

Diagnosis and management of metastatic spine disease

A review

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With continued growth of the elderly population and improvements in cancer therapies, the number of patients with symptomatic spinal metastases is likely to increase, and this is a condition that commonly leads to debilitating neurological dysfunction and pain. Advancements in surgical techniques of resection and spinal reconstruction, improvements in clinical outcomes following various treatment modalities, generally increased overall survival in patients with metastatic spine disease, and a recent randomized trial by Patchell and colleagues demonstrating the superiority of a combined surgical/radiotherapeutic approach over a radiotherapy-only strategy have led many to suggest increasingly aggressive interventions for patients with such lesions. Optimal management of spinal metastases encompasses numerous medical specialties, including neurosurgery, orthopedic surgery, medical and radiation oncology, radiology, and rehabilitation medicine. In this review, the clinical presentation, diagnosis, and management of spinal metastatic disease are discussed. Ultimately, the goal of treatment in patients with spinal metastases remains palliative, and clinical judgment is required to select the appropriate patients for surgical intervention.
(DOI: 10.3171/2010.3.SPINE09202)

KEY WORDS • cancer • metastasis • spine • surgery • radiation therapy

MORE than 1.4 million new cases of cancer will be diagnosed this year in the US.⁵ Roughly half of these patients will eventually die of their disease, a rate that has remained relatively unchanged for the past half century. Complications related to cancer caused 565,650 deaths in 2008. The lungs and liver are the most frequent sites of distant metastases, followed closely by the skeleton, within which the spinal column is the most common site of metastasis.^{1,19,156} As many as 30–90% of patients who die of cancer are found to have spinal metastases in cadaver studies.^{30,77,87,131,150} Symp-

tomatic secondary metastases are estimated to occur in approximately 10% of all cancer patients.¹³⁰ Up to 50% of spinal metastases require some form of treatment, and 5–10% require surgical management.^{13,17,143,152} However, as survival rates for many primary cancers continue to improve, it is likely that the prevalence of spinal metastases will increase.

The highest incidence of spinal metastases is found in individuals 40–65 years of age, corresponding to the period of highest cancer risk.¹⁰⁷ Males are slightly more prone to the development of spinal metastases, probably reflecting the slightly higher prevalence of lung cancer in men, and of prostate cancer over breast cancer.¹⁰⁷ This disparity may vanish, however, as adjuvant therapies for breast cancer increase the overall survival of patients with this disease, thus increasing the period during which lesions in the spine may arise. Spinal metastases are most

Abbreviations used in this paper: ISCM = intramedullary spinal cord metastasis; MESCC = metastatic epidural spinal cord compression; PMMA = polymethylmethacrylate; SRS = stereotactic radiosurgery; VB = vertebral body; XRT = radiation therapy.

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likely to originate from breast, lung, or prostate tumors, reflecting the high prevalence of these tumors and their tendency to metastasize to bone.^{33,70} Brihaye et al.²³ found that 16.5% of symptomatic spine metastases arose from breast cancer, 15.6% from lung cancer, and 9.2% from prostate cancer.

Characteristics of Metastatic Tumors

Metastatic lesions of the spine spread to the vertebral column by several mechanisms, including hematogenous seeding, direct extension or invasion, and by seeding in the CSF. The mechanism of spread is often closely related to the biological behavior of the primary tumor. Hematogenous spread, by venous or arterial routes, is thought to be the most common route by which primary tumors metastasize to the spine. Because of the rich arterial blood supply of the VBs, tumor cells from distant primary lesions can travel to the spine and establish deposits of metastatic disease.⁶ Spread via venous routes is often accomplished through the Batson plexus, the longitudinal network of valveless veins that connects vertebral veins with many other beds of venous drainage, including the caval, portal, azygous, intercostal, pulmonary, and renal systems. Changes in pressure within the major body cavities (for example, thorax, abdomen, and pelvis), can lead to variable flow through the plexus. As a result, tumor cells may be deposited in the spine via retrograde or antegrade venous flow.¹¹⁶ Whether by arterial or venous routes, the hematogenous spread of tumors usually results in multicentric disease of the spine.

Direct extension of primary tumors may also lead to metastases in the spine. Lesions within the thorax, abdomen, or pelvis may become locally aggressive and invade the vertebral column, leading to symptomatic spinal metastases. Tumors of the lung can extend posteriorly into the thoracic spine or superiorly to involve the cervicothoracic junction. Additionally, prostate, bladder, and colorectal cancers may invade the lumbar or sacral spine.¹¹⁶

Metastasis to the spine or spinal cord can also occur via shedding or seeding of tumor cells in the CSF. This usually occurs after surgical manipulation of cerebral or cerebellar metastatic or primary lesions, and, like hematogenous spread, often leads to multicentric disease.¹⁰⁸

Spinal tumors are classically grouped into 3 categories based on anatomical distribution: extradural, intradural-extramedullary, and intramedullary.^{84,104} The overwhelming majority of all spinal metastases are found in the extradural compartment; that is, the bony spine and associated tissues. Metastases to the extradural compartment are found most commonly in the VB, with or without extension into the posterior elements, followed by the paravertebral regions and the epidural space, respectively. Intradural and intramedullary metastases are very rare, and are often due to CSF seeding.¹⁰⁸ All segments of the vertebral column are susceptible to distant metastasis, but the thoracic spine is by far the most frequent site (70%), followed by the lumbar spine (20%), cervical spine, and sacrum, respectively.¹¹⁶

Presentation of Metastatic Tumors

Metastatic disease of the spine may cause a constellation of symptoms, including pain, motor or autonomic dysfunction, or sensory dysfunction, depending on the rate of tumor growth, degree of bone involvement or destruction, amount of neural compression, and extent of systemic disease. Tumors that grow quickly may lead to rapid progression of symptoms. Lytic tumors may lead to pathological fractures or deformities due to bone destruction. Metastatic tumors may also lead to nerve root impingement or spinal cord compression, leading to radiculopathy or myelopathy, respectively. Additionally, signs of systemic disease may be present, including weight loss, anorexia, or organ dysfunction. Physical examination may reveal palpable paraspinal or even rectal masses in the case of large sacral metastases.¹⁴⁵

Pain Symptoms

The most common presenting symptom of patients with symptomatic spinal metastases is pain, which occurs in 83–95% of patients, and may precede the development of other neurological symptoms by weeks or months.^{10,70,113,145,152} Pain related to spinal metastases may actually be the initial symptom in as many as 10% of cancer patients.⁹² Three classically defined types of pain often affect patients with symptomatic spinal metastases, including local, mechanical, and radicular pain. Patients may be affected by only one of these types of pain, or they may experience various combinations of these different entities. Distinguishing the type of pain a particular patient has is a pivotal part of the evaluation process. Local pain is thought to result from periosteal stretching and inflammation caused by tumor growth, and is described as a deep “gnawing” or “aching” pain. It may improve with activity, is often nocturnal, and is responsive to antiinflammatory or corticosteroid medications.⁶³ Percussion or palpation over the spinous process may elicit tenderness in patients with this type of pain.

Unlike local pain, mechanical back pain is often refractory to antiinflammatory and pain medicines, and varies with position or activity. This type of pain is ascribed to impending or established instability. Tumors that cause deformity or collapse of the affected VBs often lead to spinal instability and increased strain on the support and stability elements of the spine; that is, muscles, tendons, ligaments, and joint capsules. This strain leads to characteristic pain with movement or axial loading of the spine. Alternatively, this pain may be elicited by lying prone or supine, but is often relieved with lying down, usually on one’s side. Mechanical pain often responds well to stabilization of the spine with bracing or surgical fixation.

Radicular pain related to spinal metastases occurs when tumors compress nerve roots as the roots exit the spine, or is due to pathological fractures that obliterate the neural foramina, leading to nerve root impingement. Like radicular pain associated with intervertebral disc herniation, it is often described as sharp, shooting, or stabbing in nature. Intradural extramedullary metastases may cause irritation or impingement of nerve roots within the dura mater, leading to dysesthetic or neuropathic pain.

Unlike typical radicular pain, this is often described as an intense, burning sensation.¹⁰⁸

Neurological Dysfunction

Motor dysfunction is the next most common symptom of patients with metastatic disease of the spine. Weakness in one or more muscle groups is found in 60–85% of patients with MESCC.^{66,70,113} This weakness may be related to myelopathy (long tract signs), radiculopathy, or some combination of the two. It is due to direct compression of neural structures by tumor, or to a pathological fracture that leads to retropulsion of bone fragments into the spinal canal or neural foramina. Patients with MESCC may also have some degree of autonomic dysfunction manifesting as bowel, bladder, or sexual abnormalities that are often not revealed to the physician unless a direct inquiry is made.¹²⁴ The most common autonomic finding in MESCC is bladder dysfunction (often urinary retention), which usually correlates well with the degree of motor impairment. Patients with motor dysfunction usually progress to complete paralysis without treatment.²⁰

Sensory disturbances including anesthesia, hyperesthesia, and paresthesia usually occur in concert with motor dysfunction and pain in the corresponding dermatomal distributions. Patients with myelopathy may report sensory abnormalities in a bandlike distribution across the chest or abdomen. In MESCC of the thoracic cord, patients may describe a feeling of discomfort in the chest that is likened to restriction by a tight shirt or corset, similar in nature to the sensory discomfort described by patients with transverse myelitis of the thoracic cord.¹²⁷

The patient's neurological function when a diagnosis of spinal cord compression is made usually correlates well with their prognosis.^{6,71} This observation underscores the importance of diagnosis before motor or autonomic deficits occur. Most patients will have pain before these deficits appear. However, because reports of back pain are very common in the general population, with a lifetime prevalence of up to 84% in some studies,²⁶ a delay in diagnosis occurs in many cases of vertebral metastasis in which the initial complaint is one of new-onset back or neck pain.¹²⁷ In 2002, Levack et al.⁸⁸ reported that in 319 patients with cancer, a median 2-month delay occurred between the report of pain to a primary care provider and the diagnosis of cord compression. Therefore, clinicians should maintain a high index of suspicion for vertebral metastases in patients with back pain and a known history of cancer, with conditions that predispose them to the development of cancer, or with high-risk profiles for cancer. Additionally, because pain due to nonneoplastic processes is less common in the thoracic spine than the cervical or lumbar spine, pain in this region should raise the suspicion of cancer.¹²⁷

Diagnostic Work-Up

Patients with suspected spinal metastasis should have a thorough diagnostic work-up, including history and physical examination. Warning signs include symptoms of vertebral lesions (nocturnal pain, neurological dysfunction, and gait disturbance) as well as those of systemic

disease (weight loss or organ dysfunction). Smoking history, environmental or occupational exposure, and travel history should be investigated. Inquiries should also be made about conditions that increase the likelihood of cancer (HIV, inflammatory conditions, carcinoma in situ) as well as recent cancer screening examinations and family history. Blood cell counts, chemistry, and prostate specific antigen should be examined, and serum and urine protein electrophoresis should be obtained when there is concern about multiple myeloma.

Imaging Studies

Plain radiographs have long been a mainstay in the initial evaluation of patients with new symptoms related to the spine. This is mainly because of the technical ease of obtaining these studies, their low cost, and widespread use. Consequently, plain radiographs are a useful screening test to identify lytic or sclerotic lesions, pathological fractures, spinal deformities, and large masses. Breast or prostate cancers may produce sclerotic or blastic lesions,²⁸ but most spinal metastases are lytic, and plain radiographs may not reveal changes until up to half of the VB is affected.^{56,102} Due to this relative insensitivity, diagnosis is often obtained with other imaging techniques.

Nuclear scintigraphy (bone scan) is a sensitive method for identifying areas of increased metabolic activity throughout the skeletal system. Whereas tumor-related changes visible on plain radiography may not be present until 30–50% of vertebral bone is eroded,^{56,102} bone scans can detect metastases earlier⁹⁶ and with resolution to as small as 2 mm.¹⁵² The sensitivity of nuclear bone scans in detecting vertebral metastases has been reported to be 62–89%.¹⁰⁹ However, because nuclear scans detect increased metabolic activity, they are not specific for metastatic lesions, because this activity may be related to inflammation or infection. Scintigraphy is also hampered by poor image resolution, and should be correlated with CT or MR imaging to exclude benign processes and to plan operative intervention when necessary.⁹⁸

A more advanced form of nuclear bone scan, SPECT, provides 3D imaging of suspected vertebral metastases. This offers more detailed images and increased sensitivity and specificity in detection of lesions than planar scans.^{24,57,69,121,122} Also, SPECT imaging can be used to differentiate between metastatic and benign lesions, which is not prominent with other modalities.^{24,49,121} When planar scans are indeterminate, SPECT is an effective and relatively inexpensive tool for surveillance of the spine in the metastatic cancer work-up.⁵⁷

Positron emission tomography with FDG is also commonly used for whole-body surveillance in the detection of metastatic disease and cancer staging.^{45,55,109} The PET modality has been demonstrated to be superior to planar scintigraphy in the discovery of spinal metastases, and may lead to earlier detection because the metabolic activity of tumors is directly measured, rather than changes in bone turnover, an indirect marker for metastases.⁵⁷ The PET scans can also be used to identify cystic or necrotic areas of tumor, information that may increase the diagnostic yield of biopsy sampling and assist planning of surgical intervention. However, the resolution of PET is

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limited, and correlation with CT or MR imaging is required. Additionally, PET scanning is time-consuming and expensive.

The latest generation of multidetector CT scanners provides highly detailed imaging of the osseous anatomy of the spine and the degree of tumor involvement. The addition of sagittal and coronal digital reconstructions further enhances the detail obtained with CT imaging. When myelography is performed in conjunction with CT imaging, a highly accurate representation of the spaces occupied by neural elements is obtained, which allows identification of compressed structures. This may facilitate determination of the cause of cord compression, whether due to tumor expansion into the spinal canal or retropulsion of osseous fragments from pathological fractures. The CT modality is highly valuable for planning surgical intervention, because a thorough understanding of the regional bony anatomy may help direct the approach and the type and extent of instrumentation. In addition to CT scans of the affected portion of the spine, patients with suspected vertebral metastases and unknown primary lesion should have CT scans of the major body cavities to identify the primary tumor. Furthermore, CT angiography may be performed to evaluate the vascular supply and drainage of spinal metastases.

Magnetic resonance imaging is considered the gold standard imaging modality for assessing metastatic disease of the spine.^{12,81,155} This type of imaging is more sensitive than standard radiographs, CT, and nuclear medicine scans in detecting lesions within the vertebral column.^{4,8} This sensitivity is due in large part to the superior resolution provided by MR imaging of soft-tissue structures of the spine, including intervertebral discs, the spinal cord and nerve roots, meninges, and spinal musculature and ligaments. The MR images also elucidate the bone-to-soft-tissue interface, providing accurate anatomical detail of tumor invasion or related compression of osseous, neural, and paraspinal structures. An MR imaging series should include T1- and T2-weighted studies obtained in the 3 standard axes (axial, sagittal, and coronal) after addition of contrast agents.⁸⁴ Additionally, because T1-weighted images produce a high-intensity signal within the fat of the bone marrow, fat suppression studies may further elucidate contrast-enhancing lesions in the bony spine.⁸⁴ Diffusion weighted studies, although not routinely used, may help distinguish benign and pathological compression fractures.⁸⁹

Conventional digital subtraction angiography is an important tool in the evaluation of spine metastases, because it can provide valuable information for diagnosis and planning of treatment. In patients with lesions that originate from primary tumors with abundant vascularity (that is, renal cell, thyroid, angiosarcoma, leiomyosarcoma, hepatocellular, and neuroendocrine tumors), knowledge of the vascular supply of metastases may prove invaluable if surgery is considered.⁶⁵ Angiography may also permit preoperative embolization of metastases, which can be an effective alternative treatment for patients who are not candidates for surgical treatment.¹⁰³ Embolization reduces intraoperative blood loss^{65,115} and facilitates complete resection of the lesion. In addition to limiting intraopera-

tive hemorrhage, reducing the vascularity of metastases can also potentially shorten operating times and prevent the development of postoperative hematomas, which can cause wound breakdown and neurological decline.

Tumor Management

The treatment of metastatic spine disease frequently involves multiple modalities of therapy and numerous medical specialties, including surgical specialists (neurosurgery, orthopedic surgery, surgical oncology), medical and radiation oncology, pain specialists, interventional radiology, and rehabilitation medicine. Curative treatment is often not possible; therefore, therapeutic objectives are focused on preservation of neurological function, pain relief, and mechanical stabilization. Surgical intervention can successfully achieve these goals, but patient variables such as age, tumor burden, life expectancy, and functional status overwhelmingly influence the choice of therapy.

Surgical Treatment and Patient Selection

Advancements in medicine have improved the treatment of many cancers and prolonged survival for numerous patients. Decisions around treatment of these patients are exceedingly complex and should follow the evidence-based medicine process, using the best available literature, clinical expertise and experience, and patient preference. Given the paucity of literature, the latter 2 components are critical, especially patient preference, due to the palliative setting. From a practical perspective, clinicians should regard 3 main domains, patient factors, stability, and neurology, when trying to make a treatment decision.

The past 2 decades have seen developments in surgical technique and anterior and posterior stabilization of the spine that allow improved decompression and tumor resection with acceptable morbidity. Long-term disease-free survival is possible in some cases, specifically in solitary renal cell carcinoma metastases,⁷⁶ but the goals of surgical treatment for most patients are preservation of neurological function, reduction of pain, and ensuring mechanical stability. Additionally, most clinicians would agree that the expected patient survival should exceed 3 months before surgical treatment of spinal metastases is considered.

Selecting patients who will benefit from resection remains a challenging undertaking. In attempts to guide the selection process, authors have developed scoring systems to evaluate patients and prognosticate survival outcomes following large decompression and fixation procedures. Tokuhashi et al.¹³⁵ developed a system based on the type of primary tumor, number of vertebral metastases, presence of extraspinal or visceral metastases, general patient condition, and neurological status. Higher values were assigned to good prognostic indicators (less aggressive tumors, solitary vertebral lesions, absence of other metastases, good overall health, and no neurological deficit). Patients with scores greater than 9 of 12 were recommended for surgical removal of their lesions. Scores lower than 5 correlated with a worse prognosis, and palliative therapy

by limited decompression and stabilization was recommended. Successful advancements in surgical technique and expanded therapeutic options prompted Tomita et al.¹³⁷ to create a similar scoring system based on the grade of the primary malignancy, presence of visceral metastases, and number of bone metastases. In this system, lower scores were assigned to good prognostic indicators. In patients with scores of 2–3, wide or marginal excision with the goal of long-term local control was recommended. Scores of 4–5 indicated marginal or intralesional excision for intermediate-term control. Palliative surgery was recommended for scores of 6–7, and supportive care only for scores greater than 8. The principles used to develop these scoring systems were designed to assist surgeons in selecting patients who may benefit from surgical intervention and to determine the extent of surgical invasiveness that is appropriate.

Practically speaking, the calculated scores from the Tomita and Tokuhashi systems are not binding in the choice of treatment, especially with the recent development of other treatment modalities like SRS. However, the fundamental principles of these prognostic scoring systems still hold true. Moreover, once patients have been deemed appropriate candidates for surgical intervention, the determination of operative approach and stabilization requires a comprehensive understanding of the anatomy and histopathological features of the metastatic tumor and its surrounding structures, as well as the biomechanics of the spine and changes induced by vertebral metastases.

Percutaneous Biopsy

Advances in imaging technology have improved the detection of cancerous lesions, but tissue from spinal masses is often still required for definitive diagnosis. Up to 10–20% of spine metastases have no known source.²⁵ If surgery and excisional biopsy are not immediately indicated, percutaneous biopsy may be required, because most treatment decisions will be dictated by the tumor histological findings. Improvements in biopsy technique have resulted in diagnostic accuracy rates approaching 90%,^{9,82,86,91} with many biopsies now performed in an outpatient setting.^{7,22} When a primary tumor is considered a possibility, the surgeon should be consulted in planning the biopsy procedure, because seeding and recurrence along the biopsy needle track can occur with some primary tumors, such as chordomas.¹⁵

Surgical Anatomy and Histopathological Tumor Type

The surgical approach to resection or decompression in spinal metastases is in large part determined by the spinal segment involved, the location of the tumor within the vertebra, the tumor's histological features, and the type of spine reconstruction necessary.

The VB is the most commonly affected portion of the spine in metastatic disease, and therefore, anterior approaches provide the greatest ability to resect the lesion and decompress the spinal canal. However, these approaches are associated with increased surgery-related morbidity and mortality. Most spine surgeons are familiar with anterior approaches to the cervical spine. Other

areas of the spine, however, can be more challenging to approach anteriorly. The upper thoracic spine (T1–4) is challenging to access anteriorly, and a combined anterolateral cervical approach with sternotomy or thoracotomy may be required.³¹ Even with these extended approaches, the great vessels of the thorax may obstruct access to the spine. Therefore, a transpedicular posterior or posterolateral approach is frequently used, and is becoming the preferred approach. Three-column decompression and stabilization can be achieved with this approach, which is also being used more and more in the thoracic and lumbar spine, especially with circumferential involvement and/or multiple levels.

A right-sided thoracotomy, which minimizes risk to the great vessels and aortic arch, permits access to the midthoracic spine (T5–12). If, however, the majority of tumor bulk is on the left, a left-sided thoracotomy is indicated.⁵³ Decompression of the thoracolumbar junction (T11–L1) may necessitate a combined thoracotomy and retroperitoneal approach. The lumbar spine (L2–5) and sacrum may be approached via anterior approaches, but posterior excision and stabilization is usually adequate in metastatic disease. Vertebral body resection requires subsequent reconstruction, often with titanium distractible or static mesh cages or with PMMA and anterolateral plating. Posterior stabilization with pedicle screw instrumentation is indicated for resections at high-stress areas, such as the cervicothoracic and thoracolumbar junction, and for patients with 2 or more adjacent vertebrectomies, kyphosis, or circumferential involvement. Decompression from a lone posterior approach may be challenging, but is often indicated due to the high surgery-related morbidity of transcostal operations. Several studies have proposed a bilateral transpedicular approach via costotransversectomy to access the anterior elements and decompress the spinal cord.^{3,52,74,126,128,144} Posterior reconstruction of the anterior column can then be performed with autologous structural bone graft, titanium mesh cage,⁴³ expandible titanium cage (Fig. 1),^{74,126,128} PMMA and chest tube⁵² or Steinman pins,^{3,144} or polyetheretherketone cages. Many authors have reported lower complication rates with this technique.^{74,126,128,144} This approach is anatomically complex, and therefore requires some training. It is not strongly recommended when operating through a previously irradiated field.

Instability Secondary to Spinal Metastasis

Spinal instability secondary to metastatic disease was previously not defined. Two systematic reviews revealed no clear guidelines on impending or established instability of the cervical or thoracolumbar spine. Presently it is determined by a constellation of clinical and imaging parameters, none of which have been validated. Studies of the biomechanical properties of the spine show that the VBs support up to 80% of the axial load of the spine.⁹⁴ Consequently, osteolytic lesions of the VB, the most common site of metastasis, can significantly impact the loading capacity of the spine. The degree of impact is determined by the size of the lesion, cross-sectional area of the intact VB, and overall bone mineral density. As lytic lesions grow in size, they can undermine the integ-

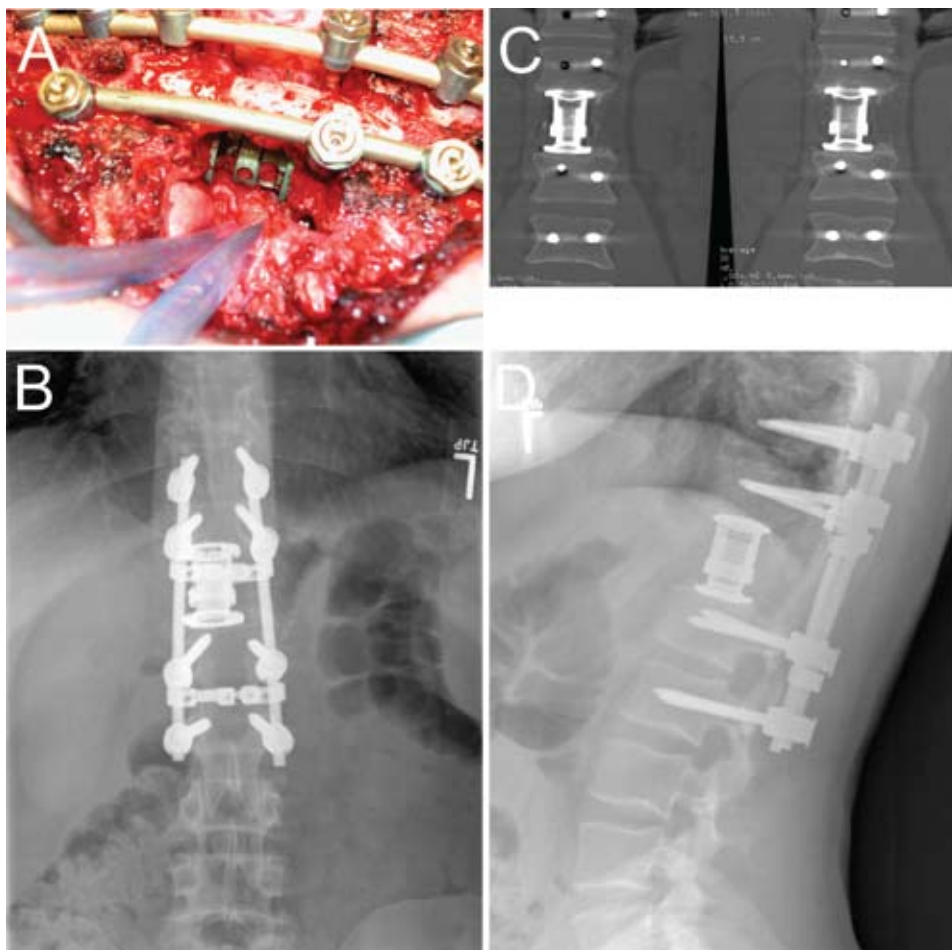


Fig. 1. **A:** Intraoperative photograph of thoracic spondylectomy and anterior reconstruction with distractible titanium cage and posterior pedicle screw stabilization. **B:** Postoperative anteroposterior radiograph of thoracic spondylectomy and anterior reconstruction with distractible titanium cage and posterior pedicle screw stabilization. **C:** Postoperative coronal CT scan of thoracic spondylectomy and anterior reconstruction with distractible titanium cage and posterior pedicle screw stabilization. **D:** Postoperative lateral radiograph of thoracic spondylectomy and anterior reconstruction with distractible titanium cage and posterior pedicle screw stabilization.

rity of the VB and can lead to compression or burst fractures. These fractures can force bone fragments or tumor debris into the spinal canal or neural foramina, causing compression of neurological structures and pain or motor/autonomic impairment. In a cadaveric study, Windhagen et al.¹⁴⁷ determined that the likelihood of pathological fracture could be predicted by calculating the product of cross-sectional area of the intact bone and bone mineral density. Taneichi et al.¹³³ showed that collapse was predicted by 50–60% VB lysis in the thoracic spine and 35–45% in the lower thoracic/lumbar spine. Segments of high mobility or stress, such as the cervicothoracic and thoracolumbar junctions, are likely to be subject to fracture with less tumor burden. Metastases to the dorsal elements of the spinal column, especially the facet joints, are believed to predispose patients to pathological dislocation, spondylolysis, and translational instability. These are uncommon, though, because metastasis to the posterior elements is much less common than to the VB.

Characterizing the degree and nature of instability

can assist the selection of surgical approach and extent of reconstruction. This remains somewhat unclear in patients with neoplasia. The indications for fixation and decompression in instability secondary to neoplastic processes are less clear, because the mechanisms of injury are different. Cybulski³⁶ proposed imaging criteria for the assessment of spine instability due to tumors; these were as follows: 1) anterior and middle column destruction (> 50% collapse of VB height); 2) collapse of 2 or more adjacent VBs; 3) tumor involvement of the middle and posterior columns (possibility of forward shear deformity); and 4) previous surgical laminectomy, with failure to recognize anterior and middle column disease. This study recommended surgical decompression and fixation when one of these instability criteria is met or when neural compression is present in patients with a life expectancy of > 5–6 months, competent immune and nutritional status, incomplete neurological deficit, and a radioresistant tumor or a tumor that failed to respond to previous treatment. Clearly, much more research is needed in the area

of defining impending or established instability in the spine.

Spinal Cord Compression

Metastatic epidural spinal cord compression occurs when tumor elements or bone fragments displace the spinal cord within the canal. Approximately 25,000 symptomatic cases are reported annually in the US,¹²⁴ and when such lesions cause neurological compromise, it is generally a surgical emergency. This condition is found in 5–10% of cancer patients, and in up to 40% of patients with other bone metastases.^{11,61,123} Corticosteroids and XRT are mainstays of treatment. Historically, surgical options were limited to decompressive laminectomy, but this technique does not address anterior compression from the VB, and it destabilizes the posterior elements, often leading to spinal instability, worsened neurological function, and pain.^{52,64} Hence, aggressive surgical techniques for circumferential decompression of the spinal cord have been used more frequently.

In 2006, Witham et al.¹⁴⁹ presented a review of the literature on the treatment of MESCC published from 1964 to 2005, and demonstrated improved outcomes over time (Table 1). These improved outcomes were associated with the evolution of increasingly aggressive surgical strategies. Studies of patients who received only XRT showed a mean 36% improvement and 17% decline in neurological function. Those patients who received laminectomy with or without XRT showed similar results: a mean 42% improvement and a 13% decline, with a slight increase in the 30-day mortality rate (mean 6%). Studies of patients who received posterior stabilization in addition to laminectomy and XRT showed improved outcomes in motor function (mean 64%) and pain relief (mean 88%), with a mortality rate comparable to laminectomy alone (mean 5%). The greatest improvements in motor function were reported in studies of patients who received anterior decompression with stabilization (mean 75%), although a higher surgical mortality rate was also observed (mean 10%).

In 2005, Patchell et al.¹⁰⁵ reported the results of the first prospective randomized controlled trial of direct decompressive resection with adjuvant XRT versus XRT alone as treatment of patients with MESCC (Table 2). Their study showed surgery with XRT to be far superior to XRT alone, and the trial was stopped after 50% recruitment. Both groups of patients received 30 Gy of external-beam radiation delivered in 10 fractions, and the surgical group underwent operations intended to decompress the spinal cord, resect tumor bulk, and stabilize the spine. Surgery with XRT was statistically superior to XRT alone in posttreatment ambulatory rate (84% vs 57%, $p = 0.001$), duration of ambulation (median 122 days vs 13 days, $p = 0.003$), maintenance of ambulation after treatment (94% vs 74%, $p = 0.024$), and return of ambulation after treatment (62% vs 19%, $p = 0.012$). Additionally, patients treated with surgery and XRT experienced significantly more improved functional ability (Frankel scores), muscle strength (American Spinal Injury Association scores), continence, and survival time than those treated with XRT alone. The median survival time in the

TABLE 1: Metastatic epidural spinal cord compression—treatment outcomes*

Treatment	Mean Improvement in Neurological Function (%)	Mean Op-Related Mortality (%)
XRT alone	36	NA
laminectomy & XRT†	42	6
laminectomy & stabilization, w/ XRT†	64	5
ant decompression & stabilization, w/ XRT†	75	10

* Based on data from Witham et al. Abbreviations: ant = anterior; NA = not applicable.

† Treatment was with or without XRT.

surgery with XRT group was 126 days, versus 100 days in the XRT alone group ($p = 0.033$). With these results, Patchell et al. concluded that, for select patients, surgery and XRT are superior to XRT alone in the treatment of MESCC.

Although the results of the Patchell et al. study¹⁰⁵ are indeed impressive, it is important to consider the selection criteria of the study. Notably, patients with highly radiosensitive tumors, such as lymphoma, myeloma, and small cell lung carcinoma, were excluded from both groups. In these patients, XRT alone is still indicated for MESCC presenting without spinal instability. Additionally, XRT alone may be indicated for patients with rapidly progressive neurological decline without significant bone intrusion of the spinal canal, or with expected survival time < 3 months. Surgical decompression and stabilization is indicated in patients with spinal instability, bony cord compression, rapid decline, or recurrent tumor despite XRT, MESCC caused by radioresistant tumors, and cases in which tissue diagnosis is necessary (Fig. 2). Furthermore, total en bloc resection and spondylectomy may be indicated, with curative resection possible for patients with solitary metastases of relatively indolent course, such as renal cell carcinoma without systemic metastases.^{119,132,136,138}

Cost-Effectiveness of Surgical Treatment for MESCC

A recent study by Thomas et al.¹³⁴ compared the cost-effectiveness of decompressive surgery plus radiotherapy with radiotherapy alone for treatment of MESCC. They performed an incremental cost-effectiveness analysis from a societal perspective by estimating the costs related to treatment and posttreatment care, and extending these costs to the lifetime of the cohort. The incremental cost-effectiveness ratio was \$60 (all prices in 2003 Canadian dollars) per additional day of ambulation, with a 95% CI of $-\$72.74$ to $\$309.44$. In short, each day of ambulation gained with surgery plus radiotherapy cost an extra \$60, with a range (95% CI) of \$72.74 savings to \$309.44 cost per additional day. With survival as the measure of effectiveness, the group found that the incremental cost-effectiveness ratio was \$30,940 per life-year

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gained. The authors concluded that these figures provide strong evidence for the cost-effectiveness of surgery plus radiotherapy with respect to additional days of ambulation and survival.

Adjuvant Therapies

Pharmacotherapy Agents

Pharmacotherapies used in the treatment of spinal metastases can be classified into 2 groups: agents that act directly against the tumor, and those that minimize the secondary effects of the tumor.¹⁵⁴ Because many metastases to the spine are largely insensitive to cytotoxic agents, the role of antitumor drugs remains limited in the treatment of these lesions, except in cases of chemosensitive tumors such as Ewing sarcoma, osteosarcoma, and neuroblastoma. Conversely, drugs that prevent or ameliorate the effects of spinal tumors, including pain, inflammation, and bone destruction, are widely used.

Chemotherapy Agents

Although advancements in chemotherapeutic regimens have improved the treatment of cancer over the past several decades, these therapies are commonly limited in the treatment of metastatic spine disease, because spine metastasis is often a late complication of cancer. However, certain metastases have improved outcomes with neoadjuvant therapies followed by resection, including germ cell tumors, high-risk neuroblastomas,¹²⁰ Ewing sarcoma,⁷⁵ and osteogenic sarcomas.¹⁶ Additionally, some tumors previously considered unresectable are now treated surgically following neoadjuvant therapy. For example, superior sulcus non-small cell lung carcinomas (Pancoast tumors) with extension to the spine were previously considered unresectable due to the high rate of surgical morbidity and limited possibility of significant improvement. However, with neoadjuvant chemotherapy (etoposide and cisplatin) and XRT, two-thirds of patients with these tumors have minimal tumor mass at operation, and the likelihood of negative margin resection is increased.¹¹⁷ Other pharmacological therapies are effective in the treatment of spine metastases.

Hormone Therapy

Some spine metastases, specifically those arising from breast and prostate cancer, may have hormone receptors and respond to treatment directed at these receptors. Selective estrogen receptor modulators such as tamoxifen, and aromatase inhibitors such as letrozole, anastrozole, and exemestane have been shown to be effective against breast cancer.⁹⁹ For prostate cancer, androgen suppression with gonadotropin-releasing hormone agonists and/or flutimide is an effective therapy.³⁴ Even if the primary tumor is responsive to hormone therapy, metastases may not possess the same hormone receptor composition and, therefore, may be unresponsive to hormone therapy.

Bisphosphonate Agents

These drugs inhibit osteoclastic activity and sup-

TABLE 2: Outcomes following treatment with XRT alone versus surgery with XRT*

Treatment	Posttreatment Ambulatory Rate (%)	Ambulation			Mean Survival (days)
		Retained (days)	Maintained (%)†	Re-gained (%)‡	
op & XRT	84	122	94	62	126
XRT alone	57	13	74	19	100

* Based on data from Patchell et al.

† Patients who were ambulatory before treatment and who maintained ambulation.

‡ Patients who were nonambulatory before treatment and who regained ambulation.

press bone resorption associated with spinal metastases. They have been shown to reduce the risk of pathological fracture,⁷³ relieve local pain caused by lytic lesions,⁷² and reduce malignancy-associated hypercalcemia. They have been proven effective for metastatic breast cancer, multiple myeloma, and some other osteolytic metastases.^{14,17,154}

Corticosteroid Agents

Corticosteroids remain a fundamental component of the pharmacological therapy for pain associated with vertebral metastases and for the acute management of neurological decompensation that often accompanies spinal cord compression from metastatic tumors. Corticosteroids decrease inflammation and thereby reduce tumor-associated pain. They also decrease spinal cord edema, which can improve short-term neurological function. Finally, corticosteroids may also be directly oncolytic in tumors such as lymphoma, multiple myeloma, and breast cancer.¹¹³ Animal models have confirmed clinical observations that patients treated with dexamethasone recover motor function faster than untreated controls.^{40,41,139} There is currently no consensus for the optimal dosing regimen of corticosteroids; that is, high dose (96 mg/day) versus low dose (16 mg/day). Vecht et al.¹⁴⁰ showed no differences in pain, ambulation, and bladder function when initial intravenous bolus doses of 10 and 100 mg were compared.

Analgesic Agents

Spinal metastases cause intense mechanical or neuropathic pain, and analgesia is an important goal of any therapy regimen. Poorly managed cancer pain contributes to depression, anxiety, and fatigue, and undertreatment of cancer pain persists despite efforts to improve delivery of analgesics.⁸⁰ The management of cancer pain is usually done in a stepwise fashion that includes an additive progression from NSAIDs, to mild opioid therapy, and morphine opioid therapy.^{37,106} First-line agents should be nonopioid analgesics such as acetaminophen, aspirin, or other NSAIDs. The American Pain Society recommends combining long- and short-acting opioids with a con-

comitant bowel regimen and avoidance of meperidine.⁹⁷ When morphine therapy is initiated, oral administration is first attempted, with a progression to increasingly invasive forms, including neuraxial analgesia. This stepwise “ladder approach” is used in conjunction with adjuvant therapy for analgesia side effects and psychiatric comorbidities.^{146,151} Additionally, many patients with spinal metastases will have neuropathic pain due to involvement of paravertebral nerve plexuses. This type of pain can be very difficult to treat with opioids and may require alternative strategies,^{111,112} including continuous nerve root block with indwelling catheter–delivered anesthetics,¹⁴² or cryoablation.⁴⁸ Other pharmacological agents may also be effective treatments for neuropathic pain; these include anticonvulsants, neuroleptics, and lidocaine patches.⁴⁴

Many of these analgesic medications can cause troublesome side effects that must be monitored and treated. Opioid analgesics commonly cause gastrointestinal symptoms, which include constipation and nausea, so a proper bowel regimen and antiemetics may be necessary when using these agents. Opioids may also exacerbate gait disturbance and cognitive impairments in the elderly, necessitating safety precautions. Patients may develop physical dependencies with long-term opioid therapy, and abrupt discontinuation should be avoided. Anticonvulsants may cause somnolence and dizziness, and neuroleptics can lead to sedation, anticholinergic effects, postural hypotension, and weight gain. Patients undergoing treatment for cancer pain must be monitored for these side effects, the effectiveness of pain relief, functional status, and quality-of-life parameters.

Radiation Therapy

Radiation therapy is a mainstay of treatment for spinal metastases, and continues to play an important role in pain relief, prevention of pathological fractures, and stabilization of neurological function. Several studies published in the 1960s and 1970s showed that patients treated with surgical decompression with or without XRT fared no better than those treated with XRT alone.^{62,83,95,141,153} Surgical treatment in these studies most often was limited to laminectomy, which is now almost never done in isolation because of destabilizing and inadequate decompression, so these studies are of historical interest only.

The XRT dosage is usually given in fractionated sessions over 10–14 days, with a total of 25–40 Gy delivered.⁸⁵ The affected level and a 5-cm margin, which typically includes 2 vertebral levels above and below the metastatic lesion, are usually targeted for therapy.⁹⁰ The ability to obtain local control is determined by the dose delivered to the target lesion and the tumor’s histological type. However, conventional XRT is imprecise and cannot deliver large single-fraction doses to the spine due to the proximity of radiosensitive neural structures. Consequently, the dose delivered to the target is often inadequate, and therefore not recommended in a histological tumor type that is radioresistant.^{50,93,118}

Unlike conventional wide-field XRT, spinal SRS precisely focuses numerous cross-fired beams of radiation to the designated target. This limits the dose delivered to

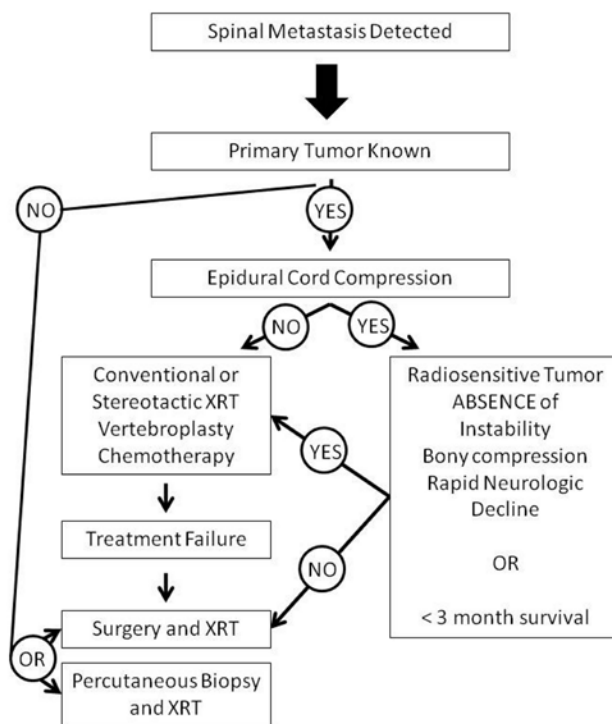


FIG. 2. Flowchart for the management of spinal metastases.

the spinal cord, skin, and other radiosensitive structures. Fractionation permits the delivery of higher single-session doses to the targeted tissues, allowing SRS to be administered in 1–2 sessions in an outpatient setting. Both rigid external frame–based and image-guided frameless systems are currently in use. Image-guided systems (CyberKnife, Accuray) use internal or external fiducial markers to provide near real-time updates of patient positioning to focus the radiation, thus obviating the need for external fixation. This is especially relevant in the spine, where fixation can be cumbersome and uncomfortable. Studies of these systems have demonstrated favorable outcomes, including halted tumor progression, improved pain, and few adverse events.^{27,59,60} Degen et al.³⁹ found that in patients with MESCC treated with the CyberKnife, neurological function was improved or stabilized in 78%, pain control was significantly improved, and quality of life was maintained. Treatment-related morbidity was relatively low, and 100% tumor control was achieved at 1-year follow-up. Additionally, Gerszten et al.⁵⁸ presented similar findings in a larger prospective longitudinal cohort study of 500 patients with spinal metastases treated with SRS. They showed that 86% of patients experienced long-term pain improvement, 90% experienced long-term tumor control, and 27 (84%) of 32 patients with a progressive neurological deficit experienced some clinical improvement.

Long-term outcomes after treatments performed using focused radiation are essential for accurate assessment of the strengths and weaknesses of such technology. For instance, there are early accounts of pathological

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fractures occurring after SRS is completed, potentially due to the rapid and effective tissue destruction caused by the focused radiation. Nonetheless, the ability to apply highly conformal XRT in high doses to target lesions while minimizing exposure of surrounding tissues permits the treatment of tumors classically considered “radiation insensitive,” and the reirradiation of select lesions. As a result, the advent of SRS has led to a fundamental change in the treatment paradigm for spine metastases.

Proton beam therapy was initially developed for cancer treatment in the 1940s, but was not widely used. In the past 2 decades, several centers have constructed proton beam facilities, and thus, it has gained popularity in cancer treatment. Rather than the x-ray and gamma-ray photons emitted in conventional and stereotactic radiotherapy, proton beam therapy uses protons to destroy cancer cells. Like SRS, proton beam therapy can be delivered close to critical structures in the CNS with minimal adverse effects. This is mainly due to the unique physical properties of protons, namely the minimal scattering and sharp peak of maximal energy (known as the Bragg effect).¹¹⁴ Proton beam therapy is limited in its role for most patients, however, because of its limited availability and high cost. As more centers develop the technology, it is likely to become more prevalent.

Although conventional XRT, SRS, and proton beam therapy provide local disease control, preservation of neurological function, and pain relief, these modalities cannot correct spinal instability or deformity and the resultant pain or dysfunction caused by metastatic lesions. Nor can these therapies correct cord compression caused by pathological fracture and retropulsion of bone fragments into the spinal canal or neural foramina. The timing of XRT must also be carefully considered when used as adjuvant or neoadjuvant therapy for resection. Detrimental consequences of XRT include impaired wound healing and graft incorporation after surgical reconstruction.^{21,47} Therefore, a 3–4-week delay in beginning radiotherapy after surgery is advised.

Percutaneous Vertebro- and Kyphoplasty

Extensive, multifocal metastatic disease of the spine has been traditionally treated with conservative measures, which include conventional XRT, corticosteroids, analgesics, bracing, and bed rest. However, XRT may not provide significant pain relief for up to 2 weeks posttreatment, and bone strengthening may not be observed for up to 4 months, if at all.¹⁸ Although it was developed for treatment of painful vertebral hemangiomas, percutaneous vertebro- and kyphoplasty has emerged as an effective treatment for painful pathological fractures caused by metastatic spine disease.

Vertebroplasty is performed by directly injecting PMMA cement into the VB, whereas in kyphoplasty, an expandable balloon is first placed into the VB and inflated to create a cavity into which PMMA is injected. The balloon expansion in kyphoplasty may in fact improve kyphotic deformity caused by VB collapse, but this has not been well documented in the literature. However, kyphoplasty has been shown to prevent further kyphotic

deformity.¹¹⁰ The injection of PMMA cement into a collapsed VB has been demonstrated to provide effective pain relief.⁵⁴ It is assumed that correction of the deformity is responsible for this relief of mechanical pain, but it is possible that PMMA may itself have direct analgesic properties.²

The indications for vertebro- and kyphoplasty in metastatic disease of the spine are currently evolving. These techniques have been proven to be effective and safe interventions for the treatment of pain from vertebral fractures resulting from metastases,¹¹⁰ and when combined with XRT, can provide pain relief in patients who are deemed poor surgical candidates.⁷⁸ However, vertebro- and kyphoplasty are relatively contraindicated in spinal cord compression due to pathological fractures, because the techniques do not relieve cord compression, and may in fact increase it by forcing bone fragments into the spinal canal. Complications from these procedures, although rare, usually result from leakage or misplacement of PMMA that leads to compression of neurological structures or hematogenous embolization to the lungs.²⁹ Although vertebro- and kyphoplasty are effective minimally invasive treatments for pain in metastatic spine disease, they are limited in their ability to stabilize the spine, correct deformities, and relieve spinal cord compression—elements that are better addressed in surgical decompression and stabilization.

Intramedullary Spinal Cord Metastases

The ISCM is a rare entity that is found in approximately 2% of cancer patients at autopsy.³⁵ Of these, approximately 5% are identified before patient death secondary to systemic disease.¹⁰¹ The most common source of ISCMs is lung carcinoma, especially small cell lung carcinoma.^{32,67,125} Intramedullary metastasis occurs less frequently in other tumors that commonly metastasize to the spine, including breast and prostate carcinoma, lymphoma, melanoma, and renal cell carcinoma.^{32,67}

Distinguishing intramedullary metastasis from other lesions such as epidural metastasis or paraneoplastic necrotizing myelopathy can be difficult because the symptoms and clinical findings can be indistinguishable.¹⁰⁰ An ISCM should be considered in patients with a history of malignancy and new onset of unilateral motor or sensory impairments, because asymmetry of spinal dysfunction suggests an intramedullary tumor.⁶⁸ Additionally, Brown-Sequard or pseudo-Brown-Sequard syndrome is estimated to occur in 30–45% of patients with ISCMs.^{42,125} A hallmark of metastatic intramedullary tumors is the rapid progression of neurological symptoms, in contrast to primary intramedullary tumors, which are typically slow growing and present with a gradual progression of symptoms. Approximately 75% of reported patients experienced progression to full neurological deficit within 1 month of the initial development of neurological symptoms.^{67,79} Additionally, although muscle atrophy is a common feature of primary intramedullary tumors, it is uncommon in metastatic lesions.¹⁰⁰

Intramedullary metastases are generally a late finding in the course of cancer, and patients usually have

other systemic metastases. Therefore, the development of intramedullary metastases is frequently associated with a poor prognosis;^{35,46,67} without treatment, the average survival is less than 1 month.¹²⁹ For this reason, several authors have advocated in favor of XRT over excision.^{46,67,148} Radiation therapy may prove effective in certain radiosensitive tumors, such as small cell lung or breast carcinoma, or lymphoma, but it may provide no relief for patients with radioresistant metastases. In these patients, microsurgical resection combined with treatment of the primary tumor and other secondary metastases may help to stabilize or reverse neurological dysfunction, prolong survival, and improve patient quality of life.^{38,51,129}

Resection may be accomplished by vaporization of the tumor with a CO₂ laser, which facilitates excision while reducing manipulation of the spinal cord. Furthermore, intramedullary metastases are often discrete, well-circumscribed deposits that are amenable to standard microsurgical resection.^{32,51}

Future Directions

With a substantial body of literature dedicated to managing possible traumatic instability of the spine, there is now interest in identifying the parameters that lead to instability of the spine in the presence of tumors. The Spinal Oncology Study Group—a collaborative group of neurosurgery, orthopedic surgery, radiation oncology, and medical oncology—is currently working to elucidate the factors that may indicate mechanical instability of the spine due to neoplastic processes. The guidelines proposed by this group may aid many primary care physicians and community oncologists in the management of spinal metastases in their patients. This is especially important because many patients initially present to primary physicians, and their treatment will be managed long term by oncologists without advanced training in spine oncology or biomechanics of the spine.

Furthermore, although significant advancements have been made on many fronts in the treatment of spine metastases, one thing is clear: progress will continue to be made. From improved surgical technique and spinal reconstruction, to focused XRT and new local or systemic chemotherapy regimens, it is important to understand that the landscape is shifting, and we must continue to reassess our management paradigms for metastatic spine disease.

Conclusions

As technical and technological advances have been incorporated in the management of metastatic spine disease, the armamentarium of therapeutic options has become increasingly complex and multidisciplinary in nature. Advanced imaging now allows earlier detection and superior characterization of spine metastases. Advances in surgical stabilization devices and technique now allow more aggressive resection and decompression of the spinal cord. Minimally invasive therapies, such as vertebroplasty and kyphoplasty, and advances in stereotactic and other modalities of radiotherapy have also proven to be increas-

ingly effective in the treatment of metastatic spine disease. As advances continue to be made, more therapeutic options will become available to the growing number of patients with metastatic spine disease. A comprehensive understanding of the treatment options available to patients with spine metastases will allow optimized matching of patients to the appropriate treatment modalities.

Disclosure

Dr. Sciubba reports receiving an honorarium from Depuy Spine courses and participating in the Spinal Oncology Study Group. Dr. Ondra reports participating in the Spinal Oncology Study Group. Dr. Gokaslan reports having stock in US Spine and Spinal Kinetics; receiving clinical/research support from AO North America, Depuy, Johnson & Johnson, Medtronic, and Integra; and receiving fellowship support from AO North America. The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Sciubba and Petteys. Acquisition of data: Sciubba and Petteys. Analysis and interpretation of data: Sciubba and Petteys. Drafting the article: Petteys. Critically revised the article: Sciubba. Reviewed final version of the manuscript and approved it for submission: Dekutoski, Fisher, Fehlings, Ondra, Rhines, Gokaslan.

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Manuscript submitted August 28, 2009.

Accepted March 3, 2010.

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