

Treatment of spine metastases in cancer: a review

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Abstract

As a consequence of the improvements in diagnostic technology along with gains in life expectancy of cancer patients, the incidence of spine metastases has increased. Spine metastases can affect the patient's quality of life and negatively impact on their prognosis. Multidisciplinary treatments involve surgery, chemotherapy, radiosurgery and radiotherapy. Spine metastases should be treated using a multidisciplinary and integrated approach that involves spinal surgeons, medical oncologists and radiologists. More research is required to elucidate the pathological mechanisms involved in the aetiology of spine metastasis. This review describes the current situation regarding the diagnosis of spine metastasis, what is understood about the pathological development of spine metastasis and the evolution of the multidisciplinary treatments that are available for patients with spine metastases.

Keywords

Spine metastases, diagnosis, mechanisms, treatments, cancer

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Introduction

Approximately 20–50% of patients with cancer have spine metastases.¹ Spine metastases are common in many different types of cancer, but are particularly common in patients with lung cancer and breast cancer.² The risk of spine metastases increases with age, time since diagnosis and the number of comorbidities present.² With the prolongation of the life expectancy of cancer patients and improvements in diagnostic methods, the prevalence of spine metastases has increased concomitantly.³ Patients with spine metastases usually present with pain, spinal instability and nerve function deficit, all of which can affect their quality of life.³ This current review will summarize the treatment options for spine metastases in cancer.

Spine metastases in cancer

Cancer cells can metastasize to the spine from a range of cancers including breast cancer,^{4,5} myeloma,^{4,6} uterine cervix carcinoma,⁷ basal cell carcinoma,⁸ peripheral cholangiocarcinoma,⁹ follicular thyroid carcinoma,¹⁰ thymic carcinomas¹¹ and lung cancer.¹² Different tumour types can affect the prognosis of patients with spinal metastases.¹³ It has been reported that patients with colon cancer, hormone-refractory prostate cancer, nonsmall-cell lung cancer and hepatocellular carcinoma have a short postoperative survival time if they have spine metastases.¹³

The early diagnosis of spine metastases is important to improve prognosis and preserve nerve function.¹⁴ Spine metastases can be detected by computed tomography (CT),^{15,16} magnetic resonance imaging (MRI),^{16,17} 2-deoxy-2-F-18 fluoro-D-glucose (FDG) imaging,¹⁸ FDG positron emission tomography (PET),¹⁹ technetium-99m bone scintigraphy²⁰ and F-18 fluoromethylcholine PET CT.²¹ MRI combined with perfusion parameters can predict local

control after stereotactic body radiation therapy (SBRT) in sarcoma spine metastases.²²

Mechanisms of spine metastases in cancer

The processes involved in the establishment of spine metastases include transportation from the primary tumour, arrest within the spine and growth of cancer cells.³ Cancer cells need to pass through the pre-existing cells and stroma within the primary tumour, detaching from these cells and stroma by reducing their levels of cell surface adhesion molecules and opening the epithelial basal lamina, in order to reach and penetrate the blood vessels that will facilitate their transportation around the body.²³ The tumour cells also need to escape the defence mechanisms of the immune system.²³ If these mechanisms are successful, then the primary cancer cells can metastasize to the spine where they grow within the bone marrow.²³ The venous, arterial and lymphatic systems are the principal routes used to facilitate the metastatic colonization of the spine.^{8,12} Invasion of cancer cells in the bone stimulates the production of growth factors, which can activate the osteoblastic or osteolytic processes.²³ Many molecules are involved in osteoblastic and osteolytic processes, including matrix metalloproteinases, proteoglycans, interleukin-1, transforming growth factor- β and vascular endothelial growth factor,¹² but there is limited information on the specific mechanisms involved in the development of metastases in the spine. Further research into the mechanisms involved in spinal metastases is urgently required.

Treatment evolution of spine metastases

From the 1970s, physicians tried to treat spine metastases using a Halo cast,²⁴ a

Halo vest and radiotherapy²⁵ and surgery.^{4,5,26–29} Currently, a multidisciplinary approach is the most common treatment strategy for spine metastases, which usually includes surgery,^{29–36} radiotherapy,^{15,37–48} bone cement,^{49,50} bisphosphonates⁵¹ and chemotherapy.⁵¹ Radiotherapy is an efficient therapeutic approach for symptomatic spine metastases patients that has a low morbidity rate.^{41,52–56} Surgery remains the standard treatment for patients with rapidly progressive spinal cord compression or patients with a high risk of fracture, but it can cause postoperative complications and delay the initiation of other anticancer therapies.^{28,31,57} Minimally-invasive techniques can improve spine stabilization and reduce the morbidity of spine metastases.^{1,30,34,58–64} It is clear that there are several treatments available for spine metastases but not every method is suitable for every patient. The different methodologies have their own characteristics, offering both advantages and disadvantages according to the clinical situation (Table 1). The subsequent sections of this review will summarize the advantages, limitations and some indications of the different treatment modalities that are currently available for spine metastases.

External stabilization is a choice for spine metastasis. With the assistance of orthoses, biomechanical stabilization can be achieved at different spinal levels. However, it can cause some skin complications and may not provide sufficient pain relief in spine metastasis. Thus, it is mainly used in those patients who are awaiting surgery or those that cannot have surgery.⁶³

Radiotherapy is also a common therapeutic approach for cancer patients with spine metastasis. Conventional external beam radiation can provide some palliative effects,⁴² but this conventional method uses a two-dimensional technique and has a large margin. This increases the risk of

unnecessary irradiation to the adjacent normal tissues, so in order to limit the risk of toxicity the radiation is given in fractionated doses, but this can be extremely inconvenient to patients.^{55,65} To improve radiation therapy, three-dimensional conformal radiation therapy was developed.⁵⁵ This technique is based on CT simulation, so there is a better dose-volume calculation that reduces unnecessary irradiation to adjacent organs and provides a more homogeneous irradiation of the target tumour, but the dosage can still not be high enough even with this technique.⁵⁵ With the advancement of radiation therapy technology, radiosurgery that can provide pain relief and improve neurological function has been developed. For example, stereotactic radiosurgery with the help of an image-guidance system can provide a precise high dosage of radiation on the target vertebra while sparing the neighbouring vertebrae and normal tissue especially the spinal cord.⁴² Even in some radio-resistant tumours, stereotactic radiosurgery can be more efficient than external beam radiation.⁵⁴ In the treatment of relapsed vertebral metastasis, external beam radiation only can deliver a modest dose due to the need to avoid radiation-induced injury, but image-guided intensity-modulated radiotherapy can deliver a higher dose of radiation that can better control the recurrent tumour.⁴³ Compared with conventional external beam radiation, stereotactic radiosurgery can preserve more bone marrow, which can be important for the tolerance of chemotherapy.⁵² Moreover, stereotactic radiosurgery is given in one session, which is convenient for patients and does not disturb any ongoing chemotherapy.⁵² Furthermore, it had been demonstrated that single-session stereotactic radiosurgery can provide a higher rate of long-term pain control than multisession stereotactic radiosurgery, but multisession stereotactic radiosurgery provides better local tumour control.⁴²

Table 1. Treatment options for spine metastases.

Author and year	Method	Outcomes
Danzig 1980 ²⁴	Halo cast	Halo cast could protect the cord when patients were treated with chemotherapy and radiotherapy.
Grillo Ruggieri 1988 ²⁵	Halo-vest and radiotherapy	Halo-vest and radiotherapy could be an alternative treatment for cervical spine metastases.
Ono 1988 ²⁶	Prosthetic replacement surgery	Patients with single vertebral body metastases, suffering from severe pain and compression of the nerve root and/or spinal cord could get benefit from prosthetic replacement surgery.
Jonsson 1994 ⁴	Surgery	Surgery was well tolerated and could relieve the pain caused by spine metastases.
Jonsson 1996 ⁵	Surgery	Surgery could decompress and reconstruction improved stabilization. The functional performance was improved in about 50% of patients.
Schulte 2000 ²⁷	Vertebral body replacement	The new radiolucent vertebral body replacement provided sufficient long-term stability and improved prognosis.
Huang 2006 ³⁰	Minimal access spinal surgery	Minimal access spinal surgery was a safe and effective method for thoracic spine metastases.
Gagnon 2007 ³⁷	CyberKnife	Cyber Knife treatment was as effective as conventional external beam radiotherapy and had the similar toxicity.
Jin 2007 ³⁸	Intensity modulated radiotherapy (IMRT) and X-ray based image-guided radiotherapy (IGRT)	IMRT and IGRT could reduce pain and improve nerve function in spinal cord compression patients. IMRT and IGRT were well tolerated methods to treat cancer patients with focal spine metastases.
Amdur 2009 ³⁹	Radiosurgery	Radiosurgery was a good choice for symptomatic spine metastases in areas previously irradiated.
Fehlings 2009 ³¹	Surgery	Posterior techniques were preferred for spine metastases at the occipitocervical junction. Anterior techniques were favoured in the subaxial cervical spine. Either anterior or posterior approaches were recommended in cervicothoracic junction spine metastases.
Moulding 2010 ⁴⁰	Spine radiosurgery after surgical	Spine radiosurgery after surgery was an effective and safe method that could control the disease. Patients receiving a higher radiosurgical dose could get a better outcome.
Haley 2011 ⁴¹	External beam radiation therapy (EBRT) or stereotactic body radiation therapy (SBRT)	EBRT was more likely to have acute toxicity and require additional interventions at the treated sites. SBRT was more expensive, but the efficacy and side-effects were similar to EBRT.
Ryu 2011 ⁵²	Radiosurgery	The phase II study (RTOG 0631) demonstrated radiosurgery is a feasible and accurate method to treat spinal metastases.

(continued)

Table 1. Continued

Author and year	Method	Outcomes
Cho 2012 ²⁸	Surgery	Surgery was an effective method for pain control and neurological recovery in subaxial cervical spinal metastases. Surgical treatment plus adjuvant therapy could control the local disease.
Heron 2012 ⁴²	Single-session (SS) and multise-session (MS) stereotactic radiosurgery (SRS)	SS and MS SRS were effective in spinal metastases treatment. SS SRS was better for pain control. MS SRS was better at delaying tumour progression.
Zairi 2012 ³⁴	Minimally invasive treatment	Minimally invasive treatment was an effective and safe option for thoracolumbar spine metastases. It could improve the quality of life and limit morbidity.
Donanzam 2013 ⁴⁹	Bone cement	Multiphasic calcium phosphates bioceramics with holmium and samarium phosphates composites could release suitable radiation.
Katsoulakis 2013 ⁴³	Third course of IMRT	In patients with multiply recurrent spine metastases, the third course of IMRT was well tolerated and associated with lower toxicity.
Kim 2013 ⁴⁴	SBRT with helical tomotherapy (HT)	SBRT with HT is a safe treatment strategy that could control the local tumour and pain in patients with spine metastases.
Lee 2013 ⁴⁵	Cyber Knife	Cyber Knife was a safe, noninvasive, feasible and effective strategy for inoperable solitary spine metastases.
Lee 2013 ⁴⁶	IMRT and volumetric modulated arc therapy (VMAT)	IMRT and VMAT offered different benefits in dose delivery. IMRT had better pre-treatment verification results and shorter planning times.
Liang 2013 ³⁶	Surgery	In spine metastases patients older than 60 years, surgery could relieve pain and improve neurological function, but the risk of complications was high.
Rao 2014 ⁵⁷	Surgery	Palliative surgery for cervical spine metastases was a safe and low complication method. It could improve neck pain and neurological function.
Sohn 2014 ⁵⁴	SRS and radiation therapy (RT)	SRS provided better control of pain and local disease than RT in renal cell carcinoma spine metastases.
Yang 2015 ⁶¹	Minimal access spinal surgery and open spinal surgery	Both minimal access spinal surgery and open spinal surgery could relieve pain and improve neurological dysfunction for spine metastases. Minimal access spinal surgery had fewer major complications and higher survival rates compared with open spinal surgery.

(continued)

Table 1. Continued

Author and year	Method	Outcomes
Yeo 2015 ⁵⁵	Three-dimensional conformal radiation therapy (3DCRT)	3DCRT could reduce the unnecessary irradiation of critical organs in mid-to-low thoracic spine metastases.
Bagla 2016 ⁵⁰	Radiofrequency ablation (RFA) with cement	RFA with cement augmentation was a safe and effective method to reduce pain and disability in patients with vertebral body metastases.
Guzik 2016 ¹⁶	Surgery	Surgery was a treatment option for cervical spine metastases patients.
Sohn 2016 ⁵⁶	SRS and radiotherapy	SRS and radiotherapy had the similar clinical outcomes in treating spine metastases patients. SRS had fewer side-effects.
Bao 2017 ⁶²	Percutaneous vertebroplasty (PVP)	PVP could effectively treat the pain in cervical metastases patients.
Bernard 2017 ⁶³	Long-segment pedicle-screw fixation and radiotherapy	Less-invasive palliative treatment was a promising treatment in advanced spinal metastases patients. Percutaneous surgery quickly improved the quality of life and walking ability in thoracolumbar instability patients. Long-segment percutaneous screw fixation could provide stability and improve quality of life in spine metastases patients who had early radiation therapy.
Yang 2017 ⁵¹	Surgery and chemotherapy	Surgery for upper cervical spine metastases patients was an effective treatment with low mortality. Surgery combined with an adjuvant therapy could relieve the regional pain and enhance the neurological function, improve the quality of life and prolong the survival period in atlantoaxial metastases patients.
Zairi 2017 ⁶⁴	Long-segment pedicle-screw fixation and radiotherapy	Long-segment percutaneous screw fixation followed by early radiation therapy was an effective and safe treatment option to improve the stability and control the local tumour in spine metastases patients.

It should be noted that radiosurgery cannot solve all the problems and it has its own associated complications. For example, if the pain is caused by the loss of mechanical stability of the spine, radiotherapy is unlikely to relieve that because it lacks the ability to stabilize the spine.⁶³ In addition, radiosurgery is associated with the risk of vertebral compression fractures. Stereotactic body radiotherapy, a type of stereotactic

radiosurgery, is associated with a crude risk rate of vertebral compression fracture of 14%.⁶⁶ Baseline compression fracture, lytic tumour and misalignment are risk factors for stereotactic body radiotherapy-induced vertebral compression fracture.⁶⁶

Surgery is another common choice for spine metastasis treatment. Surgery for patients mainly aims to restore spine stability, relieve pain, decompress the spinal cord

and retrieve tissue samples for pathological diagnosis.⁵⁷ Indications for open surgery are severe pain or significant fracture with displacement, rapidly progressing neurological deficits, failure of conservative treatment, necessary pathological diagnosis, relatively long life expectancy and a relatively good general condition.^{28,51} The surgical approaches and reconstructions that can be used are various and determination of which to use depends on the location of the tumour, the infiltration of the tumour, experience of the surgeons and general condition of the patients.⁵¹ For reconstruction surgery, a new radiolucent system has been developed that can effectively restore the stability of the spine without causing any disturbance to CT, MRI and radiotherapy when compared with a traditional metal system.²⁷ However, most patients with spine metastases are at a late stage of the disease with many comorbidities, malnutrition and poor immune status. Open surgery can cause considerable damage to muscles, blood loss during surgery and it is associated with a high risk of postoperative infections. Patients may not be able to tolerate open surgery. Thus, minimally invasive approaches have been developed and offer several advantages. For example, corpectomy that is used to treat thoracic spine metastasis can be applied through video-assisted thoracic surgery (VATS).³⁰ VATS can limit the damage to soft tissue and provide a good field of vision for surgeons.³⁰ The VATS approach is not indicated in patients that cannot tolerate single lung ventilation or have severe pleural adhesions.³⁰ Another minimally invasive approach, which uses expandable working tubes and percutaneous pedicle screws, was reported to provide stabilization and decompression for treating thoracolumbar spine metastasis.³⁴ This method can relieve pain and improve neurological function whilst causing less injury and having a

lower complication rate.³⁴ Moreover, patients can start adjuvant therapies earlier after surgery.³⁴ But this approach is only indicated in patients with anterior compression that is limited to one level and in those without kyphosis that needs anterior column reconstruction.³⁴ Percutaneous vertebroplasty, percutaneous kyphoplasty and percutaneous osteosynthesis are also minimally invasive surgical options for spine metastasis.⁶³ Percutaneous vertebroplasty is indicated in patients that do not tolerate surgery or radiotherapy.⁶³ It can relieve pain and enhance the strength of the vertebrae, but it has contradictions such as spinal cord compression, tumour extension to the posterior wall of the vertebra, vertebral collapse of more than 75% and recent fracture.⁶³ The use of percutaneous vertebroplasty in cervical metastasis treatment through the anterolateral approach is not indicated in extremely overweight patients and in patients that find it difficult to maintain a cervical extended position.⁶² Cement leakage, spinal cord or radicular compression and pulmonary embolism are potential complications.⁶³ Percutaneous kyphoplasty is a variant of percutaneous vertebroplasty in which kyphon balloons are used to restore the height of the vertebra.^{63,67} The risk of cement leakage is lower than with percutaneous vertebroplasty and it allows the treatment of collapsed vertebra.⁶⁷ Its absolute contradiction is spinal cord compression. Posterior wall involvement is a relative contradiction. However, because of restriction of the size of the balloon, this approach is not suitable for cervical lesions.^{63,67} The vertebral stenting system also provides an effective treatment strategy for spine metastasis. For example, compared with single kyphoplasty, vertebral stenting can improve osteointegration of the cement into the vertebral body, decrease the dose of cement used as well reducing the risk of cement leakage.⁶⁸ If posterior elements are affected or the tumour has

Table 2. Advantages and disadvantages of using radiotherapy for the treatment of spine metastasis.

Type of radiotherapy	Advantages	Disadvantages	References
Two-dimensional conventional external beam radiation therapy	Can alleviate pain using a noninvasive approach	Unnecessary irradiation of the surrounding healthy tissue; multiple fractions required that are not very convenient.	55
Three-dimensional conformal external beam radiation therapy	Provides a better view of the tumour and the surrounding anatomy than the two-dimensional technique, which can reduce unnecessary irradiation on unrelated organs.	The dosage of radiation cannot be high enough due to its inadequate precision.	55
Radiosurgery	Can relieve pain and control the local tumour effectively using a noninvasive approach; can deliver a higher dose of radiation to the tumour site with less unrelated tissue involvement; can deliver a higher dose radiation to treat recurrent spine metastasis after radiotherapy; more bone marrow can be preserved; can be applied in single session.	May increase the risk of vertebral compression fracture; does not have the ability to control the pain caused by mechanical instability.	37,38,42,43,52,56,66
Radiovertebro-plasty (radionuclides mixed into bone cement)	Combines radiotherapy with vertebroplasty; improves the ability of the implants to suppress tumour growth; limits the radiation at the local site.	Compared with most radiotherapy it is an invasive approach.	49,69,70
Systematic use of radionuclides	A noninvasive and cost-effective method and easy to apply; can alleviate pain effectively.	Temporary myelosuppression	71

infiltrated the spinal canal, the former two approaches will be not sufficient and patients will need extra instruments to restore spinal stability. Percutaneous osteosynthesis will have some difficulties in patients with osteoporosis.⁶³ In addition to improvements in surgical techniques, there have also been advancements in how materials are injected. Radioactive isotopes such as samarium-153 can be mixed into bone cement so that minimally-invasive surgery can be combined with radiation therapy. This strategy enhances the antitumour activity of the cement implant, and due to the characteristics of the emitted β radiation, the radiation can be limited to within a small local region.^{49,69,70} This will cause less radiotherapy-induced toxicity than the parenteral application of strontium-89.⁷¹ The advantages and disadvantages of various treatments are summarized in Table 2.

In conclusion, spine metastases should be treated using a multidisciplinary and integrated approach that involves spinal surgeons, medical oncologists and radiologists. More research is required to elucidate the pathological mechanisms involved in the aetiology of spine metastases.

Declaration of conflicting interest


The authors declare that there are no conflicts of interest.

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