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 active the osteoblastic or osteolytic processes.12 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 radiotherapy and surgery. Currently, a multidisciplinary approach is the most common treatment strategy for spine metastases, which usually includes surgery, radiotherapy, bone cement, bisphosphonates and chemotherapy. Radiotherapy is an efficient therapeutic approach for symptomatic spine metastases patients that has a low morbidity rate. 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. Minimally-invasive techniques can improve spine stabilization and reduce the morbidity of spine metastases. 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. 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.

Radiotherapy is also a common therapeutic approach for cancer patients with spine metastasis. Conventional external beam radiation can provide some palliative effects, 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. To improve radiation therapy, three-dimensional conformal radiation therapy was developed. 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. 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. Even in some radio-resistant tumours, stereotactic radiosurgery can be more efficient than external beam radiation. 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. Compared with conventional external beam radiation, stereotactic radiosurgery can preserve more bone marrow, which can be important for the tolerance of chemotherapy. Moreover, stereotactic radiosurgery is given in one session, which is convenient for patients and does not disturb any ongoing chemotherapy. 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.
Table 1. Treatment options for spine metastases.

| Author and year | Method                                      | Outcomes                                                                                                                                                                                                 |
|-----------------|---------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Danzig 1980     | Halo cast                                   | Halo cast could protect the cord when patients were treated with chemotherapy and radiotherapy.                                                                                                         |
| Grillo Ruggieri | Halo-vest and radiotherapy                  | Halo-vest and radiotherapy could be an alternative treatment for cervical spine metastases.                                                                                                              |
| Ono 1988        | 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    | Surgery                                     | Surgery was well tolerated and could relieve the pain caused by spine metastases.                                                                                                                        |
| Jonsson 1996    | Surgery                                     | Surgery could decompress and reconstruction improved stabilization. The functional performance was improved in about 50% of patients.                                                                       |
| Schulte 2000    | Vertebral body replacement                  | The new radiolucent vertebral body replacement provided sufficient long-term stability and improved prognosis.                                                                                         |
| Huang 2006      | Minimal access spinal surgery               | Minimal access spinal surgery was a safe and effective method for thoracic spine metastases.                                                                                                             |
| Gagnon 2007     | CyberKnife                                  | Cyber Knife treatment was as effective as conventional external beam radiotherapy and had the similar toxicity.                                                                                          |
| Jin 2007        | Intensity modulated radiotherapy (IMRT)     | 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      | Radiosurgery                                | Radiosurgery was a good choice for symptomatic spine metastases in areas previously irradiated.                                                                                                        |
| Fehlings 2009   | 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   | Spine radiosurgery after surgical treatment | 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      | External beam radiation therapy (EBRT)      | 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        | Radiosurgery                                | The phase II study (RTOG 0631) demonstrated radiosurgery is a feasible and accurate method to treat spinal metastases.                                                                                     |
Table 1. Continued

| Author and year | Method | Outcomes |
|-----------------|--------|----------|
| Cho 2012<sup>28</sup> | 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<sup>42</sup> | Single-session (SS) and multisession (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<sup>34</sup> | 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<sup>49</sup> | Bone cement | Multiphasic calcium phosphates bioceramics with holmium and samarium phosphates composites could release suitable radiation. |
| Katsoulakis 2013<sup>43</sup> | 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<sup>44</sup> | 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<sup>45</sup> | Cyber Knife | Cyber Knife was a safe, noninvasive, feasible and effective strategy for inoperable solitary spine metastases. |
| Lee 2013<sup>46</sup> | 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<sup>36</sup> | 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<sup>57</sup> | Surgery | Palliative surgery for cervical spine metastases was a safe and low complication method. It could improve neck pain and neurological function. |
| Sohn 2014<sup>54</sup> | SRS and radiation therapy (RT) | SRS provided better control of pain and local disease than RT in renal cell carcinoma spine metastases. |
| Yang 2015<sup>61</sup> | 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)
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. 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%. Baseline compression fracture, lytic tumour and misalignment are risk factors for stereotactic body radiotherapy-induced vertebral compression fracture.

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

| Author and year | Method | Outcomes |
|-----------------|--------|----------|
| Yeo 2015<sup>55</sup> | Three-dimensional conformal radiation therapy (3DCRT) | 3DCRT could reduce the unnecessary irradiation of critical organs in mid-to-low thoracic spine metastases. |
| Bagla 2016<sup>50</sup> | 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<sup>16</sup> | Surgery | Surgery was a treatment option for cervical spine metastases patients. |
| Sohn 2016<sup>56</sup> | SRS and radiotherapy | SRS and radiotherapy had the similar clinical outcomes in treating spine metastases patients. SRS had fewer side-effects. |
| Bao 2017<sup>62</sup> | Percutaneous vertebroplasty (PVP) | PVP could effectively treat the pain in cervical metastases patients. |
| Bernard 2017<sup>63</sup> | 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<sup>51</sup> | 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<sup>64</sup> | 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. |
and retrieve tissue samples for pathological diagnosis.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{30} VATS can limit the damage to soft tissue and provide a good field of vision for surgeons.\textsuperscript{30} The VATS approach is not indicated in patients that cannot tolerate single lung ventilation or have severe pleural adhesions.\textsuperscript{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.\textsuperscript{34} This method can relieve pain and improve neurological function whilst causing less injury and having a lower complication rate.\textsuperscript{34} Moreover, patients can start adjuvant therapies earlier after surgery.\textsuperscript{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.\textsuperscript{34} Percutaneous vertebroplasty, percutaneous kyphoplasty and percutaneous osteosynthesis are also minimally invasive surgical options for spine metastasis.\textsuperscript{63} Percutaneous vertebroplasty is indicated in patients that do not tolerate surgery or radiotherapy.\textsuperscript{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.\textsuperscript{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.\textsuperscript{62} Cement leakage, spinal cord or radicular compression and pulmonary embolism are potential complications.\textsuperscript{63} Percutaneous kyphoplasty is a variant of percutaneous vertebroplasty in which kyphon balloons are used to restore the height of the vertebra.\textsuperscript{63,67} The risk of cement leakage is lower than with percutaneous vertebroplasty and it allows the treatment of collapsed vertebra.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. | 37,38,42,52,56,66   |
| 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. 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. This will cause less radiotherapy-induced toxicity than the parenteral application of strontium-89. 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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References

1. Zairi F, Marinho P, Allaoui M, et al. New advances in the management of thoracolumbar spine metastasis. Bull Cancer 2013; 100: 435–441 [Article in French, English abstract].
2. Sohn S, Kim J, Chung CK, et al. A nationwide epidemiological study of newly diagnosed spine metastasis in the adult Korean population. Spine J 2016; 16: 937–945.
3. Smorgick Y, Mirovsky Y, Shalmon E, et al. Diagnosis and treatment of spine metastases. Harefuah 2007; 146: 358–363 [Article in Hebrew, English abstract].
4. Jonsson B, Jonsson H Jr, Karlstrom G, et al. Surgery of cervical spine metastases: a retrospective study. Eur Spine J 1994; 3: 76–83.
5. Jonsson B, Sjostrom L, Olerud C, et al. Outcome after limited posterior surgery for thoracic and lumbar spine metastases. Eur Spine J 1996; 5: 36–44.
6. Wegener B, Muller PE, Jansson V, et al. Cervical spine metastasis of multiple myeloma: a case report with 16 years of follow-up. Spine (Phila Pa 1976) 2004; 29: E368–E372.
7. Fisher MS. Lumbar spine metastasis in cervical carcinoma: a characteristic pattern. Radiology 1980; 134: 631–634.
8. Oram Y, Oremo I, Alford E, et al. Basal cell carcinoma of the scalp resulting in spine metastasis in a black patient. J Am Acad Dermatol 1994; 31: 916–920.
9. Yeh CN, Chen MF, Chen TC, et al. Peripheral cholangiocarcinoma with thoracic spine metastasis: a successful surgically treated case. Int Surg 2001; 86: 225–228.
10. Habra MA and Vassilopoulou-Sellin R. Cervical spine metastasis mimicking thyroid bed uptake in follicular thyroid carcinoma. *Thyroid* 2005; 15: 298–299.

11. Liu T, Qiu G and Tian Y. Thymic carcinoma with primary spine metastasis. *J Clin Neurosci* 2011; 18: 840–842.

12. Greenberger JS. The pathophysiology and management of spine metastasis from lung cancer. *J Neurooncol* 1995; 23: 109–120.

13. Robin AM, Yamada Y, McLaughlin LA, et al. Stereotactic radiosurgery: the revolutionary advance in the treatment of spine metastases. *Neurosurgery* 2017; 64: 59–65.

14. de Moraes FY, Taunk NK, Laufer I, et al. Spine radiosurgery for the local treatment of spine metastases: intensity-modulated radiotherapy, image guidance, clinical aspects and future directions. *Clinics* (Sao Paulo) 2016; 71: 101–109.

15. Mitera G, Probyn L, Ford M, et al. Correlation of computed tomography imaging features with pain response in patients with spine metastases after radiation therapy. *Int J Radiat Oncol Biol Phys* 2011; 81: 827–830.

16. Guzik G. Quality of life of patients after surgical treatment of cervical spine metastases. *BMC Musculoskelet Disord* 2016; 17: 315.

17. Liu WM, Xing R, Bian C, et al. Predictive value of pedicle involvement with MRI in spine metastases. *Oncotarget* 2016; 7: 62697–62705.

18. Shreve PD, Steventon RS and Gross MD. Diagnosis of spine metastases by FDG imaging using a gamma camera in the coincidence mode. *Clin Nucl Med* 1998; 23: 799–802.

19. Laufer I, Lis E, Pisinski L, et al. The accuracy of [18F]fluorodeoxyglucose positron emission tomography as confirmed by biopsy in the diagnosis of spine metastases in a cancer population. *Neurosurgery* 2009; 64: 107–113.

20. Sabour S and Derakhshan S. Technetium-99m bone scintigraphy in the detection of cervical spine metastases in oncological patients; methodological issues on diagnostic value. *Spine (Phila Pa 1976)*. Epub ahead of print 4 January 2018. DOI: 10.1097/BRS.0000000000002543.

21. Poulsen MH, Petersen H, Hoilund-Carlsen PF, et al. Spine metastases in prostate cancer: comparison of technetium-99m-MDP whole-body bone scintigraphy, [18F] choline positron emission tomography (PET)/computed tomography (CT) and [18F]NaF PET/CT. *BJU Int* 2014; 114: 818–823.

22. Spratt DE, Arevalo-Perez J, Leeman JE, et al. Early magnetic resonance imaging biomarkers to predict local control after high dose stereotactic body radiotherapy for patients with sarcoma spine metastases. *Spine J* 2016; 16: 291–298.

23. Maccauro G, Spinelli MS, Mauro S, et al. Physiopathology of spine metastasis. *Int J Surg Oncol* 2011; 2011: 107969.

24. Danzig LA, Resnick D and Akeson WH. The treatment of cervical spine metastasis from the prostate with a Halo cast. *Spine (Phila Pa 1976)* 1980; 5: 395–398.

25. Grillo Ruggieri F, Ruelle A, Cavazzani P, et al. Halo-vest and radiotherapy. An alternative approach to cervical spine metastases. *Panminerva Med* 1988; 30: 81–86.

26. Ono K, Yonenobu K, Ebara S, et al. Prosthetic replacement surgery for cervical spine metastasis. *Spine (Phila Pa 1976)* 1988; 13: 817–822.

27. Schulte M, Schultheiss M, Hartwig E, et al. Vertebral body replacement with a bioglass-polyurethane composite in spine metastases—clinical, radiological and biomechanical results. *Eur Spine J* 2000; 9: 437–444.

28. Cho W and Chang UK. Neurological and survival outcomes after surgical management of subaxial cervical spine metastases. *Spine (Phila Pa 1976)* 2012; 37: E969–E977.

29. Bhatt AD, Schuler JC, Boakye M, et al. Current and emerging concepts in non-invasive and minimally invasive management of spine metastasis. *Cancer Treat Rev* 2013; 39: 142–152.

30. Huang TJ, Hsu RW, Li YY, et al. Minimal access spinal surgery (MASS) in treating thoracic spine metastasis. *Spine (Phila Pa 1976)* 2006; 31: 1860–1863.

31. Fehlings MG, David KS, Vialle L, et al. Decision making in the surgical treatment
of cervical spine metastases. *Spine (Phila Pa 1976)* 2009; 34: S108–S117.

32. Imamura H, Kohno J, Kishimoto T, et al. Three patients successfully treated with orthopedic surgery for spinal paralysis due to spine metastasis of gastric cancer. *Gan To Kagaku Ryoho* 2009; 36: 2342–2344 [Article in Japanese, English abstract].

33. Crabtree KL, Anderson KK, Haynes NG, et al. Surgical treatment of multiple spine metastases from gastrinoma. *Evid Based Spine Care J* 2011; 2: 45–50.

34. Zairi F, Arikat A, Allaoui M, et al. Minimally invasive decompression and stabilization for the management of thoracolumbar spine metastasis. *J Neurosurg Spine* 2012; 17: 19–23.

35. Zairi F, Vieillard MH and Assaker R. Spine metastases: are minimally invasive surgical techniques living up to the hype? *CNS Oncol* 2015; 4: 257–264.

36. Liang T, Wan Y, Zou X, et al. Is surgery for spine metastasis reasonable in patients older than 60 years? *Clin Orthop Relat Res* 2013; 471: 628–639.

37. Gagnon GJ, Henderson FC, Gehan EA, et al. Cyberknife radiosurgery for breast cancer spine metastases: a matched-pair analysis. *Cancer* 2007; 110: 1796–1802.

38. Jin JY, Chen Q, Jin R, et al. Technical and clinical experience with spine radiosurgery: a new technology for management of localized spine metastases. *Technol Cancer Res Treat* 2007; 6: 127–133.

39. Amdur RJ, Bennett J, Olivier K, et al. A prospective, phase II study demonstrating the potential value and limitation of radiosurgery for spine metastases. *Am J Clin Oncol* 2009; 32: 515–520.

40. Moulding HD, Elder JB, Lis E, et al. Local disease control after decompressive surgery and adjuvant high-dose single-fraction radiosurgery for spine metastases. *J Neurosurg Spine* 2010; 13: 87–93.

41. Haley ML, Gerszten PC, Heron DE, et al. Efficacy and cost-effectiveness analysis of external beam and stereotactic body radiation therapy in the treatment of spine metastases: a matched-pair analysis. *J Neurosurg Spine* 2011; 14: 537–542.

42. Heron DE, Rajagopalan MS, Stone B, et al. Single-session and multisession CyberKnife radiosurgery for spine metastases – University of Pittsburgh and Georgetown University experience. *J Neurosurg Spine* 2012; 17: 11–18.

43. Katsoulakis E, Riaz N, Cox B, et al. Delivering a third course of radiation to spine metastases using image-guided, intensity-modulated radiation therapy. *J Neurosurg Spine* 2013; 18: 63–68.

44. Kim MS, Keum KC, Cha JH, et al. Stereotactic body radiotherapy with helical tomotherapy for pain palliation in spine metastasis. *Technol Cancer Res Treat* 2013; 12: 363–370.

45. Lee S, Chun M and Lee M. Stereotactic body radiotherapy for solitary spine metastasis. *Radiat Oncol J* 2013; 31: 260–266.

46. Lee YK, Bedford JL, McNair HA, et al. Comparison of deliverable IMRT and VMAT for spine metastases using a simultaneous integrated boost. *Br J Radiol* 2013; 86: 20120466.

47. Ryu S, Yoon H, Stassin A, et al. Contemporary treatment with radiosurgery for spine metastasis and spinal cord compression in 2015. *Radiat Oncol J* 2015; 33: 1–11.

48. Redmond KJ, Lo SS, Fisher C, et al. Postoperative Stereotactic Body Radiation Therapy (SBRT) for spine metastases: a critical review to guide practice. *Int J Radiat Oncol Biol Phys* 2016; 95: 1414–1428.

49. Donanzam BA, Campos TP, Dalmazio I, et al. Synthesis and characterization of calcium phosphate loaded with Ho-166 and Sm-153: a novel biomaterial for treatment of spine metastases. *J Mater Sci Mater Med* 2013; 24: 2873–2880.

50. Bagla S, Sayed D, Smirniotopoulos J, et al. Multicenter prospective clinical series evaluating radiofrequency ablation in the treatment of painful spine metastases. *Cardiovasc Intervent Radiol* 2016; 39: 1289–1297.

51. Yang J, Jia Q, Peng D, et al. Surgical treatment of upper cervical spine metastases: a retrospective study of 39 cases. *World J Surg Oncol* 2017; 15: 21.
52. Ryu S, Pugh SL, Gerszten PC, et al. RTOG 0631 phase II/III study of image-guided stereotactic radiosurgery for localized (1-3) spine metastases: phase II results. *Int J Radiat Oncol Biol Phys* 2011; 81: S131–S132.

53. Bowden PJ, See AW, Dally MJ, et al. Stereotactic radiosurgery for brain and spine metastases. *J Clin Neurosci* 2014; 21: 731–734.

54. Sohn S, Chung CK, Sohn MJ, et al. Stereotactic radiosurgery compared with external radiation therapy as a primary treatment in spine metastasis from renal cell carcinoma: a multicenter, matched-pair study. *J Neurooncol* 2014; 119: 121–128.

55. Yeo SG. Palliative radiotherapy for thoracic spine metastases: dosimetric advantage of three-dimensional conformal plans. *Oncol Lett* 2015; 10: 497–501.

56. Sohn S, Chung CK, Sohn MJ, et al. Radiosurgery compared with external radiation therapy as a primary treatment in spine metastasis from hepatocellular carcinoma: a multicenter, matched-pair study. *J Korean Neurosurg Soc* 2016; 59: 37–43.

57. Rao J, Tiruchelvarayan R and Lee L. Palliative surgery for cervical spine metastasis. *Singapore Med J* 2014; 55: 569–573.

58. Zairi F, Marinho P, Bouras A, et al. Recent concepts in the management of thoraco-lumbar spine metastases. *J Neurosurg Sci* 2017; 61: 365–370.

59. Donnelly DJ, Abd-El-Barr MM and Lu Y. Minimally invasive muscle sparing posterior-only approach for lumbar circumferential decompression and stabilization to treat spine metastasis – technical report. *World Neurosurg* 2015; 84: 1484–1490.

60. Guarnieri G, Izzo R and Muto M. Current trends in mini-invasive management of spine metastases. *Interv Neuroradiol* 2015; 21: 263–272.

61. Yang Z, Yang Y, Zhang Y, et al. Minimal access versus open spinal surgery in treating painful spine metastasis: a systematic review. *World J Surg Oncol* 2015; 13: 68.

62. Bao L, Jia P, Li J, et al. Percutaneous vertebroplasty relieves pain in cervical spine metastases. *Pain Res Manag* 2017; 2017: 3926318.

63. Bernard F, Lemee JM, Lucas O, et al. Postoperative quality-of-life assessment in patients with spine metastases treated with long-segment pedicle-screw fixation. *J Neurosurg Spine* 2017; 26: 725–735.

64. Zairi F, Vielliard MH, Bouras A, et al. Long-segment percutaneous screw fixation for thoraco-lumbar spine metastases: a single center’s experience. *J Neurosurg Sci* 2017; 61: 365–370.

65. Ryu S, Fang Yin F, Rock J, et al. Image-guided and intensity-modulated radiosurgery for patients with spinal metastasis. *Cancer* 2003; 97: 2013–2018.

66. Sahgal A, Atenafu EG, Chao S, et al. Vertebral compression fracture after spine stereotactic body radiotherapy: a multi-institutional analysis with a focus on radiation dose and the spinal instability neoplastic score. *J Clin Oncol* 2013; 31: 3426–3431.

67. Wang Y, Liu H, Pi B, et al. Clinical evaluation of percutaneous kyphoplasty in the treatment of osteolytic and osteoblastic metastatic vertebral lesions. *Int J Surg* 2016; 30: 161–165.

68. Itshayek E, Fraifeld S, Vargas AA, et al. Efficacy and safety of vertebral stenting for painful vertebral compression fractures in patients with metastatic disease. *Neurol Res* 2014; 36: 1086–1093.

69. Lu J, Deng J, Zhao H, et al. Safety and feasibility of percutaneous vertebroplasty with radioactive (153)Sm PMMA in an animal model. *Eur J Radiol* 2011; 78: 296–301.

70. Cardoso ER, Ashamalla H, Weng L, et al. Percutaneous tumor curettage and interstitial delivery of samarium-153 coupled with kyphoplasty for treatment of vertebral metastases. *J Neurosurg Spine* 2009; 10: 336–342.

71. Giammarile F, Moggetti T and Resche I. Bone pain palliation with strontium-89 in cancer patients with bone metastases. *Q J Nucl Med* 2001; 45: 78–83.