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Multidisciplinary management of metastatic spine disease: initial symptom-directed management

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Abstract

In the past 2 decades, a deeper understanding of the cancer molecular signature has resulted in longer longevity of cancer patients, hence a greater population, who potentially can develop metastatic disease. Spine metastases (SM) occur in up to 70% of cancer patients. Familiarizing ourselves with the key aspects of initial symptom-directed management is important to provide SM patients with the best patient-specific options. We will review key components of initial symptoms assessment such as pain, neurological symptoms, and spine stability. Radiographic evaluation of SM and its role in management will be reviewed. Nonsurgical treatment options are also presented and discussed, including percutaneous procedures, radiation, radiosurgery, and spine stereotactic body radiotherapy. The efforts of a multidisciplinary team will continue to ensure the best patient care as the landscape of cancer is constantly changing.

Keywords

pain | radiosurgery | spine metastases | spine metastasis | spine stability | vertebral augmentation

As cancer therapies continue to improve, survival time for patients with different types of oncologic neoplasms rises.[1] This increased prevalence of long-term cancer survivors has resulted in an amplified incidence of metastatic disease of the bone. Spinal metastases (SMs) are the most common skeletal site of metastases, affecting between 40% and 70% of terminal cancer patients and occurring between the ages of 40 to 65 years.[2,3] Autopsy studies show that the distribution of metastasis is relative to the size of the vertebrae and bone marrow.[4] Therefore, metastatic lesions are most often found in the lumbar region, followed by the thoracic and cervical spine. However, most symptomatic metastases arise in the thoracic spine. This is likely attributable to the relatively smaller thoracic spinal canal when compared to the lumbar or cervical spine.[3]

Primary tumors can metastasize to the spine in different ways. Hematologic spread is one of the most common. Tumor cells travel through the arterial system and seed favorable bone marrow in the vertebral bodies. Second, through a valveless venous system, the Batson plexus allows transmission of metastases for deposition in the epidural space and can lead to metastatic growth and compress the spinal canal and nerve roots. Third, spread through the cerebrospinal fluid can occur, leading to direct seeding of the subdural space. Last, direct inoculation through proximity spread can occur to the spinal vertebra.[1,5]

Multiple myeloma is the most common bone metastasis, followed by cancers of the breast, lung, prostate, kidney, thyroid, and gastrointestinal tract. In women and men, up to 65% of metastases occur from cancers of the breast and prostate, respectively. Most often, bony metastases occur in the spinal column 69% of the time, followed by pelvis, long bones, and the skull. Intradural extramedullary and intramedullary seeding of systemic cancer is uncommon.[6]

Initial symptom-directed management in patients with metastatic spine disease is dependent on individual patient circumstances and includes systemic therapy, radiation therapy (RT), percutaneous procedures, and surgery. These treatment

options can be used alone or in combination as clinically indicated.

Initial Evaluation of Presenting Symptoms

The evaluation of a patient with suspected SM relies on clinical, pain, and radiographic assessments. SMs typically involve the vertebral body but can also progress to the epidural space. The presence of cancer within the vertebral body can result in its collapse and spinal instability. The epidural cancer can cause direct pressure on the spinal cord. Therefore, failure to promptly recognize an SM might result in permanent neurological deficit due to spinal instability and/or progressive tumor burden resulting in cord compression.

Clinical Assessment

The clinical assessment of a patient with suspected SM should focus on motor, sensory, including radicular pain, limb numbness, trunk numbness, and saddle anesthesia. In general, radicular pain occurs in a dermatomal distribution as the tumor invades and violates the bony walls. Epidural spread of the tumor itself can compress the nerve roots or invade the nerve roots. As metastases start to grow and compress the spinal canal, severe sensory and motor changes can occur, including complete anesthesia below the level of metastases, paraparesis, quadriparesis, paraplegia, or quadriplegia, and loss of sphincter control, resulting in urinary and bowel retention and subsequently, incontinence. Neurogenic bowel and bladder symptoms are usually painless.[3,7]

Patients with SM are susceptible to the development of numerous metabolic abnormalities. Hypercalcemia is a very common finding in patients with SM, occurring in up to 30% of patients as a result of increased bone turnover and increased calcium reabsorption.[8] Clinical symptoms include weakness, vomiting, abnormal heart rhythm, kidney failure, anorexia, and coma. A rapid increase in hypercalcemia can indicate progression of cancer and thus may indicate a poor prognosis.[8]

Coagulopathies can affect this patient population as well, including neutropenia, anemia, and thrombocytopenia. Cancer-associated thrombosis is also well described. There are diverse causes of the mechanisms altering coagulation pathways, some of which can be attributed to the disease and others to treatment effect. Thrombocytopenia induced by chemotherapy is likely the most common risk for bleeding in a patient with cancer.[9] Cancer patients are also at elevated risk of DVT.[10] One study showed a 9.5% incidence of DVT in patients requiring surgery for SMs. Patients who were nonambulatory preoperatively had a 4-fold increase in DVT.[11]

Despite the fact that SM patients are among the most vulnerable to the development of venous thromboembolism (VTE), the preoperative baseline VTE risk, underlying risk factors for VTE, and the guidelines for prevention and prophylaxis are not well defined in this population.[11] Patients with SM who require surgery often undergo Doppler ultrasound of the lower extremities before surgery to rule out a DVT. Patients should be assessed for lower extremity swelling or edema with a high index of suspicion for DVT. The rate of osteoporosis has been shown to be increased in patients with cancer. This also predisposes patients with cancer to fractures and chronic pain. For this reason, a bone mineral density screening should be performed in this patient population.[12]

Pain Assessment and Pain Scales

The initial assessment of a patient with suspected SM presenting with pain includes assessment of local pain, radicular, and axial back pain. The latter often worsens at night.[7] Bone pain is one of the most common types of pain felt by cancer patients, with 60% to 84% of terminal cancer patients experiencing bone pain. However, the degree of bone pain felt by patients is highly variable. Diffuse bony lesions may cause low to moderate pain whereas focal metastases may report severe pain, making diagnosis and treatment unpredictable. Bone pain can be divided into oncologic and mechanical pain. Oncologic bone pain is defined as discomfort from the periosteal stretch caused by the tumor itself. This is the pain often felt at rest and worsens at night. Mechanical pain worsens with activity and movement and subsides at rest.[13]

Bone pain often occurs spontaneously without an exacerbating event and generally precedes radiographically detectable changes in the bone or pathological bone fracture. It begins as a dull intermittent pain and progresses to constant severe pain. Its severity cannot be predicted by tumor type, size, or level of dissemination. Bone pain generally intensifies with movement and palpation and is increased at night. This bone pain is mediated by sensory fibers, commonly thin myelinated and unmyelinated sensory fibers. Once tumor cells settle in the spine, the tumor cells divide and result in progressive bone damage. Inflammatory cells, in response to tumor cell invasion, release mediators including endothelin, proteases, TNF α, serotonin, prostaglandins, and nerve growth factor, which activate bone-innervating sensory nerve endings, leading to an increased sensation of pain.[14]

At later stages of tumor invasion, the destruction of bone can become extensive, leading to pathologic fractures. Patients with compression fractures often have pain when lying flat; this is likely due to the extension that occurs in recumbence, which aggravates the unstable kyphotic segment. As the metastasis continues to invade the bone, it may violate the constraints of bone and result in compression and damage to the nervous and vascular system, including the spinal cord, nerve roots, and vascular structures.[15]

The assessment and measurement of pain is an important factor to help tailor the best treatment option. The Brief Pain Inventory (BPI) was developed as an assessment tool for use cancer patients and measures both the intensity of pain and interference of pain in the patient's life (Table 1). It quantifies both the acute and chronic stages of pain.[16] The McGill Pain questionnaire–short form (MPQ-SF) was developed to include the sensory and affective dimension

Table 1. Brief Pain Inventory-Short Form (BPI-SF)[16] and McGill Pain Questionnaire-Short Form (MPQ-SF)[17] Elements for Pain Assessment

BPI-SF	MPQ-SF
Pain time	Pain description
Pain location	Fatigue
Medications	Sick
Mood	Fear
Ambulation	
Work	
Sleep	

of pain and the present pain intensity (PPI). When directly compared in cancer patients, the MPQ-SF and the BPI-SF were internally consistent, but the BPI-SF was more valid than the MPQ-SF.[17] Other pain scales, including the Verbal Descriptor Scale, the visual analog scale (VAS), and the Faces Pain Scale, have shown the highest accuracy in the diagnosis of severe pain.[18]

Radiographic Assessment

Radiographic imaging of spinal disease in the metastatic patient plays an important role in assessing the extent of disease, localizing the vertebral levels involved, determining involvement of spinal canal structures, and evaluating spinal instability. A variety of imaging modalities such as MRI, CT, bone scan, and ^{18}F-fluorodeoxyglucose ([18F]-FDG) PET/CT provide information to help guide management of SMs.

MRI is the most sensitive and specific imaging modality in the assessment of osseous metastasis within the spine. T1-weighted, T2-weighted, and short-tau inversion recovery (STIR) sequences allow for the evaluation of marrow signal changes within the vertebral bodies, which improves the detection of vertebral body osseous lesions. MRI also provides excellent anatomical detail and evaluation of structures surrounding the vertebral body, including the neural foramina, epidural space, spinal canal, and spinal cord.[19] The addition of contrast allows for improved detection of tumor spread outside the margins of the vertebral body. STIR and/or contrast-enhanced sequences may show signal changes within the posterior element, pedicles, or posterior soft tissues and ligament, indicating posterior column involvement of tumor. Typical findings of osseous metastatic disease to the spine include lesions, which demonstrate low signal on T1, high signal on STIR/T2, and enhancement with contrast. Sclerotic lesions, as can be seen in prostate metastasis, may demonstrate low signal on T1, T2, and STIR sequences with variable patterns of enhancement.[15,20]

CT is helpful for evaluation of the bony structures and can be used to see the extent of osseous destruction within the vertebral body and surrounding bony structures. Although there is limited information on soft-tissue and spinal canal involvement, CT allows for assessment both of lytic and blastic changes in the bone.[15,21] Degree of cortical involvement, pedicle/posterior element involvement, and destructive changes involving the posterior wall of the vertebral body can be better appreciated on CT compared to other modalities and can assist in preintervention or presurgical planning.

Additional imaging evaluation of SM disease includes assessment of the extent of disease burden. This is very important because it is necessary to tailor the patient's specific best treatment option. MR spine survey, bone scan, and PET/CT are modalities that can help identify additional foci of metastatic deposits within the bone and spine. This can provide useful information on tumor burden, which can be helpful in guiding management.

When evaluating a patient for SMs, the sternum should be included in the radiographic evaluation. Sternal fractures, traumatic or pathologic, have been associated with kyphotic deformity of the spine. Metastatic disease of the sternum should be considered when determining global spinal stability. Sternal pathologic fractures can disrupt the stability of the innate thoracic spine because the semirigid support from the attachment of the ribs can be compromised.[4]

Evaluation of Spine Stability

New complaints of sensory changes or mechanical neck or back pain should prompt vertebral column imaging. If there is evidence of instability, a prompt consultation with an experienced spine surgeon should be initiated to provide spine stabilization by immobilization and/or surgical stabilization. Mechanical instability in the setting of SMs can be defined as a loss of spinal column integrity secondary to an oncologic process under normal physiologic parameters. The Spine Oncology Study Group developed a standardized framework, the Spinal Instability Neoplastic Score (SINS), to quickly and precisely identify instability in patients with SMs (Table 2). The SINS was designed to facilitate and standardize the classification of stable vs unstable measure of spine stability to preserve and restore neurologic function.[22]

The SINS is calculated by adding 6 radiographic and clinic parameters with a score that ranges from 0 to 18. These 6 factors include location of the tumor, type of pain, quality of bony metastases (osteolytic vs osteoblastic), spinal alignment, degree of vertebral body collapse, and

Table 2. Key Components of Spinal Instability Neoplastic Score,[22] a System That Helps Define the Spine With Metastatic Disease as Stable (0-6), Potentially Unstable (7-12), and Unstable (13-18)

Component	Score, points
Location	0-3
Mechanical pain	1-3
Bone lesion	0-2
Radiographic alignment	0-4
Vertebral body collapse	0-3
Posterolateral involvement	0-3

posterior spinal element involvement. The additive score is then subdivided into 3 categories: stable (0-6 points), potentially unstable (7-12 points), and unstable (13-18 points). Figure 1 shows a radiographic example of each. A score of less than 6 represents a stable spine and warrants observation as the recommended treatment. Multidisciplinary discussion is recommended for scores of 7 and greater. Patients with scores 7 to 12 might require bracing and/or surgery, whereas scores greater than 13 necessitate surgical intervention to ensure spine stabilization[4,22,23] (Figure 2).

The SINS has demonstrated a near perfect interobserver and intraobserver reliability in determining the 3 categories of stability, with sensitivity and specificity or 95.7% and 79.5% for a potentially unstable and unstable spine, respectively.[24,25]

The Neurologic, Oncologic, Mechanical, and Systemic (NOMS) framework can help drive treatment decisions for surgical intervention in patients with SM.[26] *Neurologic* considerations include the degree of nervous compression and epidural spinal cord compression. *Oncologic* refers to the ability to achieve local control (LC), and the characteristics of the tumor (radiosensitivity, etc) are relevant in this domain. *Mechanical* refers to instability of the SM. *Systemic* refers to the overall disease burden of the patient and his or her ability to tolerate a surgical intervention.

The Role of Multidisciplinary Conferences

The implementation of multidisciplinary tumor boards (MTBs) to evaluate cancer patients in all subspecialties has gained widespread acceptance nationally and internationally.[27] One of the earliest studies investigating the efficacy of MTBs showed a high percentage (43%) of cases in which the MTB disagreed with the management planned by the outside provider.[28] A recent study reviewed 200 cases, finding new cancers detected in 5% of patients. Additionally, in 4% of the cases, they reported avoidance of biopsies deemed unnecessary.[29]

Findings have shown MTBs to be efficacious in identifying additional cancers and preventing unnecessary harm. Thus, MTBs are the standard of care in NCI-designated cancer centers. Typically, they involve meetings between specialists within a specific cancer field such as brain and spine tumors and include radiation oncologists, neurosurgeons, neuro-oncologists, medical oncologists, pathologists, interventional neuro-radiologists, and radiologists.

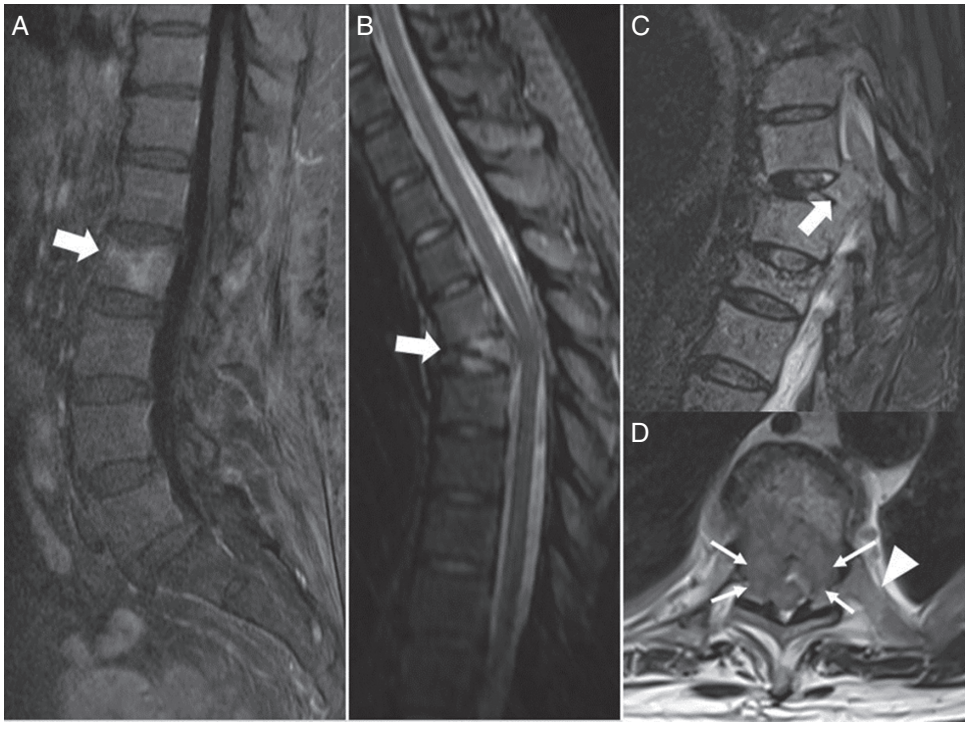

Figure 1. A, Patient with mild nonmechanical back pain presented with metastatic prostate cancer to the L2 vertebral level with a blastic lesion on CT (not shown) and mild compression fracture of less than 50% on MRI short-tau inversion recovery sequence (red arrow). Spinal alignment is maintained and there is no involvement of posterior elements. Spinal Instability Neoplastic Score (SINS) = 6; stable. B, Patient with severe back pain and metastatic adenocarcinoma presents with severe (> 50%) compression fracture of T9 (arrow) on MRI. CT (not shown) revealed a lytic lesion with the bone. Spinal alignment demonstrates moderate kyphotic angulation. No posterior element involvement was noted. SINS = 11; potentially unstable. C and D, Patient with metastatic breast cancer presents with severe back pain and neurological deficit. MRI reveals severe (> 50%) compression fracture of the T9 vertebra (white arrow) with retropulsion and presence of subluxation at T8 to T9. Axial MRI sequence demonstrates tumor involvement of the bilateral pedicles (small arrows) and left costotransverse joint (arrowhead). SINS = 16; unstable.

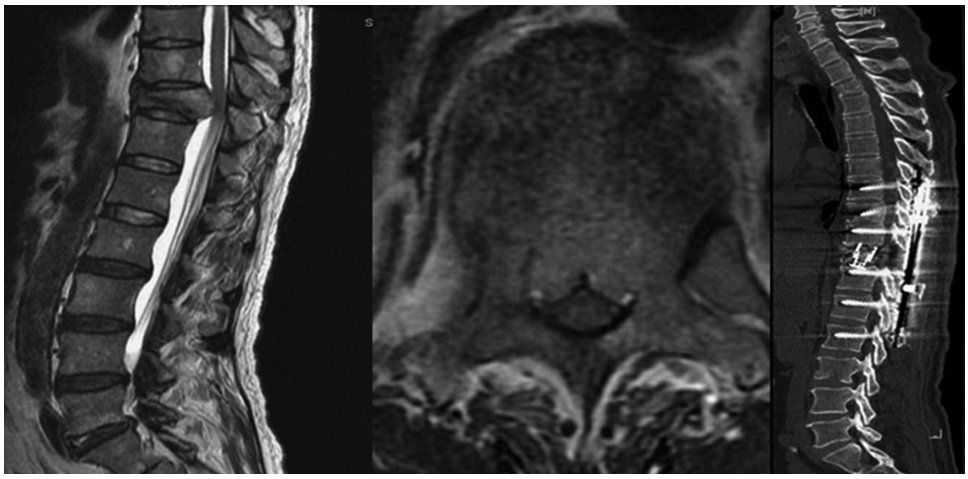

Figure 2. A 64-year-old man with gastric cancer who presented to the emergency department with paraplegia and urinary incontinence. MRI showed a metastatic lesion at T11 causing severe cord compression with SINS score = 14, A, sagittal and B, axial. He underwent T10 to T12 laminectomy, T11 costotransversectomy, and transpedicular corpectomy with posterior instrumentation and fusion, as shown in C, his postoperative CT scan.

For patients with SM in particular, an MTB's specific clinical approach is quintessential. The complexity of the disease and the options for treatment are multiple. Additionally, the local disease is only "one of the trees in the forest" and its treatment should not jeopardize the treatment of the systemic disease. At our institution, since we started providing spine stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) in 2007, all cases are discussed at our weekly MTB unless they are life-threatening emergencies. Even in those cases, a preliminary rapid discussion with the different teams occurs to ensure that a multidisciplinary approach is always considered.

Treatment Options Other Than Open Surgery

The Use of Steroids for Patients with Spinal Metastasis

The benefits of corticosteroids in patients with SM are thought to originate from their ability to reduce compression from edema within the tumor and their ability to decrease pain secondary to pathologic bone fractures.[30] The dosing of steroids remains controversial.[31]

A class I evidence study reported the benefits of corticosteroid in patients with acute spinal cord compression, showing an improvement in ambulation status (but also an increase in serious side effects).[32] The controversies around the use of steroids have been recently reviewed.[33]

Conservative Pain Management

Pain from SM can be treated and/or palliated with multiple interventions, including medications, radiation, radiosurgery, and percutaneous procedures. Medications are the best option in the acute setting and can be used for chronic pain. Although a detailed description on pain medications for SM is outside the scope of this review, the latter are described as follows.

Approximately 15% to 40% of chronic cancer pain has a component of neuropathic pain, and some studies have suggested the use of neuromodulation for palliation.[34] Spinal cord stimulation (placing electrodes on the spinal cord to deliver impulses that may reduce pain) is the most common method of neuromodulation. There are no randomized, controlled trials addressing the efficacy of spinal cord stimulation for cancer pain.[35] Less-invasive interventional options such as paravertebral nerve block, erector spinae blocks, medial branch blocks, and epidural steroid injections should always be considered; however, there is a lack of literature to guide the use of these modalities. The use of advanced neuroaxial procedures, such as intrathecal pumps, may be a secondary option for pain control.[36] A consultation with pain management specialists for inpatients to consider these options can be beneficial.

Rehabilitation plays an important role in pain relief in patients with SM and is a critical player in the treatment of pain in and out of the hospital setting. In the absence of instability, rehabilitation can assist with bracing and/or strengthening of muscle to improve function and maximize independence.[37]

Percutaneous Interventional Treatments

Minimally invasive, percutaneous interventional treatment of SM includes vertebral augmentation (vertebroplasty and kyphoplasty) and ablative therapy. These treatment options have emerged as safe and effective for management of pain control, vertebral body stabilization, and for local tumor control. In addition, vertebral augmentation can play a role in the

management of patients who are not candidates for surgical intervention. Patients who have undergone medical therapy resulting in osteopenia or RT may be at increased risk for developing vertebral compression fractures. In these instances, vertebral augmentation can be an effective tool in vertebral body stabilization and pain control.

Vertebral augmentation refers to the placement of cement, typically a polymer such as polymethylmethacrylate (PMMA), within the vertebral body. This can be performed without (vertebroplasty) or with (kyphoplasty) the creation of a cavity. Cavities created with kyphoplasty allow for the placement of cement into a low-pressure space with the goals both of improving control of cement deposition and reducing the risk of cement leakage outside the vertebral body. With the use of balloon kyphoplasty, vertebral body height restoration and kyphotic reduction may also be achieved.[38]

Benefits of vertebroplasty and kyphoplasty have been studied extensively in the literature. Numerous studies in patients with metastatic vertebral compression fractures have shown improvement in VAS, functional outcomes, and opioid analgesic use after vertebral augmentation compared with medical management alone.[39] Complications resulting in clinical sequelae in cancer patients treated with vertebral augmentation are exceedingly rare.[40]

Vertebral tumor ablative therapy can be performed in conjunction with vertebral augmentation with the purpose of additional pain control and local tumor control (Figure 3).

A variety of ablative techniques, including radiofrequency (RF), microwave, and cryoablation can be used. RF and microwave techniques provide energy transfer into tissues to create heat within the local tumor environment to produce coagulation necrosis within the tumor. Cryoablation uses argon gas, which rapidly cools and results in a decrease in temperature to approximately –100°C, resulting in tissue death. This technique is typically employed when there is extraosseous extension of tumor into surrounding soft tissues. Cement is typically deposited within the vertebral body after the tumor ablation procedure is performed.

Because of its relatively newer treatment algorithm, studies evaluating the combination of cement augmentation and tumor ablation are emerging within the literature.

This combined therapy has been suggested in some studies to provide superior pain relief compared to vertebral augmentation alone and may result in the added benefit of local tumor control.[41] The Metastatic Spine Working Group has developed an algorithm providing combined therapy as an option for pain control and vertebral body stabilization in patients with painful metastatic vertebral compression fractures and uncomplicated painful metastatic spinal disease.[42] Given the overall safety profile

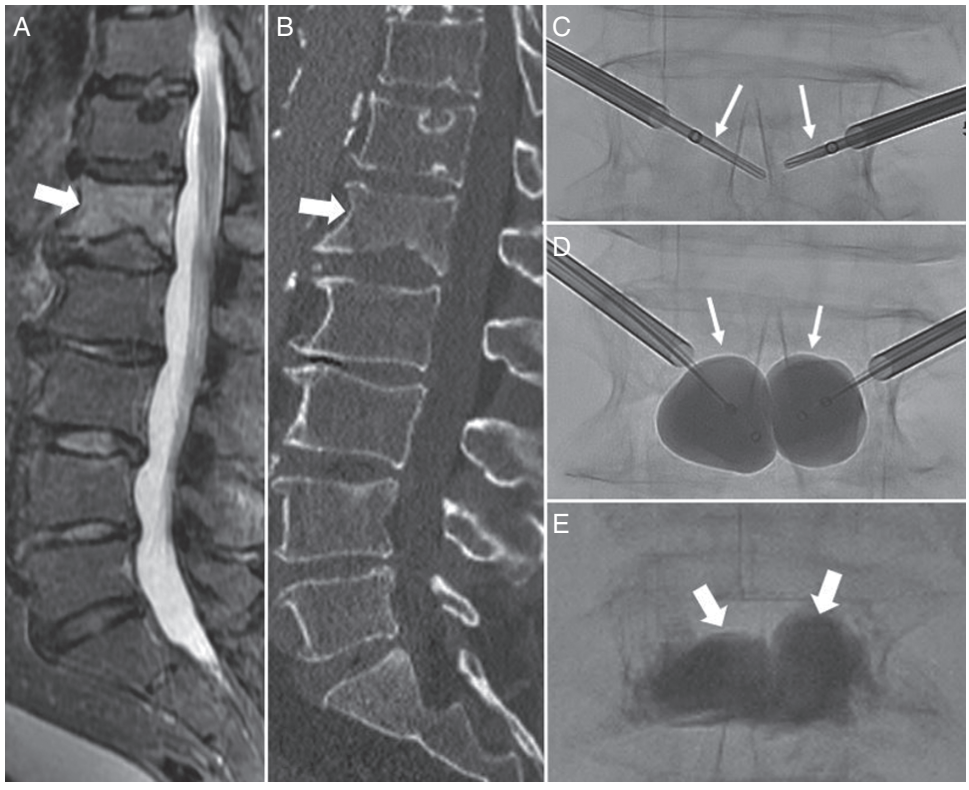

Figure 3. Patient with history of metastatic breast cancer and severe low back pain. A, MRI and B, CT demonstrate a mild compression fracture of the L1 vertebral body (arrow) with diffuse short-tau inversion recovery signal changes on MRI and mixed lytic and sclerotic regions on CT consistent with metastasis. Radiofrequency ablation probes are shown in C (arrows). After ablation was complete, D, balloon kyphoplasty (yellow arrows) was performed followed by E, cement augmentation (arrows) for pain relief and vertebral body stabilization.

of both augmentation and ablation with improved VAS scores, combined therapy should be consider when evaluating a patient with SM disease for percutaneous treatment.

Radiation Therapy

RT is an integral component of treatment for patients with SM. The goals of radiation treatment include durable tumor control, palliation of pain, and adjuvant treatment after surgical resection. Tumor control results in prevention of local disease progression and halting of new neurological symptoms and progressive vertebral body destruction. Both halting disease progression and alleviating pain result in a significant improvement in patient quality of life and a potential decrease in health care costs.

External beam radiation treatment.—The mainstay treatment for patients with SM, external beam radiation treatment (EBRT) for SM has typically been delivered using a limited number of radiation beams with the goal of delivering at least 95% of the prescription dose to the tumor. To achieve this, the radiation dose is unavoidably delivered to the adjacent normal tissues and organs at risk (OARs) such as the spinal cord, esophagus, heart, bowel, and kidney. The effectiveness of conventional EBRT (cEBRT) is therefore limited by the tolerance of adjacent normal tissues.[43]

Current recommendations for external beam radiation treatment dose and fractionation schedules.—Several dose and fractionation regimens have been evaluated. Class I evidence supports several short-course (8 Gy × 1, 8 Gy × 2 split course, 4 Gy × 5) and long-course (3 Gy × 10, 5 Gy × 3, and 3 Gy × split course) treatment regimens offering equivalent pain relief, as well as ambulatory and functional outcomes for patients with SM.[44] Because re-treatment rates may be higher following single-fraction (SF) radiation, selection of dose and fractionation choices should consider the patient's prognosis, the impact of daily radiation treatment, and the risk of requiring re-treatment.

External beam radiation treatment pain palliation.—EBRT achieves pain reduction in 50% to 80% of patients with painful spine bone metastases. Approximately 30% of patients will achieve complete resolution of pain. Up to 15 clinical trials have demonstrated that short-course radiation is as effective as more protracted courses in achieving palliation, although it is more frequently associated with a need for re-treatment.[45] In Radiation Therapy Oncology Group (RTOG) 97-14, a randomized trial of short- vs long-course radiation treatment, an SF of 8 Gy provided equivalent pain relief to more multiple fractions (MFs) with achievement of partial/complete pain response in 70% and 62% of patients treated with SF and MFs, respectively. Lower rates of acute toxicity were seen in the short-course arm.[45]

External beam radiation treatment local tumor control.—LC in patients treated for palliation of SM has been defined as the absence of recurrent cord compression in the radiated field. Nonrandomized and prospective data have reported mean crude rates of LC of 77%. In a study using myelogram evaluation post-EBRT, 80% of patients demonstrated an improvement of epidural disease.[46]

Re-treatment rates are higher in patients with more protracted survival receiving SF treatment, 20% in SF and 8% in MFs; however, recurrence rates are not substantially different for the first 2 to 3 months posttreatment.[47] Additional studies suggest that patients undergoing long-course radiation have better LC, improved motor function, as well as more durable responses compared to those treated with SF.[48] Administration of 8 Gy in 1 fraction may be more convenient, cost-effective, and appropriate for patients with limited life expectancies, and the American Society for Radiation Oncology (ASTRO) has endorsed its use.[49] For patients with a longer life expectancy, such as those with breast or prostate cancer, longer-course radiation should be considered. However, for radioresistant tumors, including renal cell carcinoma (RCC), conventionally fractionated radiation has been shown to lead to suboptimal LC.[50]

External beam radiation treatment toxicity.—Acute side effects secondary to EBRT include fatigue, mucositis, esophagitis, and bowel and bladder irritation. These usually resolve shortly after treatment and respond to supportive measures. Patients may experience a transient pain flare, which typically occurs in the first few days after RT and generally lasts 1 to 2 days. Treatment with dexamethasone may reduce the flare. Long-term side effects of SF radiation treatment appear to be low. Pathologic fractures developed in approximately 5% of patients treated with either SF or MF regimens.[45] More serious adverse effects, such as radiation myelopathy, which typically take years to manifest, are seen infrequently, particularly considering the limited life expectancy of this patient population. Based on the doses of radiation delivered with SF or MF EBRT, the risk of radiation myelopathy is likely less than 5% at 5 years.[51]

Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

In recent years, significant technological advances have allowed for the delivery of high-dose, precisely targeted radiation to a tumor while minimizing the radiation delivered to OARs (Figure 4). These include advances in patient immobilization, radiation targeting, and precision delivery techniques including image-guided radiation therapy and intensity modulated radiation therapy (IMRT).[52] IMRT uses multiple beam angles of variable intensity and shape. IMRT delivery was further enhanced by the introduction of volumetric arc therapy (VMAT), which is radiation delivery combining dynamic arcs and IMRT. The main advantage of VMAT is the substantial reduction in treatment delivery time. When using precise delivery techniques, treatment

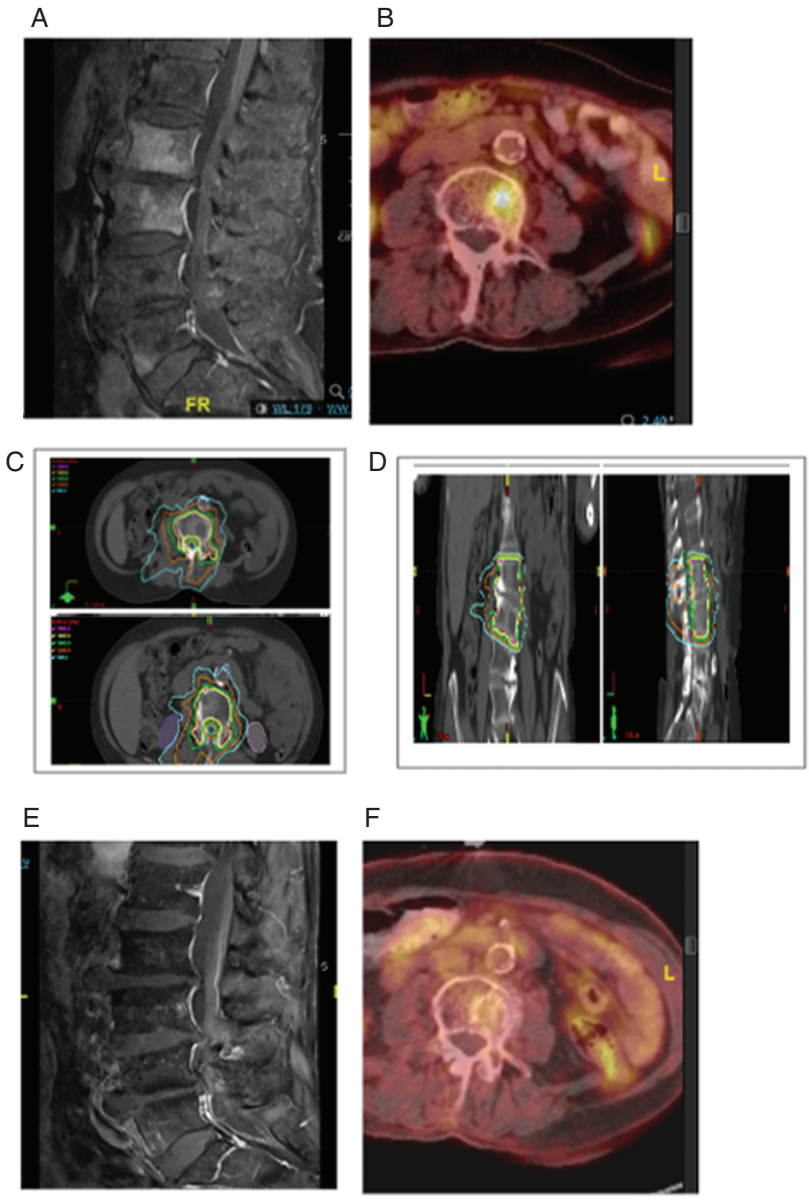

Figure 4. This 67-year-old woman with a history of stage IV non–small cell lung cancer presented with new symptoms of low back pain while undergoing systemic treatment. A, Sagittal T1-weighted lumbar spine MR image after contrast showing metastatic disease within the L2 to L3 vertebral bodies, B, ^{18}F-fluorodeoxyglucose (18F FDG) PET/CT axial image showing avid FDG activity at L3 (standard uptake value, 9.2). C, Axial and D, (left) coronaland (right) sagittal stereotactic radiosurgery (SRS) planning screenshots showing isodose curves and organs at risk outlined. The 1800-cGY prescription dose is in yellow. E, Follow-up MRI 6 months after SRS, sagittal T1-weighted lumbar spine MR image after contrast showing disease control at L2 to L3. F, 18F FDG PET/CT axial image showing decreased FDG activity at L3.

for small or moderate-sized SMs can be safely and effectively delivered in 1 to 5 fractions, and is termed *spine stereotactic radiosurgery* (sSRS) when the treatment is delivered in an SF and *spine stereotactic body radiotherapy* (sSBRT) when delivered in up to 5 fractions.[53] The more-targeted treatment approach with sSRS or sSBRT allows for delivery of a potentially higher biologically equivalent radiation dose to the target with relative sparing of the adjacent neural structures as well as nearby critical organs, and thus should allow for improved therapeutic outcomes.

Potential additional benefits of treatment with sSRS and sSBRT include minimizing the number of vertebral bodies exposed to radiation (with potential for bone marrow suppression) and allowing for more rapid initiation and minimizing interruptions in systemic therapy.

Stereotactic radiosurgery and stereotactic body radiotherapy indications.—SRS and SBRT are used in the treatment of patients with metastatic spine disease for management of pain arising from a specific metastatic

lesion, for treatment of radiographic tumor progression, or to prevent/manage neurologic deficits. SRS has also been delivered postsurgery. The SRS data reported have been based on retrospective, nonrandomized prospective studies and one prospective trial.

Stereotactic radiosurgery/stereotactic body radiotherapy pain palliation.—SRS is highly effective at reducing pain associated with a symptomatic SM, with approximately 85% of patients achieving significant pain reduction, even in patients treated with prior EBRT. Significant pain reduction is usually achieved within days to weeks of sSRS. Pain control rates of 84% to 90% at 1 year in patients treated with SRS with no prior radiation have been reported.[54] Pain control appears to vary depending on primary histology, with long-term pain improvement in more than 90% of patients with breast, lung, or melanoma primaries, with lower rates in patients with RCC, varying between 63% and 94%.[55] sSBRT has also demonstrated efficacy in palliation of pain. There is a paucity of data comparing outcomes with sSRS vs sSBRT, with one study reporting no significant difference in pain alleviation at 4 to 6 months; however, a trend of more rapid pain relief was seen in patients treated with an SF.[56]

Pain control comparison of external beam radiation treatment to stereotactic radiosurgery/stereotactic body radiotherapy.—RTOG 0631 was a prospective phase 3 trial for patients with limited SM involving 1 to 3 separate sites (with no more than 2 contiguous spine segments involved) that randomly assigned (2:1 randomization in favor of SRS/SBRT) more than 300 patients to receive either SRS/SBRT 16 or 18 Gy in one fraction to the involved spine segment(s), with rigorous dose constraints and quality assurance, or cEBRT 8 Gy in one fraction to the involved spine, including one additional spine segment above and below the index level. The primary end point was patient-reported pain control at 3 months. The 3-month change in pain score at the index site was –3.00 (SD = 3.34) in the SRS/SBRT arm compared to –3.83 (SD = 2.97) in the cEBRT arm. There was no difference in pain response between SRS and EBRT at 3 months (40.3% vs 57.9%, respectively, one-sided $P = .99$). There was no significant difference between the treatment arms in rates of adverse events or in quality of life measures.[57] The specified end point of this trial may not have optimally allowed for determining the potential benefit of sSRS.

Stereotactic radiosurgery/stereotactic body radiotherapy local tumor control.—Conventional EBRT remains the recommended upfront treatment for patients with SM. Certain patient groups may, however, benefit from initial treatment with sSRS/SBRT in view of the higher biological equivalent dose for SRS/SBRT. These include patients with symptomatic bone metastases from relatively radioresistant tumors as well as patients with vertebral body metastases presenting as oligometastatic disease (OMD). Studies have demonstrated long-term radiographic tumor control rates ranging from 75% (for melanoma metastases) to 100%.[54–56] Prospective phase 2 randomized trials have reported that stereotactic ablative radiation therapy may provide progression-free and overall survival improvement in patients with OMD, with one of these trials including patients with SM greater than 3 mm from the spinal cord.[57,58] Phase 3 trials are in progress to ascertain the role of ablative therapy in patients with OMD.

Patients who have been treated with prior fractionated EBRT and present with radiographic tumor progression are candidates for treatment with sSRS or sSBRT. Because the spinal cord will have already received a significant dose of radiation, targeted radiation with spinal cord sparing may offer benefit in terms of LC and neurologic control. Several prospective series have demonstrated high LC rates of 84% to 100%, with lower rates of LC, ranging from 75% to 85% seen when treating recurrences of radioresistant histology, such as RCC.[52,55] Patients with neurologic symptoms due to recurrence post-EBRT appear to have improvement following treatment with sSRS. In a single series, 90% of patients demonstrated improvement in weakness and 92% experienced improvements in paresthesia post-sSRS.[59]

Stereotactic radiosurgery/stereotactic body radiotherapy dose and fractionation schedules.—The optimal dose and fractionation approach for spinal radiosurgery has not been definitively determined. Prescribed doses have varied depending on prior radiation dose, tumor histology, and the tolerance of adjacent critical normal tissues. A range of prescribed doses have been reported, with SRS doses varying between 16 and 24 Gy × 1 and SBRT dose regimens including 8 to 9 Gy × 3, 5 Gy × 6, and 6 Gy × 5.[56–59] Higher doses appear to correlate with improved LC. Toxicity does not appear to vary significantly among these dose/fractionation regimens.

Stereotactic radiosurgery/stereotactic body radiotherapy toxicity.—Acute side effects postradiosurgery include mucositis, dysphagia, laryngitis, esophagitis, nausea, diarrhea, paresthesia, and transient radiculitis. Most side effects are mild, self-limiting, and effectively managed with supportive measures. Postradiosurgery vertebral body compression fractures occur in 15% to 40% of patients.[60] Prophylactic kyphoplasty prior to SRS has been used, but its efficacy remains to be determined.

The incidence of radiation-induced spinal cord injury and radiation myelitis postradiosurgery has been reported as a rare event. Current guidelines and dose constraints, including a maximal dose of 14 Gy to any portion of the spinal cord as well as limiting no more than 10 Gy delivered to 10% of the partial spinal cord volume (defined as 6 mm above and below the radiosurgery target) are associated with extremely low levels of cord injury.[57]

Surgery vs stereotactic radiosurgery.—Surgery remains the recommended treatment for patients with spine instability and for those with metastatic epidural spinal

cord compression, with concern for SRS in this setting due to need to deliver high-dose radiation immediately adjacent to the spinal cord.[61] Separation surgery has been used to partially resect tumors and provide a safe margin for SRS. This approach has been associated with low complication rates, while providing rapid neural decompression and allowing for early postoperative SRS treatment because of the minimal skin dose delivered with SRS.[62] Because SRS has demonstrated very high LC rates, the feasibility of SRS for epidural spinal cord compression is being explored in select patient groups.[63] In addition, the role of surgery and SRS as ablative therapies in patients with OMD is currently being explored.[58,64]

Proton beam treatment.—As opposed to photon radiation delivered by SRS and SBRT, proton beam therapy (PBT) can deliver a large dose of energy with a sharply localized peak, with resultant less radiation to nearby OAR, and has demonstrated superior efficacy in management of primary spine tumors, such as chordomas. There is currently a paucity of data regarding sSRS delivery with PBT.

Conclusion

The initial evaluation of SM patients includes a timely assessment of pain and spine stability. This ensures that the multidisciplinary discussion achieves the best initial symptom-directed management. Palliation and cure remain fundamental goals when caring for patients with SM. The therapeutic approaches to SM patients are multifaceted and continue to expand. It is impossible for a single specialty to master them all. Hence, the importance for a multidisciplinary approach.

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