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Future advances in spine surgery
Spine Oncology – Advances in the surgical management of metastatic spine tumors.

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Running title

Advances in metastatic spine tumor surgery

Abstract

Surgery for spinal metastases remains the mainstay treatment for pain, instability and neurological deterioration due to tumor infiltration of the spine. However, several new therapies are emerging which may improve outcomes further, and in some cases even replace the need for surgery. We now have a better understanding of which factors influence survival and quality of life after surgery, and this underpins the development and application of new treatments, and assessment of outcome.

Depending on genetic subtyping of tumors, novel immunotherapies and chemotherapies may be very effective in prolonging quality of life. New surgical techniques allow smaller, quicker and safer operations with less blood loss, pain, and quicker recovery after surgery. Radiation treatments have also leapt forwards with more accurate beams and higher doses possible from intensity modulated photon radiation, stereotactic body radiation treatment, proton beam therapy, or carbon ion treatment. Combined with more advanced materials for vertebral body stabilization, computer navigation systems and robotics, more can be done at earlier or later stages of the spinal disease than previously possible, resulting in more options and improved outcomes for patients.

Introduction

Surgery for symptomatic spinal metastases can improve pain, neurological function, and quality of life.[1-3] In recent years there have been several advances which contribute to better outcomes for this common disease. Understanding the factors which influence duration of survival and quality of life can help doctors and patients to make appropriate treatment decisions[2,4-6] and genetic subtyping, novel immunotherapies, and advances in radiation techniques have allowed personalized treatment for patient benefit. Advances in surgical techniques permit minimally invasive augmentation of vertebral body integrity without resorting to larger open surgeries, and thereby decrease pain and allow rapid recovery from surgery. Percutaneous cement augmentation, vertebral body stenting or support, and percutaneous instrumentation have increased the accessibility of surgical treatments to patients with poorer prognosis. New materials and devices for spine reconstruction can make surgery easier, and radiolucent materials permit more effective radiation treatments and radiological surveillance after surgery. Three-dimensional printing allows bespoke manufacture of components to reconstruct the spine, or produce patient-specific models of the spine to allow the surgeon to plan tumor resection and reconstruction more effectively. The availability of computer navigation systems and robotic guidance allows accurate placement of pedicle screws, and better appreciation of abnormal anatomy.

Personalized treatment

Genetic subtype analysis

Genetic analysis of tumors has revolutionized medical management of metastatic tumours, particularly breast carcinoma, melanoma, and certain lung carcinomas.[7,8]

For Non-small cell lung cancer, if genetic analysis is positive for EGFR mutation then patients may respond well to immunotherapy (Erlotinib[9]) and chemotherapy (Pemetrexed-Cisplatin[10]) with a favourable median survival of greater than 2 years. If genetic analysis is positive for ALK-EML fusion then immunotherapy with Crizotinib may be used.[11]

Renal cell carcinoma can be resistant to radiotherapy and traditional chemotherapy, but may respond well to new immunotherapies (Sunitinib and Pazopanib) with more than 50% disease control rate.[12]

Melanoma with positive BRAF mutation may also respond well to immunotherapies with improved survival even in advanced metastatic disease.[13]

Prognostication and risk assessment

Prognostic scores allow an estimation of survival and quality of life which may guide treatment decisions. It is important to tailor the most appropriate operation for an individual patient; too much surgery, or performing surgery too late, may not benefit a patient, and conversely, too conservative an approach may deny a patient the chance to walk. Prognostic scoring systems allow a better understanding of the risk of the spine tumor to the patient, estimating survival and quality of life. In general, larger operations may potentially improve long-term outcomes, but are perhaps more likely to be associated with surgical complications that could negate the benefits of surgery. To select appropriate operations, it is useful (although not always easy) to estimate whether a patient may not live long enough to appreciate the effects of surgery.

The most cited scoring systems for metastatic spine tumors are the Tomita score[4] and the Tokuhashi score[5] which comprise the primary tumor type, presence of visceral metastases, number of spinal metastases, and in addition the Tokuhashi score incorporates the neurological function and Karnofsky functional status into the score. These systems have been validated[2,14,15] and although there are limitations to their application they remain useful tools to aid surgical decision making. Other prognostic scoring systems follow similar methodologies, but place emphasis and weighting on different variables.[16]

However in this present decade, genetic subtype analysis has allowed the prognosis of certain tumor types to be estimated more specifically for an individual. Prognosis of some tumors are defined more by their genetic subtype analysis rather than other factors at presentation. Although generalized prognostic scoring systems still have their uses, wider acceptance and adoption into clinical practice has been limited and some surgeons have questioned their validity,[17] particularly since prognosis is perhaps more influenced now by genetic subtyping. For example, if a melanoma metastasis has a BRAF mutation in the genetic phenotype of the primary tumor, then survival is influenced by the response to immunotherapy rather than by the number of spinal and visceral metastases at presentation. The same can be said for EGFR receptor status in non-small cell lung carcinoma, and Estrogen, Progesterone or HER2 receptor status in breast carcinoma. Therefore, rather than rely on prognostic scoring systems, the more “modern” approach would be to create a risk stratification model including the genetic subtype of the metastasis, as well as the Tomita or Tokuhashi elements, to determine a median survival for an individual patient at the time that they present to the surgeon. It is important for the modern spine surgeon to understand primary tumor biology and how this impacts on prognosis and consequently the choice of surgery.

Advances in radiation and heavy particle therapies

Traditionally, surgical management would precede adjunctive radiation treatments. However with the advent of modern radiotherapy, including Intensity Modulated Radiotherapy (IMRT), Stereotactic Radiosurgery and Radiotherapy (SRS, SBRT), and heavy particle therapies, the landscape has shifted. If there is no imminent instability or symptomatic spinal cord compression, these techniques may be used before or instead of surgery. Surgery, rather than aiming to completely excise a tumor, may now be performed with the objective of "separation surgery" to create sufficient space around crucial structures such as the spinal cord to allow dose escalation of radiotherapy techniques whilst limiting collateral damage to the spinal cord.

Radiation treatments have seen a revolution in the past decade, with the introduction of stereotactic radiotherapy, SBRT[18,19] and heavy particle therapy such as Proton beam or Carbon Ion treatments. Whereas there is little published evidence for the efficacy of heavy particle treatment for spinal metastases, the principal benefits would be similar to SBRT, with higher delivered dosage and less collateral damage. SBRT has been used for primary treatment, post-operative treatment, and for salvage re-irradiation. A treatment dose of stereotactic radiotherapy can be given to early metastases to minimize progression to spinal cord compression or mechanical instability, particularly for radioresistant tumors such as renal cell carcinoma, sarcoma, melanomas. If there is significant instability or spinal cord compression, primary surgical management is preferable to SBRT, although SBRT may be used as a post-operative adjunct after minimal access surgery.[18] In addition to local disease control, SBRT may also have a significant role in palliative treatment of patients with end-stage disease, resulting in pain control in 80-85% of patients.[20] However, one must bear in mind that focused high dose radiation therapies such as SBRT can be associated with delayed vertebral fracture in 11-39% of patients and therefore strategies to anticipate and mitigate this risk, including prophylactic vertebroplasty, should be considered.[21]

Advances in surgical technique

Several new techniques have been developed over the past decade to make surgery for spinal metastases safer and more acceptable to patients by decreasing post-operative pain and length of hospital stay. Minimal access techniques are a useful addition to the range of techniques that a spine tumor surgeon should be familiar with. However "one size does not fit all" and the choice of technique will depend on surgeon-related factors such as technical ability and familiarity with newer techniques, and patient-related factors including the reason for surgery (pain control, stability, decompression, or separation surgery) and the patient's prognosis. Pre-operative MRI and CT imaging of the spine are essential to appreciate the anatomical goals of surgery and the potential limitations of certain approaches. Minimal access techniques in general are associated with a learning curve and require additional training, due to the relatively narrow working channels or approaches, longer working distances and challenges posed by excessive bleeding or CSF leakage.

Percutaneous vertebral body augmentation

Less invasive techniques potentially allow quicker recovery, lower complication rates, and increased versatility for treating palliative patients who have a poorer prognosis. The introduction of percutaneous cement techniques for osteoporotic vertebral body compression fractures has been successfully applied to pathological fractures due to spinal metastases. Vertebroplasty involves the injection of viscous Polymethylmethacrylate (PMMA) bone cement in situ to provide structural integrity within the weakened vertebral body.[22,23] Xie et al reported decreased pain visual analogue score from around 8,4 to 3.4 after vertebroplasty in 47 patients with spinal metastases.[22] Kyphoplasty, by temporarily inflating a balloon within the affected vertebral body, creates a cavity which can be filled with bone cement at lower injection pressure than vertebroplasty, and may also permit reduction of a wedge fracture.[24] Alternative techniques to improve pathological wedging include mechanical elevation of the end plate using an expandable jack[25] or using a titanium mesh vertebral body stent that expands over an inflatable balloon.[26]

Percutaneous radiofrequency ablation

With the development of percutaneous access to the vertebral body for cement augmentation, other techniques have been developed to ablate tumor in an attempt to improve spinal pain and possibly decrease the risk of cord compression. Radiofrequency ablation can be performed at the same time as percutaneous cement augmentation, or as an independent procedure to destroy tumor tissue within the vertebral body.[27,28] Long term outcomes are unclear, but this technology may be a useful addition to the minimally invasive methods available for palliative treatment.

Minimal access retractor systems

Anterior approaches to the vertebral body in the thoracolumbar spine is facilitated by minimal access retractor systems which allow smaller skin incisions and direct approaches to the surgical target. Corpectomy and stabilization with an expandable vertebral body replacement prosthesis is now possible with minimal tissue damage, allowing rapid patient mobilization and discharge from hospital, without the morbidity of major thoracotomy or anterolateral abdominal approaches. Transferring open surgical skills to using minimally access retractors is relatively straightforward and intuitive, unlike the steeper learning curve of endoscopic surgical techniques.[29] Uribe et al reported a mean operating time of 117 minutes, 291mls of blood loss, and hospital stay of 2.9 days for minimal access thoracic spine surgery. Although there is limited evidence of efficacy, and most published series are uncontrolled and report small numbers of patients, the general consensus is that these approaches decrease bleeding and pain compared to traditional open approaches, as discussed in two thorough reviews.[30,31]

Posterior minimal access approaches are perhaps easier to adopt due to familiarity of anatomy with traditional open approaches. Several minimal access retractor systems have been engineered to allow insertion of pedicle screws and vertebral body replacement cages with minimal disruption of normal anatomy by posterior transpedicular approaches.[32,33]

Thoracoscopic procedures

Endoscopic procedures for minimal access to thoracic spine metastases allows surgery to be performed without the major morbidity of an open thoracotomy, and a lower risk of intercostal neuralgia, pleural effusions and hematoma.[34,35] However the learning curve for these techniques is steeper than mini-open approaches, and may involve more blood loss and length of surgery than conventional techniques.[29] Thoracoscopic surgery necessitates additional investment in equipment, surgeon and staff training, and requires an experienced assistant who is familiar with the technique. A study of thoracoscopic vertebral body resection found a mean operating time of 4.9 hours, and patient stay of 8.2 days.[36]

Advances in pedicle screw technology

Percutaneous pedicle screws

Percutaneous pedicle screws, placed using a Jamshidi bone needle and Kirschner guide wires, have revolutionized the indications for posterior fixation. Previously, surgery would be discouraged in patients with an anticipated life expectancy of less than 3 months. However, clinicians often do not correctly estimate a patient's life-expectancy,[37] and patients with a poor life expectancy may nevertheless benefit from stabilization to help back pain. Percutaneous pedicle screws may be offered to patients with poor prognosis for palliative stabilization and pain relief, and have effectively moved the goal-posts for offering fixation surgery. Percutaneous screws have been used often for the treatment of lumbar degenerative disk disease, and small series have demonstrated lower complication rates and less atrophy of the Multifidus spinal muscles compared to open approaches.[38,39]

Figure 1

Carbon fiber screws

Carbon fiber reinforced PEEK (Poly-ether-ether-ketone) pedicle screws are now available from several manufacturers, with a high (greater than 60%) carbon fiber proportion. Strength is uniquely provided by unidirectional extruded carbon fibers, and is equivalent to standard titanium screws. Short non-metal carbon fiber rods are also available, allowing a radiolucent fixation system to be employed for spinal metastases. These systems have two main advantages: by decreasing the artifact on MRI or CT imaging, screw placement and surveillance for tumor recurrence is easier to observe; and carbon fiber constructs are associated with less shielding and scattering of radiotherapy which is often used for patients with spinal metastases after surgery, allowing higher and more accurate dose delivery.

Figure 2

Figure 3

Over the past few decades the proportion of elderly patients in society has increased. Combined with better medical treatment of primary tumors and improved survival, it is now more common for patients to present with metastatic disease and co-existent osteoporotic vertebrae. Pedicle screws have been developed with fenestrations that allow

Polymethylmethacrylate bone cement to be injected through the screw into the vertebral body to decrease the risk of screw pull-out and failure.[40,41]
An alternative strategy to minimize screw failure is to use expandable screws. After insertion of the pedicle screw, an internal mechanism shortens the screw and allows the slotted tip to expand, thereby increasing the purchase of the screw within osteoporotic bone.[42]

Interdisciplinary team-working

The majority of patients with metastatic spine disease should be discussed in a multidisciplinary forum, including spine surgeons, oncologists, radiotherapists, radiologists, pathologists, nurse practitioners, and ultimately with the patient, to determine the best treatment modality. Often surgery may not be the preferred treatment option, and in particular, elderly patients or patients with a poor prognosis require considerable thought prior to surgical management.[43] A major advance in the treatment of spinal metastases has been the widespread realization that collective decision-making is essential to determine the best management for this complex patient group, and the development of weekly spine tumor meetings to discuss patient options is now common. In addition, multidisciplinary discussion and consultation can be facilitated using a "virtual consult" system using electronic communications techniques.[44]

Advances in materials

PEEK, and Carbon fiber re-inforced PEEK are now widely available materials used for vertebral body replacement cages, and pedicle screw-rod systems. They have excellent resilience and similar strength to titanium constructs, but with the advantage of radiolucency for subsequent imaging, and improved radiation treatment delivery.[45] Modern engineering of expandable cages allows easier insertion of a smaller cage which is then expanded in situ, and can be filled with bone graft or artificial bone substitutes. Titanium products continue to be used widely, with excellent handling characteristics, and visibility on x-ray which allows easy insertion and surveillance.
In many units, the use of PMMA bone cement is re-emerging, allowing custom shaping of supports and constructs at the time of surgery, secured in situ by press-fit or the use of Kirschner wires to stabilize the cement block, or containing the cement within mesh or block cage.[46]

Three-dimensional printing of plastic polymer or titanium constructs is a new development which allows custom shapes and supports to be created for individual patients, after CT-scan planning. This technique is of particular value for regions with complex anatomy including the upper cervical spine and craniovertebral junction.[47] Polymer or titanium powder is built up in successive two-dimensional layers to create a computer generated three-dimensional structure which can be used as a custom implant.

Advances in spine navigation and robotic guidance

Traditionally, pedicle screws can be inserted using two-dimensional x-ray screening for accurate placement. In cases of small pedicles, obese patients, and surgery at the cervicothoracic junction, it can be difficult to accurately visualize the relevant anatomy with an intra-operative image intensifier x-rays, and in these circumstances, a navigation system may have advantages.

Frameless spine navigation and robot-assisted guidance rely on an intra-operative CT scan or image intensifier image which can be cross-referenced to the patient by optical or infrared camera registration. The trajectory of screws can then be calculated using the computer system, with potentially better accuracy and less radiation exposure than conventional pedicle screw techniques.[48,49]

Conclusion

Surgery plays a pivotal role in the management of patients with symptomatic spinal metastases. Good technical surgery performed in appropriate situations can dramatically improve quality of life and survival. However, occasionally, complications of surgery can have a negative impact on the patient, particularly in those patients with a poor prognosis and limited life expectancy. Although improvements in the medical management of cancer potentially may decrease the need for surgery in the future, it may also have the opposite effect: to increase the number of patients presenting to surgeons in advanced age and with more extensive spinal metastases. Navigated minimal access surgery, with fewer complications and less post-operative pain, is likely to have an important role in the future, hand-in-hand with advances in immunotherapy and radiation techniques. The multimodality treatment of spinal metastases requires close communication across several medical and surgical specialties, and open discussion with the patient to decide the most appropriate treatment plan in each case.

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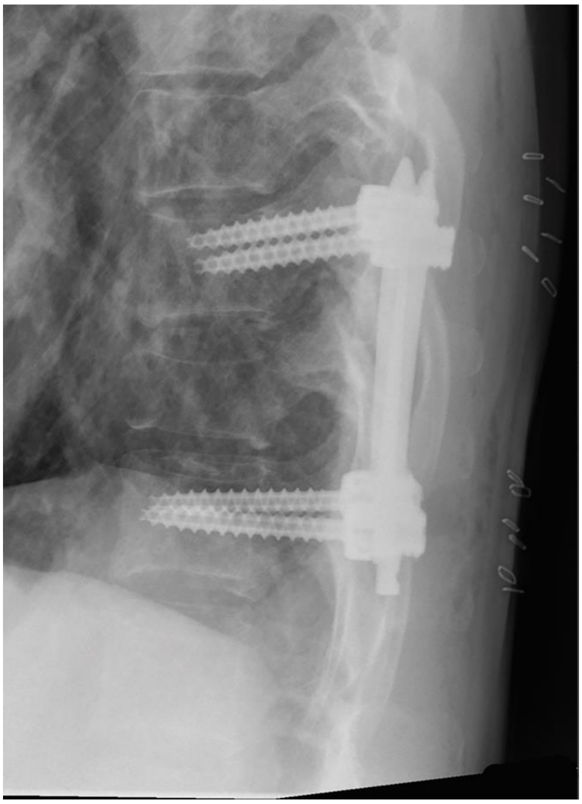
FIGURE LEGENDS

Figure 1

Percutaneous pedicle screw stabilization.

A. MRI of T11 melanoma metastasis, in a patient with multiple skin lesions, liver, lung and brain metastases, presenting with back pain.

B. Lateral X-ray showing percutaneous pedicle screws as palliative treatment for pain



C. Antero-posterior X-rays

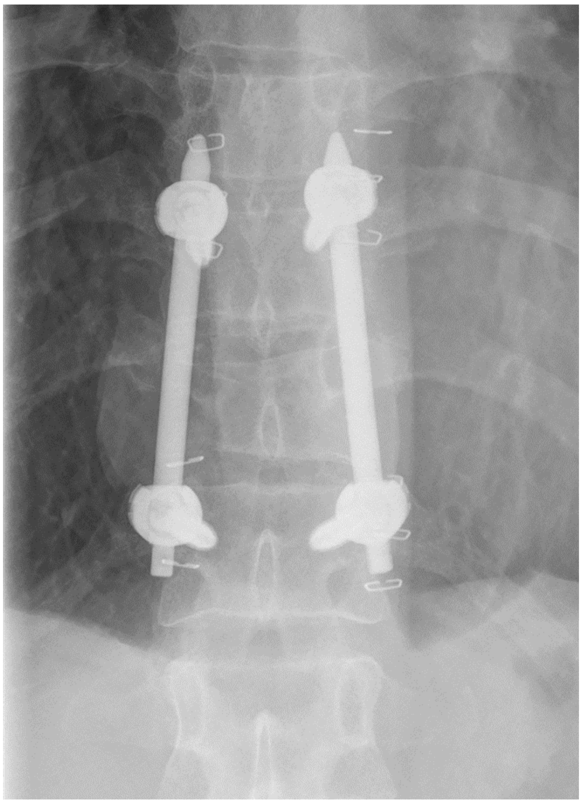


Figure 2

Carbon-fiber reinforced PEEK pedicle screws.

A. Carbon fiber screws with titanium polyaxial head, and carbon fiber reinforced rods.

B. Axial CT scan of a patient with left sided titanium pedicle screw (right side of picture) compared to less artifact of a right sided carbon fiber screw.

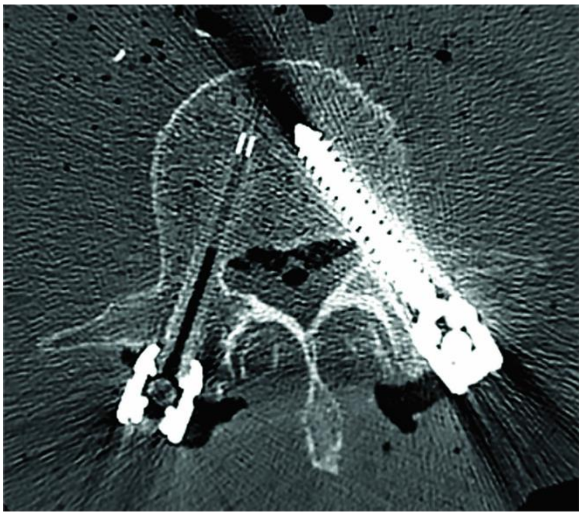


Figure 3

Radiological evaluation of carbon fiber components after C3 and C4 corpectomy, anterior cage and plate, and posterior C2 and C5 pedicle screws. Radiolucency allows more accurate dose planning for subsequent radiotherapy.

A. Sagittal CT scan showing anterior carbon fiber plate and locking screws, cage and bone graft

B. Lateral cervical X-ray demonstrating radiolucency of components. The titanium polyaxial heads of the C2 screws, and the standard titanium C5 screws are visible. All carbon fiber components are represented by small radio-opaque markers at the corners of the vertebral body replacement cage, tips of screws, and marking the ends of the anterior plate and posterior rods.

C. Anteroposterior X-ray