National Institute for Health and Care Excellence

Final

Spinal metastases and metastatic spinal cord compression

[A] Evidence reviews for service configuration and delivery – investigations

NICE guideline number NG234

Evidence review underpinning recommendations 1.1.5 to 1.1.10, 1.1.13, 1.1.15 to 1.1.20, 1.2.6 and 1.5.2 to 1.5.4 in the NICE guideline (see also the related economic model in evidence review B)

September 2023

Final

These evidence reviews were developed by NICE

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ISBN: 978-1-4731-5311-0

Contents

Service configuration & delivery (investigations)

Review question

What service configuration and delivery arrangements are effective for the investigation and referral of adults with suspected or confirmed spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Introduction

The configuration of services for the investigation and referral of people with suspected or confirmed spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression raises a number of challenges. People may present at different locations (for example at their GP or at secondary care), they may present as an emergency needing urgent investigations, and they may require transfer to another place for investigations such as MRI. This review aims to compare different ways in which these services can be configured effectively.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

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

Intervention	Any service delivery models (approaches, configurations of resources and services) for the investigation and referral of people with suspected malignant spinal cord compression or suspected spinal metastases, for example:
	• Delivery arrangements:
	  ○ How and when investigations are done, for example:
	  - 2 week wait pathway
	  - Urgent investigation within 24 hours
	  - 7 day scans
	  ○ Where investigations are done, for example
	  - Rapid diagnostic centres
	  - Community diagnostic hubs
	  - Emergency department
	  ○ Who does investigations & how the workforce is managed
	  - Role expansion or task shifting
	  - Staffing models
	• Coordination of care and management of care processes, for example:
	  ○ MSCC coordinators
	  ○ Early involvement of oncology
	  ○ Early involvement of relevant surgical department
	  ○ Communication / referral between providers (for example, from primary care)
	  ○ Multidisciplinary teams

	• Coordination of investigations amongst different providers
Comparison	Interventions compared with: • Each other • Combinations of interventions

Outcomes	**Critical**
	• Overall survival
	• Quality of life
	• Patient satisfaction
	• Neurological and functional status including:
	  ○ Bowel and bladder function
	  ○ Mobility or ambulatory status
	  ○ Time to paralysis (paralysis-free survival)
	
	Important
	• Emergency admission to hospital and length of hospital stay
	• Access to services:
	  ○ Local availability (for example, time/distance travelled to access services)
	  ○ Waiting times for services
	  ○ Time to diagnosis
	  ○ Time to treatment

MSCC: metastatic spinal cord compression

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.

Service delivery evidence

Included studies

Four observational studies were included for this review, all 4 were retrospective cohort studies (Crnalic 2013, McGivern 2014, Mattes 2020, Pease 2004).

The included studies are summarised in Table 2.

One study compared outcomes according to referral source (Crnalic 2013), two studies compared outcomes before and after implementation of a care pathway (Mattes 2020, Pease 2004), and 1 study assessed compliance with guidance from the Royal College of Radiologists at two time points (McGivern 2014).

Two studies were conducted in the United Kingdom, 1 was conducted in Sweden, and 1 was conducted in the United States.

For the related review of clinical evidence and economic model on service configuration and delivery for management and early rehabilitation see evidence review B.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

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

Summary of included studies

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

Table 2: Summary of included studies.

Study	Population	Intervention	Comparison	Outcomes
Crnalic 2013 Retrospective cohort study Sweden	N=68 Men with prostate cancer referred for surgery due to MSCC Mean age (SD): overall age not reported, but age in two different subgroups was provided – median (range) years: • hormone-naïve: 77 (60 – 88) • hormone refractory: 68 (45 – 86) Sex: male = 68	Referred from local hospital	Directly presented to cancer centre	• Access to services: ○ delays related to surgery
Mattes 2020 Retrospective cohort study United States	N=65 People treated with spinal RT for MSCC Mean age (SD): not reported Sex: not reported	No clinical care pathway (2015 - 2017 audit)	Clinical care pathway (2018 - 2019 audit)	• Access to services ○ time to MRI and time to other investigations and treatments
McGivern 2014 Retrospective cohort study United Kingdom	N=919 People treated with spinal RT for MSCC Mean age (SD): not reported Sex: female=187; male=605	Before NICE MSCC guidance (2008 audit)	After NICE MSCC guidance[1] (2012 audit)	• Access to services ○ number of people who were treated in accordance of the guidance provided (in relation to timescale and treatments received)
Pease 2004 Retrospective cohort study United Kingdom	N=148 Inpatients diagnosed with MSCC Mean age (SD): overall age not	No clinical care pathway (1997 audit)	Clinical care pathway (2000 audit)	• Access to services (number of people nursed flat) • Mortality

Study	Population	Intervention	Comparison	Outcomes
	provided but reported by group – median (range) years: • no care pathway: 66 years 6 months (37 – 82); • care pathway: 65 years, 6 months (27 – 88). Sex: female=49; male=68			• Neurological and functional status (mobility)

MSCC: metastatic spinal cord compression; NICE: National Institute for Health and Care Excellence; RT: radiotherapy
1. NICE published guidance for the management of MSCC in November 2008 with recommendations for timely access to MRI, appropriate surgery and radiotherapy, actively managed by an MSCC coordinator. Cancer networks were then tasked with developing referral and care pathways (as part of the development and implementation of Acute Oncology Services) to optimise outcomes for all patients with MSCC and identify those at high risk of MSCC for early intervention.

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

Summary of the evidence

There was very low quality evidence of an important benefit in terms of reduced delays to surgery (general reduced delay to surgery as well as reduced delay to surgery from MRI diagnosis) when patients were able to present directly to a cancer centre rather than being referred by a local hospital.

There were important benefits in one study with the use of a clinical care pathway in terms of improved mortality rate and decreased number of people nursed flat. However, another study showed no important difference in waiting times between services/procedures after the implementation of a clinical care pathway (with the exception of timing between MRI and radiotherapy consultation). This evidence was very low to low quality.

Very low to low quality evidence from a UK national audit showed improvements from 2008 to 2012 in access to services (coinciding with the development of referral and care pathways informed by the NICE 2008 MSCC guidance). There were improvements in the number of people with MSCC who had MRI within 24 hours of referral for radiotherapy, who were discussed with a surgeon, and who had radiotherapy within 24 hours of referral for radiotherapy.

There were no studies identified which reported on quality of life, patient satisfaction, time to paralysis, or emergency admission and length of hospital stay.

See the evidence profiles in appendix F.

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.

Summary of included economic evidence

No economic studies were identified which were applicable to this review question.

Economic model

An economic model was developed for this topic looking at the cost effectiveness of uptraining staff to make complex decisions around people referred to a regional MSCC centre. This was within an MSCC service that was working in accordance with NICE's 2008 guideline principles including the MSCC coordinator model. As the economic model also covered the review questions in evidence report B, the full economic model is reported in appendix I of that report.

The economic model was based on audit data from January 2018 (the launch of the service) to May 2022 from Clatterbridge Cancer Centre regional MSCC service. The MSCC service was set-up based on recommendations made in the previous guideline.

A before and after study design was used to look retrospectively at differences in survival, QALYs and costs following uptraining of staff to make complex decisions around people referred to the centre. The model was also designed to look at trends in survival and costs since the launch of the service to make inferences about improvements over time. The model also used English Indices of Multiple Deprivation to investigate whether these outcomes differed based on levels of deprivation.

The economic analysis found that after uptraining staff survival increased and costs reduced. Length of survival also increased over the time of the service showing steady improvement. These benefits were not evenly distributed across all deprivation groups with the largest benefits coming in the second and third least deprived quintiles.

There were a number of weaknesses with the economic model which are discussed in detail in the full report in evidence report B (appendix I).

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Overall survival, quality of life, patient satisfaction and neurological and functional status were chosen as critical outcomes. This is because efficient referral and care pathways should lead to quicker diagnosis and treatment of metastatic spinal disease leading to better patient outcomes. Emergency admission to hospital and length of stay were important outcomes because an inefficient or delayed referral pathway could increase emergency hospital admissions and result in longer hospital stays. Access to services was chosen as an important outcome to capture service availability in terms of geographic location and waiting times for services. Different configurations (for example centralised versus local) mean that patients may have to travel or wait longer for services.

The quality of the evidence

The quality of the evidence was assessed using GRADE, with all outcomes being rated as low or very low quality. This was predominately due to a very serious overall risk of bias in the studies which contributed to each outcome (mainly due to the risk of confounding), and serious or very serious levels of imprecision in the effect estimates.

No evidence was identified which evaluated the impact of different service configuration and delivery systems on quality of life, patient satisfaction, time to paralysis, or emergency admission and length of hospital stay. Even though the evidence was mainly low quality the committee decided that some of the studies were directly applicable to the UK context using data from audits that compare services for example pre and post implementation of the previous NICE guideline (McGivern 2014) and an audit of an MSCC service that was implemented in accordance with the previous guideline and has since evolved to bring in further refinements which showed steady improvements in length of survival over time (audit of the Clatterbridge Cancer Service - see evidence report B for the related clinical and economic evidence). They therefore gave this evidence more weight in their discussion but also used their expertise and experience and considered recommendations from the previous guideline.

Benefits and harms

The committee discussed that the previous guideline set service configuration standards for care with some detailed recommendations about how they should function. The guideline also led to a NICE quality standard for MSCC which featured service configuration as an important driver for improvements in MSCC care with 2 standards relating to the importance of the role of the MSCC coordinator (statements 4 and 5 - Metastatic spinal cord compression in adults – QS56) and two studies referring to the timing of MRI (statements 2 and 3 - Metastatic spinal cord compression in adults – QS56). The committee agreed that these standards ought to be maintained and improved upon where variation still exists. They therefore used the previous guideline's recommendations as a starting point for their discussion.

Providing a coordinated MSCC service

There was some evidence that referral pathways were associated with better outcomes particularly related to quicker access to services. Whilst it was not clear in the evidence which exact part of the pathway was driving the faster access to services the committee discussed their experience of the care of people with suspected or confirmed spinal metastases or MSCC and that it requires clear pathways and services to address the complex nature and needs of people with the condition. They noted that the evidence was low quality but agreed that having an MSCC service is consistent with previous guidance which set important standards. However, they noted that many such services currently only accept referrals for suspected or confirmed MSCC rather than spinal metastases. Due to this wider group than in the previous guideline the committee recommended that referrals should be made to this service with an appropriate level of urgency (as described in other recommendations related to other evidence reviews – see for example evidence review D for a discussion on timings around recognition) so that services are not overwhelmed. They noted the number of different specialties that have to be involved in the person's care and that access to all of the different investigations and referral to specialties requires one coordinated service to address the person's needs, deal with emergency situations and prevent serious adverse events. They agreed that this can only be achieved if a service is well organised and coordinated. Therefore they decided that there has to be an MSCC service and that it needs to be clear how to refer into it so that people with suspected or confirmed spinal metastases, direct malignant infiltration (DMI) of the spine or MSCC receive prompt diagnosis and treatment in a coordinated way. The committee noted that it is particularly important that referral processes into an MSCC service are clear because this is where delays can lead to serious adverse outcomes. So, they decided to specifically highlight referral processes which is an addition to what was in previous guidance and should improve care.

They discussed that have a designated person as the first point of contact is also very important for the MSCC service. This would be the MSCC coordinator or a designated senior clinician. They acknowledged that usually there would only be one MSCC coordinator in most services and therefore when the MSCC coordinator is not working it would usually be the responsibility of a designated clinician with appropriated expertise to carry out this role. They discussed that some knowledge of cancer or MSCC would be needed so usually that would be an on-call oncology registrar, but they decided to give this as an example rather than being prescriptive about this. This would ensure that referrals into the service and coordination of care within the service take place as promptly and efficiently as possible. Some evidence from a UK audit before and after NICE's 2008 recommendation (which introduced the role of the MSCC coordinator) showed an improvement in access to services with shorter delays to MRI diagnosis and radiotherapy or surgical treatment. The committee noted that there are uncertainties in the evidence because improvements could be a result of many different components of a service. However, they decided that the coordinator role is particularly important to help the person with the condition and the healthcare professionals treating them to navigate the care pathway. Based on their experience of services and how they have evolved and improved since the previous guideline, they recommended that the designated contact is based in the oncology service, as direct access to this speciality can help to minimise delays in triage and treatment planning. The committee agreed that this has clear advantages with ease of access to expertise and knowledge related to a person's primary tumour and prognosis so that this information can then be disseminated quicker to other specialties that are also involved in the MSCC care pathway.

In line with the previous guideline and based on their experience and knowledge of services in which the role of the MSCC coordinator has become an important part (including the Clatterbridge Cancer service - see the de novo analysis of the audit data in evidence report B), the committee agreed to recommend that each MSCC service should ensure that the role of the MSCC coordinator is covered at all times (24 hours a day, 7 days a week) which would be carried out by the designated clinician with appropriated expertise to carry out this role when the MSCC coordinator is not working.

The committee acknowledged, based on experience, that there is still variation in practice in relation to how the coordination of care for people with MSCC is implemented. They noted that the range of clinical specialities involved in care for people with this condition makes this even more difficult. The committee therefore agreed to recommend that MSCC services make clear arrangements to promote coordinated care, for example, by ensuring that referral criteria and processes are clarified, and that communication and information sharing protocols are understood. This would lead to a more effective collaboration between specialties and between primary care and specialist settings which can speed up investigation and diagnosis which ultimately also leads to timely management.

On the basis of their own experience, the committee agreed that MSCC services work most effectively when a multidisciplinary approach is in place, given the number of specialities involved in the care of people with spinal metastases or MSCC. The committee therefore agreed to recommend that MSCC services use a multidisciplinary approach and that each specialty should designate an individual point of contact (which could be a designated person or designated phone number). Having such a single point of contact makes coordination between specialties easier so that the designated first contact knows who to contact when advice or referral is needed. The committee agreed that this would help to make decision making and care planning more efficient and holistic. There was discussion whether all specialities would have to come together in in-person meetings to make decisions which could cause logistical problems and that it is also possible that not all specialties are needed for every discussion. The committee noted that there are now commonly processes in place to make virtual or phone attendance in meetings possible. They did not want to be prescriptive

about the way the multidisciplinary approach is implemented because working practices are generally evolving so they did not specify this.

The committee also considered a new analysis conducted for this guideline of an audit of all people referred to an MSCC service between January 2018 until end of May 2022 in the UK Clatterbridge Cancer Centre (covering a population of 2.4 million people across Cheshire, Merseyside, and the surrounding areas), the details of which are described in the related evidence report B. The committee discussed the analysis of deprivation data in the Clatterbridge Cancer Centre audit data (see the de novo economic model in evidence report B) which showed that people in the higher quintiles of deprivation benefited less from service improvements than people in less deprived areas. They agreed that there were many possible explanations that could lead to such findings, for example having less time or experiencing challenges in accessing health services. However, they also acknowledged that this was not restricted to MSCC alone but also relevant to other conditions. They also discussed this in relation to the equality impact assessment conducted during scoping of the guideline which listed a number of factors including socioeconomic status that lead to different health outcomes in cancer. The committee noted that a lot of the factors that could relate to deprivation and health outcomes are general public health concerns that cannot be addressed in a single guideline but agreed that it is important for healthcare professionals to be aware of the impact of health inequalities on outcomes on particular groups of people with spinal metastases, DMI of the spine or MSCC in their local area (for example deprivation). The committee decided that local services should collect and analyse information related to their services because this could help to identify groups that may access services less or may experience other service inequalities. Investigating such information is important because inequalities vary by region. They acknowledged that healthcare professionals are not always aware of the specific inequalities in their area and that education is therefore needed. They thought that this information and education would enable services to make reasonable adjustments to be made in line with the Equality Act 2010 to help address and reduce inequalities.

Roles in a coordinated MSCC service

The committee agreed on the basis of their own experience, that MSCC services are most effective when roles and responsibilities are clearly defined. They discussed that the condition is an oncological emergency where timing is crucial to prevent serious long term neurological deficits. Having clear roles and responsibilities will speed up processes and make them more efficient so that the person is triaged more quickly to the services they require. They therefore agreed to set out in the recommendations some of the key tasks that the MSCC coordinator would carry out to provide clarity about the role and standardise it. Based on their knowledge of effective coordinated care the committee agreed that having a clear record of all investigations and assessments is one important responsibility of the coordinator. Having this information in one place and being able to provide it to the relevant speciality when needed is an efficient way to support decision making. The MSCC coordinator should ensure that the initial triage regarding the person's care is carried out . In this way the person will get the investigations and management they need in a timely manner. Information sharing is also a responsibility of the coordinator so that the specialties have all the details of the investigations and assessment ready to plan treatment. The committee also discussed that safe and timely discharge is important and that this would require a lot of coordination between services. They therefore agreed that the planning in relation to this should also be included in the role of the MSCC coordinator.

The committee discussed that MSCC is a condition with many facets and complexities and therefore referring clinicians would need advice on topics that are covered in other sections of the guideline. This would be initial information that is immediately needed to assess the urgency of actions, such as the options for pain management, the factors that may indicate that there is spinal instability, when to immobilise someone, when or whether corticosteroids should be given, and whether or not transfer to specialist services may be needed. The

committee discussed that the initial advice could be given by an MSCC coordinator because the role requires a clinical background.

Based on experience the committee noted that being clear that developing a personalised care plan is part of the role of the senior clinician from the multidisciplinary MSCC team would contribute to better coordinated care. They should work with the person and relevant other healthcare professionals to tailor the care plan to the specific identified needs. They agreed that there were a number of potential specialities that have to be contacted for advice (and they gave examples of these) and having someone with a clear responsibility for making a treatment plan would make liaising between specialties more efficient which would also lead to quicker implementation of the plan. They acknowledged that the previous guideline was prescriptive about the time frame for a personalised care plan within 24 hours. The committee decided that it was important to tailor the planning to the individual and gather all relevant information and advice. They also discussed that the previous guideline focused on MSCC only with regards to a treatment plan within 24 hours and that the current guideline also included people with suspected or confirmed spinal metastases which then required more flexibility around timing. They noted that it could take longer for someone with suspected spinal metastases than someone with MSCC who would need an urgent treatment plan and therefore decided not to specify the timing around this.

The committee also agreed to recommend that due to the emergency nature of conditions such as metastatic spinal cord compression; specialist services treating spinal metastases, direct malignant infiltration of the spine, or MSCC should ensure that a senior clinician is available at all times to provide advice to MSCC services. This would ensure the safety of the person so that prompt action can be taken to prevent serious adverse events.

Providing urgent imaging services

Although there were uncertainties in the evidence on the timing of MRI assessments, the committee agreed that earlier scans for people with suspected MSCC, for example, within 24 hours of admission, led to improved patient outcomes. As this was consistent with their own experience and is well established in practice, the committee agreed to be consistent with the 24 hour timeframe of the previous guideline's recommendation to ensure prompt diagnosis and maintain standards. Based on the audit data which organised services consistent with the previous guideline and knowledge of other current practices they made service organisation recommendations to enable this, for example in relation to availability of MRI outside normal working hours and planning appointment lists.

Providing support

Based on evidence related to the new analysis of audit data (particularly related to deprivation) and the equality impact assessment conducted during scoping of the guideline (raising issues such as different outcomes by age, sex, ethnicity and other factors) the committee noted that there are many potential inequalities in how people access services and how they experience their care once in a service. They acknowledged that it is often difficult to pinpoint what people may experience as barriers when accessing services and that it can be easy for healthcare professionals to make assumptions according to broad group characteristics. The committee decided that services have to learn from people's experiences which can only happen by having mechanisms to ask for feedback from people with lived experience and their family or carers. This may highlight particular concerns that people have about any parts of the pathway as well as any other circumstances that create difficulties for them which could be social or practical (for example finding it hard to physically get to the service or having disabilities that may impact how they experience services). They agreed that the MSCC service could adapt to better meet the needs of the people using it, by discussing with people and their family or carers about their experience of the service and any concerns that they may have.

Timing of MRI assessments

The committee noted that the previous guideline's 24 hour MRI turnaround which they decided to adopt because of the emergency nature of the condition, was also based on the previous guideline's economic model which was consulted on and published alongside the guideline and was found to be cost effective. The committee discussed, based on experience, that currently too many people with suspected MSCC are transferred to specialist centres for MRI investigations. They agreed that this would not be needed and that MRI should if possible be at the local hospital or appropriate centre with direct access imaging facilities, as this would usually be quicker and avoid lengthy and potentially painful transfers for the patient. They acknowledged that local hospitals may not always have the capacity to perform MRIs at short notice and in this case transfer to a tertiary centre would be needed.

The committee agreed that less urgency was required for those with suspected spinal metastases or DMI of the spine but without suspicion of MSCC, and that a 1-week timeframe was reasonable. This is due to the much lower risk of disability in case of a few days' treatment delay in this group. Given the less urgent nature they agreed that it should be possible to schedule this MRI at the local hospital.

The committee agreed, based on their experience, that most MRIs could be done in-hours but acknowledged that in some cases an out-of-hours MRI would be appropriate in emergency situations where treatment has to start immediately, for example when there are concerns about a potential spinal column collapse.

How the recommendations might affect services

The committee acknowledged that many MSCC services currently only accept referrals for suspected or confirmed MSCC but not for people with spinal metastases without MSCC. This means that the new recommendations will increase activities for MSCC services significantly. The committee discussed that MSCC services should have spinal oversight and bring together the relevant critical expertise which would have clinical and survival benefits. The evidence from the economic model based on a service that was already set up and providing full spinal oversight showed that once implemented it resulted in cost savings per person and increased overall survival, prevented people losing function and maintained their independence (for key points see the section below and for the full economic model see evidence review B). The committee noted that many services already provide advice on the treatment of spinal metastases or suspected MSCC so relevant experience already exists that would help implement this. There have been substantial improvements since the publication of the previous guideline that recommended MSCC services including the role of the MSCC coordinator. One example of how services have developed and improved is that they have their first contact within oncology which makes services quicker and more efficient because knowledge about the primary cancer and the prognosis can be disseminated to other specialists more quickly aiding decision making. Also, the availability of MRI scanning in local hospitals has improved since the previous guideline and so the committee recommended that people are not transferred unnecessarily. The committee noted that there is still variation in the way the roles within the service are implemented and so recommended the roles and responsibilities for key members of the MSCC service should be to provide clarity about their own role as well as to everyone within the team. Having designated contacts for each specialty within the MSCC service is not current practice everywhere but the committee agreed that this would make information sharing and collaboration across teams quicker and more efficient.

Cost effectiveness and resource use

No previous economic evidence was identified in the review of the economic evidence. Therefore, all considerations around cost effectiveness and resource use were drawn from the bespoke economic model developed for this and Evidence Report B and the committee's own experience and knowledge. The bespoke economic model for the evidence report was a

'before and after' study. The 'before' service was fully compliant with the previous NICE guideline and the 'after' included some upskilling of staff, from a range of disciplines, to become trained MSCC coordinators and strengthen the current working practices. The economic model found that upskilling staff to become MSCC coordinators and be able to make complex decisions around patients referred to a regional MSCC service led to higher survival, greater QALYs and reduced costs. The committee thought these outcomes were plausible even though there were weaknesses with the study due to being unable to adequately control for confounding factors. Extrapolating from this, the committee considered that these cost savings and health improvements came from quicker diagnosis and treatment and that similar interventions to improve these areas would also lead to similar results. The committee also highlighted from the 'before and after' study that survival had improved year on year since the creation of the service. This was used as support for a number of recommendations which mirrored the Clatterbridge Cancer Centre MSCC service.

The bespoke economic model for this guideline did not include any costs for setting-up a coordinated service or training more MSCC coordinators. These costs will include the creation of computer systems (to manage people referred to the service, collect audit data and allow for virtual multidisciplinary team meetings), pathways, referral forms and regional guidelines. A new centre will also need communication, engagement and training events with referring organisations to explain and teach the new processes. This will lead to a large one-off cost. There will be opportunities for learning from other centres, like the Clatterbridge Cancer Centre MSCC service, which will provide efficiencies. The bespoke economic model showed that costs decreased per person after the creation of the service and therefore it could be inferred that implementation costs should be regained over the first few years of a newly set up service.

A number of recommendations were made that mirrored the Clatterbridge regional MSCC centre including a designated point of contact for services available 24 hours a day, 7 days a week and coordinated care including common referral criteria and processes clearly communicated to referring centres. Whilst the economic model did not explicitly look at all these interventions it was noted by the committee that the audit data used in the model started at the creation of the regional service (including the aspects above) and that length of survival had increased and cost per person had decreased over time. Pathways need to make sure that people with suspected MSCC are referred promptly to up-trained staff for a treatment or referral decision to realise the benefits of an MSCC coordinator and having more people trained to this level is one way of achieving this. As above there will be some upfront costs from implementing these recommendations such as running events to promote and explain the pathway, but these should be short term and regained from later cost savings.

The committee raised concerns that whilst there would be benefits from these recommendations that they may not be spread equally across all socioeconomic groups based on the health inequalities analysis in the economic model. Recommendations were therefore made that local services should collect, analyse and disseminate information on local health inequalities and that feedback should be sought from service users and their families so that potential concerns about access to services can be addressed. As auditing of services will already be happening for MSCC services this should not require any additional time or resources. Socio-economic data can be added easily to the audit data for example through matching Indices of Multiple Deprivation data to an individual's postcode.

The committee also recommended that 24-hour MRI should be available locally for urgent cases which potentially require treatment immediately. The committee acknowledged that providing this 24-hours a day leads to higher costs. Out-of-hours services are also difficult to staff. The committee therefore only made this recommendation for these urgent cases where more rapid intervention could lead to large survival and quality of life gains and where costly adverse events (such as paralysis) can be averted.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.1.5 to 1.1.10, 1.1.13, 1.1.15 to 1.1.20, 1.2.8 and 1.5.2 to 1.5.4 in the NICE guideline (see also the related economic model in evidence review B).

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Service delivery

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Appendices

Appendix A Review protocol

Review protocol for review question: What service configuration and delivery arrangements are effective for the investigation and referral of adults with suspected or confirmed spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022303711
1.	Review title	Effective service configuration and delivery arrangements in the investigation and referral of adults with suspected or confirmed spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression
2.	Review question	What service configuration and delivery arrangements are effective for the investigation and referral of adults with suspected or confirmed spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?
3.	Objective	To establish effective service configuration and delivery arrangements for the investigation and referral of adults with suspected or confirmed spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Cumulative Index to Nursing and Allied Health Literature (CINAHL) • Embase • Emcare • Epistemonikos • International Health Technology Assessment (IHTA) database

ID	Field	Content
		• MEDLINE & MEDLINE In-Process Searches will be restricted by: • Systematic review/meta-analysis study design filter • RCT/non-randomised controlled trials study design filter • Date: 1990 onwards (see rationale under Section 10) • English language studies • Human studies Other searches: • Reference searching • Citation searching • Inclusion lists of systematic reviews • Websites The searches will be re-run 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	Service configuration and delivery arrangements in the investigation and referral of adults with suspected or confirmed MSCC

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

ID	Field	Content
		○ 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	Any service delivery models (approaches, configurations of resources and services) for the investigation and referral of people with suspected malignant spinal cord compression or suspected spinal metastases. For example: • Delivery arrangements: ○ How and when investigations are done, for example: - 2 week wait pathway - Urgent investigation within 24 hours - 7 day scans ○ Where investigations are done, for example - Rapid diagnostic centres - Community diagnostic hubs - Emergency department ○ Who does investigations & how the workforce is managed - Role expansion or task shifting - Staffing models • Coordination of care and management of care processes, for example: ○ MSCC coordinators ○ Early involvement of oncology ○ Early involvement of relevant surgical department

ID	Field	Content
		○ Communication / referral between providers (for example from primary care) ○ Multidisciplinary teams • Coordination of investigations amongst different providers
8.	Comparator/Reference standard/Confounding factors	Interventions compared with: • Each other • Combinations of interventions
9.	Types of study to be included	Randomised controlled trials • Non-randomised comparative studies (including before and after designs) • Systematic reviews/meta-analyses. • Service evaluations and audits will be included in the absence of comparative randomised or non-randomised studies.
10.	Other exclusion criteria	Inclusion: • Full text papers Exclusion: • Conference abstracts • Articles published before 1990 (MRI became available in the early 1990s and is the key test for investigation of MSCC). • 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)	• Overall survival • Quality of life • Patient satisfaction • Neurological and functional status including: ○ Bowel and bladder function

ID	Field	Content
		○ Mobility or ambulatory status ○ Time to paralysis (paralysis-free survival)
13.	Secondary outcomes (important outcomes)	• Emergency admission to hospital and length of hospital stay • Access to services: ○ Local availability (for example, time/distance travelled to access services) ○ Waiting times for services ○ Time to diagnosis ○ Time to treatment
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 inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. The full set of records will not be dual screened because the population, interventions and relevant study designs are relatively clear and should be readily identified from titles and abstracts. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.

ID	Field	Content
15.	Risk of bias (quality) assessment	Risk of bias of individual studies will be assessed using the preferred checklist as described in Appendix H of Developing NICE guidelines: the manual: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs • The non-randomised study design appropriate checklist. For example Cochrane ROBINS-I tool for non-randomised controlled trials and cohort studies; the EPOC RoB tool for controlled before and after studies. The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. <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. If sufficient RCTs are available forming a network of relevant interventions, network meta-analysis will be done using MetaInsight V3 (Owen, RK, Bradbury, N, Xin, Y, Cooper, N, Sutton, A. MetaInsight: An interactive web-based tool for analyzing, interrogating, and visualizing network meta-analyses using R-shiny and netmeta. Res Syn Meth. 2019; 10: 569-581) <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.

ID	Field	Content	
		Minimal important differences (MIDs) Default MIDs will be used for risk ratios and continuous outcomes only, unless the committee pre-specifies published or other MIDs for specific outcomes • For risk ratios: 0.8 and 1.25. • For continuous outcomes: ○ MID is calculated by ranking the studies in order of SD in the control arms. The MID is calculated as +/- 0.5 times median SD. ○ For studies that have been pooled using SMD (meta-analysed): +0.5 and -0.5 in the SMD scale are used as MID boundaries. Validity The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/	
17.	Analysis of sub-groups	Evidence will be stratified by: • None 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
		☐	Prognostic

ID	Field	Content		
		☐	Qualitative	
		☐	Epidemiologic	
		☒	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	24 January 2022		
22.	Anticipated completion date	23 August 2023		
23.	Stage of review at time of this sub-mission	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 Guideline Alliance 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) and National Guideline Alliance	
25.	Review team members	NGA Technical Team	
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from 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: [NICE guideline webpage].	
29.	Other registration details		
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=303711	
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	Metastatic spinal cord compression, service, delivery, early rehabilitation and management.	
33.	Details of existing review of same topic by same authors		
34.	Current review status	☒	Ongoing

ID	Field	Content	
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]	
36.	Details of final publication	www.nice.org.uk	
	Relevant papers	N/A	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimal important difference; MSCC: metastatic spinal cord compression; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation

Appendix B Search strategy (clinical/economic)

Literature search strategies for review question: What service configuration and delivery arrangements are effective for the investigation and referral of adults with suspected or confirmed spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Database: Medline – OVID interface

#	Searches
1	Spinal Cord Compression/
2	((spine or spinal or vertebr*) and (metast* or oligometastasis)).tw.
3	(mescc or mscc).tw.
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	or/1-4
6	Case Management/ or "Continuity of Patient Care"/ or Critical Pathways/ or "Delivery of Health Care"/ or "Delivery of Health Care,Integrated"/ or Models, Organizational/ or Patient Care Management/ or Patient Care Planning/ or Patient Care Team/ed, og or Patient-Centered Care/
7	Community-Institutional Relations/ or Hospital-Patient Relations/ or Hospital-Physician Relations/ or Interdepartmental Relations/ or Interinstitutional Relations/ or exp Interprofessional Relations/ or Intersectoral Collaboration/ or Public Relations/
8	(collaboration or team work* or teamwork*).tw.
9	((collaborat* or coordinat* or co ordinat* or integrat* or shared or stepped or systematic) adj2 (care or effort* or health* or interven* or liais* or manag* or model* or pathway* or service* or work*)).ti,ab.
10	((configur* or model*) adj5 (care or healthcare or organi?ation* or practice* or service*)).ti,ab.
11	((case or disease or user*) adj (manag* or plan*)).ti,ab. or (patient* adj5 (mana* or plan*)).ti. or (patient? adj3 manag*).ab. /freq=2
12	(((enhanced or managed) adj care) or multi component or multicomponent).tw.
13	(algorithm* or care manag* or chronic care* or complex intervention* or consultation liais* or cooperative behav* or co operative behav* or multifacet* or multi facet* or multiintervention* or multiple intervention* or organi?ation* intervention* or transdisciplin* or trans disciplin*).tw.
14	(interdisciplin* or inter disciplin* or interinstitutional or inter institutional or interpersonal relation* or inter personal relation* or interprofession* or inter profession* or intraprofession* or intra profession* or (joint adj (disciplin* or profession* or working)) or multidisciplin* or multi disciplin* or multiprofession* or multi profession*).tw.
15	((joint or inter or intra or multi*) adj3 (disciplin* or profession*) adj5 (collaborat* or communicat* or conversation* or educat* or learn* or taught or teach* or train*)).ti,ab.
16	(patient? adj3 care adj3 team?).tw.
17	((communicat* or refer*) adj5 (professional* or disciplin* or interdisciplin* or provider*)).tw.
18	(continuity adj3 (care or healthcare)).tw.
19	((care or healthcare or service*) adj5 delivery).tw.
20	(interprofessional relation* or inter professional relation* or managed care program* or (measur* adj2 care) or ((patient care adj (management or planning or team*)) or professional patient relation*)).ti,ab.
21	((leader* adj2 style*) or ((team or unit) adj2 (culture or lead* or manager*)) or ((human resources or nurs* or rn or personnel or staff*) adj2 leader* adj2 manag*) or (nurs* adj team*)).ti,ab.
22	(((nurs* or staff* or workforce or work force or worker*) adj2 (delivery or high intensity or model* or staffing or system*)) or (model* adj3 integrat*) or ((allocation or modular or team*) adj2 model*) or planning model*).ti,ab.
23	((associate director* or deputy head or doctor? or health professional? or lead? or leader? or manager? or member? or nurs* or registrar? or staff or team?) adj3 communicat*).ti,ab.
24	(efficien* adj2 practice*).ti,ab.
25	((effectiv* or facilitat* or improv*) adj3 (communicat* or team*)).ti,ab.
26	((team* or role* or workforce* or work force*) adj2 (flex* or reflex*)).ti,ab.
27	((rapid* adj3 communicat*) or (enhanc* adj3 (communicat* or team*))).ti,ab.
28	or/6-27
29	exp Health Personnel/ or Health Workforce/
30	(allied health professional* or AHP*1 or clinician* or consultant* or coordinator* or co ordinator* or general practitioner* or GP*1 or h?ematologist* or medic* or neurologist* or neurosurgeon* or nurse* or occupational therapist* or oncologist* or OT*1 or physician* or physiotherapist* or physical therapist* or radiologist* or registrar* or surgeon* or worker* or workforce or work force).ti. or ((allied health professional* or AHP*1 or clinician* or consultant* or coordinator* or co ordinator* or general practitioner* or GP*1 or h?ematologist* or medic* or neurologist* or neurosurgeon* or nurse* or occupational therapist* or oncologist* or OT*1 or physician* or physiotherapist* or physical therapist* or radiologist* or registrar* or surgeon* or worker* or workforce or work force).ab. adj7 ((manag* or rehab* or ablat* or log?roll* or corticosteroid* or dexamethasone or gastric protection or immobili* or kyphoplast* or occupational therap* or physical therap* or physiotherap* or physio therap* or radiotherap* or surgery or surgical or vertebroplast*).ti,ab. or rh.fs.))
31	or/29-30
32	exp Hospitals/ or exp Hospital Units/ or Rehabilitation Centers/

#	Searches
33	((centre* or center* or hospital* or unit? or ward?) adj7 (manag* or neurorehab* or rehab* or ablat* or logroll* or log roll* or corticosteroid* or dexamethasone or gastric protection or immobili* or kyphoplast* or physical therap* or physio-therap* or physio therap* or occupational therap* or radiotherap* or surgery or surgical or vertebroplast*)).ti,ab.
34	(general* adj3 (physiotherap* or physio therap* or physical therap*)).tw.
35	MDT*1.tw.
36	((physio* or orthotic*) adj5 train*).tw.
37	((specialist or tertiary) adj3 (centre* or center* or hospital* or unit*)).tw.
38	(rehab* adj3 (centre* or center*)).tw.
39	or/32-38
40	or/28,31,39
41	exp Emergency Service, Hospital/
42	((community adj2 diagnos* adj (centre* or center* or hub*)) or cdh or one stop shop*).ti,ab.
43	(faster diagnostic standard* or fds).ti,ab.
44	(((express or same day or one stop) adj2 clinic*) or rapid diagnostic centre* or rapid diagnostic center* or rdc).ti,ab.
45	(a&e or (emergency adj (department* or room* or unit*)) or immediate management or ((emergency or urgen*) adj2 (manag* or refer* or treatment* or ward*))).ti,ab.
46	(accident adj2 emergenc*).ti,ab
47	(((((“2" or two) adj week*) or "14 day*") and pathway*) or ((two or "2") adj week wait)).ti,ab.
48	(("7 day" adj7 scan*) or (one week adj3 present*)).ti,ab.
49	(mscc adj (coordinat* or co ordinat*)).ti,ab.
50	(early adj2 (involv* or rehab*)).ti,ab.
51	or/41-50
52	"Personnel Staffing and Scheduling"/ or Shift Work Schedule/ or Work-Life Balance/ or Work Schedule Tolerance/ or Workload/ or og.fs.
53	(handover* or hand over* or handoff* or hand off* or ((nurs* or staff*) adj2 (delivery or mix* or model*)) or roster* or rota? or shift? or skill?mix* or (skill* adj2 mix) or staffing or team brief* or teambuild* or (team* adj2 build*)).ti,ab.
54	(patient* adj2 ratio*).ti,ab.
55	((advance? practice adj2 nurs*).ti,ab.
56	(nurs* adj (advisor* or clinician* or consultant* or practitioner* or specialist*)).ti,ab.
57	((alter* or chang* or expand* or expansion* or shift* or staff*) adj2 (activit* or duty or duties or responsibilit* or role* or task*)).ti,ab.
58	or/52-57
59	or/51,58
60	or/40,59
61	5 and 60
62	exp ANIMALS, LABORATORY/ or exp ANIMAL EXPERIMENTATION/ or exp MODELS, ANIMAL/ or exp RODENTIA/ or (rat or rats or mouse or mice).ti.
63	LETTER/ or EDITORIAL/ or NEWS/ or exp HISTORICAL ARTICLE/ or ANECDOTES AS TOPIC/ or COMMENT/ or CASE REPORT/ or (letter or comment*).ti.
64	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
65	63 not 64
66	62 or 65
67	61 not 66
68	limit 67 to (english language and yr="1990 -Current")

Health economics search

Database: Medline – OVID interface

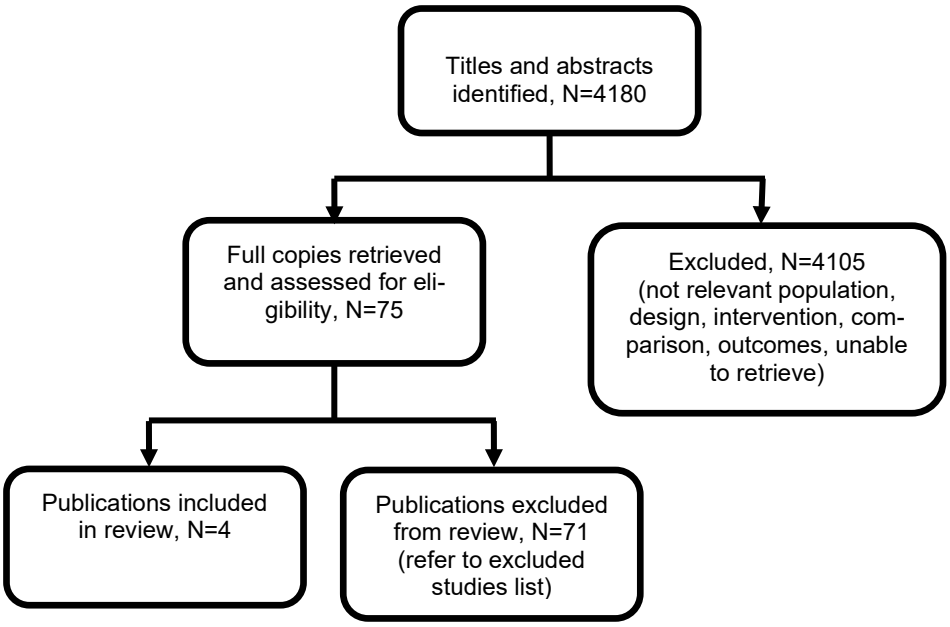
#	Searches
1	exp Spinal Cord Neoplasms/ or Spinal Neoplasms/
2	((spine or spinal or vertebr*) adj2 (adeno* or cancer* or carcinoma* or intraepithelial* or intra epithelial* or malignan* or neoplas* or tumo?r*)).tw.
3	((spine or spinal or vertebr*) and (metast* or oligometast*)).tw.
4	or/1-3
5	Spinal Cord Compression/
6	((cauda equina or cervical* or cervicothoracic or cord* or coccyx or duralsac* or dural sac* or intervertebr* or lumbar or lumbosac* or lumbo sac* or medulla* or orthothoracic or sacral or sacrum or spinal or spine* or thecal sac* or thoracic or vertebr* or epidural or extradural or extra dural or ((axon* or neuron* or nerve*) adj2 root)) and (collaps* or 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 ((axon* or neuron* or nerve*) adj2 root))).tw.
11	or/4,9-10

#	Searches
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 Service delivery evidence study selection

Study selection for: What service configuration and delivery arrangements are effective for the investigation and referral of adults with suspected or confirmed spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What service configuration and delivery arrangements are effective for the investigation and referral of adults with suspected or confirmed spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Table 4: Evidence tables

Crnalic, 2013
Crnalic, Sead; Hildingsson, Christer; Bergh, Anders; Widmark, Anders; Svensson, Olle; Lofvenberg, Richard; Early diagnosis and treatment is crucial for neurological recovery after surgery for metastatic spinal cord compression in prostate cancer.; Acta oncologica (Stockholm, Sweden); 2013; vol. 52 (no. 4); 809-15

Study details

Country/ies where study was carried out	Sweden
Study type	Retrospective cohort study
Study dates	September 2003 to September 2010
Inclusion criteria	Men with prostate cancer referred for surgery as a result of neurological deficit due to metastatic spinal cord compression
Exclusion criteria	Not reported
Patient characteristics	N=68 Patients referred from local hospital (N = 55); directly presented to cancer centre (N = 13) Age at diagnosis of primary tumour, years (range): overall age not reported Hormone-naïve: 77 (60 – 88) Hormone refractory: 68 (45 – 86) Age at surgery for MSCC (years): Hormone-naive: 77 (60 – 88); hormone refractory: 71 (54 – 88)
Intervention(s)/control	Patients were either referred from local hospital or directly presented to cancer centre
Duration of follow-up	Functional outcome was assessed one month after surgery.
Sources of funding	This work was supported by grants from the Swedish Cancer Society and the County Council of Vasterbotten.
Sample size	N=68 Referred from local hospital N=55

	Directly presented to cancer centre N=13

Outcomes

Outcome	Referred from local hospital, 1 month, n=55	Directly presented to cancer centre, 1 month, n=13
Access to services - delay to surgery, days, median (range). IQR not reported.	2 (0 – 24)	1 (0 – 4)
Access to services - delay to surgery from MRI diagnosis, days, median (range). IQR not reported.	1 (0 – 14)	0 (0 – 3)
Access to services - delay to surgery from loss of ambulation, days, median (range). IQR not reported.	1 (0 – 7)	1 (0 – 3)

Critical appraisal – ROBINS-I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Serious. *No adjusting for confounders.*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious. The study has some important problems (no adjusting for confounders).
Overall bias	Risk of bias variation across outcomes	None
Overall bias	Directness	Directly applicable

Mattes, 2020

Mattes M and Nieto J; Quality Improvement Initiative to Enhance Multidisciplinary Management of Malignant Extradural Spinal Cord Compression. JCO Oncology Practice, 16, e829-e83, 2020

Study details

Country/ies where study was carried out	United States.
Study type	Retrospective cohort study
Study dates	2015 - 2019.
Inclusion criteria	All patients diagnosed with malignant extradural spinal cord compression who were treated with radiotherapy to the spine between 2015 and 2017 at the West Virginia University department of radiation oncology.
Exclusion criteria	• Referred for radiotherapy from an outside hospital. • Referred for intramedullary metastasis, leptomeningeal carcinomatosis, or primary central nervous system tumour.
Patient characteristics	N=65 Age: not reported Sex: not reported Primary tumour type: *p* = .425 Lung - initial cohort n=9; follow-up cohort n=2. Prostate - initial cohort n=8; follow-up cohort n=5. Breast - initial cohort n=3; follow-up cohort n=3. Lymphoma - initial cohort n=5; follow-up cohort n=1. Multiple myeloma - initial cohort n=4; follow-up cohort n=5. Other - initial cohort n=11; follow-up cohort n=9. Setting: *p* = .686 Inpatient - initial cohort n=32; follow-up cohort n=21. Outpatient - initial cohort n=8; follow-up cohort n=4. Presenting symptoms: *p* = .118 Pain only - initial cohort n=21; follow-up cohort n=18. Pain plus other neurologic symptoms - initial cohort n=19; follow-up cohort n=7. Previously established diagnosis of malignancy: *p* = .564 Yes - initial cohort n=21; follow-up cohort n=15. No - initial cohort n=19; follow-up cohort n=10. Steroid use: *p* = .403 Yes - initial cohort n=32; follow-up cohort n=22. No - initial cohort n=8; follow-up cohort n=3.

	Surgical consultation: p = .568 Yes - initial cohort n=37; follow-up cohort n=24. No - initial cohort n=3; follow-up cohort n=1. Surgical management: *p* = .965 Initial cohort n=11; follow-up cohort n=7. Initial cohort n=29; follow-up cohort n=18.
Intervention(s)/control	Quality improvement initiative/educational campaign aiming to expedite and improve multidisciplinary care for extradural spinal cord compression patients. A retrospective record review was conducted to record timescales of treatments. This was reviewed by a multidisciplinary group of clinicians who used the findings to develop an internal clinical pathway supported by National Comprehensive Cancer Network recommendations. The proposed clinical pathway, along with the data and practical information about how to consult relevant clinicians and expedite MRI and biopsy studies and their interpretations, was approved by the hospital cancer committee and presented to all relevant departments. Additional feedback was collected from these groups, and the finalized clinical pathway was then e-mailed to each department and published online to allow easy access at any time. This pathway was implemented between 2018 and 2019 and compared to previous years 2015 to 2017.
Duration of follow-up	N/A.
Sources of funding	Not reported.
Sample size	N=65. Initial cohort n=40; follow-up cohort n=25.

Outcomes

Outcome	**No care pathway (2015 - 2017 audit), n=40**	**Care pathway (2018 - 2019 audit), n=25**
Time from hospital admission to MRI, (initial MRI showing extradural spinal cord compression), days, median (IQR):	1 (0 – 1)	1 (0 – 1)
Time from MRI to steroid administration, (initial MRI showing extradural spinal cord compression), days, median (IQR):	0 (0 – 1)	1 (0 – 3)
Time from MRI to initial pathology obtained, (initial MRI showing extradural spinal cord compression), days, median (IQR):	2 (0.5 – 3)	2 (1 – 4.75)
Time from MRI to surgical consultation, (initial MRI showing extradural spinal cord compression), days, median (IQR):	0 (1 – 0)	0 (-1 – 1)
Time from MRI to radiation oncology consultation, (initial MRI showing extradural spinal cord compression), days, median (IQR):	3 (0.75 – 7)	1 (0 – 2)
Time from surgical consultation to surgery, (initial MRI showing extradural spinal cord compression), days, median (IQR):	3 (1.5 – 6.5)	4 (3.5 – 6)

Outcome	No care pathway (2015 - 2017 audit), n=40	Care pathway (2018 - 2019 audit), n=25
Time from radiation oncology to first fraction, (initial MRI showing extradural spinal cord compression), days, median (IQR):	1 (0 – 2)	1 (1 – 1)

Critical appraisal – ROBINS-I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Critical *(Analysis method unlikely to control for all important confounders)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate. *Control group were treated in 2015-2017, intervention group treated 2018-2019: other factors may explain differences in outcomes.*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate. *Unclear whether data were available for all participants - or whether participants were selected because they had available data.*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Critical
Overall bias	Directness	Directly applicable

McGivern, 2014

McGivern, U M; Drinkwater, K J; Clarke, J I M; Locke, I; A royal college of radiologists national audit of radiotherapy in the treatment of metastatic spinal cord compression and implications for the development of acute oncology services.; Clinical oncology (Royal College of Radiologists (Great Britain)); 2014; vol. 26 (no. 8); 453-60

Study details

Country/ies where study was carried out	United Kingdom.
Study type	Retrospective cohort study.

Study dates	First audit - September 2008 - December 2008. Second audit- August 2012.
Inclusion criteria	First audit - all patients with a diagnosis of metastatic spinal cord compression receiving radiotherapy in all UK National Health Service cancer centres. Second audit - All patients presenting to radiotherapy centres with metastatic spinal cord compression.
Exclusion criteria	Not reported.
Patient characteristics	N=919 Age: not reported First audit - Male n=401; female n=195. Second audit - Male n=204 male; female n=92. Number of patients with a previous diagnosis of cancer: Total – 2008 n=448; 2012 n=246. Bladder - 2008 n=9; 2012 n=7. Breast - 2008 n=68; 2012 n=28. Central nervous system - 2008 n=0; 2012 n=2. Colorectal - 2008 n=24; 2012 n=6. GI (upper/lower) - 2008 n=20; 2012 n=8. Gynaecological - 2008 n=4; 2012 n=2. Head and neck - 2008 n=4; 2012 n=8. Lung - 2008 n=69; 2012 n=34. Lymphoma (including leukaemia and myeloma) - 2008 n=39; 2012 n=13. Prostate - 2008 n=146; 2012 n=95. Sarcoma - 2008 n=9; 2012 n=1. Skin - 2008 n=9; 2012 n=7. Unknown primary - 2008 n=6; 2012 n=8. Other (including renal, germ cell, etc.) - 2008 n=38; 2012 n=27. No information - 2008 n=3; 2012 n=0. Number of patients by initial referral source: Total – 2008 n=596; 2012 n=323. Cancer centre - 2008 n=89; 2012 n=67. Cancer unit - 2008 n=74; 2012 n=37. District general hospital (non-cancer unit) - 2008 n=179; 2012 n=70. GP - 2008 n=50; 2012 n=25. Haematology - 2008 n=16; 2012 n=3. Hospice - 2008 n=21; 2012 n=10. Medical oncology - 2008 n=43; 2012 n=16.

	Other hospital speciality - 2008 n=89; 2012 n=67. Other - 2008 n=11; 2012 n=16. No information – 2008 n=24; 2012 n=12. Number of patients by ECOG performance status: Total – 2008 n=596; 2012 n=323. 0 - 2008 n=16; 2012 n=15. 1 - 2008 n=129; 2012 n=59. 2 - 2008 n=132; 2012 n=84. 3 - 2008 n=159; 2012 n=97. 4 - 2008 n=63; 2012 n=22. Number of patients by neurological status Total – 2008 n=596; 2012 n=323 Unaided - 2008 n=173; 2012 n=96. With help - 2008 n=261; 2012 n=153. Paraplegic - 2008 n=98; 2012 n=37. No information - 2008 n=64; 2012 n=37. No information - 2008 n=97; 2012 n=46. Place of discharge (number of patients): Total – 2008 n=596; 2012 n=323 Hospice - 2008 n=50; 2012 n=29. Nursing home - 2008 n=15; 2012 n=8. Own home - 2008 n=238; 2012 n=158. Referring hospital - 2008 n=102; 2012 n=31. Other - 2008 n=21; 2012 n=18. No information - 2008 n=170; 2012 n=79.
Intervention(s)/control	The audits assessed compliance with the following outcomes (derived from the Royal College of Radiation dose-fractionation guidance, based on the NICE guideline 2008) in particular: • Patients with symptoms suggestive of spinal cord compression should have access to an urgent MRI (within 24 h of presentation and referral for radiotherapy). • Patients immobile for <24 h or ambulant or performance status 0, 1 or 2 (‘good prognosis’) should be discussed with neuro/spinal surgeons. • Radiotherapy, if prescribed, should start within 24 h of diagnosis. • Fractionated treatment should be prescribed for patients immobile for <24 h or ambulant and performance status 0, 1 or 2. • Poor prognosis patients, for example, those with established paraplegia for >24 h should only receive radiotherapy for pain relief. Outcomes were measured before and after implementation of the NICE guideline (2008 compared to 2012)

Duration of follow-up	N/A.
Sources of funding	Not reported.
Sample size	First audit - data from n=596 cases received from 42/57 radiotherapy centres. The number of cases received from contributing centres varied from two to 41 (median 11). Second audit - data from n=323 cases received from 52/58 cancer centres. (No details reported regarding number of cases from each centre).
Other information	Second audit - An MSCC coordinator was available in just over 50% of cases (164/323) and involved in patient management in 26% of cases in 2012. No details reported regarding this in relation to the first audit.

Outcomes

Outcome	2012 audit, n=323	2008 audit, n=596
Access to services - number of patients who had an MRI scan within 24 hours of referral for radiotherapy	n = 205/212	n = 358/387
Access to services - number of patients where discussion with a surgeon took place	n = 94/228	n = 111/350
Access to services - number of patients where radiotherapy was started within 24 hours of referral for radiotherapy	n = 243/300	n = 369/512
Access to services - number of patients who received fractionated treatment	n = 132/153	n = 242/275
Access to services - number of patients who received radiotherapy for pain relief	n = 30/114	n = 50/227
Access to services - number of patients who had an MRI at the weekend or outside normal hours	n = 58/323	n = 86/596
Access to services - time between date of referral to oncology and first radiotherapy treatment, days, median (IQR)	1 (0 to 1)	1 (0 to 2)
Access to services - number of patients where discussion of surgical intervention with surgical team was included	n = 104/323	n = 148/596
Access to services - number of patients with ECOG performance status of 0 – 2 (potentially suitable for surgery) where discussion of surgical intervention was recorded	n = 56/158	n = 79/277
Access to services - number of patients with ECOG performance status of 3 – 4 (surgery unlikely to be beneficial) referred to surgical team	n = 43/119	n = 51/222
Access to services - number of patients whose case was discussed with surgical team who went on to have surgical intervention	n = 10/104	n=15/148

Compliance with audit criteria (derived from 2006 Royal College of Radiologists dose-fractionation guidance)

Critical appraisal – ROBINS-I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Critical *(Analysis method unlikely to control for all important confounders)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate (*Control group were treated in 2008, intervention group treated 2012: other factors (beyond service configuration) may explain differences in outcomes.)*
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	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Critical
Overall bias	Directness	Directly applicable

Pease, 2004

Pease, N, Development and audit of a care pathway for the management of patients with suspected malignant spinal cord compression. Physiotherapy, 90, 2004

Study details

Country/ies where study was carried out	United Kingdom.
Study type	Retrospective cohort study. Comparison of 2 audits.
Study dates	1997 and 2000.
Inclusion criteria	Inpatients with a diagnosis of cord compression. Patient identification was done via review of hospital physiotherapy records as all patients with cord compression are referred to the hospital physiotherapy team.
Exclusion criteria	Not reported.

Patient characteristics	N=148 Age, years, and months, median (range): No care pathway 66 years 6 months (37 – 82); care pathway 65 years, 6 months (27 – 88). Sex: No care pathway – female n=17, male n=36; care pathway female n=32, male n=62. Primary cancer site: Prostate - no care pathway n=16; care pathway n=27. Breast - no care pathway n=10; care pathway n=13. Lung/bronchus - no care pathway n=9; care pathway n=18. Gastro-intestinal - no care pathway n=4; care pathway n=7. Unknown - no care pathway n=7; care pathway n=15. Myeloma - no care pathway n=3; care pathway n=6. Other - no care pathway n=4; care pathway n=9. Number of patients on who mobility scores recorded in notes: no care pathway n=35; care pathway n=80. Length of stay, days, median (range): no care pathway 13 (2 – 35); care pathway 12 (1 – 105).
Intervention(s)/control	Care pathway versus no care pathway. The care pathway was implemented in June 1999 by a copy of the pathway being attached to the notes of each patient admitted with suspected cord compression. Decisions made at each stage were dated and signed by medical staff on the relevant section of the pathway, thereby facilitating its monitoring and use. The care pathway was designed to standardise the way in which patients with spinal cord compression were managed and in particular to: • Define the indications and timing for mobilising patients with malignant spinal cord compression. • Clarify who should be referred for an orthopaedic surgery opinion. • Minimise the potential risk of complication as a result of flat bed rest. The care pathway uses guidance from Campbell and Hotchkiss and The Welsh Assembly and was developed by physiotherapy and medical staff. Prior to implementation of the care pathway, patients were nursed supine until completion of their radiotherapy which lasted at least 5 days.
Duration of follow-up	1997 audit - 12 months duration. 2000 audit - 14 months duration. Patient outcomes measured at 60/78 weeks. The second audit did not include inpatients managed on the pathway for its first month of implementation (May 1999), to allow ward staff to become familiar with its use.
Sources of funding	Not reported.
Sample size	N=148.
Other information	**Results** Number of patients nursed flat: 2000 audit n=62/95 (65.3%); 1997 audit 44/52 (84.6%); $\chi 2=5.33$, $p=0.021$. Mortality rate: 2000 audit n=12/95 (12.6%); 1997 audit 18/53 (34%); $\chi 2=8.3$, $p=0.0044$. Mobility: Maintained - 2000 audit n=70/80 (91%); 1997 audit 30/35 (86%); $p=0.79$.

	Improved - 2000 audit n=3/80 (91%); 1997 audit 0/35 (86%); *p*=0.6. Deteriorated - 2000 audit n=7/80 (91%); 1997 audit 5/35 (86%); *p*=0.57.

Outcomes

Outcome	Care pathway (2000 audit), n=53	No care pathway (1997 audit), n=95
Overall survival - mortality rate (follow-up 60 weeks)	n=12	n=18
Neurological and functional status – mobility – maintained or improved (follow-up 60 weeks)	n=73	n=30
Access to services - number of patients nursed flat	n=62	n=44

Critical appraisal – ROBINS-I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Critical *(Analysis method unlikely to control for all important confounders)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate*. (Outcome data not available for all participants, unclear whether missingness is balanced between the 2 groups.)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Critical
Overall bias	Directness	Directly applicable

Appendix E Forest plots

Forest plots for review question: What service configuration and delivery arrangements are effective for the investigation and referral of adults with suspected or confirmed spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

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

Appendix F GRADE tables

GRADE tables for review question: What service configuration and delivery arrangements are effective for the investigation and referral of adults with suspected or confirmed spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Table 5: Evidence profile for comparison between referral from local hospital versus presented directly to cancer centre

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Referred from local hospital	Presented directly to cancer centre	Relative (95% CI)	Absolute		
Access to services - delay to surgery, days, median												
1 (Crnalic 2013)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	n=55 (Median 2, range 0 – 24)	n=13 (Median 1, range 0 – 4)	not estimable	1 day fewer with direct referral (p=0.004)	VERY LOW	IMPORTANT
Access to services - delay to surgery from MRI diagnosis, days, median												
1 (Crnalic 2013)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	n=55 (Median 1, range not reported)	n=13 (Median 0, range 0 – 3)	not estimable	1 day fewer with direct referral (p=0.017)	VERY LOW	IMPORTANT
Access to services - delay to surgery from loss of ambulation, days, median												
1 (Crnalic 2013)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	n=55 (Median 1, range 0 – 7)	n=13 (Median 1, range 0 – 3)	not estimable	0 days fewer with direct referral (p=0.107)	VERY LOW	IMPORTANT

CI: confidence interval; MID: minimal important difference; MRI: magnetic resonance imaging; n: number; SD: standard deviation.
1 Very serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I.
2 Sample size < 100

Table 6: Evidence profile for comparison between clinical care pathway versus no clinical care pathway

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clinical care pathway	No clinical care pathway	Relative (95% CI)	Absolute		
Access to services - time from hospital admission to MRI, days, median (initial MRI showing malignant extradural spinal cord compression)												
1 (Mattes 2020)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	n=40 (Median 1, IQR 0 – 1)	n=25 (Median 1, IQR 0 – 1)	not estimable	0 days fewer with clinical care pathway (p=0.4)	VERY LOW	IMPORTANT
Access to services - time from MRI to steroid administration, days, median (initial MRI showing malignant extradural spinal cord compression)												
1 (Mattes 2020)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	n=40 (Median 0, IQR 0 – 1)	n=25 (Median 1, IQR 0 – 3)	not estimable	1 day fewer with clinical care pathway (p=0.2)	VERY LOW	IMPORTANT
Access to services - time from MRI to initial pathology obtained, days, median (initial MRI showing malignant extradural spinal cord compression)												
1 (Mattes 2020)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[22]	none	n=40 (Median 2, IQR 0.5 – 3)	n=25 (Median 2, IQR 1 – 4.75)	not estimable	0 days fewer with clinical care pathway (p=0.71)	VERY LOW	IMPORTANT
Access to services - time from MRI to surgical consultation, days, median (initial MRI showing malignant extradural spinal cord compression)												
1 (Mattes 2020)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	n=40 (Median 0, IQR 1 – 0)	n=25 (Median 0, IQR −1 – 1)	not estimable	0 days fewer with clinical care pathway (p=0.38)	VERY LOW	IMPORTANT
Access to services - time from MRI to radiation oncology consultation, days, median (initial MRI showing malignant extradural spinal cord compression)												
1 (Mattes 2020)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	n=40 (Median 3, IQR 0.75 – 7)	n=25 (Median 1, IQR 0 – 2)	not estimable	2 days fewer with clinical care pathway (p=0.03)	VERY LOW	IMPORTANT
Access to services - time from surgical consultation to surgery, days, median												
1 (Mattes 2020)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	n=40 (Median 3, IQR 1.5 – 6.5)	n=25 (Median 4, IQR 3.5 – 6)	not estimable	1 day more with clinical care pathway (p=0.25)	VERY LOW	IMPORTANT
Access to services - time from radiation oncology consultation to first fraction, days, median												

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clinical care pathway	No clinical care pathway	Relative (95% CI)	Absolute		
1 (Mattes 2020)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	n=40 (Median 1, IQR 0 – 2)	n=25 (Median 1, IQR 1 – 1)	not estimable	0 days fewer with clinical care pathway (p=0.64)	VERY LOW	IMPORTANT

CI: confidence interval; IQR: interquartile range; MRI: magnetic resonance imaging; n: number; SD: standard deviation.

1 Very serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I.
2 Sample size < 100

Table 7: Evidence profile for comparison between clinical care pathway (2000 audit) versus no clinical care pathway (1997 audit)

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clinical care pathway (2000 audit)	No clinical care pathway (1997 audit)	Relative (95% CI)	Absolute		
Overall survival – mortality rate (follow-up 60 weeks)												
1 (Pease 2004)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	n=12/95 (12.6%)	n=18/53 (34%)	RR 0.37 (0.19 to 0.71)	340 fewer per 1000 (from 340 fewer to 340 fewer)	LOW	CRITICAL
Neurological and functional status – mobility – maintained or improved (follow-up 60 weeks)												
1 (Pease 2004)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	n=73/80 (91.2%)	n=30/35 (85.7%)	RR 1.06 (0.92 to 1.24)	51 more per 1000 (from 69 fewer to 206 more)	LOW	CRITICAL
Access to services – number of patients nursed flat												
1 (Pease 2004)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	n=62/95 (65.3%)	n=44/52 (84.6%)	RR 0.77 (0.64 to 0.93)	846 fewer per 1000 (from 846 fewer to 846 fewer)	VERY LOW	IMPORTANT

CI: confidence interval; n: number; RR: risk ratio.
1 Very serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I.
2 95% CI crosses 1 MID

Table 8: Evidence profile for comparison between 2008 audit versus 2012 audit

Quality assessment							No. of patients		Effect			
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**2012 audit (referral & care pathways implemented by cancer networks)**	**2008 audit**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Access to services - number of patients who had an MRI scan within 24 hours of referral for radiotherapy												
1 (McGivern 2014)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	205/212 (96.7%)	358/387 (92.5%)	RR 1.05 (1.01 to 1.09)	46 more per 1000 (from 9 more to 83 more)	LOW	IMPORTANT
Access to services - number of patients where discussion with a surgeon took place												
1 (McGivern 2014)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	94/228 (41.2%)	111/350 (31.7%)	RR 1.30 (1.05 to 1.62)	95 more per 1000 (from 16 more to 197 more)	VERY LOW	IMPORTANT
Access to services - number of patients where radiotherapy was started within 24 hours of referral for radiotherapy												
1 (McGivern 2014)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	243/300 (81%)	369/512 (72.1%)	RR 1.12 (1.04 to 1.21)	86 more per 1000 (from 29 more to 151 more)	LOW	IMPORTANT
Access to services - number of patients who received fractionated treatment												
1 (McGivern 2014)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	132/153 (86.3%)	242/275 (88%)	RR 0.98 (0.91 to 1.06)	18 fewer per 1000 (from 79 fewer to 53 more)	LOW	IMPORTANT
Access to services - number of patients who received radiotherapy for pain relief												
1 (McGivern 2014)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30/114 (26.3%)	50/227 (22%)	RR 1.19 (0.81 to 1.77)	42 more per 1000 (from 42 fewer to 170 more)	VERY LOW	IMPORTANT
Access to services - number of patients who had an MRI at the weekend or outside normal hours												

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2012 audit (referral & care pathways implemented by cancer networks)	2008 audit	Relative (95% CI)	Absolute		
1 (McGivern 2014)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	58/323 (18%)	86/596 (14.4%)	RR 1.24 (0.92 to 1.69)	35 more per 1000 (from 12 fewer to 100 more)	VERY LOW	IMPORTANT
Access to services - time between date of referral to oncology and first radiotherapy treatment, days, median												
1 (McGivern 2014)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	N=311 (median 1 day, IQR 0 to 1 days)	N=512 (median 1 day, IQR 0 to 2 days)	not estimable	No difference (P not reported)	LOW	IMPORTANT
Access to services - number of patients where discussion of surgical intervention with surgical team was included												
1 (McGivern 2014)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	104/323 (32.2%)	148/596 (24.8%)	RR 1.30 (1.05 to 1.60)	74 more per 1000 (from 12 more to 149 more)	VERY LOW	IMPORTANT
Access to services - number of patients with ECOG performance status of 0 – 2 (potentially suitable for surgery) where discussion of surgical intervention was recorded												
1 (McGivern 2014)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	56/158 (35.4%)	79/227 (34.8%)	RR 1.02 (0.77 to 1.34)	7 more per 1000 (from 80 fewer to 118 more)	VERY LOW	IMPORTANT
Access to services - number of patients with ECOG performance status of 3 – 4 (surgery unlikely to be beneficial) referred to surgical team												
1 (McGivern 2014)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	43/119 (36.1%)	51/222 (23%)	RR 1.57 (1.12 to 2.21)	131 more per 1000 (from 28 more to 278 more)	VERY LOW	IMPORTANT
Access to services - number of patients whose case was discussed with surgical team who went on to have surgical intervention												
1 (McGivern 2014)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	10/104 (9.6%)	15/148 (10.1%)	RR 0.95 (0.44 to 2.03)	5 fewer per 1000 (from 57 fewer to 104 more)	VERY LOW	IMPORTANT

CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; IQR: interquartile range; MID: minimal important difference; n: number; RR: risk ratio
1 Very serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I.
2 95% CI crosses 1 MID
3 95% CI crosses 2 MIDs

Appendix G Economic evidence study selection

Study selection for: What service configuration and delivery arrangements are effective for the investigation and referral of adults with suspected or confirmed 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: What service configuration and delivery arrangements are effective for the investigation and referral of adults with suspected or confirmed 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: What service configuration and delivery arrangements are effective for the investigation and referral of adults with suspected or confirmed spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

An economic evaluation relevant to this evidence report is reported in appendix I of evidence report B.

Appendix J Excluded studies

Excluded studies for review question: What service configuration and delivery arrangements are effective for the investigation and referral of adults with suspected or confirmed spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Excluded service delivery studies

Table 9: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Neurosurgical National Audit Programme (NNAP) https://www.nnap.org.uk/.	Publication type does not match review protocol – conference abstract
Ashcroft, J., Duran, I., Hoefeler, H. et al. (2018) Healthcare resource utilisation associated with skeletal-related events in European patients with multiple myeloma: Results from a prospective, multinational, observational study. European Journal of Haematology 100(5): 479-487	Population does not match review protocol
Barzilai, Ori, Boriani, Stefano, Fisher, Charles G et al. (2019) Essential Concepts for the Management of Metastatic Spine Disease: What the Surgeon Should Know and Practice. Global spine journal 9(1suppl): 98s-107s	Intervention does not match review protocol
Beiser, Erez, Soyfer, Viacheslav, Novikov, Ilyia et al. (2019) A critical assessment of the quality of radiation therapy in Israel: time to initiation of treatment of spinal cord compression as an index of efficiency. Journal of neuro-oncology 143(2): 329-335	Intervention does not match review protocol
Bollen, Laurens, Dijkstra, Sander P D, Bartels, Ronald H M A et al. (2018) Clinical management of spinal metastases-The Dutch national guideline. European journal of cancer (Oxford, England : 1990) 104: 81-90	Study design - does not match review protocol
Brooks, F M, Ghatahora, Ameet, Brooks, M C et al. (2014) Management of metastatic spinal cord compression: awareness of NICE guidance. European journal of orthopaedic surgery & traumatology : orthopedie traumatologie 24suppl1: 255-9	Study design - does not match review protocol
Charlton, P., Sabbagh, A., Shakir, R. et al. (2018) Implementation of the Oxford Acute Referral System (OARS) an Electronic System to Document and Manage the Acute Referral of Patients with Metastatic Spinal Cord Compression (MSCC). Clinical Oncology 30: 12-s13	Study design - does not match review protocol
Chen, Albert C; Bonnen, Mark D; Mok, Henry (2017) Onsite versus offsite radiation treatment of malignant spinal cord compression: lessons from a safety net health system. The British journal of radiology 90(1072): 20160922	Study design - does not match review protocol
Choy, W.J.; Phan, K.; Mobbs, R.J. (2019) Editorial on the integrated multidisciplinary algorithm for the management of spinal metastases.	Study design - does not match review protocol

Study	Reason for exclusion
Translational Cancer Research 8(supplement2): 152-s155	
Curtin, Mark, Piggott, Robert P, Murphy, Evelyn P et al. (2017) Spinal Metastatic Disease: A Review of the Role of the Multidisciplinary Team. Orthopaedic surgery 9(2): 145-151	Intervention - does not match review protocol
Dasenbrock, Hormuzdiyar H, Clarke, Michelle J, Thompson, Richard E et al. (2012) The impact of July hospital admission on outcome after surgery for spinal metastases at academic medical centers in the United States, 2005 to 2008. Cancer 118(5): 1429-38	Study design - does not match review protocol
Dasenbrock, Hormuzdiyar H, Pradilla, Gustavo, Witham, Timothy F et al. (2012) The impact of weekend hospital admission on the timing of intervention and outcomes after surgery for spinal metastases. Neurosurgery 70(3): 586-93	Study design - does not match review protocol
Debono, Bertrand, Braticevic, Cecile, Sabatier, Pascal et al. (2019) The "Friday peak" in surgical referrals for spinal metastases: lessons not learned. A retrospective analysis of 201 consecutive cases at a tertiary center. Acta neurochirurgica 161(6): 1069-1076	Study design - does not match review protocol
Dhamija, B.; Batheja, D.; Balain, B. S. (2021) A systematic review of MIS and open decompression surgery for spinal metastases in the last two decades. Journal of clinical orthopaedics and trauma 22: 101596	Intervention - does not match review protocol
Dunbar, E.M. (2020) Multidisciplinary spine oncology care across the disease continuum. Neuro-Oncology Practice 7: i1-i4	Study design - does not match review protocol
Eleraky, Mohammed; Papanastassiou, Ioannis; Vrionis, Frank D (2010) Management of metastatic spine disease. Current opinion in supportive and palliative care 4(3): 182-8	Intervention - does not match review protocol
Fenton, M. et al. An electronic proforma to improve documentation for cases of metastatic spinal cord compression: A quality-improvement project. Clinical Oncology, Volume 31, e6	Publication type does not match review protocol – conference abstract
Gao, Z. Y., Zhang, T., Zhang, H. et al. (2021) Effectiveness of pre-operative embolization in patients with spinal metastases: a systematic review and meta-analysis. World neurosurgery	Intervention - does not match review protocol
Gasbarrini, Alessandro, Li, Haomiao, Cappuccio, Michele et al. (2010) Efficacy evaluation of a new treatment algorithm for spinal metastases. Spine 35(15): 1466-70	Intervention - does not match review protocol
Gebhardt, B.J., Rajagopalan, M.S., Gill, B.S. et al. (2015) Impact of dynamic changes to a bone metastases pathway in a large, integrated, National Cancer Institute-designated comprehensive cancer center network. Practical Radiation Oncology 5(6): 398-405	Publication type does not match review protocol – conference abstract
Greif, Dylan N, Ghasem, Alexander, Butler, Alexander et al. (2019) Multidisciplinary Management of Spinal Metastasis and Vertebral	Intervention - does not match review protocol

Study	Reason for exclusion
Instability: A Systematic Review. World neurosurgery 128: e944-e955	
Groenen, Karlijn H J, van der Linden, Yvette M, Brouwer, Thea et al. (2018) The Dutch national guideline on metastases and hematological malignancies localized within the spine; a multidisciplinary collaboration towards timely and proactive management. Cancer treatment reviews 69: 29-38	Study design - does not match review protocol
Gutt, R., Malhotra, S., Hagan, M.P. et al. (2021) Palliative Radiotherapy within the Veterans Health Administration: Barriers to Referral and Timeliness of Treatment. JCO Oncology Practice 17(12): e1913-e1922	Study design - does not match review protocol
Guzik, Grzegorz (2018) Analysis of factors delaying the surgical treatment of patients with neurological deficits in the course of spinal metastatic disease. BMC palliative care 17(1): 44	Intervention - does not match review protocol
Hanchanale S, Neoh K, Waldock J, et al MANAGEMENT OF METASTATIC SPINAL CORD COMPRESSION: AUDIT. BMJ Supportive & Palliative Care 2014;4:A54.	Study design - does not match review protocol
Hinojosa-Gonzalez, D. E., Roblesgil-Medrano, A., Villarreal-Espinosa, J. B. et al. (2021) Minimally Invasive versus Open Surgery for Spinal Metastasis: A Systematic Review and Meta-Analysis. Asian spine journal	Intervention - does not match review protocol
Hsiue, Peter P, Kelley, Benjamin V, Chen, Clark J et al. (2020) Surgical treatment of metastatic spine disease: an update on national trends and clinical outcomes from 2010 to 2014. The spine journal : official journal of the North American Spine Society 20(6): 915-924	Intervention - does not match review protocol
Huang, C.W.C., Ali, A., Chang, Y.-M. et al. (2019) Performance of on-call radiology residents in interpreting total spine MRI studies for the detection of spinal cord compression or cauda equina compression. American Journal of Roentgenology 213(6): 1341-1347	Population - does not match review protocol
Khan, H.A., Rabah, N.M., Chakravarthy, V. et al. (2021) Predictors of nonelective surgery for spinal metastases: Insights from a national database. Spine 46(24): e1334-e1342	Population - does not match review protocol
Kim, Ellen, McClelland, Shearwood 3rd, Jaboin, Jerry J et al. (2021) Disparities in Patterns of Conventional Versus Stereotactic Body Radiotherapy in the Treatment of Spine Metastasis in the United States. Journal of palliative care 36(2): 130-134	Outcomes - do not match review protocol
Kumar, Naresh, Thomas, Andrew Cherian, Ramos, Miguel Rafael David et al. (2021) Readmission-Free Survival Analysis in Metastatic Spine Tumour Surgical Patients: A Novel Concept. Annals of surgical oncology 28(5): 2474-2482	Intervention - does not match review protocol
Kurisunkal, Vineet; Gulia, Ashish; Gupta, Srinath (2020) Principles of Management of Spine	Study design - does not match review protocol

Study	Reason for exclusion
Metastasis. Indian journal of orthopaedics 54(2): 181-193	
Lacey, Craig, Ockwell, Clare, Locke, Imogen et al. (2015) A prospective study comparing radiographer- and clinician-based localization for patients with metastatic spinal cord compression (MSCC) to assess the feasibility of a radiographer-led service. The British journal of radiology 88(1055): 20150586	Intervention - does not match review protocol
Lawton, Andrew J, Lee, Kathleen A, Cheville, Andrea L et al. (2019) Assessment and Management of Patients With Metastatic Spinal Cord Compression: A Multidisciplinary Review. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 37(1): 61-71	Study design - does not match review protocol
Levack, P., Graham, J., Collie, D. et al. (2002) Don't wait for a sensory level - Listen to the symptoms: A prospective audit of the delays in diagnosis of malignant cord compression. Clinical Oncology 14(6): 472-480	Comparator - does not match review protocol
Lo, S.S.-M., Ryu, S., Chang, E.L. et al. (2015) ACR Appropriateness Criteria Metastatic Epidural Spinal Cord Compression and Recurrent Spinal Metastasis. Journal of Palliative Medicine 18(7): 573-584	Study design - does not match review protocol
Lo, Wan-Yu and Yang, Shu-Hua (2017) Metastatic spinal cord compression (MSCC) treated with palliative decompression: Surgical timing and survival rate. PloS one 12(12): e0190342	Comparator - does not match review protocol
Macdonald, A Graham, Lynch, Daniel, Garbett, Ian et al. (2019) Malignant spinal cord compression. The journal of the Royal College of Physicians of Edinburgh 49(2): 151-156	Comparator - does not match review protocol
McLinton A, Hutchison C. Malignant spinal cord compression: a retrospective audit of clinical practice at a UK regional cancer centre. Br J Cancer. 2006 Feb 27;94(4):486-91	Comparator - does not match review protocol
Newman, William Christopher, Patel, Ankur, Goldberg, Jacob L et al. (2020) The importance of multidisciplinary care for spine metastases: initial tumor management. Neuro-oncology practice 7(suppl1): i25-i32	Study design – does not match review protocol
Paulino Pereira, N. R., Groot, O. Q., Verlaan, J. J. et al. (2021) Quality of Life Changes After Surgery for Metastatic Spinal Disease: A Systematic Review and Meta-analysis. Clinical spine surgery	Intervention – does not match review protocol
Pease, N.J et al. Development and audit of a care pathway for the management of patients with suspected malignant spinal cord compression. Physiotherapy, Volume 90, Issue 1, 27 - 34	Other protocol criteria - duplicate publication
Pease, N.J.; Harris, R.J.; Finlay, I.G. (2004) Development and audit of a care pathway for the management of patients with suspected	Other protocol criteria - duplicate publication

Study	Reason for exclusion
malignant spinal cord compression. Physiotherapy 90(1): 27-34	
Pennington, Zach, Porras, Jose L, Larry Lo, Sheng-Fu et al. (2021) International Variability in Spinal Metastasis Treatment: A Survey of the AO Spine Community. Global spine journal: 21925682211046904	Population – does not match review protocol
Philipps, L. et al. An Audit of Metastatic Cord Compression Pathways. Clinical Oncology, Volume 30, S4	Publication type does not match review protocol – conference abstract
Pipola, Valerio, Terzi, Silvia, Tedesco, Giuseppe et al. (2018) Metastatic epidural spinal cord compression: does timing of surgery influence the chance of neurological recovery? An observational case-control study. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 26(9): 3181-3186	Intervention – does not match review protocol
Rades, Dirk, Janssen, Stefan, Conde-Moreno, Antonio Jose et al. (2017) Role of the overall treatment time of radiotherapy with 10 x 3 Gy for outcomes in patients with metastatic spinal cord compression. Journal of medical imaging and radiation oncology 61(3): 388-393	Intervention – does not match review protocol
Ratanatharathorn, V. and Powers, W.E. (1991) Epidural spinal cord compression from metastatic tumor: Diagnosis and guidelines for management. Cancer Treatment Reviews 18(1): 55-71	Study design – does not match review protocol
Richards, Lena, Misra, Vivek, Verma, Rajat et al. (2017) 86 - Metastatic Spinal Cord Compression (MSCC) – Collaborative Work between the Tertiary Cancer Centre and the Specialist Spinal Centre Since the Introduction of the MSCC Coordinator Service Has Seen a Marked Increase in Surgical Rates, with 20% of Patients Who Presented with MSCC in the First 24 Months Having Spinal Surgery. This Has Resulted in Improved Survival Rates for MSCC Patients in Greater Manchester and Cheshire. Spine Journal 17: 30-s31	Publication type does not match review protocol – conference abstract
Rudra, Soumon, Lauman, Mary K, Stowe, Hayley et al. (2020) Evaluation of the Metastatic Spine Disease Multidisciplinary Working Group Algorithms as Part of a Multidisciplinary Spine Tumor Conference. Global spine journal 10(7): 888-895	Comparator – does not match review protocol
Schilling, Andrew, Pennington, Zach, Ehresman, Jeff et al. (2021) Impact of Multidisciplinary Intraoperative Teams on Thirty-Day Complications After Sacral Tumor Resection. World neurosurgery 152: e558-e566	Population – does not match review protocol
Services, NHS and Mike Hutton GIRFTClinical Lead for, Spinal (2019) Spinal Services GIRFT Programme National Specialty Report.	Population – does not match review protocol
Shah, S. et al. (2021) Management of Metastatic Spinal Cord Compression in Secondary Care: A	Other protocol criteria – duplicate publication

Study	Reason for exclusion
Practice Reflection from Medway Maritime Hospital, Kent, UK. J. Pers. Med.	
Shah, Sidrah, Kutka, Mikolaj, Lees, Kathryn et al. (2021) Management of Metastatic Spinal Cord Compression in Secondary Care: A Practice Reflection from Medway Maritime Hospital, Kent, UK. Journal of personalized medicine 11(2)	Comparator – does not match review protocol
Souchon, R., Wenz, F., Sedlmayer, F. et al. (2009) DEGRO practice guidelines for palliative radiotherapy of metastatic breast cancer : BBBone metastases and metastatic spinal cord compression (MSCC). Strahlentherapie und Onkologie 185(7): 417-424	Study design – does not match review protocol
Spratt, Daniel E, Beeler, Whitney H, de Moraes, Fabio Y et al. (2017) An integrated multidisciplinary algorithm for the management of spinal metastases: an International Spine Oncology Consortium report. The Lancet. Oncology 18(12): e720-e730	Study design – does not match review protocol
Steinberger, Jeremy M, Yuk, Frank, Doshi, Amish H et al. (2020) Multidisciplinary management of metastatic spine disease: initial symptom-directed management. Neuro-oncology practice 7(suppl1): i33-i44	Study design – does not match review protocol
Tabacof, L., Delgado, A., Dewil, S. et al. (2021) Safety and Feasibility of Outpatient Rehabilitation in Patients with Secondary Bone Cancer: A Preliminary Study. Rehabilitation Oncology 39(3): e42-e50	Comparator – does not match review protocol
Tarawneh, Ahmad M; Pasku, Dritan; Quraishi, Nasir A (2021) Surgical complications and re-operation rates in spinal metastases surgery: a systematic review. 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 30(10): 2791-2799	Intervention – does not match review protocol
Tsukada, Y., Nakamura, N., Ohde, S. et al. (2015) Factors that delay treatment of symptomatic metastatic extradural spinal cord compression. Journal of Palliative Medicine 18(2): 107-113	Intervention – does not match review protocol – study shows treatment is delayed if patients present on weekend
van Tol, Floris R, Choi, David, Verkooijen, Helena M et al. (2019) Delayed presentation to a spine surgeon is the strongest predictor of poor postoperative outcome in patients surgically treated for symptomatic spinal metastases. The spine journal : official journal of the North American Spine Society 19(9): 1540-1547	Intervention – does not match review protocol – study shows poorer outcomes for patients where treatment was delayed
van Tol, Floris R, Massier, Julie R A, Frederix, Geert W J et al. (2021) Costs Associated With Timely and Delayed Surgical Treatment of Spinal Metastases. Global spine journal: 2192568220984789	Intervention – does not match review protocol
Vellayappan, B.A., Kumar, N., Chang, E.L. et al. (2018) Novel multidisciplinary approaches in the	Study design – does not match review protocol

Study	Reason for exclusion
management of metastatic epidural spinal cord compression. Future Oncology 14(17): 1665-1668	
Wallace, Adam N, Robinson, Clifford G, Meyer, Jeffrey et al. (2019) The Metastatic Spine Disease Multidisciplinary Working Group Algorithms. The oncologist 24(3): 424	Study design – does not match review protocol
White, B D, Stirling, A J, Paterson, E et al. (2008) Diagnosis and management of patients at risk of or with metastatic spinal cord compression: summary of NICE guidance. BMJ (Clinical research ed.) 337: a2538	Study design – does not match review protocol
Zaveri, Gautam R, Jain, Reetu, Mehta, Nishank et al. (2021) An Overview of Decision Making in the Management of Metastatic Spinal Tumors. Indian journal of orthopaedics 55(4): 799-814	Study design – does not match review protocol
Zehri, Aqib H, Peterson, Keyan A, Lee, Katriel E et al. (2022) National trends in the surgical management of metastatic lung cancer to the spine using the national inpatient sample database from 2005 to 2014. Journal of clinical neuroscience: official journal of the Neurosurgical Society of Australasia 95: 88-93	Intervention – does not match review protocol

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: What service configuration and delivery arrangements are effective for the investigation and referral of adults with suspected or confirmed spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

No research recommendations were made for this review question.