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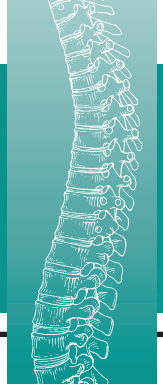

Spinal Metastatic Disease: Current Treatment Algorithms

Daniel K. Park, MD, Justin Munns, BS, Omar Hassanein, BS, and Kern Singh, MD

LEARNING OBJECTIVES: After participating in this activity, the surgeon should be better able to:

1. Interpret the common clinical presentation and work-up for a patient with metastatic lesions to the spine.
2. Use a treatment algorithm for patients with metastatic lesions.
3. Apply the current concepts behind treatments related to spinal metastases.

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Metastatic spinal disease represents a frequently encountered oncologic condition. With global advancements in current cancer treatment allowing for an increase in patient life expectancy, there has been a congruent rise in patients presenting with metastases to the spine.[1] Clinical suspicion, especially in any patient with a history of cancer, should prompt the clinician to perform a thorough workup, including laboratory screening tests as well as imaging studies.[2,3] If left untreated, spinal metastases can rapidly progress potentially resulting in neurologic and functional sequelae. The following review will discuss several important factors in the presentation, and diagnosis of spinal metastases as well as current medical and surgical treatment options. The following review will discuss several important factors in the presentation and diagnosis of spinal metastases as well as current medical and surgical treatment options. It is hoped that readers can utilize an algorithm to help simplify treatment and management of patients who present with metastasis to the spine.

EPIDEMIOLOGY

In the United States, it is estimated that more than 18,000 patients per year are diagnosed with spinal metastases.[4] The vertebral column is the most common musculoskeletal site for metastatic dissemination, and it is thought that more than 70% of cancer patients will eventually demonstrate evidence of micrometastases to the spine. Fortunately, only a small percentage (10%) will become symptomatic.[1,5] The most common primary tumors responsible for metastatic spread are lung, breast, prostate, and hematopoietic cancers. Metastases originating from the kidney, gastrointestinal tract, and thyroid are less frequent causes.[6] Most patients diagnosed with spinal metastatic disease have a prior cancer diagnosis, although 20% of patients have no oncologic history.[7]

It is thought that the three main routes for tumor dissemination to the spine are via the arterial system, the Batson venous plexus, and direct tumor expansion and invasion through the intervertebral foramen. It was previously thought that the most common route for tumor embolization was through the valveless venous plexus of Batson.[8,9] However, more recent studies have shown that spread through the arterial system is the more common route for tumor dissemination.[10]

CLINICAL PRESENTATION

Overwhelmingly, pain, typically nonmechanical in origin, is the most common initial presenting symptom, occurring in greater than 95% of patients at diagno-

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Table 1. Harrison's Criteria for Treatment of Spinal Metastases

Stage	Vertebral Stability	Neurologic Symptoms	Treatment	
I	No evidence of tumor involvement in bone/ soft tissue, stable	Negative	Radiation, pain management	
II	Bone/soft tissue involvement, stable			
III	Bone/soft tissue involvement, stable	Positive	Radiation, decompression, stabilization, especially if tumor is radioresistant or if symptoms to not improve	
			Radiosensitive	Radioresistant
IV	Vertebral instability/collapse	Negative	Intralesional excision and reconstruction, postop radiation	Anteroposterior or posterolateral decompression and stabilization
V		Positive		

sis.[11] Patients with more advanced disease frequently present with mechanical pain.[1,2] Increased suspicion for metastatic disease should be exercised in any patient with a previous diagnosis of cancer presenting with clinically suspicious neck or back pain.[1] On examination, localized pain presenting as point tenderness is the earliest sign of spinal metastasis. This pain is thought to be caused by tumor invasion into the periosteum.

Less common presenting examination findings in patients with spinal metastases include weakness and neurologic deficits. Radicular pain or signs and symptoms consistent with myelopathy may be caused by tumor impingement of the neural elements. These symptoms typically present after pain.[2,11] Although sensory deficits commonly appear after pain, bowel or bladder dysfunction and incontinence are present in more than half of patients with spinal metastases at the time of diagnosis.[6,11]

DIAGNOSIS

Radiography with anteroposterior and lateral views is commonly performed as an initial imaging test. For abnormalities to be visualized, however, more than 50% of the bone must be resorbed.[12] Common radiographic abnormalities that suggest tumor invasion include pedicle erosion (the "winking-owl sign"), paraspinal soft tissue shadows, and compression/burst fractures.

Advanced imaging may be ordered to elucidate the radiologic findings further or if index of suspicion is high and x-rays are normal. MRI is the gold standard. With a sensitivity of 95% and a specificity of 93%, MRI is the most effective imaging study to diagnose a patient with a suspicious clinical presentation.[13] MRI also provides the ability to scan the entire spine for clinically silent areas of tumor invasion. Recent studies have shown that an MRI scan should be obtained first in patients with a high clinical suspicion of spinal metastases to allow for a rapid course of action should the diagnosis be positive.[2,3]

CT is used adjunctively to analyze bone integrity in patients suspected of having spinal metastases. CT may provide better detail regarding bony involvement

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Table 2. Tokuhashi Scoring System

Category	Options	Score
General condition (Karnofsky Performance Scale)	Poor (10%–40%)	0
	Moderate (50%–70%)	1
	Good (80%–100%)	2
Number of extraspinal bone metastases	≥3	0
	1–2	1
	0	2
Number of metastases in the spine	≥3	0
	2	1
	1	2
Metastases to major internal organs	Irremovable	0
	Removable	1
	No metastases	2
Primary site of cancer	Lung, stomach	0
	Kidney, liver, uterus	1
	Thyroid, prostate, breast, rectum	2
Myelopathy	Complete	0
	Incomplete	1
	None	2

Table 3. Tomita Surgical Strategy for Spinal Metastases[18]

Malignancy Grade		Visceral Metastases		Bone Metastases	
Slow	1	None	0	Solitary	1
Moderate	2	Treatable	2	Multiple	2
Rapid	4	Untreatable	4		

Sum Total Score	Treatment	Prognosis
2–3	Wide/marginal excision	Long-term control
4–5	Marginal/intralesional excision	Middle-term control
6–7	Palliative surgery	Short-term control
8–10	Nonoperative	Supportive care

and vertebral stability. In addition, CT is often used in for a more precise assessment and mapping of the tumor invasion.[14] Furthermore, patients who cannot undergo MRI but have neurologic deficits may benefit from CT myelography.

Once the diagnosis of a spinal lesion is made in patients without a history of metastatic disease, simple laboratory tests, including complete blood cell count, electrolyte assessment, prostate specific antigen, urine/serum protein levels, and kidney and liver function tests should be measured to identify if the lesion is primary or metastatic in nature. Clinical abnormalities such as hypercalcemia and proteinuria, common in patients with multiple myeloma, can assist in establishing the diagnosis of a primary cancer.[1] Further imaging studies that may be helpful in identifying the primary tumor also include plain chest x-rays and chest, abdomen, and pelvic CT scans. A technetium-99m bone scan may also assist in identifying whether the spinal lesion is isolated or widespread.[15] Technetium scans are sensitive to areas of increased osteoid formation. Bone scans can identify lesions as small as 2 mm, provided an osteoblastic response occurs in the surrounding bone. If multiple lesions are found in the skeleton, the likelihood of metastatic disease is high. If only one spinal lesion is found, the onus is on the clinician to exclude a primary spinal tumor.

TREATMENT

Patients diagnosed with spinal metastases have a generally poor overall prognosis, as the primary malignancy is typically widespread at the time of diagnosis. The average lifespan for these patients is 3 to 6 months.[16] Several factors associated with the patient's prognosis have been shown to result in longer survival times after treatment: the patient's ability to walk before and after treatment; positive response to radiation therapy; absence of further metastases throughout the body; and a single isolated spinal lesion.[16,17]

Various treatment modalities have been used to treat spinal metastases including corticosteroids; chemotherapy; radiation, including evolving radiotherapies; and surgical intervention.[19–23] To help guide treatment, various classification systems have evolved (Tables 1–3). Furthermore, many different modalities are combined to help alleviate pain and decrease morbidity in these patients (Figure 1).

Noninvasive Modalities

In patients with cord compression associated with metastatic disease, corticosteroids may be used to help improve neurologic outcomes.[2] The mechanism of action is thought to involve the drug's ability to reduce peritumoral vasogenic spinal cord edema.[1] Furthermore, combined corticosteroid therapy prior to radiation therapy in patients with neurologic compromise has been shown to improve the duration of walking in patients after treatment.[20] It should be noted, however, that in patients with vertebral instability who lack neurologic deficits, corticosteroids have not been proven beneficial, and their use in this patient population remains controversial.[22]

Invasive Modalities

Radiation therapy with external high beam radiation has been another mainstay therapy for the treatment for spinal metastasis (Table 4). In patients with primary tumors that are radiosensitive, such as hemopoietic and prostate tumors, a significant percentage of tumor reduction can be expected. Overall, up to 30% of patients will demonstrate a positive response following radiation therapy.[1] There is debate as to whether larger doses for shorter duration would be more beneficial. Specific radiation treatment regimens are tailored to the type of cancer involved and the patient's overall clinical scenario. In addition to traditional radiotherapy, evolving methods of radiation delivery—including intensity-modulated radiotherapy (IMRT) and stereotactic radiosurgery (SRS)—are increasingly being utilized as a means to focus beams of radiation directly at specific targets of interest while limiting radiation toxicity to important structures such as the spinal cord. A study by Gerszten and colleagues used image-guided SRS (CyberKnife, Accuray, Inc.) in 115 patients with spine metastases and reported no neurologic deficits or radiation

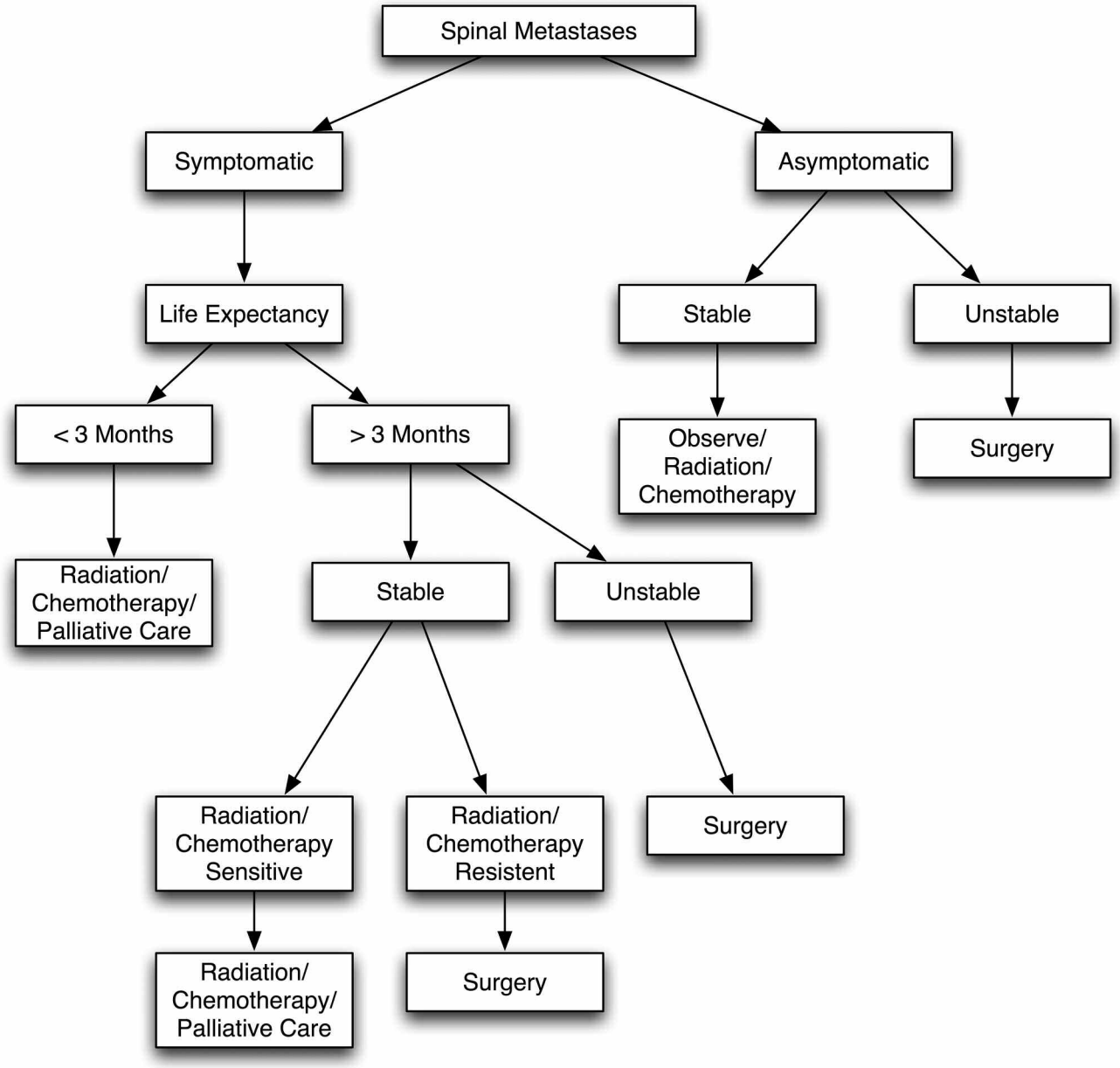

Fig. 1 *Algorithm for treatment of patients with spine metastases.*

Table 4. Relative Indications for Surgery or Radiation as a Primary Treatment Modality

Radiation	Surgery
Radioresponsive tumor	Retropulsed bone producing neural compression
Moderately radioresponsive tumor in patient with minimal deficit/limited pain	Spinal deformity producing pain/neural compression
Isolated epidural neural compression	Spinal instability from bony/ligamentous destruction
Isolated local pain	Progressive neurologic deficit
Expected survival less than 3 months	Failure of radiation
Poor operative candidate	Progressive deficit/pain during radiation
Complete neurologic deficit	Previous radiation with recurrence/progression
	Unknown primary

Fig. 2 *Surgical decompression and reconstruction in a 64-year-old woman with metastatic breast cancer. The patient presented with a 3-month history of worsening back pain and a 7-day history of difficulty walking secondary to increasing back pain and bilateral lower extremity dysesthesia. Preoperative MRI (A) and CT (B) scans demonstrate a pathologic burst fracture at T12 with 40% canal compromise (C). A minimally invasive corpectomy via a lateral approach with an expandable cage was performed with 75 mL blood loss. A percutaneous posterior spinal fusion with instrumentation was accomplished from T10-L2 with 50 mL blood loss (D and E).*

toxicity in 9 to 30 months of posttreatment follow-up. Also in that study, 74 of 79 patients with axial or radicular pain reported improved symptoms after therapy.[22] Despite the successful results reported in this study, there remains a lack of research that directly compares SRS and IMRT with standard radiation therapy or surgery. Currently, SRS and IMRT are used as adjuncts to surgery, alone in patients deemed inoperable, or when there are recurrent metastatic lesions after other treatment options have been exhausted.[22]

Surgery remains an integral part of the treatment plan in patients with symptomatic radioresistant tumors, spinal instability, neural compression secondary to retropulsed bone, deformity, or intractable pain, and when radiotherapy has failed (Table 4). Typically patients with a life expectancy of more than 3 months who present with metastatic spine cancer are considered possible surgical candidates.

Various surgical techniques, including minimally invasive surgery, have been developed, but they are beyond the scope of this review (Figure 2). Recent clinical studies have provided some guidance regarding when surgery is most effective as a treatment option. In comparing surgery combined with radiation versus radiation alone, investigations by Patchell and colleagues demonstrated that patients with symptomatic spinal compression had significant benefits in posttreatment outcomes after they received surgical excision with radiation as opposed to radiation alone.[24] In this study, patients who received surgery with radiation had a higher rate of walking after treatment (84% vs. 57%), and they walked for a longer duration (122 days vs. 13 days), compared with patients who received radiation therapy alone. Patients who received surgery also had longer survival (126 days vs. 100 days). In the study, 16 patients in each treatment group were unable to walk before therapy, and 10 of the 16 patients regained the ability to walk after surgery compared with three of 16 patients who received

radiation alone.[24] Furthermore, a systematic review of the literature demonstrated radiotherapy alone should be directed primarily toward patients with complete paraplegia or paralysis or those who have a radiosensitive tumor.[25]

As stated previously, surgery is usually combined with radiation therapy. Regarding order of treatment protocol, recent studies have analyzed whether administration of radiation before or after surgery affects patient outcomes and postsurgical complications. A study by Ghogawala and colleagues suggests that surgery on an irradiated field may exponentially increase the rate of postsurgical wound complications.[26] The study analyzed 85 patients divided into three groups: radiation therapy alone; surgery after radiation; and surgery before radiation. In patients who underwent surgery before radiation therapy, only 12% had wound complications, compared with 32% of patients who received radiation before surgery. Additionally, 75% of patients who underwent surgery first retained the ability to walk and remained continent 30 days after treatment, compared with 50% of the patients who had radiation therapy first.[26] The results from Sundaresan et al. also supported the findings of Ghogawala et al., demonstrating that wound breakdown was higher in patients treated preoperatively with radiation.[27]

CONCLUSION

With increasing medical advances in the diagnosis and treatment of cancers, patients with metastatic disease to the spine are experiencing improved prognoses at diagnosis. Therefore, clinical suspicion of spinal involvement of tumor is essential in providing care to these patients, as untreated spinal metastases have been shown to lead to rapidly worsening symptoms including eventual sensory loss, paraplegia, and bladder and bowel incontinence. MRI is the gold standard for establishing the diagnosis, although other imaging modalities can assist.

Classification of disease severity by use of one or more classification systems assists in the formation of an appropriate therapy regimen. Corticosteroid therapy and radiation have been used frequently as first-line treatments and have been shown to reduce tumor size and improve symptoms in a significant number of patients. Newer advancements in radiotherapy delivery are on the horizon to decrease radiation side effects.

Despite these neoadjuvant therapies, the mainstay of treatment remains surgery, particularly in patients with neurologic compromise and/or instability. Typically, a combination of various treatment modalities is used to provide the patient the best quality of life; therefore, a coordinated team of various physicians is critical to deliver optimal care to these patients. With the article by Patchell et al.,[24] surgery has emerged as an important tool to help maintain or increase the quality of life of these patients. The surgeon's role in the team of physicians is increasing, and the onus is on the surgeon to help recommend whether surgery or a nonsurgical modality is warranted.

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1. The smallest-sized lesion that can be identified on a technetium-99m bone scan is typically
A. 1 mm
B. 2 mm
C. 3 mm
D. 4 mm

2. A 57-year-old woman with a medical history of breast carcinoma has a positive MRI scan for a metastatic tumor lesion at the L4 vertebrae. Which one of the following is the *most* likely method of tumor spread to the spine?
A. Direct tumor invasion from the breast to the vertebrae
B. Emboli from the arterial system
C. Emboli from the Batson's venous plexus
D. Emboli from the lymphatic system

3. A 63-year-old man with no significant medical history presents with lower back pain of 3 months' duration that is suspicious for metastatic spinal disease. The most important first steps in his workup are
A. anteroposterior and lateral x-rays of his lumbar spine to identify a vertebral lesion
B. MRI of his spine to confirm the diagnosis of spinal metastatic cancer
C. blood studies and imaging of his chest, abdomen, and pelvis looking for a primary tumor
D. all of the above

4. Which one of the following is the *most* common clinical presentation of a metastatic tumor lesion to the thoracic spine?
A. Myelopathy
B. Bilateral radicular pain along the chest wall
C. Unilateral numbness along a thoracic dermatome
D. Bowel incontinence

5. A 72-year-old African-American man with a 40-pack-year smoking history presents with increasing severe lower lumbar pain of 2 months' duration that does not improve with rest or nonsteroidal anti-inflammatory use. On further workup, the patient is found to have significant hypercalcemia and Bence-Jones protein in the urine. Which one of the following is the *most* likely diagnosis?
A. Multiple myeloma
B. Primary malignancy of the spine
C. Squamous cell lung carcinoma with metastases to the spine
D. Renal cell carcinoma with metastases to the spine

6. Which one of the following is the *most* likely explanation for the increasing incidence of spinal metastases in the United States?
A. More effective therapy for cancer patients allowing for a longer life span
B. Carcinogenic properties of newer cancer therapies increasing the incidence of spinal carcinomas
C. Unknown but most likely related to an environmental toxin
D. Increased tobacco consumption in the United States

7. A 55-year-old woman in remission for 3 years after treatment for breast carcinoma presents with a 2-month history of severe lower lumbar back pain and weakness of the lower extremities. MRI confirms the presence of a tumor lesion at the L4 vertebrae without evidence of vertebral instability but with compression of the spinal cord. On the basis of the Harrison criteria, which of the following options is the most likely course of treatment for this patient?
A. Corticosteroid therapy followed by radiation therapy alone
B. Surgical treatment with en bloc spondylectomy without radiation
C. Surgical en bloc resection and decompression with reconstruction followed by radiation
D. Chemotherapy alone

8. A 77-year-old man with stage IV colon cancer and multiorgan failure secondary to metastatic disease presents with severe back pain. The patient is receiving palliative care with an expected life expectancy of 1 to 2 months following failed chemotherapy. Which one of the following options is the best course of treatment for this patient's spinal metastases?
A. Chemotherapy and radiation followed by surgical decompression at the locations of spinal tumors
B. Emergency posterolateral decompression and stabilization at the tumor lesions followed by postoperative corticosteroid therapy
C. Increasing palliation if possible to relieve the patient's pain with consideration for corticosteroid and radiation therapy
D. Elective decompression surgery of lesions only at the thoracic spine

9. Sagittal MRI reveals a mass in the intervertebral foramen. The differential diagnosis should include metastatic spinal disease and which of the following primary tumor(s)?
A. Melanoma
B. Nerve sheath tumor
C. Renal cell carcinoma
D. All of the above

10. A 65-year-old woman with a history of breast carcinoma presents with vague lower back pain of 4 months' duration as well as a 2-month history of severe bilateral arm weakness and numbness. MRI reveals a single tumor lesion at the T4 vertebrae, and x-rays and CT scans demonstrate vertebral instability. No other signs of systemic metastases are present. Radiation therapy is administered, and the tumor fails to decrease in size. According to the Harrison criteria, which one of the following options is the *best* treatment for this patient after radiation?
A. Anteroposterior or posterolateral decompression and stabilization
B. Intralesional excision and reconstruction
C. Chemotherapy alone
D. Begin chemotherapy and repeat radiation therapy if the tumor increases in size