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Review

Spine metastases: Current treatments and future directions

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ABSTRACT

Spinal metastases are the most frequently encountered spinal tumour and can affect up to 50% of cancer patients. Both the incidence and prevalence of metastases are thought to be rising due to better detection and treatment options of the systemic malignancy resulting in increased patient survival. Further, the development and access to newer imaging modalities have resulted in easier screening and diagnosis of spine metastases. Current evidence suggests that pain, neurological symptoms and quality of life are all improved if patients with spine metastases are treated early and aggressively. However, selection of the appropriate therapy depends on several factors including primary histology, extent of the systemic disease, existing co-morbidities, prior treatment modalities, patient age and performance status, predicted life expectancy and available resources. This article reviews the currently available therapeutic options for spinal metastases including conventional external beam radiation therapy, open surgical decompression and stabilisation, vertebral augmentation and other minimally invasive surgery (MIS) options, stereotactic spine radiosurgery, bisphosphonates, systemic radioisotopes and chemotherapy. An algorithm for the management of spine metastases is also proposed. It outlines a multidisciplinary and integrated approach to these patients and it is hoped that this along with future advances and research will result in improved patient care and outcomes.

1. Introduction

The World Health Organisation (WHO) estimates that 10 million people were diagnosed with cancer worldwide in 2000 and expects cancer rates to increase by 50% to 15 million by 2020. As treatment options improve and patients have an increased survival,[1,2] the incidence and prevalence of spinal metastases, which are known to occur in 30–50% of cancer patients,[3–5] will also rise. Often, these tumours can significantly impact a patient's quality of life as a result of disabling pain, fractures or even paralysis due to spinal cord compression.[6,7] Both early detection and appropriate intervention are essential to minimise the sequelae of spinal metastases and maximise patient function and quality of life.

2. Demographics

The vast majority of spinal metastases arise from breast, lung, prostate or renal primaries reflecting both the prevalence of these cancer types and their predilection to bone.[8–10] Metastatic tumours are the most frequent spine tumours and are estimated to be 20 times more frequent than primary spine tumours.[11] Whilst spinal metastases can develop at any age, the highest incidence is between 40 and 70 years of age

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related to an increased cancer risk during this time. There is also a male predominance of spine metastases,[12,13] however, this is believed to be related to the higher incidence of prostate cancer relative to breast cancer.

Metastatic involvement of the spine arises in the thoracic region 70% of the time followed by the lumbar and then the cervical spine.[8,9,14] Spinal metastases from tumour can spread via the arterial system, Batson's venous plexus, cerebrospinal fluid and direct extension from paraspinous disease. The posterior vertebral body (ventral to the spinal cord) is the initial site of involvement in two-thirds of the cases with the posterior elements being involved typically later and seldom in isolation. Spinal metastases are extradural in 94–98% of patients, predominantly arising in the vertebral column and secondarily extending into the epidural space. Intradural metastases are rare overall with only 0.5% of spine metastases occurring in the intradural/intramedullary compartment.[15,16]

Patients with spinal column metastases are reported to have median overall survival of 7 months, ranging from 3 to 16 months,[17–20] whilst those with epidural spread have median survival of 3–6 months.[20,21] A short life expectancy and the presence of systemic disease are most consistent with palliative treatment regimens rather than a curative treatment. However, with recent advances in cancer treatment and care, patients have longer overall survival, thus elevating the risk for systemic metastases, but also emphasising the importance of treating these lesions to prevent undesired sequelae.[1,22]

3. Signs and symptoms

Up to 10% of cancer patients present with spinal metastases as the initial disease presentation.[22] Pain is the most common manifestation, occurring in 90% of the patients.[8,23,24] Spinal tumour pain can present as local pain exaggerated by palpation or percussion, radicular in nature, implying compression or invasion of the nerve roots, or mechanical pain that is relieved by rest, provoked by movement and warranting spinal instability precautions.[8,22,25,26] Night pain or pain when recumbent is a classic feature of spine malignancy, resulting from lengthening of the spine and distension of the spinal epidural venous plexus.[20] The history of every patient complaining of back pain should include specific questions addressing these symptoms, and their presence is a red flag that should prompt further investigation.

Motor dysfunction is the second most common finding in metastatic spine patients at presentation, ranging 35–75%.[10,17] Patients usually complain of extremity heaviness and the physical examination is positive for motor deficits. Sensory deficits often accompany the motor ones, and sphincter control is frequently preserved at the initial stages of the disease.[10,20,22]

4. Diagnostic evaluation

All cancer patients complaining of back pain or neurological involvement and patients presenting with symptoms and positive "red flags" should be evaluated by laboratory studies and proper imaging. Routine blood studies consisting of a complete blood count, albumin, electrolyte panel, liver enzyme assays, blood urea nitrogen and serum creatinine can shed light on the general and metabolic condition of the patient, and occasionally hint towards a diagnosis or metastatic spread.[10,27]

Several imaging modalities of varying sensitivity are helpful in identifying bony metastases. Whilst plain X-rays (Fig. 1a) are often used as an initial screening step as they are readily available and inexpensive, their role is limited in the early detection of metastatic skeletal involvement as nearly 50% of the normal vertebral body needs to be destroyed before tumour involvement can be clearly identified.[10,28,29] Computed tomography (CT) (Fig. 1b–d) provides high-resolution imaging useful in evaluating the osseous elements of the spine and any associated osteolytic or sclerotic changes as well as vertebral collapse. It is useful in surgical planning and often complements the information provided by Magnetic Resonance Imaging (MRI) to evaluate the bony changes related to the spinal tumour. The main disadvantages of CT, however, are its inability to differentiate soft tissue structures and the need for myelographic contrast to visualise the subarachnoid space. The sensitivity and specificity of CT to detect bony involvement ranges between 90% and 100%, however, epidural and soft tissue diseases are detected only in 50% of cases.[10,28]

MRI (Fig. 2a and b) is superior to CT for evaluating tumours of the spine.[30] MRI provides high-resolution multiplanar imaging of all aspects of the spine including the osseous structures and differentiation of soft tissue to allow visualisation of the spinal cord, nerve roots, meninges, intervertebral discs and the paraspinous musculature. Daldrup-Link et al.[31] reported the sensitivity of whole-body MRI to be 82% for marrow metastases screening, higher than bone scan and lower than fluorodeoxyglucose positron emission tomography (FDG-PET), and recommended using MRI as primary screening modality.

Bone scintography is routinely used to screen for bone involvement in cancer patients. The sensitivity of bone scan is reported to be 62–89%.[29,31,32] Other nuclear studies such as FDG-PET and single-photon emission computed tomography (SPECT) are used for better localisation and are associated with higher sensitivity and specificity (90% and 97.6%, respectively, for FDG-PET).[29,31] Suggested algorithms for bone metastases screening in cancer patients have never been validated and guidelines are not available. One consideration is to use bone scintography as the primary screening tool in all patients diagnosed with cancer. Asymptomatic patients with negative bone scan can then be followed in clinic but no additional skeletal surveys should be performed. However, symptomatic patients or patients with positive bone scans should be imaged with additional modalities according to the findings on bone scans or the level of symptoms.[29,30]

5. Steroids

Corticosteroids are used routinely in the treatment of spine tumours, especially when spinal cord compression occurs, although indications for their use and the appropriate dose

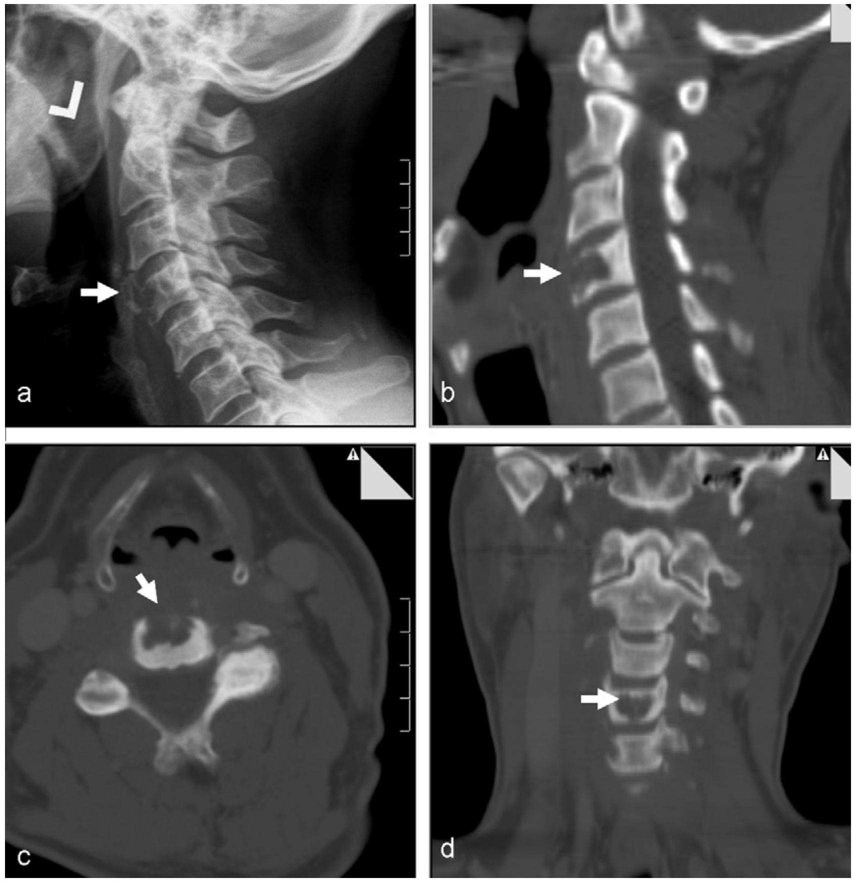

Fig. 1 – (a–d): Sixty-three-year-old male, previously diagnosed and treated for bladder carcinoma, presents with progressive neck pain and stiffness over nine months. 1(a): Lateral X-ray demonstrates erosion of the ventral C4 body (arrow). 1(b–d): CT scan on the same patient demonstrates a lytic lesion in the ventral portion of C4 (arrows).

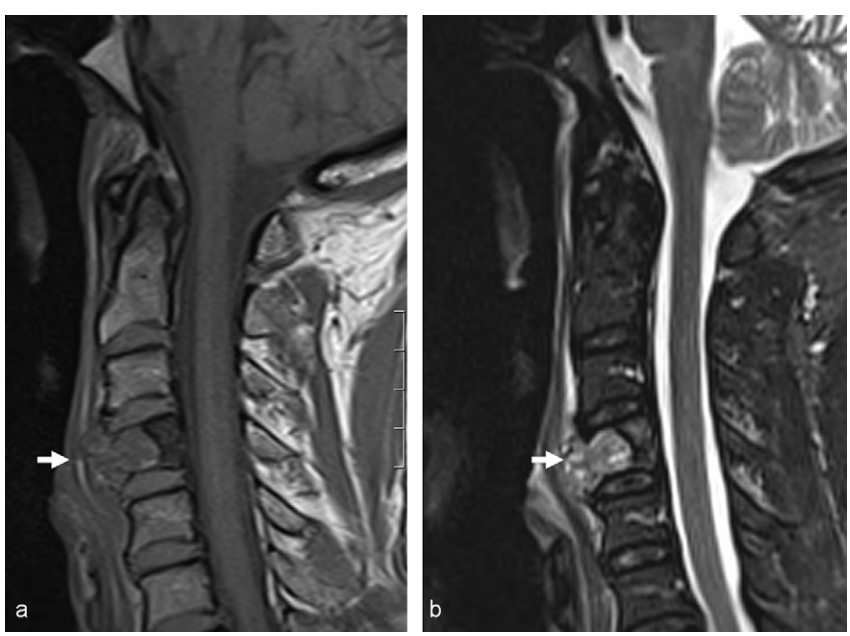

Fig. 2 – (a–b): A sagittal MRI (T1(2a) and T2(2b)) performed on the same patient demonstrates the ventral C4 lesion again where it can be seen destroying the ventral elements and extending to the retropharyngeal region (arrows). No compromise of the spinal canal or spinal cord compression is noted.

remain controversial. Steroids reduce oedema in the spinal cord and have been shown to reduce the size of metastases from haematogenous tumours and, occasionally, of breast cancer.[8,20] Vecht et al.[33] conducted a randomised trial in patients with metastatic epidural spinal cord compression (MESCC) comparing dexamethasone treatment regimens and found no statistical difference between treatment regimens and so advocated lower treatment dosages. This is in contrast with the Class I evidence from Sorensen et al.[34] who showed a statistically significant improvement in ambulation rates at three to six months when high-dose steroids were given for MESCC prior to radiotherapy compared to radiotherapy alone. In contrast, Maranzano et al.[35] challenged the need to utilise steroids in MESCC patients and found that all patients demonstrated stable or improved neurologic status and 85% had improved pain scores when treated with radiation and no steroids. Currently there are no guidelines for steroid treatment of the metastatic spine patient and the decision whether to treat and the preferred dosing are determined by the treating physician.

6. Radiation therapy

Before radiation therapy became available, surgical dorsal decompression in the form of laminectomy was the only alternative for patients with metastatic cord compression. Spine radiotherapy was introduced in the 1950s and several large retrospective studies and one small prospective randomised trial comparing it to laminectomy failed to show benefit of surgical decompression.[36–39] As a result, for many years, conventional radiation alone for patients with metastatic spine tumours was considered the standard of care. Radiation therapy has never been directly compared to supportive therapy alone nor compared to surgery with no adjuvant radiation.[7,20,39] However, the benefits of radiation for spinal metastases were repeatedly confirmed in large-scale retrospective studies showing improved or retained function.[20,21,40–43]

Despite the general acknowledgement that radiotherapy has a major role in the treatment of spine metastatic disease, there is no consensus regarding the appropriate daily dose and the fraction number. Whilst patients are typically treated with 30 Gy divided into 10 fractions in the USA, patients in Europe are treated with shorter protocols with higher fraction dose.[20,44,45] A randomised trial on behalf of the Bone Pain Trial Working Party compared single 8 Gy radiation therapy to 20 Gy divided in five fractions and to 30 Gy divided in 10 fractions.[46] Seven hundred and sixty-five patients were treated with overall equivalent results in survival, pain control, pathological fractures, spinal cord compression and side-effects. However, the low-dose group had shorter progression free survival and increased risk for re-treatment. Rades et al. [47] retrospectively evaluated 1304 patients treated with five different radiation regiments. They also found no statistical difference between the groups when survival, pain control and side-effects were compared. However, they did find significantly higher recurrence rate in the lower dose protocols after one year follow-up. The authors concluded that patients with short estimated survival should be treated with one 8 Gy fraction, whilst those with better prognoses should receive 30 Gy in 10 fractions. Maranzano et al.[48] prospectively compared single 8 Gy dose with a split course of three fractions of 5 Gy followed by five fractions of 3 Gy in 276 patients with short life expectancy. No statistical difference was noted and the authors recommended the single fraction protocol. A study conducted by the same group comparing single 8 Gy dosing to two fractions of 8 Gy also demonstrated no difference.[49] A meta-analysis conducted by Chow and colleagues[45] encompassed 19 randomised trials examining the optimal dosing regimen. As previously shown, the hypo-fractionated regimens had the same results with regard to pain control and tumour control, but had significant increase in re-treatment rates. As no guidelines exist, treatment regimens will probably remain a geographical choice although higher dosing does appear to offer some advantages related to longer local recurrence free intervals.

7. Systemic therapies

7.1. *Chemotherapy*

The long-term control of spine metastases entails systemic chemotherapy. Chemotherapy can be administered as monotherapy or involve a combination of agents and largely depends on the histology of the tumour and its chemosensitivity or specific receptor status.[50,51] Typically, hormonal drugs are used for prostate and breast metastases, and cytotoxic agents for most other cancers and also when hormonal therapy begins to fail in patients initially treated with it.

7.2. *Bisphosphonates*

Bisphosphonates are a group of drugs that bind to the surface of the bone and impair osteoclast-mediated bone resorption and reduce the tumour-associated osteolysis. They are used as co-analgesics in cases of moderate and severe bone pain and can reduce the frequency of skeletal-related events such as pathologic fractures, hypercalcemia, spinal cord compression or the need for surgery or radiation therapy.[20,52,53] Multiple studies have demonstrated a statistically significant decrease in fracture rate or skeletal events with bisphosphonates relative to placebo.[54–57] With respect to the specific impact of bisphosphonates on spinal cord compression, there is a paucity of data and no specific conclusions can be drawn.

7.3. *Radioisotopes*

Systemically administered drugs can also act as local radiation therapy to the spine. Radioisotopes such as strontium-89 or rhenium-186 can be injected intra-venously and are characterised by affinity to osteoblastic bone. Multiple studies, although not specifically limited to the spine, have shown benefit in terms of pain reduction in the treatment of multiple bone metastases. However, severe side-effects including irreversible bone marrow suppression have limited the use of these isotopes to patients with multiple synchronous painful metastases, good marrow function and when no further treatment modalities are available.[18,58,59]

8. Surgical treatment

Spinal stability must be maintained in order to achieve the normal spine functions of a body support system and a protective housing for the neural elements. Infiltration of the spinal column with metastases results in the replacement of the bony architecture with tissue lacking weight-bearing properties. The initial treatments described for spinal column tumours were in an era before radiotherapy was introduced. Decompressing of the spinal cord was performed via a dorsal approach laminectomy that theoretically relieved the pressure on the spinal cord and potentially reversed neurological deficits. However, most spinal metastases occur in the ventral spinal elements, causing ventral column instability. When combined with the surgical dorsal decompression this resulted in significant and rapid destabilisation of the entire spinal column, vascular insufficiency in the spinal cord and direct cord compression from loss of spinal column integrity. Not surprisingly dorsal decompression followed by conventional radiation provided no neurological preservation or advantage over radiation treatment alone and thus surgery for spine metastases was widely abandoned.[37–39,60]

However, surgeons continued to operate on spinal metastases patients who presented with progressive neurological deterioration after radiation therapy. In 1983, Constans et al.[12] published a surgical series describing a single institutional experience of 600 metastatic patients who were neurologically deteriorating and needed further surgery and were predominantly treated initially with decompressive laminectomy followed by irradiation. This additional surgery resulted in neurological improvement in 44% of the patients and 41% had stabilisation of their neurological progression.

Beginning in the 1980s, advances in surgical techniques and development of new and improved spinal instrumentation options began to shift the paradigm for spinal metastases treatment.[6,61,62] Further, it was recognised that surgical decompression if performed without instrumentation, whether via a ventral or dorsal approach, caused further instability to the metastatic spine.[9,63] A meta-analysis evaluating 24 surgical papers and 4 radiation papers was performed where operative results in the new era combined with radiation therapy were compared against conventional radiation therapy alone. The study demonstrated that surgical patients had better odds of remaining ambulatory or even regaining ambulation.[43] In 2005, Patchell et al.[7] published a pivotal randomised multi-centre trial comparing surgery and radiation with radiation only for the treatment of spinal epidural metastases. This study showed a clear benefit of surgical management in terms of maintaining and regaining ambulation and associated lower consumption of corticosteroids and analgesia. The authors' conclusion was that surgical intervention should be the first line of treatment for these patients. Further analysis of the data showed surgery to be cost effective as well.[64] These studies changed the treatment algorithms in many centres but their conclusions are controversial. Criticism of Patchell's study centres around patient selection where 101 patients were recruited over a 10 year period. Critics also point out that the control arm, treated by radiation only, had poorer outcomes relative to other radiation monotherapy series.[65,66]

Surgical resection can be en-bloc (removal of the tumour in one piece with wide excisional margins), an approach suitable for a solitary spine metastases in patients with a good performance status and good prognosis, debulking (piecemeal resection with no significant margins) or palliative (partial removal of tumour to relieve cord compression).[6,67–69] Approaches to achieve each of these degrees of resection and instrumentation/fusion for spine stabilisation have been performed ventrally (Fig. 3a and b), dorsally or combined ventral/dorsal throughout the entire spine. Consensus and data are lacking as to the optimal surgical approaches and procedures and are at the discretion of the treating surgeon.[9,67,68,70–72]

9. Surgical advancements

As the prevalence of surgery for spinal metastases is rising, new techniques are utilised to ease the procedure and diminish the risks to the patient.

9.1. *Embolisation*

Spine metastases resection has been reported to be associated with extensive blood loss during the procedure, especially in much vascularised tumours such as renal cell carcinoma.[73,74] Pre-operative angiography can demonstrate the tumour vascular supply and tumour blood flow can be reduced by embolisation with particles, coils or ONYX.[75,76] Surgery should be performed within 48 h of embolisation and the surgical and anaesthesia teams should be aware that successful embolisation does not preclude the possibility of excessive blood loss.[73–77] Of note, whilst embolisation has been shown to reduce extensive blood loss in many patients, it is not an option in some cases mainly because of anatomical variations.[77]

9.2. *Minimally invasive surgery*

Metastatic spine patients often suffer from co-morbidities, malnourishment, diminished immune system, considerable pain and limited overall survival. Extensive surgical procedures or prolonged hospital stays are neither acceptable nor feasible in many patients. Recent advances in visualisation solutions and percutaneous instrument placement have led to the development of minimally invasive approaches for the treatment of spinal metastases[78–82] and are associated with less pain, shorter intensive care unit (ICU) stays and shorter overall hospital stays.

Another important surgical adjunct is the image guided intraoperative navigation system. Tumours tend to envelop the normal anatomical structures and distort them, making the localisation challenging and the routine use of anatomical landmarks for hardware placement at times impossible. Navigation systems (analogous to global positioning systems) rely on pre-operative or intra-operative imaging and assist in three-dimensional structure localisation. With experience, navigation system use shortens the surgical time, reduces skin incision size and soft tissue resection, achieves higher tumour resection rates and allows for more accurate hardware placement.[83,84]

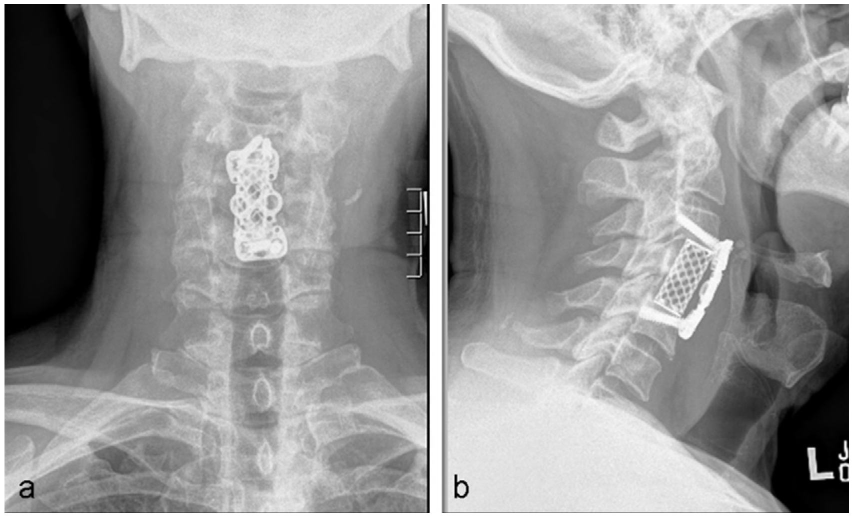

Fig. 3 – (a–b): The patient was operated via a ventral cervical approach for a C4 corpectomy and fusion with mesh cage and anterior cervical plating. Post-operative anterior–posterior (3a) and lateral (3b) X-rays demonstrate hardware position and alignment of the spine.

9.3. *Vertebral augmentation procedures*

Pathologic compression fractures are often encountered in metastatic spine tumour patients and can be associated with pain, deformity and, occasionally, neurologic compromise. The risk for compression fractures is inversely correlated with the residual intact vertebra and the bone density.[85,86] Further, the location of tumour within the vertebra, the spinal region involved, local kyphosis or lordosis and the position of the instantaneous axis of rotation all play a role in determining the risk for a pathologic fracture.[85–87]

Vertebral augmentation is a percutaneous minimally invasive procedure initiated by inserting a needle under fluoroscopic guidance through the pedicle to the vertebral body and filling the fractured body with polymethyl methacrylate (PMMA)/bone cement.[88–90] The PMMA hardens within the porous bone of the vertebral body thereby strengthening and internally stabilising the pathological compression fracture related to localised metastatic involvement. The PMMA can be injected either under high pressure (a procedure known as vertebroplasty)[88–90] or after creating a cavity for the cement en-lay and potential vertebral height restoration with an internally inflated balloon (kyphoplasty).[89,91] Vertebroplasty[88–90] and kyphoplasty[89,91] are typically single session outpatient procedures and can be performed with local anaesthesia, intravenous sedation or under general anaesthesia depending on patient and surgeon preference. Both methods have been shown to substantially reduce pain from metastatic vertebral compression fractures with very low associated complication rates.[92]

10. Stereotactic spine radiosurgery

The role of radiation is well established in the treatment of metastatic spine tumours where it has been shown to reduce pain, control local disease progression and potentially prevent or reverse neurological dysfunction.[3,93] Further, it has been found that a higher radiation dosage to the tumour area results in a greater tumour control rate.[48] Yet, one of the main limitations associated with conventional radiotherapy for spinal metastases is the low radiation tolerance of the spinal cord and cauda equina, since exposure of the cord to radiation can lead to myelopathy or oedema.[3,48,94] Unfortunately, because the dose required for the eradication of many spinal metastases exceeds the maximal dose the surrounding tissue can receive, tumours are often under-treated with conventional radiation. This “undertreatment” may result in poorer outcomes in terms of pain relief, prevention of neurological deterioration, tumour control, increased steroid use and decreased overall survival in these patients.[7,95–97]

In contrast, stereotactic radiosurgery (SRS) to the spine is a novel treatment modality that delivers an accurate and conformal high radiation dose to the tumour in 1–5 sessions and the steep fall-off dose gradients associated with the treatment protect the adjacent normal structures. Whilst the concept of stereotactic radiosurgery is not new and was initially conceived by the Swedish neurosurgeon Lars Leksell in 1951,[98] with the development of the Gamma Knife for intracranial targets, the transition of this technology to extra-cranial targets took several further decades to mature. However, technological advancements in appropriate patient immobilisation,[99–101] radiation targeting and precision delivery with image guided radiation therapy (IGRT)[99,102–104] and intensity modulated radiation therapy (IMRT)[105,106] have made extra-cranial radiosurgery feasible in recent years. Thus radiation can now be delivered to a spinal tumour resulting in effective pain and tumour control whilst at the same time minimising the radiation to adjacent normal structures thereby decreasing both the acute and delayed morbidity related to the treatment (Fig. 4).[102,103,107–111]

SRS is typically delivered as an outpatient procedure. Pretreatment, a patient is immobilised in an external stabilisation device and undergoes a high resolution CT and MRI scan. These images are transferred to the SRS planning software

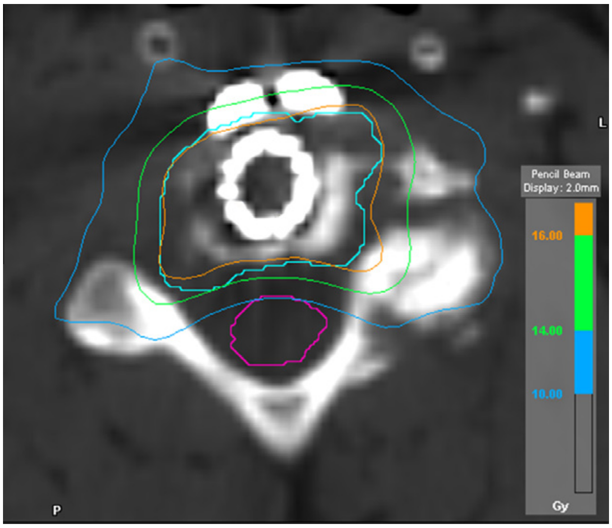

Fig. 4 – One month post-operatively, the patient was treated with adjuvant stereotactic radiosurgery (SRS). The turquoise outline is the target region (CTV) and the magenta the spinal cord. The orange is the 16 Gy prescription isodose line, the green is the 14 Gy isodose line and the blue is the 10 Gy dose fall-off region from the targeted tumour.

where they are reconstructed into three-dimensional images. These images are used to identify and plan the targeting of the tumour with radiation and identify and exclude other adjacent normal tissue structures, especially the spinal cord from the proposed radiation delivery. On the treatment day, the patient is immobilised in the identical position in which the planning CT was obtained using various methods to confirm setup accuracy and track patient motion including fluoroscopy, kilovolt or megavolt radiographs, cone beam computed tomography and infrared stereoscopic cameras. Bony landmarks and internally or externally placed fiducials are tracked during the treatment session in this manner. Treatment is delivered using a linear accelerator dedicated for radiosurgery that is capable of delivering small shaped beams of radiation that can provide shaped radiation delivery. There is no recovery time related to the treatment and patients are immediately able to resume their pre-treatment level of activity. Treatment can be administered within a couple weeks of open spine surgery (as the radiation dose is typically deposited deep to the healing soft tissue of the wound) and systemic chemotherapy requires minimal, if any, disruption during spine radiosurgery.

The most common indication for spine radiosurgery is pain and typically 70–90% of all patients treated present with localised oncologic pain. Other indications for the procedure include: (1) initial tumour treatment, (2) treatment after surgery for residual tumour, (3) progression after other treatment modalities such as surgery, conventional radiation and chemotherapy have failed and perhaps (4) radiation boost following conventional treatment for more radioresistant tumours.

Several studies have reported very promising results with SRS resulting in a high percentage of pain relief. Pain relief, either partial or complete, is achieved in 85–92% of patients treated with spine radiosurgery often within a few days to weeks of treatment.[102,107,112–114] This clinical response is typically more extensive and faster than results achieved with conventional radiation.[97] In our series of 108 patients (154 spine metastases), we prospectively evaluated the impact of treatment on pain and quality of life in patients treated with spine radiosurgery. Pain scores were improved over baseline pain score in 77% of patients ($p < 0.001$) as early as week one post treatment and at 12 months post treatment 89% of the patients had continued pain improvement ($p < 0.008$) over baseline. Independent quality of life functional scores were also significantly improved relative to baseline as early as one month post treatment.[114]

Spine radiosurgery allows for the delivery of "ablative" radiation doses with minimal side-effects and results in local control rates between 77 and 94%.[113,115–119] Included in these series were patients with tumours considered to be more radioresistant such as colon or renal cell carcinoma.[107,112,113,120–123] This treatment option also results in several distinct and significant advantages over other treatment options for metastatic spine tumours highlighted in Table 1.

Although a relatively new treatment modality, SRS offers a promising major advancement in clinical medicine for the treatment and palliation of spine tumours. Its dose–response/toxicity ratio is favourable both in terms of tumour control and rapid and durable pain relief and it is associated

Table 1 – Advantages of spine radiosurgery.

- Non-invasive out-patient treatment with no recovery time
- Highly effective for both pain palliation and local tumour control
- Single fraction treatment beneficial to patients with limited life expectancy
- Rapid pain control meaningfully improves patient's quality of life
- More rapid pain relief and better tumour control over conventional radiation
- Greater efficacy in radioresistant histopathologies
- Allows for the treatment of tumours previously irradiated using conventional beam radiotherapy
- Larger radiobiological dose can be delivered compared to external beam radiation
- Early treatment may obviate the need for extensive spinal surgery
- Avoids irradiation of a large segment of the spinal cord as well as delivers minimal radiation to adjacent normal tissues
- Precludes the need to irradiate large segments of vertebral column that negatively impacts bone marrow reserves
- Averting open surgery as well as preserving bone marrow function facilitates continuous chemotherapy
- Associated with a negligible dose of radiation to the fascia and skin, so no impact on wound healing and can be performed very soon after open surgery
- No significant impact on tissue handling, healing or infection rates if done pre-operatively in contrast to the effects of convention radiation
- May decrease fusion/instrument failure when delivered after surgery compared with post operative conventional radiation.

with limited post radiation spinal myelopathy.[124] Continued research will help further define its role and impact in the management of spine metastases in terms of both short- and long-term outcomes.

11. Proposed treatment algorithm

Standard guidelines for treating spinal metastases are not available, and treatment regimens vary widely according to availability of treatment modalities, geographical variations, health insurance coverage and medical costs, as well as personal and religious beliefs. We share here our spine tumour treatment algorithm used successfully at our institution over the past five years. It outlines a general approach to managing patients with suspected spinal metastases and we believe it could be implemented in any institution with spine surgery and irradiation capabilities (Fig. 5). Others have also proposed similar treatment algorithms.[18,125]

One very essential aspect of spine tumour management as emphasised in the algorithm presented here is the presence or absence of neurological deficits. This dictates the acuity and nature of the intervention, as neurologic deficits before treatment are correlated with poor prognosis.[7,18,20] Further, complete loss of neurological function or loss of bowel and bladder function for 24–48 h is irreversible and also potentially preventable if patients with "red flags" are closely and promptly evaluated.[126,127] Another fundamental feature in the management of patients with spine metastases is that the approach should be multidisciplinary and well integrated. Our algorithm outlines the primary consultant for the various patient clinical presentations and outlines the general treatment flow for most patients with spinal metastases.

12. Future directions incorporating combination therapies

Although patients with spinal metastases are perceived to have a short survival time, recent studies have shown the benefit of aggressive treatment for sub-populations.[6,7,61,62] As cancer treatment improves, and patients live longer, the benefits of aggressive treatment outweigh the associated risks and costs.[1,19] Successful cancer treatment combines the use of surgery, chemotherapy and irradiation.[128] Combining surgical resection and stabilisation with irradiation has been shown to be superior to irradiation alone[7] but has never been compared to surgical resection and SRS. The combination treatment of SRS following surgery offers several potential advantages related to limiting the radiation dose to the surrounding normal tissues. Hence, there is not only reduced irradiation to the spinal cord but the surgical wound and the fusion site are also subjected to less radiation, thus limiting the risk of wound breakdown[129–131] and increasing the

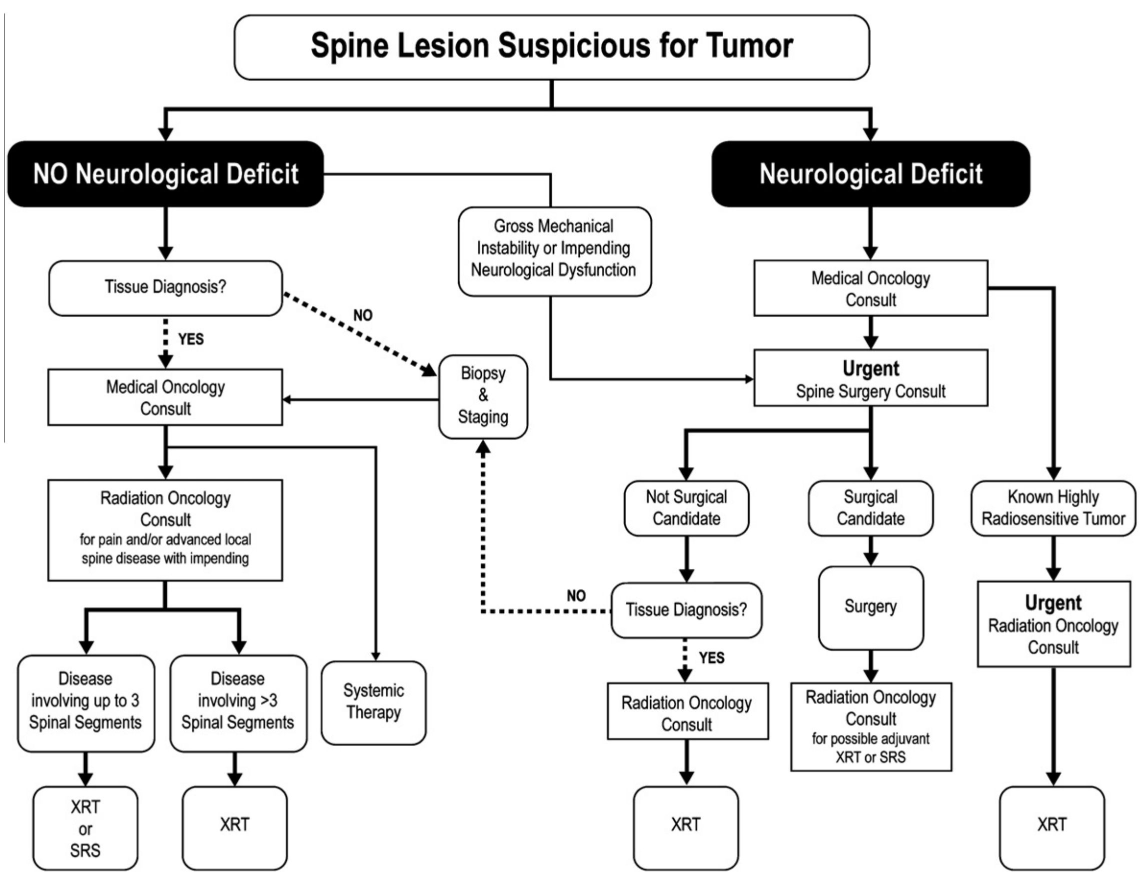

Fig. 5 – Treatment algorithm for patients with spine lesions suspicious for a metastatic tumour. The presence or absence of neurological deficits, tissue confirmation and multi-disciplinary integration are key features in the appropriate and effective management of these patients.

chances for spine fusion. In an unpublished series, surgical patients receiving adjuvant SRS had less instrumentation failures and higher fusion rates when compared to patients undergoing surgery followed by adjuvant conventional radiation therapy (Harel, R., Angelov, L.: Cleveland Clinic).

Other combination procedures for metastatic spine tumours include percutaneous vertebral augmentation techniques in conjunction with SRS for painful pathological fractures. These two minimally invasive techniques result in marked pain relief, improved spinal stability and local tumour control when performed in combination.[132] Other combination approaches such as partial tumour resection using percutaneous radiofrequency transmitters or laser technology followed by augmentation of the vertebra with PMMA have been described[133,134] Further, the administration of radioactive particles (samarium-153 or Iodine -125) through a percutaneous cannula during vertebral augmentation is another described technique,[25,26] however, no significant benefit in terms of time to progression has been shown.

13. Conclusion

In the future, advancements in imaging modalities, surgical skills and instruments, chemotherapy and radiation therapy will continue to improve the quality of life and overall survival of patients with spine metastases. However, improved systemic control of many malignancies, increased surgical treatment options and proliferation of novel spine tumour treatment modalities have resulted in patient referrals to an ever-broadening variety of specialists. Yet, patients with spine tumours frequently present with complex diagnostic or therapeutic challenges requiring integrated multi-step and multidisciplinary care. In managing these patients, every effort should be made to provide appropriate patient care orchestration and integration. This integrated care in conjunction with standardised algorithms, treatment guidelines, institutional tumour boards, multi-centre prospective studies and institutional collaborations will all be essential to improve patient outcomes as well as patient satisfaction, resulting in superior patient care.

Conflict of interest statement

None declared.

REFERENCES

1. Winstead ER. After treatment: the needs of cancer survivors. *NCI Cancer Bull* 2005;**2**(43):1–2.
2. Hayat MJ, Howlader N, Reichman ME, Edwards BK. Cancer statistics, trends, and multiple primary cancer analyses from the surveillance, epidemiology, and end results (SEER) program. *Oncologist* 2007;**12**(1):20–37.
3. Wong DA, Fornasier VL, MacNab I. Spinal metastases: the obvious, the occult, and the impostors. *Spine* 1990;**15**(1):1–4 [Phila Pa 1976].
4. Heidecke V, Rainov NG, Burkert W. Results and outcome of neurosurgical treatment for extradural metastases in the cervical spine. *Acta Neurochir (Wien)* 2003;**145**(10):873–80 [discussion 880–1].
5. Ortiz Gomez JA. The incidence of vertebral body metastases. *Int Orthop* 1995;**19**(5):309–11.
6. Ibrahim A, Crockard A, Antonietti P, et al. Does spinal surgery improve the quality of life for those with extradural (spinal) osseous metastases? An international multicenter prospective observational study of 223 patients. Invited submission from the joint section meeting on disorders of the spine and peripheral nerves, March 2007. *J Neurosurg Spine* 2008;**8**(3):271–8.
7. Patchell RA, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. *Lancet* 2005;**366**(9486):643–8.
8. Camins MB, Jenkins AL, Singhal A, Perrin RG. Tumors of the vertebral axis: benign, primary malignant, and metastatic tumors. In: Winn RH, Youmans JR, editors. *Youmans neurological surgery*. 5th ed. Philadelphia: W.B. Saunders Company; 2004. p. 4835–68.
9. Steinmetz MP, Mekhail A, Benzel EC. Management of metastatic tumors of the spine: strategies and operative indications. *Neurosurg Focus* 2001;**11**(6):e2.
10. Jacobs WB, Perrin RG. Evaluation and treatment of spinal metastases: an overview. *Neurosurg Focus* 2001;**11**(6):e10.
11. Perrin RG, Laxton AW. Metastatic spine disease: epidemiology, pathophysiology, and evaluation of patients. *Neurosurg Clin N Am* 2004;**15**(4):365–73.
12. Constans JP, de Divitiis E, Donzelli R, et al. Spinal metastases with neurological manifestations. Review of 600 cases. *J Neurosurg* 1983;**59**(1):111–8.
13. Gilbert RW, Kim JH, Posner JB. Epidural spinal cord compression from metastatic tumor: diagnosis and treatment. *Ann Neurol* 1978;**3**(1):40–51.
14. Holman PJ, Suki D, McCutcheon I, et al. Surgical management of metastatic disease of the lumbar spine: experience with 139 patients. *J Neurosurg Spine* 2005;**2**(5):550–63.
15. Schick U, Marquardt G, Lorenz R. Intradural and extradural spinal metastases. *Neurosurg Rev* 2001;**24**(1):1–5 [discussion 6–7].
16. Perrin RG, Livingston KE, Aarabi B. Intradural extramedullary spinal metastasis. A report of 10 cases. *J Neurosurg* 1982;**56**(6):835–7.
17. van der Linden YM, Dijkstra SP, Vonk EJ, Marijnen CA, Leer JW. Prediction of survival in patients with metastases in the spinal column: results based on a randomized trial of radiotherapy. *Cancer* 2005;**103**(2):320–8.
18. Bartels RH, van der Linden YM, van der Graaf WT. Spinal extradural metastasis: review of current treatment options. *CA Cancer J Clin* 2008;**58**(4):245–59.
19. Bartels RH, Feuth T, van der Maazen R, et al. Development of a model with which to predict the life expectancy of patients with spinal epidural metastasis. *Cancer* 2007;**110**(9):2042–9.
20. Cole JS, Patchell RA. Metastatic epidural spinal cord compression. *Lancet Neurol* 2008;**7**(5):459–66.
21. Loblaw DA, Laperriere NJ, Mackillop WJ. A population-based study of malignant spinal cord compression in Ontario. *Clin Oncol (R Coll Radiol)* 2003;**15**(4):211–7.
22. Witham TF, Khavkin YA, Gallia GL, et al. Surgery insight: current management of epidural spinal cord compression from metastatic spine disease. *Nat Clin Pract Neurol* 2006;**2**(2):87–94 [quiz 116].
23. Helweg-Larsen S, Sorensen PS. Symptoms and signs in metastatic spinal cord compression: a study of progression from first symptom until diagnosis in 153 patients. *Eur J Cancer* 1994;**30A**(3):396–8.

24. Bach F, Larsen BH, Rohde K, et al. Metastatic spinal cord compression. Occurrence, symptoms, clinical presentations and prognosis in 398 patients with spinal cord compression. *Acta Neurochir (Wien)* 1990;**107**(1–2):37–43.
25. 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**(4):336–42.
26. Yang Z, Yang D, Xie L, et al. Treatment of metastatic spinal tumors by percutaneous vertebroplasty versus percutaneous vertebroplasty combined with interstitial implantation of 125I seeds. *Acta Radiol* 2009;**50**(10):1142–8.
27. Ruckdeschel JC. Early detection and treatment of spinal cord compression. *Oncology (Williston Park)* 2005;**19**(1):81–6 [discussion 86, 89–92].
28. Guillevin R, Vallee JN, Lafitte F, et al. Spine metastasis imaging: review of the literature. *J Neuroradiol* 2007;**34**(5):311–21.
29. Costelloe CM, Rohren EM, Madewell JE, et al. Imaging bone metastases in breast cancer: techniques and recommendations for diagnosis. *Lancet Oncol* 2009;**10**(6):606–14.
30. Andreula C, Murrone M. Metastatic disease of the spine. *Eur Radiol* 2005;**15**(3):627–32.
31. Daldrup-Link HE, Franzius C, Link TM, et al. Whole-body MR imaging for detection of bone metastases in children and young adults: comparison with skeletal scintigraphy and FDG PET. *AJR Am J Roentgenol* 2001;**177**(1):229–36.
32. Ohta M, Tokuda Y, Suzuki Y, et al. Whole body PET for the evaluation of bony metastases in patients with breast cancer: comparison with 99Tcm-MDP bone scintigraphy. *Nucl Med Commun* 2001;**22**(8):875–9.
33. Vecht CJ, Haaxma-Reiche H, van Putten WL, et al. Initial bolus of conventional versus high-dose dexamethasone in metastatic spinal cord compression. *Neurology* 1989;**39**(9):1255–7.
34. Sorensen S, Helweg-Larsen S, Mouridsen H, Hansen HH. Effect of high-dose dexamethasone in carcinomatous metastatic spinal cord compression treated with radiotherapy: a randomised trial. *Eur J Cancer* 1994;**30A**(1):22–7.
35. Maranzano E, Latini P, Beneventi S, et al. Radiotherapy without steroids in selected metastatic spinal cord compression patients. A phase II trial. *Am J Clin Oncol* 1996;**19**(2):179–83.
36. Stark RJ, Henson RA, Evans SJ. Spinal metastases. A retrospective survey from a general hospital. *Brain* 1982;**105**(Pt 1):189–213.
37. Sherman RM, Waddell JP. Laminectomy for metastatic epidural spinal cord tumors. Posterior stabilization, radiotherapy, and preoperative assessment. *Clin Orthop Relat Res* 1986;**207**:55–63.
38. Hirabayashi H, Ebara S, Kinoshita T, et al. Clinical outcome and survival after palliative surgery for spinal metastases: palliative surgery in spinal metastases. *Cancer* 2003;**97**(2):476–84.
39. George R, Jeba J, Ramkumar G, et al. Interventions for the treatment of metastatic extradural spinal cord compression in adults. *Cochrane Database Syst Rev* 2008;**4**:CD006716.
40. Helweg-Larsen S, Sorensen PS, Kreiner S. Prognostic factors in metastatic spinal cord compression: a prospective study using multivariate analysis of variables influencing survival and gait function in 153 patients. *Int J Radiat Oncol Biol Phys* 2000;**46**(5):1163–9.
41. Maranzano E, Latini P. Effectiveness of radiation therapy without surgery in metastatic spinal cord compression: final results from a prospective trial. *Int J Radiat Oncol Biol Phys* 1995;**32**(4):959–67.
42. Helweg-Larsen S. Clinical outcome in metastatic spinal cord compression. A prospective study of 153 patients. *Acta Neurol Scand* 1996;**94**(4):269–75.
43. Klimo Jr P, Thompson CJ, Kestle JR, Schmidt MH. A meta-analysis of surgery versus conventional radiotherapy for the treatment of metastatic spinal epidural disease. *Neuro Oncol* 2005;**7**(1):64–76.
44. Loblaw DA, Laperriere NJ. Emergency treatment of malignant extradural spinal cord compression: an evidence-based guideline. *J Clin Oncol* 1998;**16**(4):1613–24.
45. Chow E, Harris K, Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: a systematic review. *J Clin Oncol* 2007;**25**(11):1423–36.
46. 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up. Bone Pain Trial Working Party. *Radiother Oncol* 1999;**52**(2):111–21.
47. Rades D, Stalpers LJ, Veninga T, et al. Evaluation of five radiation schedules and prognostic factors for metastatic spinal cord compression. *J Clin Oncol* 2005;**23**(15):3366–75.
48. Maranzano E, Bellavita R, Rossi R, et al. Short-course versus split-course radiotherapy in metastatic spinal cord compression: results of a phase III, randomized, multicenter trial. *J Clin Oncol* 2005;**23**(15):3358–65.
49. Maranzano E, Trippa F, Casale M, et al. 8Gy single-dose radiotherapy is effective in metastatic spinal cord compression: results of a phase III randomized multicentre Italian trial. *Radiother Oncol* 2009;**93**(2):174–9.
50. Landreneau FE, Landreneau RJ, Keenan RJ, Ferson PF. Diagnosis and management of spinal metastases from breast cancer. *J Neurooncol* 1995;**23**(2):121–34.
51. Mercadante S, Fulfaro F. Management of painful bone metastases. *Curr Opin Oncol* 2007;**19**(4):308–14.
52. Costa L, Major PP. Effect of bisphosphonates on pain and quality of life in patients with bone metastases. *Nat Clin Pract Oncol* 2009;**6**(3):163–74.
53. Berenson JR, Rajdev L, Broder M. Managing bone complications of solid tumors. *Cancer Biol Ther* 2006;**5**(9):1086–9.
54. Heun JM, Jatoi A. Osseous metastases: drugs that enhance bone integrity and prevent adverse skeletal events. *Expert Opin Pharmacother* 2009;**10**(5):723–6.
55. Rosen LS, Gordon D, Tchekmedyian S, et al. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial – the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol* 2003;**21**(16):3150–7.
56. Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2002;**94**(19):1458–68.
57. Theriault RL, Lipton A, Hortobagyi GN, et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Group. *J Clin Oncol* 1999;**17**(3):846–54.
58. Finlay IG, Mason MD, Shelley M. Radioisotopes for the palliation of metastatic bone cancer: a systematic review. *Lancet Oncol* 2005;**6**(6):392–400.
59. Bauman G, Charette M, Reid R, Sathya J. Radiopharmaceuticals for the palliation of painful bone metastasis – a systemic review. *Radiother Oncol* 2005;**75**(3):258–70.
60. Young RF, Post EM, King GA. Treatment of spinal epidural metastases. Randomized prospective comparison of laminectomy and radiotherapy. *J Neurosurg* 1980;**53**(6):741–8.

61. Tomita K, Kawahara N, Kobayashi T, et al. Surgical strategy for spinal metastases. *Spine (Phila Pa 1976)* 2001;**26**(3):298–306.
62. Patil CG, Patil TS, Lad SP, Boakye M. Complications and outcomes after spinal cord tumor resection in the United States from 1993 to 2002. *Spinal Cord* 2008;**46**(5):375–9.
63. Harrington KD. Anterior cord decompression and spinal stabilization for patients with metastatic lesions of the spine. *J Neurosurg* 1984;**61**(1):107–17.
64. Thomas KC, Nosyk B, Fisher CG, et al. Cost-effectiveness of surgery plus radiotherapy versus radiotherapy alone for metastatic epidural spinal cord compression. *Int J Radiat Oncol Biol Phys* 2006;**66**(4):1212–8.
65. van den Bent MJ. Surgical resection improves outcome in metastatic epidural spinal cord compression. *Lancet* 2005;**366**(9486):609–10.
66. Maranzano E, Trippa F. Be careful in getting cost-effectiveness conclusions from a debatable trial! *Int J Radiat Oncol Biol Phys* 2007;**68**(1):314 [author reply 314–5].
67. Vrionis FD, Small J. Surgical management of metastatic spinal neoplasms. *Neurosurg Focus* 2003;**15**(5):E12.
68. Mazel C, Balabaud L, Bennis S, Hansen S. Cervical and thoracic spine tumor management: surgical indications, techniques, and outcomes. *Orthop Clin North Am* 2009;**40**(1):75–92, vi–vii.
69. Chi JH, Sciubba DM, Rhines LD, Gokaslan ZL. Surgery for primary vertebral tumors: en bloc versus intralesional resection. *Neurosurg Clin N Am* 2008;**19**(1):111–7.
70. Fehlings MG, David KS, Vialle L, et al. Decision making in the surgical treatment of cervical spine metastases. *Spine (Phila Pa 1976)* 2009;**34**(22 Suppl.):S108–17.
71. Jonsson B, Jonsson Jr H, Karlstrom G, Sjostrom L. Surgery of cervical spine metastases: a retrospective study. *Eur Spine J* 1994;**3**(2):76–83.
72. Liu JK, Apfelbaum RI, Chiles 3rd BW, Schmidt MH. Cervical spinal metastasis: anterior reconstruction and stabilization techniques after tumor resection. *Neurosurg Focus* 2003;**15**(5):E2.
73. Sundaresan N, Choi IS, Hughes JE, Sachdev VP, Berenstein A. Treatment of spinal metastases from kidney cancer by presurgical embolization and resection. *J Neurosurg* 1990;**73**(4):548–54.
74. Berkefeld J, Scale D, Kirchner J, Heinrich T, Kollath J. Hypervascular spinal tumors: influence of the embolization technique on perioperative hemorrhage. *AJNR Am J Neuroradiol* 1999;**20**(5):757–63.
75. Rehak S, Krajina A, Ungermann L, et al. The role of embolization in radical surgery of renal cell carcinoma spinal metastases. *Acta Neurochir (Wien)* 2008;**150**(11):1177–81 [discussion 1181].
76. Gore P, Theodore N, Brasiliense L, et al. The utility of onyx for preoperative embolization of cranial and spinal tumors. *Neurosurgery* 2008;**62**(6):1204–11 [discussion 1211–2].
77. Guzman R, Dubach-Schwizer S, Heini P, et al. Preoperative transarterial embolization of vertebral metastases. *Eur Spine J* 2005;**14**(3):263–8.
78. McLain RF, Lieberman IH. Endoscopic approaches to metastatic thoracic disease. *Spine (Phila Pa 1976)* 2000;**25**(14):1855–8.
79. Logroscino CA, Proietti L, Tamburrelli FC. Minimally invasive spine stabilisation with long implants. *Eur Spine J* 2009;**18**(Suppl. 1):75–81.
80. Ofluoglu O. Minimally invasive management of spinal metastases. Orthop Clin North Am 2009;**40**(1):155–68, viii.
81. Huang TJ, Hsu RW, Li YY, Cheng CC. Minimal access spinal surgery (MASS) in treating thoracic spine metastasis. *Spine (Phila Pa 1976)* 2006;**31**(16):1860–3.
82. Rosenthal D, Marquardt G, Lorenz R, Nichtweiss M. Anterior decompression and stabilization using a microsurgical endoscopic technique for metastatic tumors of the thoracic spine. *J Neurosurg* 1996;**84**(4):565–72.
83. Haberland N, Ebmeier K, Hliscs R, et al. Neuronavigation in surgery of intracranial and spinal tumors. *J Cancer Res Clin Oncol* 2000;**126**(9):529–41.
84. Kalfas IH. Image-guided spinal navigation: application to spinal metastases. *Neurosurg Focus* 2001;**11**(6):e5.
85. Dimar 2nd JR, Voor MJ, Zhang YM, Glassman SD. A human cadaver model for determination of pathologic fracture threshold resulting from tumorous destruction of the vertebral body. *Spine (Phila Pa 1976)* 1998;**23**(11):1209–14.
86. Krishnaney AA, Steinmetz MP, Benzel EC. Biomechanics of metastatic spine cancer. *Neurosurg Clin N Am* 2004;**15**(4):375–80.
87. Tschirhart CE, Finkelstein JA, Whyne CM. Biomechanics of vertebral level, geometry, and transcortical tumors in the metastatic spine. *J Biomech* 2007;**40**(1):46–54.
88. Alvarez L, Perez-Higueras A, Quinones D, Calvo E, Rossi RE. Vertebroplasty in the treatment of vertebral tumors: postprocedural outcome and quality of life. *Eur Spine J* 2003;**12**(4):356–60.
89. Chi JH, Gokaslan ZL. Vertebroplasty and kyphoplasty for spinal metastases. *Curr Opin Support Palliat Care* 2008;**2**(1):9–13.
90. Pilitsis JG, Rengachary SS. The role of vertebroplasty in metastatic spinal disease. *Neurosurg Focus* 2001;**11**(6):e9.
91. Khanna AJ, Neubauer P, Togawa D, Kay Reinhardt M, Lieberman IH. Kyphoplasty and vertebroplasty for the treatment of spinal metastases. *Support Cancer Ther* 2005;**3**(1):21–5.
92. Hentschel SJ, Burton AW, Fourney DR, Rhines LD, Mendel E. Percutaneous vertebroplasty and kyphoplasty performed at a cancer center: refuting proposed contraindications. *J Neurosurg Spine* 2005;**2**(4):436–40.
93. Maranzano E, Bellavita R, Rossi R. Radiotherapy alone or surgery in spinal cord compression? The choice depends on accurate patient selection. *J Clin Oncol* 2005;**23**(32):8270–2 [author reply 8272–4].
94. Schultheiss TE. The radiation dose–response of the human spinal cord. *Int J Radiat Oncol Biol Phys* 2008;**71**(5):1455–9.
95. Party BPTW. 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up. Bone Pain Trial Working Party. *Radiother Oncol* 1999;**52**(2):111–21.
96. Price P, Hoskin PJ, Easton D, et al. Prospective randomised trial of single and multifraction radiotherapy schedules in the treatment of painful bony metastases. *Radiother Oncol* 1986;**6**(4):247–55.
97. Steenland E, Leer JW, van Houwelingen H, et al. The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. *Radiother Oncol* 1999;**52**(2):101–9.
98. Leksell L. The stereotaxic method and radiosurgery of the brain. *Acta Chir Scand* 1951;**102**(4):316–9.
99. Yenice KM, Lovelock DM, Hunt MA, et al. CT image-guided intensity-modulated therapy for paraspinal tumors using stereotactic immobilization. *Int J Radiat Oncol Biol Phys* 2003;**55**(3):583–93.
100. Wulf J, Hadinger U, Oppitz U, Olshausen B, Flentje M. Stereotactic radiotherapy of extracranial targets: CT-simulation and accuracy of treatment in the stereotactic body frame. *Radiother Oncol* 2000;**57**(2):225–36.
101. Lohr F, Debus J, Frank C, et al. Noninvasive patient fixation for extracranial stereotactic radiotherapy. *Int J Radiat Oncol Biol Phys* 1999;**45**(2):521–7.

102. Ryu S, Fang Yin F, Rock J, et al. Image-guided and intensity-modulated radiosurgery for patients with spinal metastasis. *Cancer* 2003;**97**(8):2013–8.
103. Ryu SI, Chang SD, Kim DH, et al. Image-guided hypo-fractionated stereotactic radiosurgery to spinal lesions. *Neurosurgery* 2001;**49**(4):838–46.
104. Murphy MJ, Chang S, Gibbs I, et al. Image-guided radiosurgery in the treatment of spinal metastases. *Neurosurg Focus* 2001;**11**(6):e6.
105. Das IJ, Cheng CW, Chopra KL, et al. Intensity-modulated radiation therapy dose prescription, recording, and delivery: patterns of variability among institutions and treatment planning systems. *J Natl Cancer Inst* 2008;**100**(5):300–7.
106. Yu CX, Amies CJ, Svatos M. Planning and delivery of intensity-modulated radiation therapy. *Med Phys* 2008;**35**(12):5233–41.
107. Gerszten PC, Burton SA, Ozhasoglu C, Welch WC. Radiosurgery for spinal metastases: clinical experience in 500 cases from a single institution. *Spine (Phila Pa 1976)* 2007;**32**(2):193–9.
108. Bilsky MH, Yamada Y, Yenice KM, et al. Intensity-modulated stereotactic radiotherapy of paraspinal tumors: a preliminary report. *Neurosurgery* 2004;**54**(4):823–30 [discussion 830–1].
109. Benzil DL, Saboori M, Mogilner AY, Rocchio R, Moorthy CR. Safety and efficacy of stereotactic radiosurgery for tumors of the spine. *J Neurosurg* 2004;**101**(Suppl. 3):413–8.
110. Medin PM, Solberg TD, De Salles AA, et al. Investigations of a minimally invasive method for treatment of spinal malignancies with LINAC stereotactic radiation therapy: accuracy and animal studies. *Int J Radiat Oncol Biol Phys* 2002;**52**(4):1111–22.
111. De Salles AA, Pedroso AG, Medin P, et al. Spinal lesions treated with Novalis shaped beam intensity-modulated radiosurgery and stereotactic radiotherapy. *J Neurosurg* 2004;**101**(Suppl. 3):435–40.
112. Ryu S, Rock J, Rosenblum M, Kim JH. Patterns of failure after single-dose radiosurgery for spinal metastasis. *J Neurosurg* 2004;**101**(Suppl. 3):402–5.
113. Gerszten PC, Burton SA, Ozhasoglu C, et al. Stereotactic radiosurgery for spinal metastases from renal cell carcinoma. *J Neurosurg Spine* 2005;**3**(4):288–95.
114. Angelov L. Stereotactic spine radiosurgery (SRS) for pain and tumor control in patients with spinal metastases from renal cell carcinoma: a prospective study. *Int J Radiat Oncol Biol Phys* 2009;**75**(3):s112–3.
115. Rock JP, Ryu S, Yin FF, Schreiber F, Abdulhak M. The evolving role of stereotactic radiosurgery and stereotactic radiation therapy for patients with spine tumors. *J Neurooncol* 2004;**69**(1–3):319–34.
116. Rock JP, Ryu S, Yin FF. Novalis radiosurgery for metastatic spine tumors. *Neurosurg Clin N Am* 2004;**15**(4):503–9.
117. Gerszten PC, Lunsford LD, Rutigliano MJ, et al. Single-stage stereotactic diagnosis and radiosurgery: feasibility and cost implications. *J Image Guid Surg* 1995;**1**(3):141–50.
118. Gerszten PC, Welch WC. Cyberknife radiosurgery for metastatic spine tumors. *Neurosurg Clin N Am* 2004;**15**(4):491–501.
119. Gerszten PC, Burton SA, Welch WC, et al. Single-fraction radiosurgery for the treatment of spinal breast metastases. *Cancer* 2005;**104**(10):2244–54.
120. Chang EL, Shiu AS, Mendel E, et al. Phase I/II study of stereotactic body radiotherapy for spinal metastasis and its pattern of failure. *J Neurosurg Spine* 2007;**7**(2):151–60.
121. Rock JP, Ryu S, Shukairy MS, et al. Postoperative radiosurgery for malignant spinal tumors. *Neurosurgery* 2006;**58**(5):891–8 [discussion 891–8].
122. Sahgal A, Chou D, Ames C, et al. Image-guided robotic stereotactic body radiotherapy for benign spinal tumors: the University of California San Francisco preliminary experience. *Technol Cancer Res Treat* 2007;**6**(6):595–604.
123. Yamada Y, Lovelock DM, Yenice KM, et al. Multifractionated image-guided and stereotactic intensity-modulated radiotherapy of paraspinal tumors: a preliminary report. *Int J Radiat Oncol Biol Phys* 2005;**62**(1):53–61.
124. Gibbs IC, Patil C, Gerszten PC, Adler Jr JR, Burton SA. Delayed radiation-induced myelopathy after spinal radiosurgery. *Neurosurgery* 2009;**64**(2 Suppl.):A67–72.
125. Cappuccio M, Gasbarrini A, Van Urk P, Bandiera S, Boriani S. Spinal metastasis: a retrospective study validating the treatment algorithm. *Eur Rev Med Pharmacol Sci* 2008;**12**(3):155–60.
126. Boogerd W, van der Sande JJ. Diagnosis and treatment of spinal cord compression in malignant disease. *Cancer Treat Rev* 1993;**19**(2):129–50.
127. Husband DJ. Malignant spinal cord compression: prospective study of delays in referral and treatment. *BMJ* 1998;**317**(7150):18–21.
128. Prosnitz RG, Patwardhan MB, Samsa GP, et al. Quality measures for the use of adjuvant chemotherapy and radiation therapy in patients with colorectal cancer: a systematic review. *Cancer* 2006;**107**(10):2352–60.
129. Tibbs MK. Wound healing following radiation therapy: a review. *Radiother Oncol* 1997;**42**(2):99–106.
130. Bernstein EF, Sullivan FJ, Mitchell JB, Salomon GD, Glatstein E. Biology of chronic radiation effect on tissues and wound healing. *Clin Plast Surg* 1993;**20**(3):435–53.
131. McPhee IB, Williams RP, Swanson CE. Factors influencing wound healing after surgery for metastatic disease of the spine. *Spine (Phila Pa 1976)* 1998;**23**(6):726–32 [discussion 732–3].
132. Gerszten PC, Monaco 3rd EA. Complete percutaneous treatment of vertebral body tumors causing spinal canal compromise using a transpedicular cavitation, cement augmentation, and radiosurgical technique. *Neurosurg Focus* 2009;**27**(6):E9.
133. Georgy BA. Metastatic spinal lesions: state-of-the-art treatment options and future trends. *AJNR Am J Neuroradiol* 2008;**29**(9):1605–11.
134. Gronemeyer DH, Schirp S, Gevargez A. Image-guided radiofrequency ablation of spinal tumors: preliminary experience with an expandable array electrode. *Cancer J* 2002;**8**(1):33–9.