Spinal Metastasis – Diagnosis, Management, and the Role of the Hospitalist

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ABSTRACT

Management of spinal metastases is a complex process which includes services ranging from neurological surgery to medical oncology to radiation oncology. Neurosurgery hospitalists increasingly play a crucial role by coordinating diagnostic and therapeutic strategies, tailoring them to each patient's individual needs. In this article, we review each step of the management of the spine mass from diagnosis to treatment. An emphasis is placed on the diagnosis and management of metastatic spinal cord compression. Finally, we review in detail the role of the neurosurgery hospitalist in this process.

INTRODUCTION

Metastatic disease in patients with solid and hematological malignancies is an important adverse prognostic factor, as it is associated with significantly higher rates of morbidity and mortality. Autopsy studies of patients with cancer reveal that up to 70% had also developed metastases to bone.[1,2,3] Greater than 80% of these bone metastases are attributable to three primary malignancies: breast, prostate, and lung (though many others, including thyroid, renal, and colon cancer also frequently metastasize to bone).[2,3] The spine is the most common site of osseous metastasis, and its increasingly high prevalence on autopsy is in large part due to the improved overall survival of patients living with cancer.[2,3]

Physiologic factors contributing to the origin and severity of spinal metastases include (a) Batson venous plexus, which is responsible for drainage of the abdominal and pelvic organs, and (b) growth factors released from bone marrow stroma by tumor-mediated structural degradation, which then induce growth and proliferation of the invading tumor cells (in addition to osteoblastic and osteoclastic activity).[2,4,5] Bone metastases are either sclerotic, lytic, or mixed, depending on the degree to which they stimulate osteoblasts, osteoclasts, or both.[5,6]

The most dreaded complication of spinal cord metastasis is metastatic spinal cord compression (MSCC), first described by William G. Spiller, MD in 1925.[7] Approximately 5% of all patients with cancer develop MSCC, while as many as 20% of patients with spinal metastases suffer MSCC4.[8] Breast, lung, prostate, and renal cancer are responsible for the majority of MSCC.[9,10] The thoracic spine (60%) is the most commonly implicated region, followed by the lumbar spine (25%), and cervical spine (15%).[4,9] When MSCC occurs, the culprit lesion is located within the vertebral body itself in about 85% of cases, whereas paravertebral spaces are the origin in 15% of cases.[4] As with spinal metastases in general, the overall incidence of MSCC has increased, which likely also is due to the increasing longevity of patients with cancer.[11]

CLINICAL PRESENTATION

The most common symptom of spinal metastases and MSCC is new or worsening back pain.[4,9,10] Bone metastasis is the most common cause of cancer-associated pain and represents multifactorial pathophysiology, including osteolysis, tumor-induced growth factor production, nerve infiltration, and periosteal distension.[4,6] The characteristics of this pain typically are somatic, neuropathic, or both. Somatic pain is localized and worsened by movement or manipulation of the affected region, while neuropathic pain typically radiates, burns, and worsens at night.[4,6] In high risk patient populations, sudden and severe worsening of pain should raise suspicion for a pathological fracture, which may result from either osteolytic or osteoblastic lesions.[4,5]

Neurological injury in MSCC is due to compression-mediated demyelination and axonal damage, along with vascular compromise leading to vasogenic edema, ischemia, and ultimately infarction of the spinal cord4. The incidence of focal extremity weakness due to MSCC ranges from 35% to 75% and represents the most common focal neurological manifestation.[4,12] It is often associated with ambulatory dysfunction, though the degree of impairment varies greatly. Sensory deficits are less common, typically preceded by pain and motor impairment, progress distally to proximally, and may be associated with more severe neurological injury[4, 12]. Bowel and bladder dysfunction are grave features of MSCC and are seen in 50-60% of cases.[4] When present, sphincter dysfunction (tested by digital rectal examination and measurement of urinary post-void residuals) represents a poor prognostic indicator and reduces the likelihood of complete functional neurological recovery.[4,13] While the characteristic syndrome of MSCC includes the above manifestations, many patients present with more general signs and symptoms, such as nonspecific pain and ambulatory dysfunction.[4,12]

CLINICAL PRESENTATION AND EVALUATION OF METASTATIC SPINAL CORD COMPRESSION

Metastatic spinal cord compression is a medical and surgical emergency requiring immediate evaluation and intervention to prevent paralysis and other irreversible neurological injury.[4,14] It is paramount that clinicians maintain a high index of suspicion and promptly evaluate symptoms that raise the possibility of spinal metastatic disease or MSCC, particularly in patients with an established diagnosis of malignancy.[6,15] Poor prognostic factors include prolonged duration of neurological deficit, severe neurological compromise, prior radiation treatment of metastatic lesions, and metastases located in the thoracic spine (although there are only few and low-quality studies to establish these prognostic features).[16] Patients who are unable to lift their legs against gravity and those who have been non-ambulatory for greater than 48 hours are at greatest risk of poor functional recovery.[16]

Ambulatory status at the time of diagnosis carries the greatest power of prognostication, as multiple studies demonstrate improved post-treatment outcomes and functional capacity for patients who were able to ambulate at the time of intervention.[10,12,17] There is insufficient standardization in the assessment of pre-treatment functional capacity and inadequate tools for quantifying the post-treatment prognosis, but experts agree that pre-treatment ambulation is strongly linked to better outcomes and reduced rates of morbidity and mortality.[16-19]

Given the preceding prognostic considerations, early detection, diagnosis, and intervention in cases of MSCC is crucial to improving patients' outcomes.[14,18] The gold-standard imaging modality to diagnose MSCC is magnetic resonance imaging (MRI), which confers a high diagnostic sensitivity (93%) and specificity (97%).[2,4,8] MRI offers detailed visualization of the spinal cord and its surrounding structures and is useful not only for surgical planning, but also for identifying targets in cases when emergent radiation treatment is necessary,[1, 2,4,8] Experts recommend MRI evaluation of the entire spine, as up to 30% of patients with MSCC have more than one metastatic lesion in the spine.[15,20]

Fortunately, data suggest that patients with MSCC today are more likely to experience significant functional recovery. A study in 2010 showed that 62% of patients with MSCC were ambulatory at the time of their diagnosis and intervention, whereas only approximately one-third of patients in the 1990s remained ambulatory by the time of intervention.[14,21,22] In addition to early diagnosis, multiple studies have demonstrated that early surgical intervention (in appropriate candidates) plus radiation therapy improves outcomes in comparison to radiation therapy alone.[2, 6,14,17,9,10,12,23,24,25]. Historically, laminectomy alone was the standard method of surgical intervention, but more recent studies and surgical advances support decompression and fusion for stabilization over decompression alone.[2,16,17,21, 23]

Overall median survival rates for patients with MSCC range between 6 to 9 months.[18,19,21,25,26] In addition to patients' functional and ambulatory condition, survival rates are greatly influenced by the type and features of the primary malignancy.[25] Lung cancer and cancer of unknown primary causing MSCC bear the worst prognoses, while prostate and myeloma are associated with more favorable outcomes.[18,19,25,26]

NEUROIMAGING IN THE DIAGNOSIS OF SPINAL METASTASES

Historically, plain film radiographs were the first imaging test used for the diagnosis of spinal metastatic disease. With the advent of more sophisticated imaging modalities, however, radiographs are no longer routinely utilized for this purpose. Radiographs require a minimum mass diameter of 1 cm and a bone density of 50% or greater to achieve adequate visualization, resulting in a very high rate of false negative tests. The development of computed tomography (CT) scans presented a significant advancement, as they can detect bony metastatic lesions up to 6 months before they are reliably identified on radiograph. Nevertheless, though excellent for detecting bony abnormalities, CT is far inferior to MRI when it comes to delineation of soft tissues and the diagnosis of spinal cord compression.

Standardized use of MRI in the evaluation of spinal metastatic disease has greatly impacted the management and outcome expectations for patients. In addition to its superior visualization of the spinal cord and surrounding soft tissue, MRI remains the only modality capable of evaluating the bone marrow and its constituent elements with high resolution. T1-weighted MR scans are particularly useful for the evaluation of bone marrow due to the hyperintense signal generated by its high fat content, which enables detection of focal hypointense lesions relative to the surrounding normal tissue. In contrast, T2-weighted MR images show metastatic lesions as hyperintense compared to bone marrow, due to their relatively high water content. The addition of intravenous contrast further aids detection of lesions in the epidural space, as well as MSCC. A limitation of MRI, however, is its inability to differentiate conclusively between changes resulting from tumor versus those from surgery.

Biopsy is the gold standard test to determine the primary origin of any metastatic lesion. Neuroimaging can play a role in identifying the tissue of origin during the early stages of a metastatic evaluation, as many malignancies cause either lytic (osteoclast-predominant) or sclerotic (osteoblast-predominant) bony lesions (though some are characterized by mixed features). Primary cancers of the lung, breast, thyroid, adrenal glands, and melanoma (among others) cause lytic bony metastases. In contrast, prostate, bladder, and nasopharyngeal cancers cause sclerotic metastases. Cancers of ovarian, cervical, testicular, and occasionally lung etiology may cause mixed—lytic and sclerotic—patterns. Both lytic and sclerotic lesions involving the posterior cortex may cause destruction of the cortex and pedicles. An important sign of diffuse bone marrow infiltration is a hyperintense appearance of the vertebral discs in comparison to bone on a T1-weighted MRI. A systematic grading of spinal cord compression proposed by Bilsky and colleagues is commonly used to stratify the severity of MSCC.[27]

Other imaging modalities that have proven useful in screening for bone metastases are bone scintigraphy and single-photon-emission computed tomography (SPECT). These are nuclear medicine scans that operate by injection of a radioactive tracer that accumulates in newly formed bone at the site of a metastatic lesion. Neoplastic lesions appear "hot" (indicative of increased bone turnover, including degradation and formation), but this effect may not be seen in cases where the cancer has caused excessive tissue destruction and consequently impaired blood flow to the site. One of the best modalities for visualization of bone marrow involvement is the [18F] fluoro-2-deoxy-d-glucose positron emission tomography (FDG-PET) scan, which measures glucose metabolism and thus preferentially highlights areas of increased bone cell turnover. This is particularly useful for when evaluating for multiple myeloma.[28]

MANAGEMENT OF SPINAL METASTASTIC DISEASE

General considerations of treatment

Metastatic malignancy generally is an incurable disease. Whether and how to pursue treatment requires careful consideration of several patient and disease-specific determinants. Physicians should proactively seek to understand each patient's perceptions, expectations, and preferences. In their 2017 report, the International Spine Oncology Consortium proposed a number of factors to consider prior to initiating treatment, beginning with a thorough assessment of the patient's baseline functional status.[29] The Karnofsky performance scale and the Eastern Cooperative Oncology Group (ECOG) scale are commonly used in general oncology as functional performance evaluators. Patients with 'poor functional status' are generally defined as those with a Karnofsky performance score of less than 40.

The overall burden of disease also plays a significant prognostic role, even following treatment of spinal lesions. Extensive extra-spinal metastatic disease denotes a poor prognosis for survival after spinal radiation. Some tumor types (for example, hormone-sensitive breast cancer and lung cancer with target-sensitive genomic alterations) have more favorable prognostic profiles, and this must also be factored into spine-specific treatment paradigms. Hematological cancers affecting the spine generally have well-established systemic treatment protocols that may be favored over surgery or local radiation, at times even when cord compression is present. Similarly, tumor histology is important in predicting whether conventional external beam radiation therapy (cEBRT) can achieve durable local response, as some histologies are more radiosensitive than others. Finally, mechanical stability of the spine, commonly assessed by the Spine Instability Neoplastic Score (SINS), will greatly influence treatment options as the primary goal in mechanically unstable spines is to restore structural stability.[30] SINS incorporates both clinical and radiological features and scores range from 0 to 18, with higher numbers signifying a higher degree of instability.

Radiation therapy

The two most common forms of radiation therapy for spinal metastases are external beam radiation therapy (EBRT) and stereotactic body radiation therapy (SBRT). The former is most frequently employed, while the latter often is reserved for specifically indicated circumstances. The primary goal of EBRT is palliation and it is the preferred treatment for radiosensitive tumors (e.g. lymphoma, myeloma, germ cell tumors). Practice guidelines, informed by multiple randomized controlled trials, favor shorter fractionated regimens of EBRT over more protracted ones, as they have been shown to be noninferior in their primary outcome (pain control) and associated with fewer acute post-treatment adverse effects.[31,32]

SBRT utilizes confocal beams of radiation to precisely target a specific site, while avoiding collateral radiation damage to important adjacent structures. It is particularly useful for the treatment of relatively radioresistant tumors like sarcoma, melanoma, and renal cell carcinoma. It is also used in patients who have persistent pain despite treatment with EBRT.[33] SBRT is associated with a higher risk of vertebral compression fractures. It is worth noting, however, that SBRT and EBRT have not been compared directly in prospective randomized controlled trials.

Surgery

The two main indications for surgical consultation in spinal metastatic disease are spinal instability and MSCC. Surgical consultation (by a neurosurgeon or specialized orthopedic spine surgeon) generally is recommended for any patient with a SINS greater than 72.[34,35] MSCC is a medical emergency and surgery is a critical component in the care of patients with MSCC. Surgical intervention typically is pursued in conjunction with medical and radiation therapy, as multiple clinical trials involving MSCC have demonstrated significantly better outcomes in patients treated with surgery plus radiation in comparison to radiation therapy alone.[36] These findings have led to expansion of the surgical role in the management of MSCC and advancements in surgical technique. A trial by Patchell et al. found that more patients in the surgical group (84%) were able to ambulate after treatment versus the radiation monotherapy group (57%), and they remained ambulatory for a longer duration (median 122 days versus 13 days).[37] Minimally invasive techniques like cement augmentation of vertebral bodies are increasingly used and have proven effective in the management of certain disease presentations, such as pathological fractures.[2,38]

Another benefit of surgical intervention is to facilitate safe delivery of postoperative radiation therapy. Spine separation surgery is one such procedure which creates a gap access to the tumor, allowing radiation to be administered, while sparing the spinal cord and the cauda equina from direct exposure and potential radiation damage.[39-41]

Medical management

The aspect of medical management that is most directly relevant to the hospitalist or general internist is analgesia, since pain is the most common symptom in spine metastasis. Mild bone pain is usually managed well with scheduled acetaminophen, with or without a nonsteroidal anti-inflammatory drugs (NSAID). As pain becomes more severe, the addition of an oral opioid agent

may be necessary. In the hospital, this approach can be combined with intravenous opioids for breakthrough pain, titrated to therapeutic efficacy while at the same time avoiding neurological and respiratory side effects. Glucocorticoids are frequently used to improve outcomes when there is MSCC, but they are also a useful adjunct for analgesia.[42]

Osteoclast inhibitors reverse or delay the progression of bone metastases and reduce the likelihood of skeletal-related events (SREs). Denosumab and zoledronic acid (a bisphosphonate) are the most frequently utilized agents.[43] Denosumab has been shown to have a benefit over zoledronic acid in reducing overall bone tumor burden, but comes with a significant additional cost, resulting in the more common use of the latter.[43,44] The well-known adverse effects of these agents include jaw necrosis, hypocalcemia, increased risk of atrial fibrillation and stroke (bisphosphonates), and a higher risk of infection (denosumab).

Depending on the primary tumor identified on biopsy, systemic chemotherapy and more recently developed targeted therapy or immunotherapy may play a role in controlling systemic disease burden.[29,45] Systemic chemotherapy regimens generally come with a significantly increased risk of toxicity, and the treating hospitalist should be cognizant of possible adverse effects during the course of therapy.

ROLE OF THE HOSPITALIST PHYSICIAN IN THE MANAGEMENT OF PATIENTS WITH SPINAL MASS

The medical complexity of hospitalized patients has increased substantially over time, making multidisciplinary care increasingly necessary and common. In addition, patients with disseminated cancer are likely to be older, and are thus more likely to have multiple medical comorbidities that complicate their pre- and postoperative care. Much like the primary care physician in the outpatient setting, the hospitalist physician today serves an important role in coordinating treatment plans among multiple care teams and is vital to managing medical comorbidities.

Hospitalists are often called upon to evaluate patients for their overall risk for surgery, therefore today's hospitalist needs a deep understanding of perioperative medicine, and must be well versed in the utilization of the multiple risk stratification tools. For a risk assessment of major adverse cardiac and cerebrovascular events (MACCE) the hospitalist needs to be familiar with the Gupta Score and the Revised Cardiac Risk Index (RCRI).[46,47] They also need to understand the current AHA/ACC guidelines for perioperative assessment,[48] as well as ASA classification.[49] Although the risk of MACCE is a central part of preoperative assessment, there are other tools to aid with risk stratification, such as the risk of postoperative respiratory failure estimated by ARISCAT.[50] The risk of postoperative venous thromboembolism is defined using the Caprini score.[51] Understanding which patients can proceed to surgery without delay and which patients need further testing for enhanced risk stratification is an integral skill for the current hospitalist.

In the postoperative period the hospitalist continues to play an important role, as they are often consulted to manage postoperative sequelae. In the postoperative period the hospitalist may be called upon to manage metabolic complications and electrolyte disturbances, or to manage hyperglycemia in steroid-treated patients and diabetics. Prevention, early detection and treatment of postoperative venous thromboembolic disease (VTE) are also critical management skills for the hospitalist, as are the detection and management of postoperative infections. Additionally, the hospitalist must feel comfortable managing acute postoperative pain, and working collaboratively with dedicated pain medicine services. Lastly, the hospitalist must frequently assess goals of care, and involve palliative care when indicated, after careful consultation with their surgical colleagues.

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