001) Diagnostic value of in-	Other protocol criteria -

Study	Exclusion reason
creased diffusion weighting of a steady-state free precession sequence for differentiating acute benign osteoporotic fractures from pathologic vertebral compression fractures. AJNR. American journal of neuroradiology 22(2): 366-72	study reported in an included systematic review (Thawait 2012)
Baur, A, Stabler, A, Bruning, R et al. (1998) Diffusion-weighted MR imaging of bone marrow: differentiation of benign versus pathologic compression fractures. Radiology 207(2): 349-56	Other protocol criteria - study reported in an included systematic review (Thawait 2012)
Baur, Andrea, Stabler, Axel, Arbogast, Susanne et al. (2002) Acute osteoporotic and neoplastic vertebral compression fractures: fluid sign at MR imaging. Radiology 225(3): 730-5	Other protocol criteria - study reported in an included systematic review
Bazzocchi, Alberto, Spinnato, Paolo, Garzillo, Giorgio et al. (2012) Detection of incidental vertebral fractures in breast imaging: the potential role of MR localisers. European radiology 22(12): 2617-23	Population – does not match protocol
Beeler, Whitney H, Paradis, Kelly C, Gemmete, Joseph J et al. (2019) Computed Tomography Myelosimulation Versus Magnetic Resonance Imaging Registration to Delineate the Spinal Cord During Spine Stereotactic Radiosurgery. World neurosurgery 122: e655-e666	Index test – does not match protocol
Bhugaloo, Aa, Abdullah, Bjj, Siow, Ys et al. (2006) Diffusion weighted MR imaging in acute vertebral compression fractures: differentiation between malignant and benign causes. Biomedical imaging and intervention journal 2(2): e12	Other protocol criteria - study reported in an included systematic review (Liu 2019)
Bierry, Guillaume, Venkatasamy, Aina, Kremer, Stephane et al. (2014) Dual-energy CT in vertebral compression fractures: performance of visual and quantitative analysis for bone marrow edema demonstration with comparison to MRI. Skeletal radiology 43(4): 485-92	Population – does not match protocol
Boesen, J, Johnsen, A, Helweg-Larsen, S et al. (1991) Diagnostic value of spinal computer tomography in patients with intraspinal metastases causing complete block on myelography. Acta radiologica (Stockholm, Sweden : 1987) 32(1): 1-2	Outcomes – do not match protocol
Bohdiewicz, Paul J, Wong, Ching-Yee O, Kondas, David et al. (2003) High predictive value of F-18 FDG PET patterns of the spine for metastases or benign lesions with good agreement between readers. Clinical nuclear medicine 28(12): 966-70	Outcomes – do not match protocol
Bohuslavizki, K.H., Klutmann, S., Buchert, R. et al. (1999) Value of F-18-FOG PET in patients with cervical lymph node metastases of unknown origin. Radiology and Oncology 33(3): 207-213	Population – does not match protocol
Boker, Sarah M, Adams, Lisa C, Bender, Yvonne Y et al. (2019) Differentiation of Predominantly Osteoblastic and Osteolytic Spine Metastases by Using Susceptibility-weighted MRI. Radiology 290(1): 146-154	Comparator – does not match protocol
Boogerd, W. and Kroger, R. (1991) Intravenous contrast in spinal computed tomography to identify epidural metastases. Clinical Neurology and Neurosurgery 93(3): 195-199	Outcomes – do not match protocol
Boogerd, W; van der Sande, J J; Kroger, R (1992) Early diagnosis and treatment of spinal epidural metastasis in breast cancer: a prospective study. Journal of neurology, neurosurgery, and psychiatry 55(12): 1188-93	Outcomes – do not match protocol
Borggrefe, Jan, Neuhaus, Victor-Frederic, Le Blanc, Markus et al. (2019) Accuracy of iodine density thresholds for the separation of vertebral bone metastases from healthy-appearing trabecular bone in spectral detector computed tomography. European radiology 29(6): 3253-3261	Index test – does not match protocol
Bredella, Miriam A, Essary, Brendan, Torriani, Martin et al. (2008) Use of FDG-PET in differentiating benign from malignant compression fractures. Skeletal radiology 37(5): 405-13	Other protocol criteria - study reported in an included systematic review

Study	Exclusion reason
	(Kim 2020)
Brunner, P., Chanalet, S., Sedat, J. et al. (2002) Percutaneous infiltrations of cervical, thoracic, and lumbar spine. Seminars in Interventional Radiology 19(3): 219-228	Intervention – does not match protocol
Buhmann Kirchhoff, Sonja, Becker, Christoph, Duerr, Hans Roland et al. (2009) Detection of osseous metastases of the spine: comparison of high resolution multi-detector-CT with MRI. European journal of radiology 69(3): 567-73	Population – does not match protocol - unclear how patients were identified for the study
Burns, Joseph E, Yao, Jianhua, Wiese, Tatjana S et al. (2013) Automated detection of sclerotic metastases in the thoracolumbar spine at CT. Radiology 268(1): 69-78	Population – does not match protocol - case control design
Buyukdereli, Gulgun, Ermin, Tahsin, Kara, Oguz et al. (2006) Tc-99m MIBI uptake in traumatic vertebral fractures and metastatic vertebral lesions: comparison with Tc-99m MDP. Advances in therapy 23(1): 33-8	Outcomes – do not match protocol
Byun, Woo Mok, Jang, Han Won, Kim, Sang Woo et al. (2007) Diffusion-weighted magnetic resonance imaging of sacral insufficiency fractures: comparison with metastases of the sacrum. Spine 32(26): e820-4	Outcomes – do not match protocol
Byun, Woo Mok, Shin, Sei One, Chang, Yongmin et al. (2002) Diffusion-weighted MR imaging of metastatic disease of the spine: assessment of response to therapy. AJNR. American journal of neuroradiology 23(6): 906-12	Population – does not match protocol
Castillo, M, Arbelaez, A, Smith, J K et al. (2000) Diffusion-weighted MR imaging offers no advantage over routine noncontrast MR imaging in the detection of vertebral metastases. AJNR. American journal of neuroradiology 21(5): 948-53	Population – does not match protocol
Castroneves, LA, Coura Filho, G, de Freitas, RMC et al. (2018) Comparison of 68Ga PET/CT to Other Imaging Studies in Medullary Thyroid Cancer: Superiority in Detecting Bone Metastases. The Journal of clinical endocrinology and metabolism 103(9): 3250-3259	Population – does not match protocol
Chabot, M.C. and Herkowitz, H.N. (1995) Spine tumors: Patient evaluation. Seminars in Spine Surgery 7(4): 260-268	Study design – does not match protocol
Chadwick, D.J., Gingell, J.C., Gillatt, D.A. et al. (1991) Magnetic resonance imaging of spinal metastases. Journal of the Royal Society of Medicine 84(4): 196-200	Outcomes – does not match protocol
Chan, J H M, Peh, W C G, Tsui, E Y K et al. (2002) Acute vertebral body compression fractures: discrimination between benign and malignant causes using apparent diffusion coefficients. The British journal of radiology 75(891): 207-14	Other protocol criteria - study reported in an included systematic review (Thawait 2012)
Chan, Jimmy Yu Wai, Chan, Richie Chiu Lung, Chow, Velda Ling Yu et al. (2013) Efficacy of fine-needle aspiration in diagnosing cervical nodal metastasis from nasopharyngeal carcinoma after radiotherapy. The Laryngoscope 123(1): 134-9	Population – does not match protocol
Chen, C J and Hsu, W C (1997) Imaging findings of spontaneous spinal epidural hematoma. Journal of the Formosan Medical Association = Taiwan yi zhi 96(4): 283-7	Population – does not match protocol
Chen, Hongliang, Xie, Biao, Zhong, Xin et al. (2021) Magnetic Resonance Image under Variable Model Algorithm in Diagnosis of Patients with Spinal Metastatic Tumors. Contrast media & molecular imaging 2021: 1381274	Comparator – does not match protocol
Chen, Y, Zhang, E, Wang, Q et al. (2021) Use of dynamic contrast-enhanced MRI for the early assessment of outcome of CyberKnife stereotactic radiosurgery for patients with spinal metastases. Clinical radiology 76(11): 864e1-864e6	Outcomes – do not match protocol
Chiewvit, Pipat, Danchaivijitr, Nasuda, Sirivitmaitrie, Kaewta et al. (2009) Does magnetic resonance imaging give value-added than bone	Population – does not match protocol

Study	Exclusion reason
scintigraphy in the detection of vertebral metastasis?. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 92(6): 818-29	
Cho, Se Jin, Suh, Chong Hyun, Baek, Jung Hwan et al. (2019) Diagnostic performance of CT in detection of metastatic cervical lymph nodes in patients with thyroid cancer: a systematic review and meta-analysis. European radiology 29(9): 4635-4647	Population – does not match protocol
Cho, Won-Ik and Chang, Ung-Kyu (2011) Comparison of MR imaging and FDG-PET/CT in the differential diagnosis of benign and malignant vertebral compression fractures. Journal of neurosurgery. Spine 14(2): 177-83	Other protocol criteria - study reported in an included systematic review (Kim 2020)
Ciray, I, Lindman, H, Astrom, K G et al. (2001) Early response of breast cancer bone metastases to chemotherapy evaluated with MR imaging. Acta radiologica (Stockholm, Sweden : 1987) 42(2): 198-206	Population – does not match protocol
Colletti, P M, Dang, H T, Deseran, M W et al. (1991) Spinal MR imaging in suspected metastases: correlation with skeletal scintigraphy. Magnetic resonance imaging 9(3): 349-55	Outcomes – do not match protocol
Colletti, P M, Siegel, H J, Woo, M Y et al. (1996) The impact on treatment planning of MRI of the spine in patients suspected of vertebral metastasis: an efficacy study. Computerized medical imaging and graphics : the official journal of the Computerized Medical Imaging Society 20(3): 159-62	Outcomes – do not match protocol
Cook, A M, Lau, T N, Tomlinson, M J et al. (1998) Magnetic resonance imaging of the whole spine in suspected malignant spinal cord compression: impact on management. Clinical oncology (Royal College of Radiologists (Great Britain)) 10(1): 39-43	Outcomes – do not match protocol
Cox, M., Pukenas, B., Poplawski, M. et al. (2016) CT-guided Cervical Bone Biopsy in 43 Patients: Diagnostic Yield and Safety at Two Large Tertiary Care Hospitals. Academic Radiology 23(11): 1372-1375	Outcomes – do not match protocol
Cuenod, C A, Laredo, J D, Chevret, S et al. (1996) Acute vertebral collapse due to osteoporosis or malignancy: appearance on unenhanced and gadolinium-enhanced MR images. Radiology 199(2): 541-9	Other protocol criteria - study reported in an included systematic review (Thawait 2012)
Dandekar, M R, Kannan, S, Rangarajan, V et al. (2011) Utility of PET in unknown primary with cervical metastasis: a retrospective study. Indian journal of cancer 48(2): 181-6	Population – does not match protocol
De Bruin, H.G., Algra, P.R., Kruyt, R.H. et al. (1999) Comparison of the FISP 2D sequence with spin echo T1 weighted images before and after intravenous Gd-chelates in detection and evaluation of spinal metastases. Image Decisions MRI 3(4): 10-15	Other protocol criteria – not available in English
Delpassand, E S, Garcia, J R, Bhadkamkar, V et al. (1995) Value of SPECT imaging of the thoracolumbar spine in cancer patients. Clinical nuclear medicine 20(12): 1047-51	Outcomes – do not match protocol
Demirdogen, Ezgi, Ursavas, Ahmet, Aydin Guclu, Ozge et al. (2020) Diagnostic performance of EBUS-TBNA and its interrelation with PET-CT in patients with extra-thoracic malignancies. Tuberkuloz ve toraks 68(3): 285-292	Intervention – does not match protocol
Donners, R., Hirschmann, A., Gutzeit, A. et al. (2021) T2-weighted Dixon MRI of the spine: A feasibility study of quantitative vertebral bone marrow analysis. Diagnostic and Interventional Imaging 102(78): 431-438	Population – does not match protocol
Douis, H, Davies, A M, Jeys, L et al. (2016) Chemical shift MRI can aid in the diagnosis of indeterminate skeletal lesions of the spine. European radiology 26(4): 932-40	Other protocol criteria - study reported in an included systematic review (Suh 2018)
Eissawy, M.G., Saadawy, A.M.I., Farag, K. et al. (2021) Accuracy and	Population – does not

Study	Exclusion reason
diagnostic value of diffusion-weighted whole body imaging with background body signal suppression (DWIBS) in metastatic breast cancer. Egyptian Journal of Radiology and Nuclear Medicine 52(1): 74	match protocol
Facon, David, Ozanne, Augustin, Fillard, Pierre et al. (2005) MR diffusion tensor imaging and fiber tracking in spinal cord compression. AJNR. American journal of neuroradiology 26(6): 1587-94	Outcomes – do not match protocol
Faiella, E., Santucci, D., Calabrese, A. et al. (2022) Artificial Intelligence in Bone Metastases: An MRI and CT Imaging Review. International Journal of Environmental Research and Public Health 19(3): 1880	Population – does not match protocol
Fan, Xiaojie, Zhang, Xiaoyu, Zhang, Zibo et al. (2021) Deep Learning on MRI Images for Diagnosis of Lung Cancer Spinal Bone Metastasis. Contrast media & molecular imaging 2021: 5294379	Other protocol criteria - study reported in an included systematic review (Faiella 2022)
Fan, Xin, Zhang, Han, Yin, Yuzhen et al. (2020) Texture Analysis of 18F-FDG PET/CT for Differential Diagnosis Spinal Metastases. Frontiers in medicine 7: 605746	Intervention – does not match protocol
Feroz, Imza, Makhdoomi, Rumana Hamid, Khursheed, Nayil et al. (2018) Utility of Computed Tomography-guided Biopsy in Evaluation of Metastatic Spinal Lesions. Asian journal of neurosurgery 13(3): 577-584	Outcomes – do not match protocol
Filograna, Laura, Lenkowicz, Jacopo, Cellini, Francesco et al. (2019) Identification of the most significant magnetic resonance imaging (MRI) radiomic features in oncological patients with vertebral bone marrow metastatic disease: a feasibility study. La Radiologia medica 124(1): 50-57	Other protocol criteria - study reported in an included systematic review (Faiella 2022)
Frank, J A, Ling, A, Patronas, N J et al. (1990) Detection of malignant bone tumors: MR imaging vs scintigraphy. AJR. American journal of roentgenology 155(5): 1043-8	Population – does not match protocol
Freire, A.R.S., Lima, E.N.P., Almeida, O.P. et al. (2003) Computed tomography and lymphoscintigraphy to identify lymph node metastases and lymphatic drainage pathways in oral and oropharyngeal squamous cell carcinomas. European Archives of Oto-Rhino-Laryngology 260(3): 148-152	Population – does not match protocol
Fu, Tsai-Sheng, Chen, Li-Hui, Liao, Jen-Chung et al. (2004) Magnetic resonance imaging characteristics of benign and malignant vertebral fractures. Chang Gung medical journal 27(11): 808-15	Other protocol criteria - study reported in an included systematic review (Thawait 2012)
Gabriel, Michael, Decristoforo, Clemens, Donnemiller, Eveline et al. (2003) An intrapatient comparison of 99mTc-EDDA/HYNIC-TOC with 111In-DTPA-octreotide for diagnosis of somatostatin receptor-expressing tumors. Journal of nuclear medicine 44(5): 708-16	Population – does not match protocol
Gao, Y, Fang, J, Liu, X et al. (2006) [Diagnostic value of nuclide bone imaging for bone metastasis from lung cancer and clinic analysis]. Zhongguo fei ai za zhi = Chinese journal of lung cancer 9(4): 357-61	Population – does not match protocol
Gauthe, Mathieu, Testart Dardel, Nathalie, Ruiz Santiago, Fernando et al. (2018) Vertebral metastases from neuroendocrine tumours: How to avoid false positives on 68Ga-DOTA-TOC PET using CT pattern analysis?. European radiology 28(9): 3943-3952	Population – does not match protocol
Geith, Tobias, Biffar, Andreas, Schmidt, Gerwin et al. (2015) Physiological Background of Differences in Quantitative Diffusion-Weighted Magnetic Resonance Imaging Between Acute Malignant and Benign Vertebral Body Fractures: Correlation of Apparent Diffusion Coefficient With Quantitative Perfusion Magnetic Resonance Imaging Using the 2-Compartment Exchange Model. Journal of computer assisted tomography 39(5): 643-8	Outcomes – do not match protocol
Geith, Tobias, Biffar, Andreas, Schmidt, Gerwin et al. (2013) Quantitative analysis of acute benign and malignant vertebral body fractures	Other protocol criteria - study reported in an in-

Study	Exclusion reason
using dynamic contrast-enhanced MRI. AJR. American journal of roentgenology 200(6): w635-43	cluded systematic review (Li 2019)
Geith, Tobias, Schmidt, Gerwin, Biffar, Andreas et al. (2014) Quantitative evaluation of benign and malignant vertebral fractures with diffusion-weighted MRI: what is the optimum combination of b values for ADC-based lesion differentiation with the single-shot turbo spin-echo sequence?. American journal of roentgenology 203(3): 582-8	Other protocol criteria - study reported in an included systematic review (Li 2019)
Geneidi, E.A.S.; Ali, H.I.; Dola, E.F. (2016) Role of DWI in characterization of bone tumors. Egyptian Journal of Radiology and Nuclear Medicine 47(3): 919-927	Population – does not match protocol
Ghanem, Nadir Alexander, Pache, Gregor, Lohrmann, Christian et al. (2007) MRI and (18)FDG-PET in the assessment of bone marrow infiltration of the spine in cancer patients. European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society 16(11): 1907-12	Outcomes – do not match protocol
Gosfield, E 3rd; Alavi, A; Kneeland, B (1993) Comparison of radionuclide bone scans and magnetic resonance imaging in detecting spinal metastases. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 34(12): 2191-8	Population – does not match protocol
Gravel, Guillaume, Tselikas, Lambros, Moulin, Benjamin et al. (2019) Early detection with MRI of incomplete treatment of spine metastases after percutaneous cryoablation. European radiology 29(10): 5655-5663	Outcomes – do not match protocol
Gross, N.D., Weissman, J.L., Talbot, J.M. et al. (2001) MRI detection of cervical metastasis from differentiated thyroid carcinoma. Laryngoscope 111(11i): 1905-1909	Population – does not match protocol
Gualdi, GF, Casciani, E, Di Biasi, C et al. (1999) [The role of TC and MRI in the identification, characterization and staging of tumors of the spinal vertebrae]. La Clinica terapeutica 150(1): 51-65	Other protocol criteria – not available in English
Guan, Youxin, Peck, Kyung K, Lyo, John et al. (2020) T1-weighted Dynamic Contrast-enhanced MRI to Differentiate Nonneoplastic and Malignant Vertebral Body Lesions in the Spine. Radiology 297(2): 382-389	Population – does not match protocol
Guo, Marissa, Kolberg, Kristen L, Smith, Eleanor C et al. (2018) Predominance of Spinal Metastases Involving the Posterior Vertebral Body. World neurosurgery 119: e991-e996	Outcomes – do not match protocol
Guo, Shuai, Chen, Jie, Yang, Baohui et al. (2016) Establishment and evaluation of a prognostic model for surgical outcomes of patients with atlanto-axial dislocations. The Journal of international medical research 44(6): 1474-1482	Population – does not match protocol
Gupta, A., Chaturvedi, S., Jha, D. et al. (2019) Revisiting metastatic central nervous system tumors with unknown primary using clinicopathological findings: A single neurosciences institutional study. Indian Journal of Pathology and Microbiology 62(3): 368-374	Intervention – does not match protocol
Ha, Ji Y, Jeon, Kyung N, Bae, Kyungsoo et al. (2017) Effect of Bone Reading CT software on radiologist performance in detecting bone metastases from breast cancer. The British journal of radiology 90(1072): 20160809	Population – does not match protocol
Hahn, Seok; Lee, Young Han; Suh, Jin-Suck (2018) Detection of vertebral metastases: a comparison between the modified Dixon turbo spin echo T2 weighted MRI and conventional T1 weighted MRI: a preliminary study in a tertiary centre. The British journal of radiology 91(1085): 20170782	Population – does not match protocol
Hammon, Matthias, Dankerl, Peter, Tsymbal, Alexey et al. (2013) Automatic detection of lytic and blastic thoracolumbar spine metastases on computed tomography. European radiology 23(7): 1862-70	Intervention – does not match protocol

Study	Exclusion reason
Han, L J, Au-Yong, T K, Tong, W C et al. (1998) Comparison of bone single-photon emission tomography and planar imaging in the detection of vertebral metastases in patients with back pain. European journal of nuclear medicine 25(6): 635-8	Population – does not match protocol
Hao, S P and Ng, S H (2000) Magnetic resonance imaging versus clinical palpation in evaluating cervical metastasis from head and neck cancer. Otolaryngology--head and neck surgery, 123(3): 324-7	Population – does not match protocol
Harrison, S K; Ditchfield, M R; Waters, K (1998) Correlation of MRI and CSF cytology in the diagnosis of medulloblastoma spinal metastases. Pediatric radiology 28(8): 571-4	Population – does not match protocol - medulloblastoma
Henschke, Nicholas, Maher, Christopher G, Ostelo, Raymond W J G et al. (2013) Red flags to screen for malignancy in patients with low-back pain. The Cochrane database of systematic reviews: cd008686	Intervention – does not match protocol - no imaging tests evaluated
Hoogcarspel, Stan J, Van der Velden, Joanne M, Lagendijk, Jan J W et al. (2014) The feasibility of utilizing pseudo CT-data for online MRI based treatment plan adaptation for a stereotactic radiotherapy treatment of spinal bone metastases. Physics in medicine and biology 59(23): 7383-91	Outcomes – do not match protocol
Horakova, M., Horak, T., Valosek, J. et al. (2022) Semi-automated detection of cervical spinal cord compression with the Spinal Cord Toolbox. Quantitative Imaging in Medicine and Surgery 12(4): 2261-2279	Population – does not match protocol
Hoshiai, Sodai, Masumoto, Tomohiko, Hanaoka, Shouhei et al. (2019) Clinical usefulness of temporal subtraction CT in detecting vertebral bone metastases. European journal of radiology 118: 175-180	Population – does not match protocol
Hsu, H.-C., Liao, T.-Y., Ro, L.-S. et al. (2019) Differences in Pain Intensity of Tumors Spread to the Anterior versus Anterolateral/Lateral Portions of the Vertebral Body Based on CT Scans. Pain Research and Management 2019: 9387941	Outcomes – do not match protocol
Huang, C W C, Ali, A, Chang, Y-M et al. (2020) Major Radiologic and Clinical Outcomes of Total Spine MRI Performed in the Emergency Department at a Major Academic Medical Center. AJNR. American journal of neuroradiology 41(6): 1120-1125	Population – does not match protocol
Huang, T.-W., Chao, P.-C., Ou, J.-J. et al. (2006) Cervical spine metastases secondary to colorectal carcinoma: The role of MR imaging and treatment strategy. Journal of Medical Sciences 26(6): 215-218	Outcomes – do not match protocol
Iagaru, A., Young, P., Mittra, E. et al. (2013) Pilot prospective evaluation of 99mTc-MDP scintigraphy, 18F NaF PET/CT, 18F FDG PET/CT and whole-body MRI for detection of skeletal metastases. Clinical Nuclear Medicine 38(7): e290-e296	Population – does not match protocol
Ichimaru, K., Endo, K., Ito, K. et al. (1995) Spinal cord tumours: Diagnosis with myelogram of MRI?. Journal of Orthopaedic Surgery 3(2): 35-39	Population – does not match protocol
Jacobson, A F, Cronin, E B, Stomper, P C et al. (1990) Bone scans with one or two new abnormalities in cancer patients with no known metastases: frequency and serial scintigraphic behavior of benign and malignant lesions. Radiology 175(1): 229-32	Population – does not match protocol
Kakitsubata, Yousuke, Theodorou, Daphne J, Theodorou, Stavroula J et al. (2009) Metastatic disease involving the discovertebral junction of the spine. Joint bone spine 76(1): 50-6	Population – does not match protocol - cadaveric study
Karchevsky, Michael; Babb, James S; Schweitzer, Mark E (2008) Can diffusion-weighted imaging be used to differentiate benign from pathologic fractures? A meta-analysis. Skeletal radiology 37(9): 791-5	Outcomes – do not match protocol – does not report data relevant to diagnostic accuracy
Kaufman, B A; Moran, C J; Park, T S (1995) Spinal magnetic resonance imaging immediately after craniotomy for detection of metastatic dis-	Population – does not match protocol

Study	Exclusion reason
ease. Pediatric neurosurgery 23(4): 171-81	
Kelly, Hillary R and Curtin, Hugh D (2017) Chapter 2 Squamous Cell Carcinoma of the Head and Neck-Imaging Evaluation of Regional Lymph Nodes and Implications for Management. Seminars in ultrasound, CT, and MR 38(5): 466-478	Population – does not match protocol
Kerslake, R W; Jaspan, T; Worthington, B S (1991) Magnetic resonance imaging of spinal trauma. The British journal of radiology 64(761): 386-402	Population – does not match protocol
Khan, A., Gao, A., Hall, E. et al. (2017) Do Routine Computed Tomography Scans Detect Early Spinal Cord Compression in Patients with Castrate Resistant Prostate Cancer? Implications for the PROMPTS Trial. Clinical Oncology 29(3): e87-e87	Publication type – does not match protocol
Kim, D.W., Kim, S.C., Krynyckyi, B.R. et al. (2005) Focally increased activity in the lateral aspect of the mid cervical spine on bone scintigraphy is almost always benign in nature. Clinical Nuclear Medicine 30(9): 593-595	Outcomes – do not match protocol
Kim, Seong-Jang and Lee, Jung Sub (2020) Diagnostic Performance of F-18 Fluorodeoxyglucose Positron Emission Tomography or Positron Emission Tomography/Computed Tomography for Differentiation of Benign and Malignant Vertebral Compression Fractures: A Meta-Analysis. World neurosurgery 137: e626-e633	Other protocol criteria – duplicate publication
Kizilay, F., Sahin, M., Simsir, A. et al. (2020) Predictive value of bone scintigraphy in the diagnosis of prostate cancer bone metastases and comparison of verification methods. Kuwait Medical Journal 52(4): 368-374	Population – does not match protocol
Kosuda, S, Kaji, T, Yokoyama, H et al. (1996) Does bone SPECT actually have lower sensitivity for detecting vertebral metastasis than MRI?. Journal of nuclear medicine, 37(6): 975-8	Outcomes – do not match protocol
Krabbe, Christiaan A, van der Werff-Regelink, Gerreke, Pruim, Jan et al. (2010) Detection of cervical metastases with (11)C-tyrosine PET in patients with squamous cell carcinoma of the oral cavity or oropharynx: A comparison with (18)F-FDG PET. Head & neck 32(3): 368-74	Population – does not match protocol
Kubota, Takao, Yamada, Kei, Ito, Hirotoshi et al. (2005) High-resolution imaging of the spine using multidetector-row computed tomography: differentiation between benign and malignant vertebral compression fractures. Journal of computer assisted tomography 29(5): 712-9	Outcomes – do not match protocol
Lang, Ning, Su, Min-Ying, Yu, Hon J et al. (2013) Differentiation of myeloma and metastatic cancer in the spine using dynamic contrast-enhanced MRI. Magnetic resonance imaging 31(8): 1285-91	Reference standard – does not match protocol
Lauenstein, T.C., Freudenberg, L.S., Goehde, S.C. et al. (2002) Whole-body MRI using a rolling table platform for the detection of bone metastases. European Radiology 12(8): 2091-2099	Index test – does not match protocol
Lee, Eugene, Lee, Joon Woo, Lee, Jinyoung et al. (2016) Acute benign vertebral compression fractures: "see-through sign" on contrast-enhanced MR images. European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society 25(11): 3470-3477	Outcomes – do not match protocol
Li, X F, Yang, Y, Lin, C B et al. (2016) Assessment of the diagnostic value of diffusion tensor imaging in patients with spinal cord compression: a meta-analysis. Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas 49(1): e4769	Outcomes – do not match protocol
Libshitz, H I, Malthouse, S R, Cunningham, D et al. (1992) Multiple myeloma: appearance at MR imaging. Radiology 182(3): 833-7	Population – does not match protocol

Study	Exclusion reason
Lin, Fan; Lei, Yi; Li, Yang-bin (2009) Influence of lesion ratio on diagnostic performance of in-phase/opposed-phase imaging and apparent diffusion coefficient for differentiating acute benign vertebral fractures and metastases. Chinese medical journal 122(11): 1293-9	Other protocol criteria - study reported in an included systematic review (Suh 2018)
Liu, H., Jiao, M., Yuan, Y. et al. (2022) Benign and malignant diagnosis of spinal tumors based on deep learning and weighted fusion framework on MRI. Insights into Imaging 13(1): 87	Comparator – does not match protocol
Liu, J., Guo, W., Zeng, P. et al. (2022) Vertebral MRI-based radiomics model to differentiate multiple myeloma from metastases: influence of features number on logistic regression model performance. European Radiology 32(1): 572-581	Comparator – does not match protocol
Liu, Peng, Liang, Yun, Bian, Chong et al. (2020) Diagnostic accuracy of MR, CT, and ECT in the differentiation of neoplastic from nonneoplastic spine lesions. Asia-Pacific journal of clinical oncology 16(5): e192-e197	Population – does not match protocol
Liu, Tao, Wang, Shenghao, Liu, Hao et al. (2017) Detection of vertebral metastases: a meta-analysis comparing MRI, CT, PET, BS and BS with SPECT. Journal of cancer research and clinical oncology 143(3): 457-465	Systematic review - included studies were assessed for relevance
Luboldt, W, Küfer, R, Blumstein, N et al. (2008) Prostate carcinoma: diffusion-weighted imaging as potential alternative to conventional MR and 11C-choline PET/CT for detection of bone metastases. Radiology 249(3): 1017-25	Outcomes – do not match protocol
Luo, Zhanpeng, Litao, Li, Gu, Suxi et al. (2016) Standard-b-value vs low-b-value DWI for differentiation of benign and malignant vertebral fractures: a meta-analysis. The British journal of radiology 89(1058): 20150384	Outcomes – does not match protocol
Lv, Mu, Zhou, Zhichao, Tang, Qingkun et al. (2020) Differentiation of usual vertebral compression fractures using CT histogram analysis as quantitative biomarkers: A proof-of-principle study. European journal of radiology 131: 109264	Intervention – does not match protocol
Maeda, Masayuki, Sakuma, Hajime, Maier, Stephan E et al. (2003) Quantitative assessment of diffusion abnormalities in benign and malignant vertebral compression fractures by line scan diffusion-weighted imaging. AJR. American journal of roentgenology 181(5): 1203-9	Other protocol criteria - study reported in an included systematic review (Thawait 2012)
Mahnken, Andreas H, Wildberger, Joachim E, Adam, Gerhard et al. (2005) Is there a need for contrast-enhanced T1-weighted MRI of the spine after inconspicuous short tau inversion recovery imaging?. European radiology 15(7): 1387-92	Outcomes – do not match protocol
Maralani, P.J., Lo, S.S., Redmond, K. et al. (2017) Spinal metastases: multimodality imaging in diagnosis and stereotactic body radiation therapy planning. Future Oncology 13(1): 77-91	Study design – does not match protocol
Matsumoto, Yoshihiro, Harimaya, Katsumi, Kawaguchi, Kenichi et al. (2016) Dumbbell Scoring System: A New Method for the Differential Diagnosis of Malignant and Benign Spinal Dumbbell Tumors. Spine 41(20): e1230-e1236	Population – does not match protocol
McKinley, W O, Conti-Wyneken, A R, Vokac, C W et al. (1996) Rehabilitative functional outcome of patients with neoplastic spinal cord compressions. Archives of physical medicine and rehabilitation 77(9): 892-5	Intervention – does not match protocol
Meena, Rajesh, Aggarwal, Ashish, Bhattacharya, Anish et al. (2019) Non traumatic vertebral lesions: incremental utility of PET-CT over MRI and FNAC in a suggested diagnostic algorithm. British journal of neurosurgery 33(1): 25-29	Population – does not match protocol
Mehta, R C, Marks, M P, Hinks, R S et al. (1995) MR evaluation of vertebral metastases: T1-weighted, short-inversion-time inversion recovery, fast spin-echo, and inversion-recovery fast spin-echo sequences. AJNR.	Outcomes – do not match protocol

Study	Exclusion reason
American journal of neuroradiology 16(2): 281-8	
Metin, M., Ergin, M., Solak, O. et al. (2012) Effectiveness of PET scan in postoperative long term follow up of patients with nonsmall cell lung cancer. Journal of Clinical and Analytical Medicine 3(1): 30-32	Population – does not match protocol
Metser, Ur, Lerman, Hedva, Blank, Annat et al. (2004) Malignant involvement of the spine: assessment by 18F-FDG PET/CT. Journal of nuclear medicine, 45(2): 279-84	Population – does not match protocol
Mihoubi Bouvier, Fadila, Thomas De Montpreville, Vincent, Besse, Benjamin et al. (2021) Can MRI differentiate surrounding vertebral invasion from reactive inflammatory changes in superior sulcus tumor?. European radiology 31(12): 8991-8999	Population – does not match protocol
Mohson, K.I.; Naief, Q.T.; Jalil, F.A. (2020) Differentiating benign from suspicious vertebral marrow lesions detected with conventional magnetic resonance imaging using apparent diffusion coefficient and diffusion-weighted image. Open Access Macedonian Journal of Medical Sciences 8(b): 114-118	Outcomes – do not match protocol
Mossa-Basha, M., Gerszten, P.C., Myrehaug, S. et al. (2019) Spinal metastasis: Diagnosis, management and followup. British Journal of Radiology 92(1103): 20190211	Study design – does not match protocol
Mostardi, P M, Diehn, F E, Rykken, J B et al. (2014) Intramedullary spinal cord metastases: visibility on PET and correlation with MRI features. AJNR. American journal of neuroradiology 35(1): 196-201	Outcomes – do not match protocol
Mubarak, Fatima and Akhtar, Waseem (2011) Acute vertebral compression fracture: differentiation of malignant and benign causes by diffusion weighted magnetic resonance imaging. JPMA. The Journal of the Pakistan Medical Association 61(6): 555-8	Other protocol criteria - study reported in an included systematic review (Li 2019)
Nakanishi, K, Kobayashi, M, Nakaguchi, K et al. (2007) Whole-body MRI for detecting metastatic bone tumor: diagnostic value of diffusion-weighted images. Magnetic resonance in medical sciences, 6(3): 147-55	Population – does not match protocol
Narin, Y., Urhan, M., Canpolat, N. et al. (2007) Lesion detectability and clinical effectiveness of dual-head coincidence gamma camera imaging in comparison with dedicated PET systems in tumour patients. Journal of International Medical Research 35(4): 467-473	Population – does not match protocol
Nozaki, T, Yasuda, K, Akashi, T et al. (2008) Usefulness of single photon emission computed tomography imaging in the detection of lumbar vertebral metastases from prostate cancer. International journal of urology : official journal of the Japanese Urological Association 15(6): 516-9	Population – does not match protocol
Ohlmann-Knafo, S, Tarnoki, A D, Tarnoki, D L et al. (2015) MR Diagnosis of Bone Metastases at 1.5 T and 3 T: Can STIR Imaging Be Omitted?. RoFo : Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin 187(10): 924-32	Population – does not match protocol
Ohno, Seiichiro, Togami, Izumi, Sei, Tetsuro et al. (2003) MR imaging of vertebral metastases at 0.2 Tesla: clinical evaluation of T1-weighted opposed-phase gradient-echo imaging. Physiological chemistry and physics and medical NMR 35(2): 145-56	Other protocol criteria - study reported in an included systematic review (Suh 2018)
Otake, S, Matsuo, M, Tamaki, T et al. (1991) [Fast MR imaging of liver metastasis using FLASH and FISP--optimal sequences for T1- and T2*-weighted images]. Nihon Igaku Hoshasen Gakkai zasshi. Nippon acta radiologica 51(1): 19-32	Population – does not match protocol
Oztekin, Ozgur, Ozan, Ebru, Hilal Adibelli, Zehra et al. (2009) SSH-EPI diffusion-weighted MR imaging of the spine with low b values: is it useful in differentiating malignant metastatic tumor infiltration from benign fracture edema?. Skeletal radiology 38(7): 651-8	Other protocol criteria - study reported in an included systematic review (Li 2019)
Park, Chankue, Lee, Joon Woo, Kim, Yongju et al. (2019) Diagnosis of	Publication type – does

Study	Exclusion reason
spinal metastasis: are MR images without contrast medium application sufficient?. Clinical imaging 55: 165-173	not match protocol
Park, Hee Jin, Lee, So Yeon, Rho, Myung Ho et al. (2016) Single-Shot Echo-Planar Diffusion-Weighted MR Imaging at 3T and 1.5T for Differentiation of Benign Vertebral Fracture Edema and Tumor Infiltration. Korean journal of radiology 17(5): 590-7	Population – does not match protocol
Park, Sang-Min, Park, Jae-Woo, Lee, Hui-Jong et al. (2017) Diagnostic Value of Technetium-99m Bone Scintigraphy in the Detection of Cervical Spine Metastases in Oncological Patients. Spine 42(22): 1699-1705	Population – does not match protocol
Park, Sun-Won, Lee, Joo-Hyuk, Ehara, Shigeru et al. (2004) Single shot fast spin echo diffusion-weighted MR imaging of the spine; Is it useful in differentiating malignant metastatic tumor infiltration from benign fracture edema?. Clinical imaging 28(2): 102-8	Other protocol criteria - study reported in an included systematic review (Li 2019)
Park, Sunghoon, Yoon, Joon-Kee, Chung, Nam-Su et al. (2018) Correlations between intravoxel incoherent motion diffusion-weighted MR imaging parameters and 18F-FDG PET/CT metabolic parameters in patients with vertebral bone metastases: initial experience. The British journal of radiology 91(1086): 20170889	Outcomes – do not match protocol
Perrin-Resche, I, Bizais, Y, Buhe, T et al. (1993) How does iliac crest bone marrow biopsy compare with imaging in the detection of bone metastases in small cell lung cancer?. European journal of nuclear medicine 20(5): 420-5	Population – does not match protocol
Petren-Mallmin, M (1994) Clinical and experimental imaging of breast cancer metastases in the spine. Acta radiologica. Supplementum 391: 1-23	Outcomes – do not match protocol
Petren-Mallmin, M, Nordstrom, B, Andreasson, I et al. (1992) MR imaging with histopathological correlation in vertebral metastases of breast cancer. Acta radiologica (Stockholm, Sweden : 1987) 33(3): 213-20	Outcomes – do not match protocol
Pongpornsup, Sopa; Wajanawichakorn, Phromphiang; Danchaivijitr, Nasuda (2009) Benign versus malignant compression fracture: a diagnostic accuracy of magnetic resonance imaging. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 92(1): 64-72	Other protocol criteria - study reported in an included systematic review (Li 2019)
Poulsen, Mads H, Petersen, Henrik, Hoilund-Carlsen, Poul F et al. (2014) Spine metastases in prostate cancer: comparison of technetium-99m-MDP whole-body bone scintigraphy, [(18) F]choline positron emission tomography(PET)/computed tomography (CT) and [(18) F]NaF PET/CT. BJU international 114(6): 818-23	Population – does not match protocol
Pozzi, G, Garcia Parra, C, Stradiotti, P et al. (2012) Diffusion-weighted MR imaging in differentiation between osteoporotic and neoplastic vertebral fractures. European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society 21suppl1: 123-7	Other protocol criteria - study reported in an included systematic review (Li 2019)
Pozzi, Grazia, Albano, Domenico, Messina, Carmelo et al. (2018) Solid bone tumors of the spine: Diagnostic performance of apparent diffusion coefficient measured using diffusion-weighted MRI using histology as a reference standard. Journal of magnetic resonance imaging, 47(4): 1034-1042	Population – does not match protocol
Prabhu, Vikram C, Bilsky, Mark H, Jambhekar, Kedar et al. (2003) Results of preoperative embolization for metastatic spinal neoplasms. Journal of neurosurgery 98(2suppl): 156-64	Intervention – does not match protocol
Qi, Na, Meng, Qingyuan, You, Zhiwen et al. (2021) Standardized uptake values of 99mTc-MDP in normal vertebrae assessed using quantitative SPECT/CT for differentiation diagnosis of benign and malignant bone lesions. BMC medical imaging 21(1): 39	Outcomes – do not match protocol
Qin, Feng, Feng, Yapei, Zhang, Panpan et al. (2022) Diagnostic Value	Index test does not

Study	Exclusion reason
of Emission Computed Tomography Combined with Computed Tomography for Metastatic Malignant Tumor of Spine. Contrast media & molecular imaging 2022: 5847589	match protocol
Reginelli, Alfonso, Silvestro, Giustino, Fontanella, Giovanni et al. (2016) Performance status versus anatomical recovery in metastatic disease: The role of palliative radiation treatment. International journal of surgery (London, England) 33suppl1: 126-31	Intervention – does not match protocol
Ren, Hong; Lin, Wei; Ding, Xianjun (2017) Surface Coil Intensity Correction in Magnetic Resonance Imaging in Spinal Metastases. Open medicine (Warsaw, Poland) 12: 138-143	Index test - does not match protocol
Runge, V.M., Bradley, W.G., Brant-Zawadzki, M.N. et al. (1991) Clinical safety and efficacy of gadoteridol: A study in 411 patients with suspected intracranial and spinal disease. Radiology 181(3): 701-709	Intervention – does not match protocol
Saidha, N K, Ganguly, M, Sidhu, Harkirat Singh et al. (2013) The Role of 18 FDG PET-CT in Evaluation of Unknown Primary Tumours. Indian journal of surgical oncology 4(3): 236-41	Population – does not match protocol
Savelli, G., Chiti, A., Grasselli, G. et al. (2000) The role of bone SPET study in diagnosis of single vertebral metastases. Anticancer Research 20(2b): 1115-1120	Population – does not match protocol
Scarabino, T, Giannatempo, GM, Popolizio, T et al. (1996) Fast spin echo imaging of vertebral metastasis: comparison of fat suppression techniques (FSE-CHESS, STIR-FSE). Radiologia medica 92(3): 180-185	Other protocol criteria – not available in English
Schiff, D and O'Neill, B P (1996) Intramedullary spinal cord metastases: clinical features and treatment outcome. Neurology 47(4): 906-12	Outcomes – do not match protocol
Schirrmeister, H, Guhlmann, A, Elsner, K et al. (1999) Sensitivity in detecting osseous lesions depends on anatomic localization: planar bone scintigraphy versus 18F PET. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 40(10): 1623-9	Population – does not match protocol
Schmidt, GP, Baur, A, Stäbler, A et al. (2005) Estimation of diffuse bone marrow infiltration of the spine in multiple myeloma: correlation of MRT with histological results. RoFo 177(5): 745-750	Other protocol criteria – not available in English
Sedonja, I and Budihna, N V (1999) The benefit of SPECT when added to planar scintigraphy in patients with bone metastases in the spine. Clinical nuclear medicine 24(6): 407-13	Outcomes – do not match protocol
Semirgin, S.U. (2019) SPECT/CT findings of suspicious vertebral metastasis on planar bone scintigraphy. Journal of Experimental and Clinical Medicine (Turkey) 36(4): 99-103	Outcomes – do not match protocol
Shah, Lubdha M and Salzman, Karen L (2011) Imaging of spinal metastatic disease. International journal of surgical oncology 2011: 769753	Study design – does not match protocol
Sharma, Punit, Dhull, Varun Singh, Reddy, Rama Mohan et al. (2013) Hybrid SPECT-CT for characterizing isolated vertebral lesions observed by bone scintigraphy: comparison with planar scintigraphy, SPECT, and CT. Diagnostic and interventional radiology (Ankara, Turkey) 19(1): 33-40	Index test – does not match protocol
Simsek, D.H., Sanli, Y., Civan, C. et al. (2020) Does bone scintigraphy still have a role in the era of 68 Ga-PSMA PET/CT in prostate cancer?. Annals of Nuclear Medicine 34(7): 476-485	Population – does not match protocol
Sugimura, K, Kajitani, A, Okizuka, H et al. (1991) Assessing response to therapy of spinal metastases with gadolinium-enhanced MR imaging. Journal of magnetic resonance imaging : JMRI 1(4): 481-4	Population – does not match protocol
Sung, Jin Kyeong, Jee, Won-Hee, Jung, Joon-Yong et al. (2014) Differentiation of acute osteoporotic and malignant compression fractures of the spine: use of additive qualitative and quantitative axial diffusion-weighted MR imaging to conventional MR imaging at 3.0 T. Radiology	Other protocol criteria - study reported in an included systematic review (Suh 2018)

Study	Exclusion reason
271(2): 488-98	
Tabotta, Flavian, Jreige, Mario, Schaefer, Niklaus et al. (2019) Quantitative bone SPECT/CT: high specificity for identification of prostate cancer bone metastases. BMC musculoskeletal disorders 20(1): 619	Population – does not match protocol
Tadros, M.Y. and Louka, A.L. (2016) Discrimination between benign and malignant in vertebral marrow lesions with diffusion weighted MRI and chemical shift. Egyptian Journal of Radiology and Nuclear Medicine 47(2): 557-569	Other protocol criteria - study reported in an included systematic review (Suh 2018)
Tan, D Y L; Tsou, I Y Y; Chee, T S G (2002) Differentiation of malignant vertebral collapse from osteoporotic and other benign causes using magnetic resonance imaging. Annals of the Academy of Medicine, Singapore 31(1): 8-14	Other protocol criteria - study reported in an included systematic review (Thawait 2012)
Tan, Hui, Xu, Hui, Luo, Feifei et al. (2019) Combined intravoxel incoherent motion diffusion-weighted MR imaging and magnetic resonance spectroscopy in differentiation between osteoporotic and metastatic vertebral compression fractures. Journal of orthopaedic surgery and research 14(1): 299	Index test – does not match protocol
Tang, Guangyu, Liu, Yong, Li, Wei et al. (2007) Optimization of b value in diffusion-weighted MRI for the differential diagnosis of benign and malignant vertebral fractures. Skeletal radiology 36(11): 1035-41	Other protocol criteria - study reported in an included systematic review (Thawait 2012)
Tariq, G., Singh, M., Feroze, S. et al. (2000) MRI-Evaluation of spinal pathology. JK Practitioner 7(3): 162-166	Study design – does not match protocol
Taskin, G.; Incesu, L.; Aslan, K. (2013) The value of apparent diffusion coefficient measurements in the differential diagnosis of vertebral bone marrow lesions. Turkish Journal of Medical Sciences 43(3): 379-387	Reference standard – does not match protocol
Taylor, B V, Kimmel, D W, Krecke, K N et al. (1997) Magnetic resonance imaging in cancer-related lumbosacral plexopathy. Mayo Clinic proceedings 72(9): 823-9	Population – does not match protocol
Thawait, Shrey K, Kim, Jihoon, Klufas, Roman A et al. (2013) Comparison of four prediction models to discriminate benign from malignant vertebral compression fractures according to MRI feature analysis. AJR. American journal of roentgenology 200(3): 493-502	Outcomes – do not match protocol
Thawait, Shrey K, Marcus, Matthew A, Morrison, William B et al. (2012) Research synthesis: what is the diagnostic performance of magnetic resonance imaging to discriminate benign from malignant vertebral compression fractures? Systematic review and meta-analysis. Spine 37(12): e736-44	Other protocol criteria - systematic review - included studies were assessed for relevance
Thomson, V., Pialat, J.-B., Gay, F. et al. (2008) Whole-body MRI for metastases screening: A preliminary study using 3D VIBE sequences with automatic subtraction between noncontrast and contrast enhanced images. American Journal of Clinical Oncology: Cancer Clinical Trials 31(3): 285-292	Population – does not match protocol
Tokuda, Osamu, Harada, Yuko, Ueda, Takaaki et al. (2011) Malignant versus benign vertebral compression fractures: can we use bone SPECT as a substitute for MR imaging?. Nuclear medicine communications 32(3): 192-8	Other protocol criteria - study reported in an included systematic review (Li 2019)
Traub-Weidinger, T, Von Guggenberg, E, Dobrozemsky, G et al. (2010) Preliminary experience with (68)Ga-DOTA-lanreotide positron emission tomography. The quarterly journal of nuclear medicine and molecular imaging : official publication of the Italian Association of Nuclear Medicine (AIMN) [and] the International Association of Radiopharmacology (IAR), [and] Section of the Society of... 54(1): 52-60	Outcomes – do not match protocol
Tzeng, Y.-H., Chang, T.-Y., Huang, G.-S. et al. (2004) Diffusion-weighted MR imaging for differentiating acute benign from pathologic compression fractures: A reinvestigation of the usefulness of diffusion-	Other protocol criteria - study reported in an included systematic review

Study	Exclusion reason
weighted imaging. Chinese Journal of Radiology 29(3): 109-115	(Thawait 2012)
Uchida, Kenzo, Nakajima, Hideaki, Miyazaki, Tsuyoshi et al. (2013) (18)F-FDG PET/CT for Diagnosis of Osteosclerotic and Osteolytic Vertebral Metastatic Lesions: Comparison with Bone Scintigraphy. Asian spine journal 7(2): 96-103	Outcomes – do not match protocol
Van Veldhuizen, P J and Stephens, R L (1993) Evaluation of neoplastic spinal cord compressions. Kansas medicine : the journal of the Kansas Medical Society 94(5): 130-2	Outcomes – do not match protocol
Venkitaraman, R, Sohaib, S A, Barbachano, Y et al. (2007) Detection of occult spinal cord compression with magnetic resonance imaging of the spine. Clinical oncology (Royal College of Radiologists (Great Britain)) 19(7): 528-31	Outcomes – do not match protocol
Venkitaraman, Ramachandran, Barbachano, Yolanda, Dearnaley, David P et al. (2007) Outcome of early detection and radiotherapy for occult spinal cord compression. Radiotherapy and oncology, 85(3): 469-72	Study design – does not match protocol
Wang, Juan, Fang, Zhiyuan, Lang, Ning et al. (2017) A multi-resolution approach for spinal metastasis detection using deep Siamese neural networks. Computers in biology and medicine 84: 137-146	Population – does not match protocol
Wang, Li-Xia, Kong, Xiang-Quan, Shi, He-Shui et al. (2007) Application value of magnetic resonance sequences in diagnosis of early spinal metastatic tumor. Chinese medical sciences journal = Chung-kuo i hsueh k'o hsueh tsa chih 22(1): 9-12	Outcomes – do not match protocol
Wang, Z., Yuan, L., Ma, D. et al. (2016) 18F-FDG PET/CT can differentiate vertebral metastases from Schmorl's nodes by distribution characteristics of the 18F-FDG. Hellenic Journal of Nuclear Medicine 19(3): 241-244	Outcomes – do not match protocol
White, Andrew P, Kwon, Brian K, Lindskog, Dieter M et al. (2006) Metastatic disease of the spine. The Journal of the American Academy of Orthopaedic Surgeons 14(11): 587-98	Study design – does not match protocol
White, N. (2016) Metastatic Spinal Cord Compression: Presentation, Diagnosis, and Management. Hospital Medicine Clinics 5(3): 452-465	Study design – does not match protocol
Wonglaksanapimon, Suwimon, Chawalparit, Orasa, Khumpunnip, Sutiporn et al. (2012) Vertebral body compression fracture: discriminating benign from malignant causes by diffusion-weighted MR imaging and apparent diffusion coefficient value. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 95(1): 81-7	Other protocol criteria - study reported in an included systematic review (Li 2019)
Wu, X., Ma, C., Zhao, X. et al. (2010) Application of whole body diffusion weighted imaging in bone metastasis. Chinese-German Journal of Clinical Oncology 9(1): 44-47	Outcomes – do not match protocol
Yang, Z., Shi, W., Zhu, B. et al. (2014) Is 18F-FDG PET/CT more reliable than 99mTc-MDP planar bone scintigraphy in detecting bone metastasis in nasopharyngeal carcinoma?. Annals of Nuclear Medicine 28(5): 411-416	Population – does not match protocol
Yao, W.W., Li, M.H., Yang, S.X. et al. (2005) Use of diffusion-weighted magnetic resonance imaging to differentiate between acute benign and pathological vertebral fractures: Prospective study. Journal of the Hong Kong College of Radiologists 8(1): 4-8	Outcomes – do not match protocol
Yilmaz Ovali, G., Duzgun, F., Farasat, M. et al. (2017) Benign versus malignant vertebral compression, chemical shift MR imaging, is it useful?. Iranian Journal of Radiology 14(2): e42016	Other protocol criteria - study reported in an included systematic review (Suh 2018)
Yueniwati, Yuyun and Widhiasi, Dhanti Erma (2015) Role of Magnetic Resonance Imaging in Differentiating Spondylitis from Vertebral Metastasis. Asian spine journal 9(5): 776-82	Outcomes – do not match protocol
Zajick, Donald C Jr, Morrison, William B, Schweitzer, Mark E et al.	Outcomes – do not

Study	Exclusion reason
(2005) Benign and malignant processes: normal values and differentiation with chemical shift MR imaging in vertebral marrow. Radiology 237(2): 590-6	match protocol
Zampa, Virna, Cosottini, Mirco, Michelassi, Chiara et al. (2002) Value of opposed-phase gradient-echo technique in distinguishing between benign and malignant vertebral lesions. European radiology 12(7): 1811-8	Other protocol criteria - study reported in an included systematic review (Li 2019)
Zeng, K Liang, Myrehaug, Sten, Soliman, Hany et al. (2019) Stereotactic Body Radiotherapy for Spinal Metastases at the Extreme Ends of the Spine: Imaging-Based Outcomes for Cervical and Sacral Metastases. Neurosurgery 85(5): 605-612	Study design – does not match protocol
Zhang, J., Chen, Y., Zhang, E. et al. (2020) Diagnosis of spinal lesions using perfusion parameters measured by DCE-MRI and metabolism parameters measured by PET/CT. European Spine Journal 29(5): 1061-1070	Population – does not match protocol
Zhang, Jiahui, Chen, Yongye, Zhang, Enlong et al. (2020) Use of monoexponential diffusion-weighted imaging and diffusion kurtosis imaging and dynamic contrast-enhanced-MRI for the differentiation of spinal tumors. European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society 29(5): 1112-1120	Population – does not match protocol
Zhang, Yiqiu, Shi, Hongcheng, Cheng, Dengfeng et al. (2013) Added value of SPECT/spiral CT versus SPECT in diagnosing solitary spinal lesions in patients with extraskeletal malignancies. Nuclear medicine communications 34(5): 451-8	Index test – does not match protocol
Zhang, Yiqiu, Shi, Hongcheng, Gu, Yushen et al. (2011) Differential diagnostic value of single-photon emission computed tomography/spiral computed tomography with Tc-99m-methylene diphosphonate in patients with spinal lesions. Nuclear medicine communications 32(12): 1194-200	Index test – does not match protocol
Zhou, X.J., Leeds, N.E., McKinnon, G.C. et al. (2002) Characterization of benign and metastatic vertebral compression fractures with quantitative diffusion MR imaging. American Journal of Neuroradiology 23(1): 165-170	Other protocol criteria - study reported in an included systematic review (Thawait 2012)
Zidan, D.Z.; Habib, L.A.; Chalabi, N.A. (2014) Quantitative chemical-shift MR imaging cutoff value: Benign versus malignant vertebral compression - Initial experience. Egyptian Journal of Radiology and Nuclear Medicine 45(3): 779-786	Other protocol criteria - study reported in an included systematic review (Suh 2018)

Excluded economic studies

No economic evidence was identified for this review. See supplement 2 for further information.

Appendix K Research recommendations – full details

Research recommendations for review question: How effective are radiological imaging techniques in the diagnosis of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

No research recommendations were made for this review question.

Appendix L Study data - diagnostic accuracy

Diagnostic accuracy data for review question: How effective are radiological imaging techniques in the diagnosis of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Key to variables:

- **Study**: study ID
- **Source**: source of data Su 2018 or Li 2019 systematic reviews or our literature search
- **Population**: population tested – people with spinal bone marrow lesions or vertebral compression fractures
- **Condition**: the condition being tested for – either malignant bone marrow lesions or malignant vertebral compression fractures
- **Imaging_group**: type of MRI sequences: chem_shift (chemical shift imaging), conv_dwi (conventional plus diffusion weighted), conv_ce (conventional plus contrast enhanced), conv (conventional sequences)
- **TP, FP, FN, TN**: true positive, false positive, false negative, true negative

study	source	population	condition	Imaging_group	TP	FP	FN	TN
Kim 2014	Suh 2018	Bone marrow lesions (BML)	Malignant BML	chem_shift_bml	18	0	3	11
Erly 2006	Suh 2018	Vertebral compression fractures (VCF)	Malignant VCF	chem_shift_vcf	19	3	1	26
Douis 2016	Suh 2018	Bone marrow lesions (BML)	Malignant BML	chem_shift_bml	11	12	1	33
El-Samie 2015	Suh 2018	Bone marrow lesions (BML)	Malignant BML	chem_shift_bml	32	0	7	24
Geith 2012	Suh 2018	Vertebral compression fractures (VCF)	Malignant VCF	chem_shift_vcf	10	3	10	23
Kim 2017	Suh 2018	Vertebral compression fractures (VCF)	Malignant VCF	chem_shift_vcf	23	1	1	19
Ogura 2012	Suh 2018	Vertebral compression fractures (VCF)	Malignant VCF	chem_shift_vcf	28	9	0	33
Ragab 2009	Suh 2018	Vertebral compression fractures (VCF)	Malignant VCF	chem_shift_vcf	19	0	1	20
Rathore 2017	Suh 2018	Bone marrow lesions (BML)	Malignant BML	chem_shift_bml	36	14	6	70
Tadros 2016	Suh 2018	Bone marrow lesions (BML)	Malignant BML	chem_shift_bml	15	4	1	10
Ovali 2017	Suh 2018	Vertebral compression fractures (VCF)	Malignant VCF	chem_shift_vcf	19	7	0	42
Mittal 2016	Suh 2018	Vertebral compression fractures (VCF)	Malignant VCF	chem_shift_vcf	18	1	2	17
Zampa 2002	Li 2019	Vertebral compression fractures (VCF)	Malignant VCF	chem_shift_vcf	40	8	5	33

study	source	population	condition	Imaging_group	TP	FP	FN	TN
Jung 2003	Li 2019	Vertebral compression fractures (VCF)	Malignant VCF	conv_ce_vcf	27	4	0	51
Bhugaloo 2006	Li 2019	Vertebral compression fractures (VCF)	Malignant VCF	conv_dwi_vcf	28	11	2	27
Oztekin 2009	Li 2019	Vertebral compression fractures (VCF)	Malignant VCF	conv_dwi_vcf	34	3	3	24
Pongorsop 2009	Li 2019	Vertebral compression fractures (VCF)	Malignant VCF	conv_ce_vcf	34	1	1	22
Biffar 2010	Li 2019	Vertebral compression fractures (VCF)	Malignant VCF	conv_dwi_vcf	13	3	7	21
Biffar2011	Li 2019	Vertebral compression fractures (VCF)	Malignant VCF	conv_dwi_vcf	19	0	1	20
Mubarak 2011	Li 2019	Vertebral compression fractures (VCF)	Malignant VCF	conv_dwi_vcf	36	4	8	15
Tokuda 2011	Li 2019	Vertebral compression fractures (VCF)	Malignant VCF	conv_vcf	50	3	3	41
Ogura 2012	Li 2019	Vertebral compression fractures (VCF)	Malignant VCF	chem_shift_vcf	20	0	8	42
Pozzi 2012	Li 2019	Vertebral compression fractures (VCF)	Malignant VCF	conv_dwi_vcf	22	1	1	9
Wonglaksanapimon 2012	Li 2019	Vertebral compression fractures (VCF)	Malignant VCF	conv_dwi_vcf	6	3	1	29
Geith 2013	Li 2019	Vertebral compression fractures (VCF)	Malignant VCF	conv_ce_vcf	12	1	7	24
Geith 2014	Li 2019	Vertebral compression fractures (VCF)	Malignant VCF	conv_dwi_vcf	17	4	3	22
Sung 2014	Li 2019	Vertebral compression fractures (VCF)	Malignant VCF	conv_dwi_vcf	30	1	0	31
Zidan 2014	Li 2019	Vertebral compression fractures (VCF)	Malignant VCF	chem_shift_vcf	14	3	1	14
Arvelo-Perez 2015	Li 2019	Vertebral compression fractures (VCF)	Malignant VCF	conv_ce_vcf	17	6	2	22
Zou 2016	Li 2019	Vertebral compression fractures (VCF)	Malignant VCF	conv_vcf	46	7	3	8
Bacher 2021	Lit search	Vertebral compression fractures (VCF)	Malignant VCF	chem_shift_vcf	31	1	1	62
Kato 2015	Lit search	Vertebral compression fractures (VCF)	Malignant VCF	conv_vcf	28	0	2	30
Maeder 2018	Lit search	Bone marrow lesions (BML)	Malignant BML	chem_shift_bml	90	1	4	26
Perry 2018	Lit search	Bone marrow lesions (BML)	Malignant BML	chem_shift_bml	23	4	2	21
Razek 2019	Lit search	Vertebral compression fractures (VCF)	Malignant VCF	conv_dwi_vcf	23	1	1	18
Schmeel 2018	Lit search	Vertebral compression fractures (VCF)	Malignant VCF	chem_shift_vcf	23	4	2	23
Schmeel 2021	Lit search	Bone marrow lesions (BML)	Malignant BML	chem_shift_bml	34	1	2	52
Shi 2017	Lit search	Bone marrow lesions (BML)	Malignant BML	chem_shift_bml	67	12	4	21
Taheri 2017	Lit search	Bone marrow lesions (BML)	Malignant BML	chem_shift_bml	87	3	0	26
Zafar 2020	Lit search	Vertebral compression fractures (VCF)	Malignant VCF	conv_dwi_vcf	17	8	15	240