Original Article

Metastatic Spinal Cord Compression

Meic H. Schmidt, MD,[1] Paul Klimo, Jr, MD, MPH,[1] and Frank D. Vrionis, MD, PhD,[2]
Salt Lake City, Utah, and Tampa, Florida

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Abstract
Approximately 70% of cancer patients have metastatic disease at death. The spine is involved in up to 40% of those patients. Spinal cord compression may develop in 5% to 10% of cancer patients and up to 40% of patients with preexisting nonspinal bone metastasis (>25,000 cases/y). Given the increasing survival times of patients with cancer, greater numbers of patients are likely to develop this complication. The role of surgery in the management of metastatic spinal cord compression is expanding. The management of metastatic spine disease can consist of a combination of surgery, radiation treatment, and chemotherapy. Treatment modalities are not mutually exclusive and must be individualized for patients evaluated in a multidisciplinary setting. (*JNCCN* 2005;3:711–719)

As many as 70% of cancer patients have evidence of metastatic disease at the time of death,[1,2] and involvement of the spine occurs in up to 40% of those patients.[3] The spine is the most common osseous site for metastatic deposits. Metastatic spine disease can result in severe back pain, spinal deformity, pathologic fractures, and neurologic compromise.[4]

Among the complications associated with metastatic spine disease, paralysis secondary to spinal cord compression is the most dreaded. Spinal cord compression may develop in 5% to 10% of cancer patients and up to 40% of patients with preexisting nonspinal bone metastasis. Of those patients with bony spinal disease, 10% to 20% develop symptomatic spinal cord compression, resulting in over 25,000 cases per year.[4] Thus, spinal cord injury from metastasis is more common than traumatic spinal cord injury (10,000 per year). Given the increasing survival times of cancer patients, more and more patients are likely to develop this complication.

The spinal region most commonly affected by metastatic spine disease is the thoracic spine (70%), followed by the lumbar spine (20%), and the cervical spine (10%).[5–7] Metastatic spine disease can involve 1 or more of 3 locations: the vertebral body (85%), the paravertebral spine (10%–15%), and, in unusual cases, the epidural or subarachnoid/intramedullary space alone(<5%).[5,7] The posterior half of the vertebral body is usually involved first; the anterior body, lamina, and pedicles are invaded later.[8] Multifocal metastatic deposits at noncontiguous levels occur in 10% to 40% of patients.[4,5,7]

Most metastatic spine disease (50%) arises from breast, lung, or prostate cancer, followed by renal-cell cancer, gastrointestinal, thyroid, sarcoma, and lymphoreticular malignancies.[5] Spinal metastatic lesions from prostate, breast, melanoma, and lung cancer occur in 90.5%, 74.3%, 54.5%, and 44.9% of patients, respectively.[9] The frequency of neurologic compromise from malignant epidural spinal cord compression (MESCC) varies also by primary cancer diagnosis: 22% with breast cancer, 15% with lung cancer, and 10% with prostate cancer.[4,6] Patients may present with malignant epidural spinal cord compression without a known history of a primary cancer.[4] About 50% of patients with this presentation are eventually diagnosed with lung cancer as the primary cancer.[6,10]

The management of metastatic spine disease is complex and consists of surgery, radiation treatment, and chemotherapy.[11,12] Most controversy exists in the role of surgery and radiation in the treatment of MESCC.[13] The NCCN CNS Cancers Clinical Practice Guidelines emphasize that treatment modalities are not mutually

From [1]Spinal Oncology Service, Department of Neurosurgery, Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah, and [2]Neuro-Oncology Program, H. Lee Moffitt Cancer Center & Research Institute, University of South Florida, Tampa, Florida.
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Correspondence: Meic H. Schmidt, MD, Spinal Oncology Service, Huntsman Cancer Institute, Department of Neurosurgery, University of Utah, 30 North 1900 East, Suite 3B-409, Salt Lake City, UT 84132-2303. E-mail: meic.schmidt@hsc.utah.edu.

exclusive. Treatment options and recommendations must be individualized for patients evaluated in a multidisciplinary setting.[11]

Chemotherapy: Steroids

Good evidence supports the use of steroids in patients with newly diagnosed metastatic spinal disease causing symptomatic spinal cord compression. Steroids have been shown to reduce vasogenic edema, protect against lipid peroxidation and lipid hydrolysis, prevent ischemia and intracellular calcium accumulation, and support cellular energy metabolism. Dexamethasone is the most widely used steroid, although methylprednisolone, more commonly used in trauma, offers an alternative. In patients presenting with an undiagnosed spinal mass with no history of cancer, especially younger patients, steroids should be avoided until the diagnosis is made. Steroids have an oncolytic effect in some tumors, particularly lymphomas and thymomas, which may delay diagnosis.[14]

The optimal dose of dexamethasone in metastatic spinal cord compression is controversial. Loading doses range from 10 to 100 mg, followed by 4 to 24 mg 4 times a day and tapered down over several weeks.[5,7,14–18] The larger doses are generally reserved for patients who present with a severe baseline or worsening neurologic examination.[19] Some clinicians advocate using the methylprednisolone dose protocol used in trauma for oncology patients who have experienced rapid neurologic deterioration.[19] In a well-designed randomized controlled trial (RCT) that compared the use of high-dose dexamethasone followed by radiotherapy with the use of radiotherapy alone, 81% of patients in the experimental group were ambulatory after treatment compared with 63% in the control group.[18]

In another RCT, however, patients with a complete myelographic block who received a 100-mg bolus of dexamethasone followed by a standard maintenance dose had no better pain relief, ambulation, or bladder function than those who received a 10-mg bolus and the same maintenance therapy.[20] Higher doses are also associated with more complications (wound dehiscence, pneumonia).[21] Therefore, on the basis of this information, we recommend that an appropriate regimen of dexamethasone would be an initial bolus of 10 mg followed by 16 mg/day tapered over several weeks.

Patients with no clinical evidence of spinal cord compression generally do not require steroid treatment. In a cohort study by Maranzano et al.,[22] 20 patients without neurologic deficit received radiation therapy without steroid treatment. None of the patients' conditions worsened.[22] Furthermore, steroids can have an oncolytic effect on tumors like lymphomas. Steroids should be withheld if possible until tissue biopsy is obtained if this diagnosis is supected.[14]

Surgical Management

Posterior Decompressive Laminectomy

For many years, laminectomy was the only surgical option offered to patients with metastatic spine disease. It can be performed quickly by a neurosurgeon, has minimal intraoperative risk, and does not require spinal column reconstruction or placement of internal stabilization devices. Despite its widespread use, its effectiveness was not viewed with consensus among surgeons. Some thought that it was the only reasonable hope for recovering neurologic deficits, whereas others found it to be of little value except for obtaining tissue to make a diagnosis and relieving pain.[23,24]

Many of the studies on decompressive laminectomy have been uncontrolled cohort studies. Success rates, defined as the ability to walk after surgery, ranged from 14% to 58% (mean = 30%) of patients who underwent the procedure.[10,25–36] In addition, significant non-neurologic complications can occur after laminectomy, specifically wound infection or dehiscence and spinal instability. Findlay's[37] review of the literature found the incidence of significant complications to be approximately 11%.

Numerous articles, including controlled cohort studies, have compared the efficacy of laminectomy alone with that of radiation alone or laminectomy followed by radiation.[7,10,23,24,34,38–41] In 1978, Gilbert et al.[7] published a single-institution, retrospective analysis involving 235 patients treated with either decompressive laminectomy followed by radiation (n = 65) or radiation alone (n = 170). Pretreatment neurologic function was the most reliable indicator of posttreatment function, because the rate of neurologic recovery between the two groups did not differ. Among patients who developed rapidly progressive weakness, none of the surgical-arm patients improved but approximately half of the radiation-arm patients did. The authors concluded that radiation alone should be the treatment of choice and that a decompressive laminectomy is indicated in only 3 situations: (1) to establish a diagnosis; (2) to treat relapse for patients unable to undergo further radiation; or (3) if symptoms progress during radiation.

Only 1 RCT has been attempted. Young et al.[41] randomized patients with a symptomatic epidural spinal lesion to receive either laminectomy followed by radiotherapy or radiotherapy alone. No significant difference was found between the groups with respect to pain relief, ambulatory status, or sphincter function. No treatment-related complications occurred in patients undergoing surgery or radiotherapy. The major limitation with the study, as the authors clearly state, was that it was too small (29 patients) to detect a difference in the treatment results. However, the study showed that a properly conducted RCT was feasible.

As a result of these studies and others, minimal neurologic benefit and significant morbidity were attributed to laminectomy, and radiation became the primary treatment. Indiscriminate use of decompressive laminectomy was prone to failure because, in most cases, the tumor lies ventral to the thecal sac, which makes meaningful decompression or tumor resection impossible without significant retraction on the thecal sac.[7,10,25–36,39,40,42,43] Furthermore, a laminectomy can cause or worsen pre-existing spinal instability. This can lead to progressive deformity, which in turn can result in pain and neurologic compromise. Based on these data, we recommend that decompressive laminectomy alone without supplemental internal fixation should not be used in patients with metastatic spinal disease, except in cases in which the pathology is strictly confined to the lamina and spinous process, or in cases with unilateral involvement of the pedicle/transverse process and in which instability is not expected.

The results of decompressive laminectomy seem to improve if internal fixation (e.g., pedicle screws) and fusion is performed as well. In a review of the results for 134 patients treated with either a laminectomy (n = 111) or laminectomy with stabilization (n = 23), Sherman et al.[43] found that the latter group had better post-treatment ambulatory status (92% vs. 57%), sphincter function, and pain control, and less recurrent neurologic dysfunction. Others studies have reported similar results.[19,44–48]

Circumferential Decompression

The limited efficacy of laminectomy and its associated complications for the treatment of metastatic spinal cord compression have meant that surgery has rarely been the primary treatment for metastatic spinal disease. As surgeons realized the limitations of the laminectomy, they began to decompress the ventral spinal cord, which is the most common site of metastatic spread.[45,49–68] Thus, a new philosophy began to emerge: direct, circumferential spinal cord decompression.

To achieve a circumferential decompression, surgical approaches must be tailored to the location of the tumor with respect to the spinal cord.[4] The common goal is to have the spinal cord free of any malignant compression. Approaches can broadly be classified as anterior (e.g., transthoracic, retroperitoneal) or posterior, including posterolateral trajectories (e.g., laminectomy, transpedicular, costotransversectomy, lateral extracavitary). In addition to decompression of the spinal cord, reconstruction and immediate stabilization of the spinal column form the pillars of modern surgical management.

Much of the literature regarding circumferential decompression over the past 20 years is from uncontrolled cohort studies. In one of the largest reports, Sundaresan et al.[63] described their results in 80 patients with solitary metastatic spinal lesions. Their approach varied depending on the anatomic and radiologic extent of the tumor: an anterior approach was used in 32 patients, a strictly posterior or posterolateral approach in 8 patients, and a combined anteroposterior approach in 40 patients. Preoperatively, 32 patients (40%) were ambulatory and 55 (69%) had significant pain. Postoperatively, 78 (98%) were ambulatory, including 94% of those who were initially unable to walk. Pain was improved in 95%, with 76% having complete relief. The overall survival was 30 months. Patients with breast or renal cell carcinoma had a median survival of 36 months, compared with 15 and 12 months for gastrointestinal and unknown primary carcinoma, respectively.

Gokaslan et al.[54] reported their results with transthoracic vertebrectomy in 72 patients. Pain was improved in 92% of patients and 93% of patients were able to walk postoperatively. Of the 13 patients who could not walk before surgery, 10 regained ambulatory ability after surgery, including 3 who regained normal function. The 1-year survival rate for the entire cohort was 62%. Complications ranging from minor atelectasis to pulmonary embolism were reported in 21 patients. The 30-day mortality rate was 3%.

Overall, the data obtained from studies of circumferential decompression suggest that neurologic outcomes are far superior to those achieved with decompressive laminectomy or radiation. On average, 90% of patients experienced an improvement in pain and 85% were ambulatory after surgery, including 60% who regained the ability. The morbidity and mortality associated with this more complex surgery are significant; however, the rates are acceptable in light of the improved neurologic and pain outcomes.

One of the most problematic surgical complications in cancer patients is a wound infection. Factors associated with wound infections are postoperative incontinence, posterior incision, morbid obesity, and preoperative radiation.[69] In patients with metastatic spine tumors, preoperative radiation (especially within 7 days of surgery), malnutrition, and steroid use are risk factors.[37,53,62,70,71] Ghogawala et al.[70] showed that major wound complications rates are threefold higher in patients who underwent radiation before surgery compared with patients who underwent surgery before radiation.

More recently, Klimo et al.[72] provided a quantitative comparison between the "new" surgery and radiotherapy, based on articles that report on ambulatory status before and after treatment, age, sex, primary neoplasm pathology, and spinal disease distribution. The meta-analysis included data from 24 surgical (999 patients) and 4 radiation (543 patients) articles, mostly uncontrolled cohort studies. Overall, surgical patients were 1.3 times more likely to be ambulatory after treatment and twice as likely to regain ambulatory function. Ambulatory success rates for surgery and radiation were 85% and 64%, respectively. Primary pathology was the principal factor determining survival. Neurologic status, overall health, extent of disease (spinal and extraspinal), and primary pathology all influenced proper treatment selection.

Analogous to the controversy of laminectomy versus radiation in the "old era," it is clear that an RCT is needed to address the question of circumferential surgery compared with radiation in this "new era." Patchell et al.[73] recently published the results of an RCT comparing direct decompressive surgical resection followed by adjuvant radiation (50 patients) with conventional radiation alone (51 patients). Patients in both groups were treated with the same steroid protocol and received the same total radiation dose (30 Gy). Patients treated with surgery retained ambulatory and sphincter function significantly longer than patients in the radiation group. Also, 56% of nonambulators in the surgical group regained the ability to walk compared with 19% in the radiation group. Patients who underwent surgery and radiation also had a significant survival advantage.

This landmark study, which represents the first good class I data in the metastatic spinal disease literature, supports a change in the current management of metastatic epidural spinal disease.[73] Traditional indications for surgery include radioresistant tumors (sarcoma, lung, colon, melanoma, renal cell); obvious spinal instability; clinically significant neural compression secondary to retropulsed bone or from spinal deformity; intractable pain unresponsive to nonoperative measures; and radiation failure (progression of deficit during treatment or spinal cord tolerance reached). Based on the results of this study, we recommend surgery as the primary treatment modality for all patients with newly diagnosed metastatic disease and spinal cord compression who do not harbor any of the indications for radiotherapy or contraindications for surgery.

Radiation

Conventional Radiotherapy

Radiosensitive tumors (lymphoma, breast, multiple myeloma, small-cell lung carcinoma, seminoma of testes, neuroblastoma, Ewing sarcoma) are a common indication for radiotherapy. In addition, patients with an expected survival of less than 3 months, those unable to tolerate surgery, those with total neurologic deficit below the level of compression for more than 24 hours, and those with multilevel or diffuse spinal involvement are also candidates for radiotherapy. The standard radiation portal involves the level of disease with a 5-cm margin that effectively includes 2 vertebral bodies above and below.[74] The total radiation dose is usually 3,000 cGy (2,000–4,000 cGy) and is administered over 10 to 14 days, with higher doses delivered in the first few days and then tapered down.[74] Patients with radiosensitive tumors (breast, myeloma, lymphoma) overall have a better functional outcome than those with more radioresistant tumors (sarcoma, lung, colon, melanoma, renal cell), especially when the diagnosis of spinal cord compression is made late. Many patients have disease isolated to the spine, usually the vertebral body, without epidural compression. For these patients, a single dose, usually 8 Gy, provides good pain relief and is as efficacious as various fractionated regimens.[75,76]

As described previously, radiotherapy was the treatment of choice when decompressive laminectomy was the predominant surgical procedure primarily because the surgery was a poorer option rather than because the radiotherapy was a strong option. Overall, the reported ambulatory success of patients receiving radiotherapy was 34% and 73%.[7,10,15,34,39,40,77–81] Several reports since then have all been uncontrolled cohort studies.[16,82–89] One of the largest reports is by Maranzano et al.,[16,85,87] who treated 209 patients with radiation (30 Gy) and steroids. Nearly all (98%) patients had pain, and 65% had some degree of neurologic dysfunction.

After radiotherapy, pain improved in 71% of patients, ambulatory function improved in 36%, and bladder function improved in 44%. Overall, 76% recovered or preserved the ability to walk. The median survival for the whole group was 6 months with a 1-year survival rate of 28% (average follow-up, 49 months). Favorable factors for survival included ambulatory status, both before and after treatment, and histology.

Helweg-Larsen[83] followed 153 patients for a median of 2.6 months. The total radiation dose was 28 Gy, given in fractions of 4 Gy on 7 consecutive days. In total, 21 of the 74 initially nonambulatory patients (12 paretic, 9 plegic) recovered some gait function, whereas 7 patients (2 with normal gait, 5 with assisted gait) progressed to a nonambulatory state because of treatment failure. Of patients who presented with sphincter dysfunction, 10 (18%) regained bladder function. The median survival was 5.4 months.

More recently Maranzano et al.[90] reported the results of a phase III, randomized, multicenter trial of radiation alone that compared 2 hypofractionation schemes. In that study, 10% of patients lost the ability to walk and 5 patients experienced local recurrence despite favorable histology for radiation. The reported response rates for pain, motor function, and sphincter control were 57%, 70%, and 89%, respectively. However, the response rates for regaining motor function and sphincter control were only 29% and 14%, respectively.

The average pain improvement, ambulatory success, and ambulatory rescue for recent radiation alone articles are 77%, 63%, and 29%, respectively.[16,82,84–89] Falkmer et al.[91] reported similar values in a recent review article. These outcomes appear to be inferior to those found in the newer surgical literature. In addition, the results of the first well-designed RCT comparing stand-alone radiotherapy to surgery with adjuvant radiotherapy shows a marked benefit for surgery.[73] Thus, for patients who meet surgical criteria radiotherapy as adjuvant therapy is more effective. Conversely, many patients either cannot tolerate surgery or are not candidates for it (e.g., highly radiosensitive tumors, short life expectancy). In these patients, radiation should still serve as the primary mode of treatment.

Non-conventional Radiotherapy

With conventional external beam radiation, a significant amount of normal tissue, including the spinal cord, is exposed to radiation, which can lead to radiation-induced myelopathy.[92–94] Therefore, if sufficient radiation could be delivered to the target while the amount delivered to normal tissue is minimized, injury to the spinal cord would theoretically be reduced. Non-conventional radiotherapy, which includes stereotactic radiosurgery (SRS) and intensity-modulated radiotherapy (IMRT), is able to do just that. The reported data thus far consist of case series. In these series, the follow-up has been short, and outcome measures such as pain and neurologic function are rarely discussed.[95–98] The research has shown it to be a safe intervention; however, it has not been rigorously tested against other current therapies (surgery or conventional radiotherapy) regarding effectiveness. Such data are needed before a treatment recommendation can be rendered. Currently, radiosurgery is recommended for recurrent tumors when all other modalities (surgery, conventional radiotherapy) have failed.

Conclusions

Significant changes have occurred in the treatment of metastatic epidural spinal disease during the past 20 years.[11] Decompressive laminectomy is no longer the only surgical treatment. Although it is appropriate in certain cases, it carries all the risks associated with an invasive procedure and offers the patient little benefit, unless it is used to remove disease isolated to the posterior elements without significant vertebral body involvement. Conversely, the existing literature suggests that surgery that frees the spinal cord at the site of compression in addition to reconstructing and stabilizing the spinal column followed by adjuvant conventional radiation is more effective at preserving and regaining neural function, notably ambulatory function and sphincter function, than conventional radiotherapy alone. It is also highly effective in relieving pain.

The results of a recently published RCT by Patchell et al.[73] provide the first class I evidence to support a significant change in the current role of surgery for metastatic spinal cord compression.[11,13,73,99] Conventional radiotherapy has a clearly defined role both as adjuvant therapy after surgery and as primary therapy in patients who cannot tolerate surgery or those with radiosensitive histology (lymphoma, etc.). The role of non-conventional radiation therapy (IMRT, SRS), particularly in the setting of MESCC, remains to be elucidated, but it might be a reasonable option for patients who have undergone prior radiation.[95] Also, the role of many minimally invasive techniques such as kyphoplasty and endoscopic surgical approaches continues to evolve.[100–103] New well-designed clinical trials are necessary to delineate the value of these new treatments.

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