Spinal Metastasis as Complication of Systemic Cancers

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Introduction

Metastatic spinal cord disease represents a common complication of systemic cancer and is a major cause of morbidity in cancer patients [1, 2]. Since the first report of spine metastasis by Dr. William Spiller in 1925 [3], this disease entity has proven to be a challenge to physicians both with regard to diagnosis and management. Symptomatic spine metastasis is seen in 5–10% of patients with cancer and such lesions must be caught early and treated in an effective manner in order to preserve residual neurologic function and to prevent new neurologic deficits [4, 5]. These patients present with signs and symptoms such as pain, weakness, autonomic dysfunction, sensory loss, and ataxia [6]. A variety of prognostic factors have been evaluated in order to adequately assess the appropriate treatment options for these patients. Such factors include extent of metastatic disease, aggressiveness of the cancer, and preoperative function. By assessing the patient's prognosis, the appropriate treatment options that minimize additional morbidity and maximize the patient's quality of life can be selected. These treatment options range from palliative measures, such as radiation therapy, to curative resection; the type of treatment must be individualized for each patient [7, 8].

Epidemiology

1.7 million new cases of cancer are expected to be diagnosed in the U.S. in 2015 [9]. Systemic neoplasia is seen in 60–70% of these patients at the time of their death with bone as the most common site for metastatic disease [10]. Post-mortem studies report the prevalence of skeletal metastasis in cancer patients to range from 7 to 27%. The prevalence is similar for both men and women [11]. Of those with skeletal metastasis, 36–70% have lesions to the spine [12–14]. Metastatic disease to the spine can present in a variety of ways and causes significant morbidity in these patients.

Metastatic lesions can be intradural intramedullary, intradural extramedullary, or extradural in location. Extradural disease can be isolated to the bony spine, or an epidural component can be present with or without compression of the spinal cord or thecal sac. Approximately 94–98% of patients with metastasis to the spine have either vertebral or epidural involvement [11]. On the other hand, intradural extramedullary and intradural intramedullary seeding are only seen in 5–6% and 0.9–2.1% of patients, respectively [15]. Intradural extramedullary lesions of metastatic origin typically arise via seeding of the spinal subarachnoid space (e.g., lymphoma). This topic will

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Table 6.1 Site of primary tumor with epidural spinal metastasis

Primary	Incidence (%)
Breast	13–22
Lung	15–19
Prostate	10–18
Lymphoma	8–10
Sarcoma	7.5–9
Kidney	6–7
Gastrointestinal	4–5
Melanoma	2–4
Myeloma	4.5–5
Unknown	4–11

primarily be discussed in another chapter. Epidural spinal metastases (ESM) are most commonly seen in the thoracic spine (70% of cases). Disease is also seen in the lumbar spine (20% of cases) and less commonly the cervical spine (10% of cases) [12, 16]. Despite the incidence of metastasis, ESM are symptomatic in only 5–10% of patients with cancer [17–19].

The incidence of metastatic spine disease varies among different tumor types. A higher index of suspicion must be maintained with particular cancer patients in an attempt to retain and possibly restore neurologic function. The most common malignancies to result in symptomatic ESM include breast cancer, lung cancer, and prostate cancer. Lymphoma, sarcoma, and renal cancers display a high prevalence as the primary source for ESM, and less frequently melanoma, myeloma, and gastrointestinal tract tumors will metastasize to the epidural spine. However, it is not infrequent that the primary site for ESM remains unknown [19–21]. Table 6.1 displays the incidence of each of these primary sites as a source of metastasis. Loblaw and colleagues analyzed the cumulative incidence of ESM in the 5 years preceding death among different cancer types and found an overall incidence of 2.5% for all cancer types with a range of 0.2% in pancreatic carcinoma to 7.9% in myeloma [22].

Pathogenesis and Pathophysiology

Batson, through his cadaveric experiments, identified the low-pressure valveless vertebral-venous plexus, which extends from epidural and perivertebral veins to veins of the thoraco-abdominal wall and veins of the head and neck. Venous blood can bypass the portal, caval, and pulmonary veins via Valsalva, venous obstruction, or increased intra-thoracic and intra-abdominal pressure resulting in flow inversion to the vertebral-venous plexus. This provides a pathway for distant organs to spread disease to the spine [23, 24].

An alternative route for metastasis to the bony spine and epidural space is via arterial emboli through the rich vascular network that supplies the bony spine. The vertebral body has a large blood supply, while the posterior elements are less highly vascular. Spinal lesions arise more often from the vertebral body; [5] however, isolated involvement of the vertebral body is rarely observed—only in 3.8% of cases—while 75% of ESM involve the vertebral body, pedicle and posterior elements [25]. These tumors can grow within the anterior or posterior bony elements or spread to the epidural space via venous drainage [26]. In addition, invasion into the spine can occur via direct extension from the paraspinal region to the nerve roots through the neural foramina [1].

The pathophysiology by which spine metastasis causes neurologic injury is a matter of some debate. Spinal cord compression is associated with endogenous neurochemical changes that lead to neuronal injury. This compression was initially thought to result in arterial ischemia. Subsequent animal and human studies have demonstrated that compression and obstruction of the vertebral-venous plexus result in vasogenic spinal cord edema, venous hemorrhage, and ischemia [20, 27]. In addition to venous obstruction, spinal auto-regulatory mechanisms induce arteriolar dilatation and increased edema via induction of such enzymes as nitric oxide synthase. Cytokine production, e.g., PGF_2, IL-1, IL-6, locally promotes an inflammatory response with vasodilatation and increased edema formation. In addition, animal studies display myelin loss secondary to ischemia and compression [28–31].

Presentation

Patients harboring spinal metastases can present in a variety of ways. Symptoms secondary to metastasis are the same symptoms by which a primary spinal malignancy is discovered. Also, 20% of patients with metastatic cancer have signs and symptoms of ESM as the initial manifestation of their disease [32]. Patients with bony spine metastasis with or without an epidural component commonly present with a prolonged period of persistent back pain with a median time course of 8 weeks. Unfortunately, although back pain is a frequent complaint among the general populace, the physician must consider spine metastasis in the differential diagnosis. This is especially true in older patients and patients with pain at the level of the thoracic spine, as pain at this level is uncommon in degenerative disc disease. Even with the diagnostic modalities available to the modern physician, patients are diagnosed very late in the course of their disease. Levack and colleagues performed a prospective observational study of 319 patients and found that 82% of patients at diagnosis of ESM were either unable to walk or only able to do so with help. 94% of these patients reported

approximately a 3-month history of axial spine pain [33]. It is important to note that patients with compression secondary to epidural disease can still present with isolated axial spine pain without neurologic deficit or radicular symptoms. Epidural spinal compression cannot be excluded because a patient with back pain does not manifest myelopathy or radiculopathy.

Pain may occur for a variety of reasons including pathologic fracture, local compression resulting in axial spine pain, or via nerve root impingement resulting in radicular pain. Radicular pain affecting the upper or lower extremities is seen in cervical and lumbar disease, whereas thoracic cord lesions present with bilateral pain radiating around the chest or upper abdomen [34].

The location of pain can help guide the physician; however, pain can be a false localizing sign and may not always correlate directly with the level of the metastasis. The differential diagnosis must also include more common entities such as herniated disc disease, which can be distinguished by a history of trauma or other inciting event as a well an acute onset of pain, rather than the more common insidious onset of pain symptoms seen in spine metastasis [35, 36].

Weakness is the second or third most common complaint of patients with spine metastasis and is both a symptom and sign of disease. Subjective weakness may be a manifestation of axial or radicular pain without true weakness evident on examination and is present in a high percentage of patients with ESM. Objective weakness is seen in 84% of patients with compressive ESM. At the time of diagnosis, approximately 50% are ambulatory, 35% are paraparetic, and 15% are paraplegic. Rapid diagnosis and treatment are critical in these patients as 30% of those individuals presenting with weakness become paraplegic within one week [21].

Patients with spinal metastasis commonly present with numbness and paresthesias such that 51% have subjective sensory symptoms on presentation, and 78% of patients have sensory deficits found on examination [21]. These deficits can assist in localizing the metastatic lesion. Dermatomal sensory loss or reflex loss is more predictive than a sensory level, as the sensory level may be apparent between one and four levels below the level of disease. Patients with cervical and thoracic disease can also present with Lhermitte's sign [37].

Bowel or bladder dysfunction is seen in as many as 57% of patients. Urinary retention is the most common form of dysfunction, more common than both urinary and fecal incontinence. The degree of autonomic abnormality often correlates with the severity of motor and sensory deficits and is considered a late finding. In addition to the aforementioned presenting signs and symptoms, patients may also present with other forms of autonomic dysfunction such as the absence of sweating below the lesion level and Horner's syndrome as well as ataxia, spasticity, and syringomyelia [20, 21].

In assessing patients with ESM, it is important to differentiate between lesions causing myelopathy from spinal cord compression and those causing deficits from cauda equina syndrome (CES) . Patients with either lesion can present with back pain, weakness, sensory deficits, or bowel and bladder dysfunction. However, the former results in upper motor neuron signs such as clonus, Babinski sign, and hyperactive reflexes. On the other hand, the latter displays unique sensory deficits such as saddle anesthesia as well as lower motor neuron signs such as hypoactive reflexes and muscle wasting [38, 39].

Diagnostic Work-up

The diagnosis of spine metastasis is continually evolving as the diagnostic tools available to the physician continue to improve. Plain X-rays are a valuable tool in analyzing the bony spine. Plain radiographs detect bony erosion better in cortical bone than in cancellous bone. The pedicle is primarily composed of cortical bone as compared to the vertebral body, so metastasis to the pedicle is identified first on plain radiographs despite the higher degree of involvement in the vertebral body [16]. Metastatic tumors are commonly lytic lesions that present with vertebral body compression. Plain radiographs also show paraspinal soft-tissue shadows and pathological fracture-dislocation [40, 41]. Despite these advantages, false-negative plain radiographs occur in 10–17% of patients with ESM [18]. The osteoblastic tumors seen in prostate and breast metastases as well as paraspinal tumors that invade the neural foramen are difficult to identify on plain radiographs.

Bone scans are more sensitive in assessing metastatic disease than plain radiographs. Bone scans use technetium diphosphonate to identify diseased bone which present as "hot spots." This diagnostic method has the advantage of providing a survey of the entire skeleton. Degenerative changes seen in elderly patients can show up as "hot spots" and complicate the diagnosis [42, 43]. As an alternative to a conventional bone scan, whole body positron emission tomography (PET) can be used to assess bony metastases. This imaging modality has been shown to have equal sensitivity and improved accuracy in detecting metastatic bone lesions when compared to a bone scan [44]. The improved accuracy is related to the mechanism by which the modalities detect tumor involvement—technetium scanning relies upon osteoblastic bone response to tumor, while PET measures glucose uptake in the tumor itself by the use of a

radiotracer [45–48]. Consequently, PET scans are more likely to detect tumors that are at an earlier stage of growth, while bone scans are less likely to detect osteolytic and slow growing metastases [48, 49].

Myelography, as first brought forward by Jean Athanase Sicard, has been an important diagnostic technique in the evaluation of spinal metastasis [50]. Prior to the advent of MRI, myelography was the gold standard for evaluation of these tumors [51]. Myelography can still be used to identify the site and extent of metastasis when MRI is not readily available, a patient is unable to tolerate MRI, or MRI is contraindicated as in patients with ferromagnetic implants [41, 52]. The relationship of the metastasis to the spinal cord, dura, and nerve roots can also be discerned. Myelography is primarily performed via lumbar injection of radio-opaque dye. However, some metastases can present in multiple locations; a tumor causing complete obliteration of the spinal canal results in failure to identify additional rostral metastases, in which case a cisternal injection is required to complete the evaluation [41].

Computed tomography (CT) can be used either as a separate modality or in combination with myelography. CT imaging is primarily useful in assessing the bony elements surrounding the spinal cord. CT in combination with myelography can greatly improve the data available from each study alone and can provide better anatomical detail of the spinal axis and extent of the tumor both inside and outside the spinal canal [41, 53].

While the aforementioned modalities can be of value in assessing spinal metastasis, magnetic resonance imaging (MRI) is considered the modality of choice. MRI provides multi-planar imaging of the spine that is noninvasive. In addition, paravertebral soft-tissue masses and bone marrow involvement can also be detected [51]. MRI has been shown to be equivalent if not superior to CT myelography in detecting cord compression in ESM as well as cord atrophy [54]. MRI has been shown to be the most accurate and noninvasive method to assess the entire spinal axis so that the appropriate treatment modality can be initiated [55].

Laboratory and radiographic assessment are important in assessing systemic disease. Metabolic panels, blood counts, and prealbumin should be obtained to assess the nutritional status and immunological status of the patient. Renal dysfunction and liver dysfunction via metastasis or primary disease can be assessed via blood urea nitrogen and creatinine and liver function tests [41]. Tumor markers such as prostate specific antigen, serum and urine protein electrophoresis for myeloma, CA-125 for ovarian cancer, and CEA for colorectal cancer can assist with diagnosis [56]. Urinalysis, chest radiography, abdominal ultrasound, and CT imaging of the chest, abdomen, and pelvis are useful screening methods for systemic malignancy [41].

Prognosis

In discussing the various treatment options of spinal metastasis, multiple factors must be considered in order to determine the patient's prognosis. Prognosis can be a key item in patient assessment that can influence how aggressive the treatment is for a particular patient. Tokuhashi generated such a system for assessing prognosis that is useful in based on length of survival (Table 6.2). This system includes such items as general condition, number of extraspinal metastasis, the number of spinal metastasis, the extent of metastasis to internal organs, the primary site of the tumor, and the degree of spinal cord injury. This scoring system has been correlated with prognosis such that patients with a score between 9 and 12 are predicted to survive greater than 12 months, while patients with a score from 0 to 5 are predicted to survive less than 3 months [57].

In general, the median time of survival after diagnosis of ESM is approximately 6 months. Patients who are ambulatory at the time of diagnosis display a median survival of 8–10 months as compared to 2–4 months for non-ambulatory patients. In addition, patients with slow growing cancers such as breast and prostate cancer tend to liver longer than faster growing cancers such as lung cancer. The former has a

Table 6.2 Tokuhashi's evaluation for prognosis

	Score		
Symptoms	0	1	2
Karnofsky score	10–40	50–70	80–100
Extraspinal metastasis	>3	1–2	0
Internal organ metastasis	Unresectable	Resectable	No metastasis
Primary site of tumor	Lung, stomach	Kidney, liver, uterus	Thyroid, prostate, breast, rectum
Spinal metastasis	>3	2	1
Spinal cord injury	Complete	Incomplete	None

median survival of 9–10 months, while the latter has a median survival of 3 months [58, 59].

Pharmacotherapy

The treatment options for spinal metastasis are divided into three categories. These options include pharmacologic therapy, radiation therapy, and surgical resection with or without fusion. Treatment of the patient's symptoms and adjuvant therapy, e.g., corticosteroids or chemotherapy, are two roles of pharmacologic therapy. The physician combines medications for analgesia as well as for the control of neuropathic pain with radiation therapy and/or surgical intervention. Opiates are the primary treatment for analgesia, while amytriptiline and gabapentin or pregabalin are effective treatment options for neuropathic pain. These medications are a key component to palliative therapy [34].

Pain develops not only from bony infiltration but also from pathologic fractures. In addition to pain, fractures can lead to spinal instability requiring surgical intervention. Pharmacotherapy directed at bone turnover can provide a method in preventing pathologic compression fractures. Bisphosphonates inhibit osteoclast activity and bony resorption, decreasing the risk of pathologic fracture. Such therapy has shown a benefit in patients with bony metastasis from multiple myeloma and breast cancer [60, 61].

Corticosteroids have been shown in experimental models to reduce peritmoral vasogenic spinal cord edema and transiently improve neurologic function. After initiation of steroid therapy, patients have significant improvement in pain symptoms [34, 41, 62]. A randomized trial by Sorensen and colleagues compared outcome in patients receiving high-dose radiation therapy with or without dexamethasone. In the former group, 81% of patients were ambulatory after treatment and 59% of patients remained ambulatory after 6 months. In contrast, only 63% of patients in the latter group were ambulatory after treatment and 33% of patients remained ambulatory after 6 months. These differences displayed statistical significance identifying the importance of corticosteroids as adjuvant treatment in patients with ESM [63].

Studies have also focused on the effect of high-dose bolus dexamethasone (100 mg) versus moderate-dose bolus dexamethasone (10 mg) versus no corticosteroid treatment. These studies displayed equivalent efficacy between doses with regard to improvement in pain, ambulatory status, and bladder function. The physician must consider the side effect profile of corticosteroids, especially at higher dosages. Significant adverse side effects include severe psychoses, gastric ulcers, rectal bleeding, and gastrointestinal perforations [63–66]. Heimdal and colleagues performed a retrospective study of patients who received radiation therapy in combination with corticosteroids. All patients received pretreatment with antacids or H2 blockers prior to high-dose corticosteroid therapy. Despite preventive measures, two patients developed gastric perforations and two patients developed gastrointestinal bleeding, one of which proved fatal. A subsequent cohort of patients received a lower dose corticosteroid regimen of 16 mg tapered over 2 weeks. These patients did not experience serious side effects and the ambulatory outcome was similar to those patients receiving the high-dose corticosteroid regimen [66]. In addition, the use of corticosteroids has been analyzed in patients with less severe metastatic disease. Maranzano and colleagues analyzed 20 consecutive patients with ESM causing less than 50% narrowing of the spinal canal and no neurologic deficit in a phase II trial. Patients treated with corticosteroids and radiation therapy showed no additional survival benefit and equivalent return of neurologic function in comparison to patients treated with radiation therapy alone [67].

Chemotherapeutic agents can be a valuable treatment option in ESM. The primary use of these agents is dependent on the chemosensitivity or chemoresistance of the particular tumor. Treatment must be designed to maintain neurologic function and maximize quality of life. Consequently, chemotherapy is typically used as adjuvant therapy along with radiation therapy and/or surgical resection in tumors with uncertain or limited chemosensitivity. On the other hand, the role of chemotherapy in chemosensitive tumors has been a matter of debate. Patients with symptomatic chemosensitive metastases have most often been given chemotherapy in combination with other therapeutic modalities. However, patients with chemosensitive tumors have shown good neurologic improvement with chemotherapy alone. Especially early in the course of the disease, chemosensitive tumors are likely to respond to chemotherapy. These tumors include germ cell tumors and hematological malignancies, such as lymphoma [68, 69]. In addition, chemotherapy can be considered as a single mode of treatment for patients who have previously received radiation or surgery and are not candidates for further treatment [34].

Radiation Therapy

Historically, decompression via laminectomy was considered the primary treatment for spinal metastasis. Studies were conducted in the 1970s and 1980s comparing radiation therapy alone to laminectomy followed by adjuvant radiation therapy. These studies displayed similar rates of neurologic improvement. Consequently, radiation therapy became the standard as primary treatment, while surgery was reserved for patients who deteriorated during or failed to improve after radiation therapy [70–72]. As more advanced surgical

techniques for resection and stabilization have been developed, the role of radiotherapy has also been modified.

Prognosis for patients with spinal metastasis receiving radiotherapy is highly dependent upon the radiosensitivity of the primary tumor. The most radiosensitive tumors that commonly metastasize to the spine include breast cancer, small cell lung cancer, prostate cancer, myeloma, and lymphoma. Patients with these tumors tend to show improved functional recovery and better tumor control rates as compared to patients with radioresistant tumors such as melanoma and renal cell carcinoma. Patients with radioresistant tumors can, however, still obtain significant pain control and quality of life improvement from radiotherapy [73–75].

A variety of techniques are available for the effective delivery of radiotherapy. Such techniques include but are not limited to conventional radiotherapy and stereotactic ablative radiation therapy. In general, the use of radiotherapy is limited by the level of radiation tolerance of the spinal cord. Hypertension, advanced age, prior spinal cord pathology, combination chemotherapy, and immunosuppression are factors which lower the spinal cord's tolerance to radiation [76]. This tolerance level is not fully understood, which makes it necessary to limit the radiation dose provided to the spinal cord in order to prevent such serious complications as radiation myelitis or myelopathy. When radiation myelopathy occurs, patients have progressive rostral spread of sensorimotor symptoms within months of radiation therapy. Within 1 year of symptomatic onset, MRI displays cord swelling as high T2 signal within the cord with gadolinium enhancement. The combination of clinical and imaging characteristics is used to differentiate between radiation toxicity and tumor recurrence [77–80].

Although utilized with decreasing frequency now, conventional external beam radiation therapy (EBRT) has been historically considered an excellent treatment option for pain associated with bony spinal metastases commonly seen in lung, breast, and prostate cancer. This pain can be treated with various dose schedules with equal efficacy [81–83]. Notably, a retrospective analysis of 1300 patients compared five different treatment regimens between 8 Gy in 1 fraction and 40 Gy in 20 fractions. Functional outcome was similar between all groups; however, the more protracted regimens were associated with a lower rate of local recurrence [84]. A protracted regimen is subsequently advantageous in patients with a longer life expectancy, versus a short course of radiation for palliation for short life expectances [85].

Stereotactic ablative body radiation therapy (SABR) provides an alternate modality for focused high-dose radiation to the tumor while minimizing radiation to the adjacent spinal cord, and has become the dominant modality of radiation delivery to spinal metastases. Accurate targeting requires localization of multiple radiation beams to converge on the lesion of interest at a high dose. The typical dose ranges from 8 to 18 Gy. This treatment can be administered over multiple sessions, which makes outpatient treatment convenient. Gerstzen and colleagues presented 500 consecutive lesions treated with high-dose (15–22.5 Gy) single-fraction SABR with a median follow-up of 21 months. They reported long-term tumor control of 88% overall with 100% for breast, lung, and renal metastases [86]. A series by Bate and colleagues followed 57 patients treated with SABR with or without surgery, the SABR-only group achieved local tumor control of 96% overall [87]. In another study, the tumor control rate was 100% in lesions without previous irradiation [88]. SABR following surgery should be considered when mechanical stability and local tumor control both are required. Laufer and colleagues reported 186 patients with ESM treated with local debulking and spinal stabilization plus SABR, and compared radiotherapy groups. Both groups of high-dose therapy following decompression surgery achieved local recurrence rates below 10% [89]. Radiosurgery is considered safer for recurrent tumors than traditional methods as repeat traditional radiotherapy poses a significant risk at surpassing the radiation tolerance of the spinal cord. Moreover, recent review of the literature advocates SABR as the first-line treatment for palliative symptom control for those with symptomatic radioresistant tumors with no neurologic deficit (Fig. 6.1a–c) [90]. Overall, SABR is becoming a common method for delivering safe doses of radiation to spinal tumors. Radiosurgery, like other forms of radiotherapy, does not address the issue of spinal instability.

Surgical Management

The role of surgery in the treatment of spine metastasis has changed as the techniques available for spinal reconstruction have improved. Despite the variety of options in a surgeon's armamentarium, the ability to maintain a patient's quality of life remains of utmost importance and extensive spinal instrumentation correlates with a longer and more painful recovery period, in addition to the recovery required for treatment of the primary disease. Consequently, prognosis is a key factor in deciding the aggressiveness of treatment for a particular patient.

Various scoring systems have been proposed to help guide treatment strategies and the role of surgical intervention. Tomita and colleagues clarified the correlation between length of survival and surgical treatment goals. In this study, they analyzed the growth rate of primary tumor, the presence of visceral metastasis, and the presence and number of bone metastasis. Slow growth tumors such as breast and thyroid cancer equated to 1 point; moderate growth tumors such as
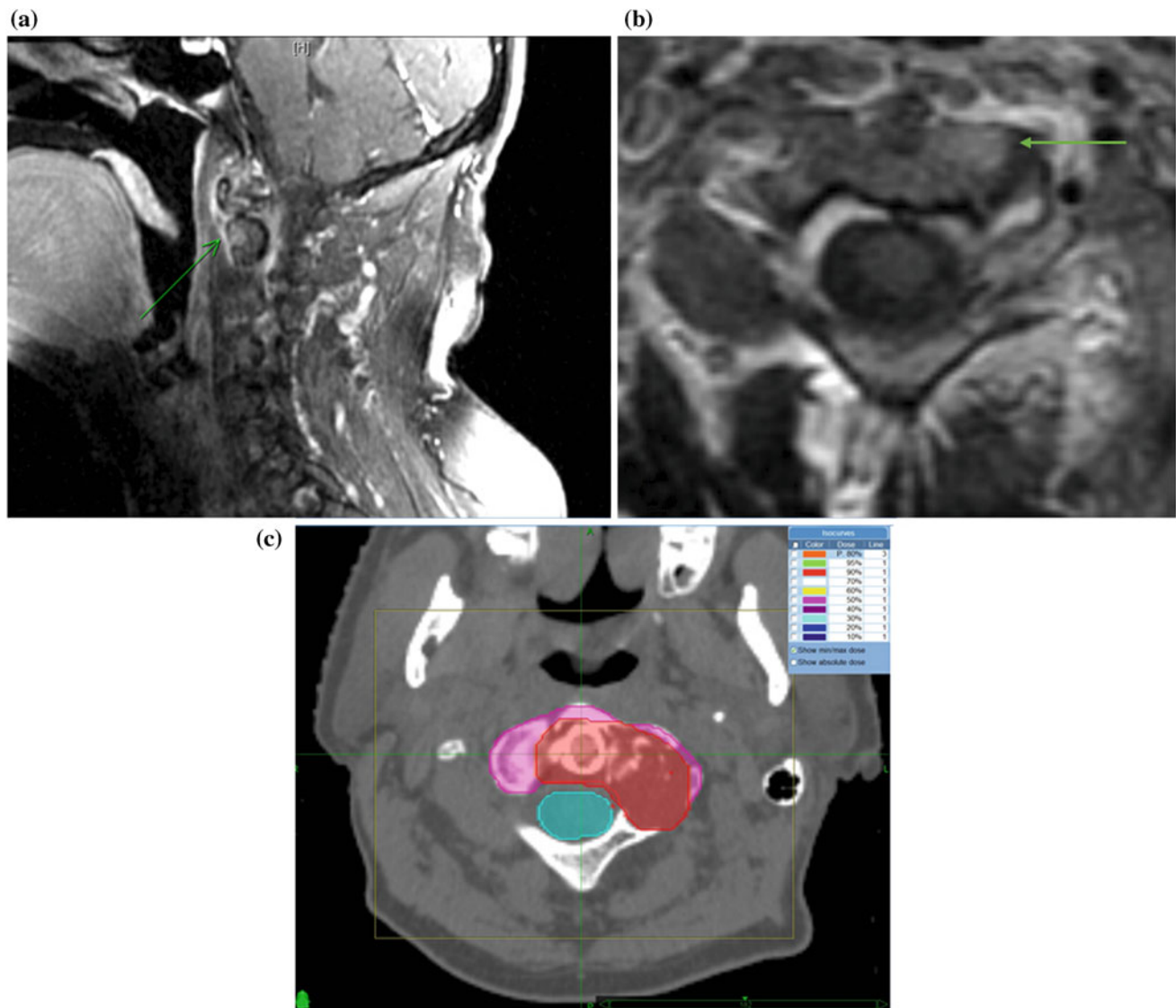
Fig. 6.1 **a–c** 61-year-old male presenting with a 2-month history of progressively worsening neck pain. The patient was neurologically intact on examination. He was recently diagnosed with metastatic thyroid carcinoma; a relatively radioresistant tumor. Pretreatment sagittal (**a**) and axial (**b**) T1 post-gadolinium MR image displaying a tumor in the left C2 vertebral body (*green arrow*). **c** CTV (*red circle*) and PTV (*purple circle*) for SABR treatment planning

renal cell carcinoma equated to 2 points; rapid growth tumors such as lung and gastrointestinal cancer equated to 4 points. Visceral metastases equated to 2 points if they were treatable, while untreatable lesions equated to 4 points. Finally, solitary or isolated bony metastasis equated to 1 point, while multiple metastases equated to 2 points. The group then separated patients into prognostic scores from 2 to 10. Patients with a prognostic score of 2–3 had a treatment goal of long-term local control via wide or marginal excision, e.g., en bloc spondylectomy, with a mean survival time of 38.2 months. Patients with a prognostic score of 4–5 had a treatment goal of middle term local control via intralesional excision with a mean survival time of 21.5 months. Patients

with a prognostic score of 6–7 had a treatment goal of short-term palliation via simple decompression and stabilization with a mean survival time of 10.1 months. Finally, patients with a prognostic score of 8–10 had supportive care only with a mean survival time of 5.3 months [7].

Bilsky and coworkers developed a scoring system that integrates neurologic assessment, oncologic assessment, assessment of mechanical instability, and an assessment of systemic disease burden and medical co-morbidity (NOMS). The neurologic component addresses myelopathy, radiculopathy, and degree of epidural compression. Oncologic assessment evaluates the radiosensitivity of the tumor. Radiosensitive tumors include multiple myeloma and

lymphoma while highly radioresistant tumors include renal cell carcinoma, thyroid carcinoma, melanoma, and sarcoma [91].

On the other hand, the Spinal Instability Score Neoplastic Score (aka, SINS) can help the surgeon predict spinal stability with respect to neoplastic lesions. A composite score of six different factors will help determine if a spine is stable (score 0–6), intermediate (score 7–12), or unstable (score 13–18). Those factors are: location of lesion in the spine, mechanical or postural pain, bone lesion quality, spinal alignment, vertebral body involvement (i.e., collapse), and the posterolateral involvement of spinal elements [92].

The simplest therapeutic option—percutaneous vertebroplasty or kyphoplasty—is a valuable option for treating pain from lesions either isolated to the vertebral body or lesions with a mild epidural component. In this treatment, the surgeon injects polymethylmethacrylate (PMMA) either directly into the vertebral body in vertebroplasty or after expansion of the collapsed vertebral body with a balloon in kyphoplasty. The surgeon usually injects bone cement via a transpedicular route; however, anterolateral, intercostovertebral, and posterolateral routes are used in the cervical, thoracic, and lumbar regions, respectively. Patients can experience pain relief within 24–48 h following therapy and have shown to maintain improved pain control upon 2-year follow-up examination [93, 94].

Compressive lesions in the vertebral body not amenable to percutaneous vertebroplasty or kyphoplasty require alternate avenues by which the spinal cord can be accessed. The surgeon typically performs decompression with a corpectomy via an anterior or anterolateral approach. Anterior approaches require access through the neck, thorax, or abdomen or retroperitoneal space, which can present a surgical challenge. For lumbar lesions, the lateral approach is also used to obtain a retroperitoneal plane to the spinal column. Following a corpectomy/vertebrectomy, the space filled by the vertebral body must be reconstructed to the appropriate height. The typical material in degenerative spine disease is autologous bone or bone allograft. Patients with metastatic lesions will or have already received radiation therapy that decreases the rate of bony fusion. PMMA is used for reconstruction in the cervical or thoracic spine or a titanium expandable cage in the thoracic or lumbar spine. The former requires the addition of a plate and screw construct to aid in stability [95]. Sawaya and coworkers studied 72 patients with thoracic spine anterior column disease that underwent a vertebrectomy and fusion procedure. 76% of these patients displayed improvement in neurologic function. In addition, 77% of patients non-ambulatory prior to surgery regained ambulatory capacity postoperatively [12].

While the anterior approach to metastatic disease can be effective in treating the majority of patients, the extent of a patient's primary disease may not warrant such an extensive tumor resection. Simple decompressive laminectomy and fusion with pedicle screw instrumentation provides a palliative surgical option. In a retrospective study by Oda e al., 32 patients with extensive metastatic disease in the cervico-thoracic spine underwent posterior decompression and fusion. 94% of these patients maintained pain relief, neurologic function, and spinal stability throughout the survival period [96–98].

Patchell's seminal paper compared 50 patients treated by the surgical procedure appropriate to the site of the metastasis followed by radiation therapy with 51 patients treated with radiation alone. In this randomized, multi-institutional, non-blinded trial, the treatment group randomly assigned patients with metastatic spinal cord compression to two different treatment arms. In comparing the two groups after treatment, 84% of patients were ambulatory in the surgery/radiation group while only 57% were ambulatory in the radiation-only group. 32 patients were non-ambulatory prior to treatment, 50% in each group. Of these patients, 62% of the combined group were ambulatory after treatment, while only 19% of the latter group were ambulatory after treatment. Finally, patients in the former group were able to retain the ability to walk for a mean of 122 days, while patients in the latter group were only able to retain the ability to walk for a mean of 13 days. This study showed that direct surgical decompression, and fusion where appropriate, followed by radiation therapy was superior to radiation therapy alone. Only patients with single levels of metastatic epidural spinal cord compression were included in this study [99].

Out of Patchell's study was born the idea of separation surgery. Separation surgery is a simple concept, but one that incorporates all the surgical techniques discussed above, as well as the efficacy of SABR. Separation surgery starts with the goal of resecting the tumor off the thecal sac and spinal cord and reconstituting the CSF space. As the majority of tumors present in the vertebral body, these tumors can commonly infiltrate the posterior longitudinal ligament (PLL). Consequently, to adequately decompress the spinal cord, a bilateral pediculectomy must be performed and the PLL must be dissected off of the overlying dura. This approach requires stabilization through the placement of pedicle screws. A gross total resection of tumor is not required as at approximately 2 weeks after surgery, SABR can be delivered to the residual tumor and resection cavity up to the dural edge. The surgical resection allows the CSF to provide an appropriate distance between the desired radiation dose and the spinal cord to minimize risk of radiation myelopathy. A CT myelogram is utilized to best identify the dural margin used for radiation planning with minimal artifact generated by the instrumentation (Fig. 6.2a–f). Studies using this technique demonstrate local progression rates less than 5% at 1 year [87, 89].
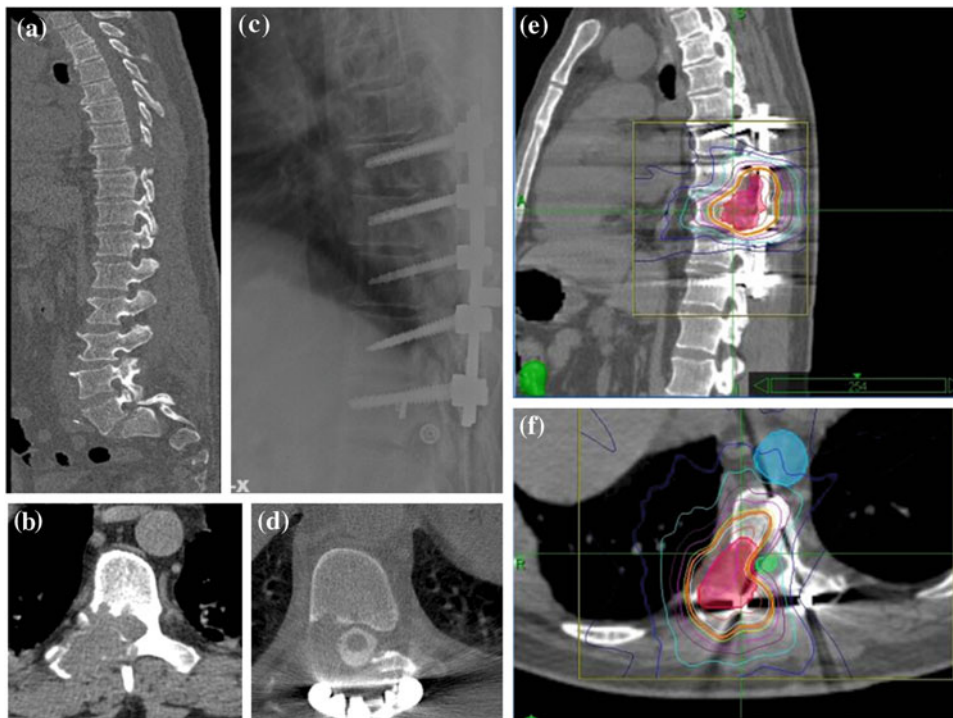
Fig. 6.2 **a**–**f** 53-year-old male presenting with progressive back pain and lower extremity weakness. The patient displayed 4+/5 weakness in the right lower extremities. He was recently diagnosed with renal cell carcinoma status-post a nephrectomy. **a** Preoperative sagittal CT displaying a tumor at T9. **b** Preoperative axial CT displaying a tumor at the right T9 pedicle and transverse process encroaching on the spinal cord. **c** Postoperative sagittal CT displaying instrumentation placed for stabilization following a T9/10 laminectomy and right T9 pediculectomy and tumor resection. **d** Postoperative axial CT myelogram image displaying reconstitution of the thecal sac. **e**, **f** GTV (*red circle*) for SABR treatment planning

Intradural Intramedullary Spinal Cord Metastasis

Intradural intramedullary spinal cord metastasis (ISCM) is an uncommon event, diagnosed in only 0.9–2.1% of cancer patients [100–102]. Approximately 50% of ISCM arise from lung carcinoma and the majority of these cases are small cell carcinoma. Breast cancer, lymphoma, kidney cancer, melanoma, gastrointestinal cancer, ovarian cancer, and tumors of unknown primary are other causes of ISCM [102–107]. Table 6.3 displays the incidence of each of these primary sites as a source of metastasis with regard to ISCM. Most ISCM are thought to spread via emboli through a secondary capillary network to penetrating arteries of the spinal cord [23, 105, 107]. Alternatively, ISCM may originate via direct extension from leptomeningeal disease and subsequently spread to the cord parenchyma [102, 107].

Pain is a common presenting sign in ISCM. In addition, patients may present with weakness and display a similar clinical course to ESM, including rapid progression to paraplegia [108]. However, true motor weakness typically follows sensory disturbances in ISCM as they are most commonly located in the posterior cord [109]. The presence of a Brown-Sequard syndrome can also be a common initial finding and help differentiate between ISCM and ESM [109]. MRI (Fig. 6.3a, b) is the primary imaging modality for detecting cord enlargement, contrast enhancement, and surrounding edema in ISCM. As in ESM, opiates for analgesia and gabapentin for neuropathic pain are commonly used. Patients have shown significant relief of pain symptoms as well as transient improvement in neurologic function with the use of corticosteroids [102].

Treatment of ISCM has primarily been based on anecdotal experience and case series, as no prospective trials on
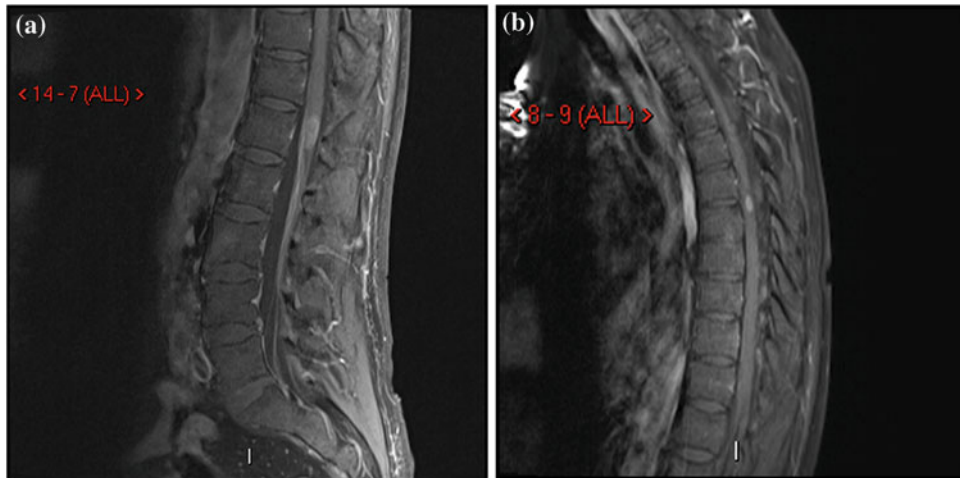
Table 6.3 Site of primary tumor with intradural intramedullary spinal metastasis

Primary	Incidence (%)
Lung	47–54
Breast	11–14.5
Lymphoma	4–12
Kidney	4–9
Melanoma	3.6–9
Gastrointestinal	3–7.3
Ovarian	0.8–1.1
Unknown	1.8–6

Fig. 6.3 a, **b** 57-year-old male with a history of a parasagittal oligodendroglioma for 10 years who presented with new bilateral numbness from the belt line down, Lhermitte's phenomenon, and radicular leg pain worsened with cough. He also noted urinary and fecal retention. Sagittal lumbar (**a**) and thoracic (**b**) post-contrast T1-weighted sequences showed ovoid ring-enhancing masses in the conus and mid-thoracic cord. Chest CT demonstrated a large left upper lobe lung mass, and bronchoscopic biopsy confirmed small cell lung cancer

treatment have been performed. EBRT with or without corticosteroids has been the most effective treatment of ISCM [107]. Clinical response primarily depends on the duration of symptoms, the degree of neurologic deficit, and the radiosensitivity of the tumor. As pathologic evidence indicates that ISCM are multifocal in as many as 30% of patients, radiation therapy to the entire spinal cord could be a treatment option [110, 111]. However, the consequences of bone marrow suppression associated with total spinal irradiation has limited this extensive treatment modality [106, 110]. Stereotactic radiosurgery has a potential role in treating these lesions; however, this modality has only been shown in the literature to be effective in primary vascular tumors [112]. The true issue is discerning the proximity of tumor to functioning spinal cord and limiting radiation exposure to this tissue.

The role of surgery in ISCM remains a matter of debate. 75% of patients with ISCM develop paraplegia within one month from the first symptom of disease. However, patients with rapidly progressive neurologic deficit have shown improved neurologic outcome with early surgical management [102]. In such patients, the objective of surgery is maximal removal of the lesion via microsurgical resection with preservation of existing neurologic function [108]. Focal radiation can then be applied to the involved area, especially in patents with evidence of residual disease [104].

Conclusions

Spinal cord metastases are a common complication of systemic malignancy. ESM most commonly stem from lung, breast, and prostate cancer, while greater than 50% of ISCM stem from lung cancer alone. Patients may present with a variety of symptoms, most notably pain and weakness. The ultimate goals in managing these patients include maximizing both length of survival and quality of life. These goals can best be reached via early, accurate diagnosis followed by the appropriate treatment for a particular patient. As imaging modalities have improved, delineating the exact location and extent of disease has become significantly more accurate. Despite the advantages of MR imaging, other imaging modalities such as CT and plain radiographs still play a valuable role in diagnosis.

Pharmacotherapy plays an important role in treatment for these patients not only for analgesia but also for treatment of edema with corticosteroids and adjuvant treatment with chemotherapy. The patient's prognosis defines the appropriate treatment for spinal metastasis, with the goal of maintaining that patient's quality of life. Radiation therapy continues to be a primary treatment option and a variety of new techniques are now available to maximize the radiation dose to the tumor while minimizing the dose to the spinal cord. Surgical resection and spinal stabilization also have critical roles in the treatment armamentarium. The combination of these different modalities will certainly continue to be a vital component in the treatment of metastatic spinal cord disease as the treatment algorithm continues to evolve with advancements from all fields.

References

1. Schiff D. Spinal cord compression. Neurol Clin N Am. 2003;21:67–87.

2. Mut M, Schiff D, Shaffrey ME. Metastasis to nervous system: spinal epidural and intramedullary metastases. J Neurooncol. 2005;75(1):43–56.

3. Spiller WG. Rapidly developing paraplegia associated with carcinoma. Arch Neurol Psychiatry. 1925;13:471.

4. Bilsky MH, Shannon FJ, Sheppard SS, Prabhu V, Boland PJ. Diagnosis and management of a metastatic tumor in the atlantoaxial spine. Spine. 2002;27(10):1062–9.

5. Barron KD, Hirano A, Araki S. Experiences with metastatic neoplasms involving the spinal cord. Neurology. 1959;9:91–106.

6. Townsend CM. Intraspinal tumors. In: Sabiston textbook of surgery, 17th ed. Philadelphia: Saunders; 2004. p. 2150–2.

7. Tomita K, Kawahara N, Kobayashi T, Yoshida A, Murakami H, Akamaru T. Surgical strategy for spinal metastasis. Spine. 2001;26(3):298–306.

8. Weigel B, Maghsudi M, Neumann C, Kretschmer R, Muller FJ, Nerlich M. Surgical management of symptomatic spinal metastasis. Spine. 1999;24(21):2240–6.

9. American Cancer Society. Cancer facts and figures 2015. Atlanta: American Cancer Society; 2015.

10. Wise JJ, Fischgrund JS, Herkowitz HN, Montgomery D, Kurz LT. Complication, survival rates, and risk factors of surgery for metastatic disease of the spine. Spine. 1999;24(18):1943–51.

11. Tubiana-Hulin M. Incidence, prevalence and distribution of bone metastasis. Bone. 1991;12(Suppl 1):9–10.

12. Perrin RG McBroom RJ. Anterior versus posterior decompression for symptomatic spinal metastasis. Can J Neurol Sci. 1987;14:75–80.

13. Raj PP. Cancer pain syndromes. In: Textbook of regional anesthesia, 1st ed. UK: Churchill Livingstone; 2002. p. 565–6.

14. Browner B. Metastatic disease of the spine. In: Skeletal trauma: basic science, management, and reconstruction, 3rd ed. Philadelphia: Saunders; 2003. p. 405–19.

15. Goetz CG. Direct metastatic disease. In: Textbook of clinical neurology, 2nd ed. Philadelphia: Saunders; 2003. p. 1042–51.

16. Gokaslan ZL, York JE, Walsh GL, McCutcheon IE, Lang FE, Putnam JB, Wildrick DM, Swisher SG, Abi-said D, Sawaya R. Transthoracic vertebrectomy for metastatic spinal tumors. J Neurosurg. 1998;89:599–609.

17. Kim RY. Extradural spinal cord compression from metastatic tumor. Ala Med. 1990;60:10–5.

18. Bach F, Larsen BH, Rohde K, Borgersen SE, Gjerris F, Boge-Rasmussen T, Agerlin N, Rasmussen B, Stjernholm P, Sorensen PS. Metastatic spinal cord compression. Occurrence, symptoms, clinical presentations and prognosis in 398 patients with spinal cord compression. Acta Neurochir (Wien) 1990;107:37–43.

19. Sorenson PS, Borgeson SE, Rasmussen B, Bach F, Boge-Rasumssen T, Stjernholm P, Larsen BH, Agerlin N, Gjerris F. Metastatic epidural spinal cord compression: results of treatment and survival. Cancer. 1990;65(7):1502–8.

20. Gabriel K, Schiff D. Metastatic spinal cord compression by solid tumors. Semin Neurol. 2004;24(4):375–83.

21. Grant R, Papadopoulos SM, Greenberg HS. Metastatic epidural spinal cord compression. Neurol Clin. 1991;9:825–41.

22. Loblaw DA, Laperriere NJ, Mackillop WJ. A population-based study of malignant spinal cord compression in Ontario. Clin Oncol. 2003;15:211217.

23. Batson OV. The role of the vertebral veins in metastatic process. Ann Intern Med. 1942;16:38.

24. Abeloff MD. Bone metastasis. In: Clinical oncology, 3rd ed. UK: Churchill Livingstone; 2004. p. 1091–123.

25. Khaw FM, Worthy SA, Gibson MJ, Gholkar A. The appearance on MRI of vertebrae in acute compression of the spinal cord due to metastases. J Bone Joint Surg Br. 1999;81-B(5):830–4.

26. Arguello F, Baggs LB, Duerst RE, et al. Pathogenesis of vertebral metastasis and epidural spinal cord compression. Cancer. 1990;65:98–106.

27. Byrne TN. Spinal cord compression from epidural metastasis. N Engl J Med. 1992;327(9):614–9.

28. Siegal T. Spinal cord compression: from laboratory to clinic. Eur J Cancer. 1995;31A(11):1748–53.

29. Siegal T, Siegal TZ, Sandback U, et al. Experimental neoplastic spinal cord compression: evoked potentials, edema, prostaglandins, and light and electron microscopy. Spine. 1987;12(5):440–8.

30. Ishikawa M, Sekizuka E, Krischek B, et al. Role if nitric oxide in the regulation of spinal arteriolar tone. Neurosurgery. 2002;50(2):371–7.

31. Kato A, Ushio Y, Hayakawa T, et al. Circulatory disturbance of the spinal cord with epidural neoplasm in rats. J Neurosurg. 1985;63(2):260–5.

32. Schiff D, O'Neil BP, Suman VJ. Spinal epidural metastasis as the initial manifestation of malignancy: clinical features and diagnostic approach. Neurology. 1997;49:452–6.

33. Levack P, Graham J, Collie D, et al. Don't wait for a sensory level—listen to the symptoms: a prospective audit of the delays in diagnosis of malignant cord compression. Clin Oncol (R Coll Radiol). 2002;14(6):474–80.

34. Spinazzé S, Caraceni A, Schrijvers D. Epidural spinal cord compression. Crit Rev Oncol Hematol. 2005;56(3):397–506.

35. Gilbert RW, Kim JH, Posner JB. Epidural spinal cord compression from metastatic tumor: diagnosis and treatment. Ann Neurol. 1978;3:40–51.

36. Love JG. The differential diagnosis of intraspinal tumors and protruded intervertebral disks and their surgical treatment. J Neurosurg. 1944;1:275–90.

37. Prasad D, Schiff D. Malignant spinal-cord compression. Lancet Oncol. 2005;6:15–24.

38. Maxwell M, Chir MB, Borges LF, Zervas NT. Renal cell carcinoma: a rare source of cauda equina metastasis. J Neurosurg (Spine 1). 1999;90:129–32.

39. Shapiro S. Medical realities of cauda equina syndrome secondary to lumbar disk herniation. Spine. 2000;25(3):348–51.

40. Brice J, McKissock WS. Surgical treatment of malignant extradural spinal tumors. BMJ. 1965;i:1341–4.

41. Jacobs WD, Perrin RG. Evaluation and treatment of spinal metastasis: an overview. Neurosurg Focus. 2001;11(6):1–11.

42. Buckwalter JA, Brandser EA. Metastatic disease of the spine. Am Fam Physician. 1997;55:1761–8.

43. Ayyathurai R, Mahaptra R, Rajasudaram R, Srinivasan V, Archard NP, Toussi H. A study on staging bone scans in newly diagnosed prostate cancer. Urol Int. 2006;76:209–12.

44. Hsia TC, Shen YY, Yen RF, Kao CH, Changlai SP. Neoplasma. 2002;49(4):267–71.

45. Thrupkaew AK, Henkin RE, Quinn IL. False negative bone scans in disseminated metastatic disease. Radiology. 1974;113:383–6.

46. Gulenchyn KY, Papoff W. Technetium-99 m MDP scintigraphy; an insensitive tool for the detection of bone marrow metastasis. Clin Nucl Med. 1987;12:45–6.

47. Moog F, Bangerter M, Kotzerke J, Guhlmann A, Frickhofen N, Reske SN. 18-F-fluorodeoxyglucose-positron emission tomography as a new approach to detect lymphomatous bone marrow. J Clin Oncol. 1998;16:603–9.

48. Wu HC, Yen RF, Shen YY, Kao CH, Lin CC, Lee CC. Comparing whole body 18F-2-deoxyglucose positron emission tomography and technetium-99 m methylene diphosphate bone scan to detect bone metastasis in patients with renal cell carcinomas—a preliminary report. J Cancer Res Clin Ocol. 2002;128:503–6.

49. Jacobson AF. Bone scanning in metastatic disease. In: Collier BD Jr, Fogelman I, Rosenthall L, editors. Skeletal nuclear medicine. St. Louis: Mosby; 1996. p. 87–123.

50. Sicard JA, Forestier J. Méthode radiographique d'expolration de la cavité épidurale par le lipiodol. Rev Neurol. 1921;37:1264–6.

51. Husband DJ, Grant KA, Romaniuk CS. MRI and the diagnosis and treatment of suspected malignant spinal cord compression. Br J Radiol. 2001;74:15–23.

52. Stark RJ, Henson RA, Evans SJ. Spinal metastasis: a retrospective survey from a general hospital. Brain. 1982 Mar;105(Pt 1):189–213.

53. Resjó M, Harwood-Nash DC, Fitz CR, Chuang S. CT metrizamide myelography for intraspinal and paraspinal neoplasms in infants and children. AJR. 1979;132:367–72.

54. Karnaze MG, Gado MH, Sartor KJ, Hodges FJ 3rd. Comparison of MR and CT myelography in imaging the cervical and thoracic spine. AJR Am J Roentgenol. 1988;150(2):397–403.

55. Cook AM, Lau TN, Tomlinson MJ, Vaidya M, Wakeley CJ, Goddard P. Magnetic resonance imaging of the whole spine in suspected malignant spinal cord compression: impact on management. Clin Oncol (R Coll Radiol). 1998;10(1):39–43.

56. Perkins GL, Slater ED, Sanders GK. Serum tumor markers. Am Fam Physician. 2003;68(6):1075–82.

57. Tokuhashi Y, Mastsuzaki H, Toriyama S, et al. Scoring system for the perioperative evaluation of metastatic spine tumor prognosis. Spine. 1990;15:1110–3.

58. Marazano E, Latini P, Beneventi S, et al. Comparison of two different radiotherapy schedules for spinal cord compression in prostate cancer. Tumori. 1998;84:472–7.

59. Maranzano E, Latini P. Effectiveness of radiation therapy without surgery in metastatic spinal cord compression: final results from a prospective trial. Int J Radiation Oncol Biol Phys. 1995;32:959–67.

60. Berenson JR, Lichtenstein A, Porter L, et al. Long-term pamidronate treatment for advanced multiple myeloma patients reduces skeletal events. Myeloma Aredia Study Group. J Clin Oncol. 1998;16:593–602.

61. Hortobagyi GN, Theriault RL, Lipton A, et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group. J Clin Oncol. 1998;16:2038–44.

62. Ushio Y, Posner R, Kim JH, et al. Experimental spinal cord compression by epidural neoplasm. Neurology. 1977;27:422–9.

63. Sorensen S, Helweg-Larsen S, Mouridsen H, et al. Effect of high-dose dexamethasone in carcinomatous metastatic spinal cord compression treated with radiotherapy: a randomized trial. Eur J Cancer. 1994;30A:22–7.

64. Loblaw DA, Perry J, Chambers A, Laperriere NJ. Systematic review of diagnosis and management of malignant extradural spinal cord compression: the cancer care Ontario practice guidelines initiative's neuro-oncology disease site group. J Neurooncol. 2005;23(9):2028–37.

65. Vecht CJ, Haaxma-Reiche H, van Putten WL, et al. Initial bolus of conventional versus high-dose dexamethasone in metastatic spinal compression. Neurology. 1989;39:1255–7.

66. Heimdal K, Hirschberg H, Slettebo H, Watne K, Nome O. High incidence of serious side effects of high-dose dexamethasone treatment in patients with epidural spinal cord compression. J Neurooncol. 1992;12:141–4.

67. Maranzano E, Latini P, Beneventi S, et al. Radiotherapy without steroids in selected metastatic spinal cord compression patients: a phase II trial. Am J Clin Oncol. 1996;19:179–83.

68. Siegal T. Spinal epidural involvement in haematological tumors: clinical features and therapeutic options. Leuk Lymphoma. 1991;5:101–10.

69. Cooper K, Bajorin D, Shapiro W, et al. Decompression of epidural metastasis from germ cell tumors with chemotherapy. J Neurooncol. 1990;8(3):275–80.

70. Barcena A, Lobato RD, Rivas JJ, Cordobes F, de Castro S, Cabrera A, et al. Spinal metastatic disease: analysis of factors determining functional prognosis and the choice of treatment. Neurosurgery. 1984;15:820–7.

71. Klimo P Jr, Kestle JR, Schmidt MH. Clinical trials and evidence-based medicine for metastatic spinal disease. Neurosurg Clin N Am. 2004;15:549–64.

72. Wu AS, Fourney DR. Evolution of treatment for metastatic spine disease. Neurosurg Clin N Am. 2004;15:401–11.

73. Helweg-Larsen S, Sorensen PS, Kreiner S. Prognostic factors in metastatic spinal cord compression: a prospective study using multivariate analysis of variables influencing survival and gait function in 153 patients. Int J Radiat Oncol Biol Phys. 2000;46:1163–9.

74. Helwig-Larsen S, Rasmussen B, Sorensen PS. Recovery of gait after radiotherapy in paralytic patients with metastatic epidural spinal cord compression. Neurology. 1990;40:1234–6.

75. Gagnon GJ, Nasr NM, Liao JJ, et al. Treatment of spinal tumors using CyberKnife fractionated stereotactic radiosurgery: pain and quality-of-life assessment after treatment in 200 patients. Neurosurgery. 2009;64:297–307.

76. Schultheiss TE. Spinal cord radiation tolerance. Int J Radiat Oncol Biol Phys. 1994;30:735–6.

77. Murakami H, Kawahara N, Yahata T, Yokoyama K, Komai K, Tomita K. Radiation myelopathy after radioactive iodine therapy for spine metastasis. Br J Radiol. 2006;79:e45–9.

78. Maddison P, Southern P, Johnson M. Clinical and MRI discordance in a case of delayed radiation myelopathy. J Neurol Neurosurg Psychiatry. 2000;69:563–4.

79. Wang PY, Shen WC, Jan JS. MR imaging in radiation myelopathy. Am J Neuroradiol. 1992;13:1049–55.

80. Michikawa M, Wada Y, Sano M, et al. Radiation myelopathy: significance of gadolinium-DTPA enhancement in the diagnosis. Neuroradiology. 1991;33:286–9.

81. Chow E, Danjoux C, Wong R, Szumacher E, Franssen E, Fung K, Finkelstein J, Andersson L, Connolly R. Palliation of bone metastasis: a survey of patterns of practice among Canadian oncologists. Radiother Oncol. 2000;56:305–14.

82. Wu JS, Wong RK, Lloyd NS, Johnston M, Bezjak A, Whelan T. Radiotherapy fractionation for the palliation of uncomplicated painful bone metastasis—an evidence-based practice guideline. BMC Cancer. 2004;4:71.

83. Rades D, Stalpers LJ, Schulte R, Veninga T, Basic H, Engenhart-Cabilic R, Schild SE, Hoskin PJ. Defining the appropriate radiotherapy regimen for metastatic spinal cord compression in non-small cell lung cancer patients. Eur J Cancer. 2006;42(8):1052–6.

84. Rades D, Stalpers LJ, Veninga T, et al. Evaluation of five radiation schedules and prognostic factors for metastatic spinal cord compression. J Clin Oncol. 2005;23:3366.

85. Marazano E, Bellavita R, Rossi R, et al. Short-course versus split-course radiotherapy in metastatic spinal cord compression: results of a phase III, randomized, multicenter trial. J Clin Oncol. 2005;23:3358.

86. Gersten PC, Burton SA, Ozhasoglu C, Welch WC. Radiosurgery for spinal metastases: clinical experience from 500 cases from a single institution. Spine. 2007;32:193–9.

87. Bate BG, Khan NR, Kimball BY, et al. Stereotactic radiosurgery for spinal metastases with or without separation surgery. J Neurosurg Spine. 2015;22:209–15.

88. Witham TF, Khavkin YA, Gallia GL, Wolinsky JP, Gokaslan ZL. Surgery Insight: current management of epidural spinal cord

compression from metastatic spine disease. Nat Clin Pract Neurol. 2006;2(2):87–94.

89. Laufer I, Iorgulescu JB, Chapman T, et al. Local disease control for spinal metastases following "separation surgery" and adjuvant hypofractionated or high-dose single-fraction stereotactic radiosurgery: outcome analysis in 186 patients. J Neurosurg Spine. 2013;18:207–14.

90. Kaloostian PE, Yurter A, Etame AB, et al. Palliative strategies for the management of primary and metastatic spinal tumors. Cancer Control. 2014;21:140–3.

91. Laufer I, Rubin DG, Lis E, et al. The NOMS framework: approach to the treatment of spinal metastatic tumors. Oncologist. 2013;18:744–51.

92. Fourney DR, Frangou EM, Ryken TC, et al. Spinal instability neoplastic score: an analysis of reliability and validity from the spine oncology study group. J Clin Oncol. 2011;29:3072–7.

93. Purkayastha S, Gupta AK, Kapilamoorthy TR, Kesavadas C, Thomas B, Krishnamoorth T, Bodhey NK. Percutaneous vertebroplasty in the management of vertebral lesions. Neurol India. 2005;53(2):167–73.

94. Huang TJ, Hsu RWW, Li YY, Cheng CC. Minimal access spinal surgery (MASS) in treating thoracic spine metastasis. Spine. 2006;31(16):1860–3.

95. Miller DJ, Lang FF, Walsh, GL, Abi-Said D, Wildrick DM, Gokaslan ZL. Coaxial double-lumen methylmethacrylate reconstruction in the anterior cervical and upper thoracic spine after tumor resection. J Neurosurg (Spine 2). 2000;92:181–90.

96. Fourney DR, Abi-Said D, Lang FF, McCutcheon I, Gokaslan ZL. Use of pedicle screw fixation in the management of malignant spinal disease: experience in 100 consecutive patients. J Neurosurg (Spine 1). 2001;94:25–37.

97. Oda I, Abumi K, Ito M, Kotani Y, Oya T, Hasegawa K, Minami A. Palliative spinal reconstruction using pedicle screws for metastatic lesions of the spine: a retrospective analysis of 32 cases. Spine. 2006;31(13):1439–44.

98. Mazel C, Hoffmann E, Antonietti P, Grunenwald D, Henry M, Williams J. Posterior cervicothoracic instrumentation in spine tumors. Spine. 2004;29(11):1246–53.

99. Patchell DA, Tibbs PA, Regine WF, Payne RP, Saris S, Kryscio RJ. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomized trial. Lancet. 2005;366(9486):643–8.

100. Chason JL, Walker FB, Landers JW. Metastatic carcinoma in the central nervous system and dorsal root ganglia. Cancer. 1963;16:781–7.

101. Costigan DA, Winkelman MD. Intramedullary spinal cord metastasis. A clinicopathological study of 13 cases. J Neurosurg. 1985;62:227–33.

102. Kalaycı M, Çağavi F, Güi S, Yenidünya S, Açıkgöz B. Intramedullary spinal cord metastasis: diagnosis and treatment— and illustrated review. Acta Neurochir (Wien). 2004;146:1347–54.

103. Connolly S, Winfree C, McCormick P, et al. Intramedullary spinal cord metastasis: report of three cases and review of the literature. Surg Neurol. 1996;46:329–39.

104. Schiff D, O'Neil BP. Intramedullary spinal cord metastasis: clinical features and treatment outcomes. Neurology. 1996;47:906–12.

105. Edelson RN, Deck MDF, Posner JB. Intramedullary spinal cord metastasis. Neurology. 1972;22:1222–31.

106. Grem JL, Burgess J, Trump D. Clinical features and natural history of intramedullary spinal cord metastasis. Cancer. 1985;56:2305–14.

107. Villegas AE, Guthrie TH. Intramedullary spinal cord metastasis in breast cancer: clinical features, diagnosis, and therapeutic consideration. Breast J. 2004;10(6):532–5.

108. Conill C, Sanchez M, Puig S, Planas I, Castel T. Intramedullary spinal cord metastasis and melanoma. Melanoma Res. 2004;14:431–3.

109. Aryan HE, Azadeh F, Nakaji P, Imbesi SG, Abshire BB. Intramedullary spinal cord metastasis of lung adenocarcinoma presenting as Brown-Sequard syndrome. Surg Neurol. 2004; 61(1):72–6.

110. Winkelman MD, Adelstein DJ, Karling NL. Intramedullary spinal cord metastasis: diagnosis and therapeutic considerations. Arch Neurol. 1987;44:526–31.

111. Siegal T, Siegal T. Spinal metastasis. In: Principles of neuro-oncology, 1st ed. USA: McGraw-Hill; 2005. p. 581–606.

112. Jawahar A, Kondziolka D, Graces YI. Stereotactic radiosurgery for hemangioblastomas of the brain. Acta Neurochir. 2000;142:641–4.