INTRODUCTION

Brain tumors encompass neoplasms that originate in the brain itself (primary brain tumors) or involve the brain as a metastatic site (secondary brain tumors). Primary brain tumors include tumors of the brain parenchyma, meninges, cranial nerves, and other intracranial structures (the pituitary and pineal glands).

Primary central nervous system lymphoma refers to non-Hodgkin lymphoma confined to the central nervous system (CNS). The site of origin of this type of tumor remains unknown.

Secondary brain tumors, which originate elsewhere in the body and metastasize to the intracranial compartment, are the most common types of brain tumors.

HISTOPATHOLOGIC CLASSIFICATION

Primary brain tumors are classified by light microscopy according to their predominant cell type and graded based upon the presence or absence of standard pathologic features.

The (World Health Organization) WHO classification system has combined a tumor nomenclature with an implied grading system so that the actual histologic diagnosis directly correlates with the histologic grade of the tumor. The most common histologies for neuroepithelial and meningeal brain tumors, along with a general estimate of the tumor grades involved in each category.

Gliomas, meningiomas, and embryonal tumors account for over 95 percent of primary intracranial neoplasms. Since there are multiple classification schemes, it is important to know what system or criteria are being used when a name is applied to a tumor, particularly glioma. Gliomas - account for over 80 percent of primary CNS malignancies and refers to tumors derived from glial cells (ie, astrocytes, oligodendrocytes, and ependymal cells).

Astrocytic tumors — The WHO system recognizes three levels of astrocytic tumors based upon histopathology.

1. **Astrocytomas** — These are low grade astrocytic tumors or gliomas with increased cellularity and atypia, but without mitoses, endothelial proliferation, or necrosis. Examples of these grade 1 and 2 gliomas include pilocytic astrocytomas, and diffuse astrocytomas.

2. **Anaplastic astrocytomas** — Anaplastic astrocytomas exhibit mitoses but no endothelial proliferation or necrosis. They are considered grade 3 astrocytomas.
3. **Glioblastomas** — Glioblastomas (the older term is glioblastoma multiforme or GBM) are grade 4 astrocytomas with high mitotic activity and either endothelial proliferation or necrosis.

Diffuse astrocytomas, the most common histologic subtype, can be subdivided further into three types — fibrillary, protoplasmic, and gemistocytic — but mixed forms can occur.

Pilocytic astrocytomas tend to occur in children and young adults and have a particular predilection for the cerebellar hemispheres. The prognosis for those tumors varies greatly, independent of histology.

The prognostic value of defining subcategories of gliomas based only upon mitotic activity, proliferation and/or necrosis is unclear.

**Oligodendroglial tumors** — appear on light microscopy as round cells with perinuclear halos (a "fried-egg" appearance) and an acutely branching (chicken-wire) capillary pattern. The WHO grading system recognizes separate categories of oligodendrogliomas and anaplastic (or "malignant") oligodendrogliomas; the latter tumors are characterized by increased cellularity, high mitotic rate, and pleomorphism. When such tumors manifest endothelial proliferation and/or necrosis, they are generally considered glioblastomas; ie, glioblastomas can arise from oligodendrogliomas as well as from astrocytomas.

**Mixed oligodendroglial and astrocytic tumors** — Oligodendrogliomas and astrocytomas are not mutually exclusive; some tumors have areas more suggestive of oligodendroglioma and other areas resembling astrocytoma. Consequently, both oligoastrocytomas and anaplastic oligoastrocytomas (sometimes called mixed anaplastic gliomas) are well recognized.

**Ependymal tumors** — arise from ependymal cells lining the ventricular system. They are generally considered low-grade tumors. High cellularity and the presence of mitoses warrant the designation "anaplastic ependymoma." It remains controversial whether anaplastic ependymomas have a markedly worse prognosis than typical ependymomas.

**Medulloblastomas** — are small, blue, round cell embryonal tumors typically arising in children in the roof of the fourth ventricle. Histologically identical tumors arise elsewhere in the brain and, depending upon their location, may be called pineoblastomas, neuroblastomas, or ependymoblastomas.

**Meningiomas** — Meningiomas arise from the arachnoidal cap cell. As with gliomas, varying grades of malignancy within meningiomas are recognized. In addition to the histologically benign meningioma occasional tumors are termed atypical and others malignant (or anaplastic).

- Atypical meningiomas have increased mitotic activity (more than four mitoses per 10 high power fields [HPFs]), or three or more of the following features:
  - Increased cellularity, small cells with high nuclear to cytoplasmic ratio
  - Prominent nucleoli, uninterrupted patternless or sheet-like growth
Foci of spontaneous or geographic necrosis.

- Anaplastic (malignant) meningiomas exhibit histological features of frank malignancy far in excess of the abnormalities present in atypical meningioma.

Both atypical and malignant meningiomas are more prone to recur following resection than the histologically benign tumors.

**MOLECULAR CLASSIFICATION** — The formation of brain tumors involves an accumulation of lesions in genes important for the regulation of cell proliferation, differentiation, and death. As with other types of cancer, both oncogenes and tumor suppressor genes play critical roles in the pathogenesis of glioma.

Glioblastoma may arise de novo (primary GBM), usually in older patients, or evolve from a low-grade glioma (secondary GBM) in younger patients. The observed molecular abnormalities differ in these two settings. Genetic abnormalities have also been associated with other types of brain tumor.

**INCIDENCE OF PRIMARY BRAIN TUMORS**

Incidence estimates differ depending upon the inclusion or exclusion of benign brain tumors and upon quality of reporting. In 2009, the American Cancer Society estimates there will have been approximately 22,070 new primary brain tumor cases in the United States but includes only malignant subtypes. The Central Brain Tumor Registry of the United States (CBTRUS) data reported 98,990 new cases of both malignant and benign brain tumors during a two year period (2004 to 2005). The annual incidence of primary brain cancer for all races from 2004 to 2005 was 18.2 per 100,000 person-years. The incidence rates of all primary non-malignant brain tumors ranged from 6.31 to 16.68 per 100,000 person-years, and incidence rates of all primary malignant brain tumors ranged from 4.52 to 8.84 per 100,000 person-years across 44 cancer registries included in the CBTRUS statistical report.

**Mortality and prognostic factors** — Although brain tumors account for only 2 percent of all cancers and are about one-fifth as common as breast or lung cancer, these neoplasms result in a disproportionate share of cancer morbidity and mortality. The annual age-adjusted mortality rate for malignant brain cancer in the United States (1997 to 2001) was 4.6 per 100,000 person-years. Including all ages and all races, the five-year survival rate for malignant brain tumors was 33 percent.

For all histologic types, pediatric and young adult populations have a better survival than do older adults. As an example, for all primary malignant brain tumors combined, the five year survival rate among children under age 14 is 62 percent, compared to 4.9 percent in adults 65 years of age and older. The five-year survival rates for the most common histologic subtypes, anaplastic astrocytoma and glioblastoma (glioblastoma multiforme, GBM), are 30 percent and 3.3 percent, respectively.
In general, young age, high performance status, and lower pathologic grade are favorable prognostic factors for primary brain tumors. Less significant predictors of favorable prognosis include long duration of symptoms, absence of mental changes at time of diagnosis, cerebellar location of tumor, small preoperative tumor size, and completeness of surgical resection.

**Gender** — There is a slight male predominance in the incidence of malignant brain tumors (8.0 versus 5.5 per 100,000 person-years for women in the years 1997 to 2001). However, when both malignant and benign tumor types are examined, the disparity between the sexes is less apparent (between 2004 to 2005, males accounted for 44 percent and females for 56 percent of cases). This difference is primarily explained by the higher incidence of meningiomas in women (7.8 versus 3.5 per 100,000 person-years in men).

**Race** — Caucasians tend to have a higher incidence of malignant brain tumors compared to blacks for both genders (8.8 versus 4.9 per 100,000 person-years in men, and 6.1 versus 3.2 per 100,000 person-years in women). In general, malignant brain tumors are less common among Asian Americans and Native Americans, while the incidence of malignant brain tumors in Hispanics is intermediate between that in Caucasians or African Americans.

In contrast, incidence rates for meningiomas do not vary substantially by race (6.9 per 100,000 person-years in non-Hispanic blacks, 6.1 per 100,000 person-years in non-Hispanic whites, and 6.5 per 100,000 person-years in Hispanics).

**Age** — The incidence of brain tumors varies with age and the specific histology. Data compiled from several tumor registries suggest a peak incidence of all primary brain tumors around age 50, although autopsy series suggest that incidence rises continuously with increasing age. Most intracranial tumors occur in people older than 45 years of age. Glioblastoma rarely occurs before the age of 15 but dramatically increases after the age of 45. In contrast, medulloblastoma, and other embryonal tumors are uncommon after the age of 20.

**Adults** — In adults, gliomas (principally astrocytoma) account for approximately 50 percent and meningioma 25 to 30 percent of symptomatic primary brain tumors. The incidence of meningioma increases to 40 percent when neuroimaging studies are included because of the large number of asymptomatic tumors. Pituitary tumors account for 10 to 20 percent, primary central nervous system lymphoma for 3 to 5 percent, and craniopharyngioma for 1 to 3 percent.

**Children** — In children under the age of 15, brain tumors are the most common solid malignancy and the second leading cause of cancer death after leukemia. Brain cancer rates are approximately 2 to 2.5 per 100,000 per year. The male-to-female ratio is approximately 1.2:1.

Pediatric brain tumors occur in the following distribution.

- Medulloblastoma — 20 to 25 percent
- Low-grade supratentorial astrocytoma — 20 to 25 percent
- Cerebellar astrocytoma — 10 percent
- High-grade supratentorial astrocytoma — 10 percent
• Brainstem glioma — 10 percent 
• Ependymoma — 10 percent 
• Craniopharyngioma — 5 to 10 percent 

Temporal trends — Multiple studies have documented rising incidence rates for brain tumors in several industrialized countries; this increase seems to be confined mainly to the elderly population, with no clear ethnic, gender or geographic differences.

The precise etiology of this increase in brain tumor incidence remains unclear.

The introduction of noninvasive diagnostic technology including magnetic resonance imaging (MRI) in the 1980s, the improvement in health care access for the elderly population improved and an increase in the availability of neurologists may have made a difference.

PATHOGENESIS — Tumor-related disruption in the blood brain barrier is caused by two major mechanisms:

The local production of factors that increase the permeability of tumor vessels such as vascular endothelial growth factor, glutamate, and leukotrienes. The absence of tight endothelial cell junctions in tumor blood vessels. These vessels develop in response to angiogenic factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor. VEGF is responsible for the loss of integrity of the blood brain barrier in brain tumors. VEGF stimulates the formation of gaps in the endothelium, a process that leads to fluid leakage into the brain parenchyma, thereby resulting in vasogenic edema. Vasogenic edema tends to spread more readily in the extracellular space of white matter rather than gray matter. Tumor-related edema may disrupt synaptic transmission, alter neuronal excitability, and contribute to headaches, seizures, focal neurologic deficits, and encephalopathy.

GLUCOCORTICOIDS — Most patients with brain tumors and peritumoral edema can be managed with glucocorticoids and are indicated in all patients who have symptomatic peritumoral edema. Reduction of intracranial pressure and improvement in neurologic symptoms usually begins within minutes to hours of treatment. A decrease in capillary permeability can be identified within six hours and changes of diffusion-weighted MRI indicating decreased edema are identifiable within 48 to 72 hours. However, adequate reduction in elevated ICP resulting from peritumoral edema may take several days with glucocorticoid therapy alone, and additional treatment may be required in the initial management of these patients.

Dexamethasone is the standard glucocorticoid agent, because its relative lack of mineralocorticoid activity and it reduces the potential for total body fluid retention. The mechanism of action of glucocorticoids for control of vasogenic edema is not fully understood but has been shown to upregulate Ang-1, a strong BBB-stabilizing factor and downregulates VEGF, a strong permeabilizing factor, in astrocytes and pericytes.
Dose and schedule — In patients with severe symptoms, the usual dexamethasone regimen consists of a 10 mg loading dose, followed by 4 mg four times per day and lower doses (1 to 2 mg four times per day) for patients without impending herniation. Although dexamethasone is typically administered in four divided daily doses, its biological half-life is sufficiently long to allow twice daily dosing and this approach is often used for maintenance therapy.

Complications — Despite the beneficial effect of glucocorticoids, they are associated with a large number of well known side effects. The frequency of these complications can be reduced by using the lowest possible dose. Common complications include insomnia, essential tremor, and hiccups. Three complications are of particular concern to patients with brain tumors: gastrointestinal complications, steroid myopathy, and opportunistic infections such as Pneumocystis carinii pneumonia.

Gastrointestinal complications — Glucocorticoids increase the risk of gastrointestinal complications such as gastritis or peptic ulcer disease, especially when used in conjunction with other drugs such as nonsteroidal antiinflammatory agents (NSAIDs). Concurrent anticoagulation therapy and a prior history of peptic ulcer disease are other factors that can increase the likelihood of gastrointestinal bleeding in patients receiving glucocorticoids.

The effectiveness of prophylactic therapy to prevent peptic ulceration in patients with brain tumors is unknown. In NSAID-treated patients, proton pump inhibitors can protect against both gastric and duodenal ulcerations. Standard doses of H2 blockers are not effective for the prevention of NSAID-induced gastric ulcers.

We usually restrict prophylactic therapy with a proton pump inhibitor to the perioperative period and to patients receiving very high doses of glucocorticoids. For other patients, prophylactic therapy is probably unnecessary unless they are at high risk for developing peptic ulceration (eg, previous peptic ulcer disease, concurrent anticoagulation, NSAID therapy). When NSAIDs are necessary, use of a selective COX-2 inhibitor or misoprostol appears to reduce the risk of gastrointestinal complications.

Steroid myopathy — Glucocorticoid-induced myopathy contributes significantly to morbidity in patients with brain tumors. Myopathy is a common complication, with an estimated incidence between 2 and 20 percent. The risk of developing steroid myopathy appears to be significantly lower in patients taking phenytoin, possibly due to induction of hepatic metabolism of dexamethasone by phenytoin.

The majority of patients develop proximal weakness between the ninth and twelfth weeks of glucocorticoid treatment, although there is marked variation in individual susceptibility. Some patients become weak after a low dose of glucocorticoids for a few weeks, while others never develop myopathy despite receiving large doses of glucocorticoids for months or years. The onset is usually subacute, occurring over several weeks. Muscle pain is not a feature and tendon reflexes are preserved.
Treatment of steroid myopathy is difficult. Ideally, glucocorticoids should be discontinued but the lowest possible dose should be used if this is not feasible. Recovery after discontinuation of glucocorticoid therapy can be expected within two to three months but may be much slower if treatment is continued, even at a reduced dose.

Another treatment approach is to change the glucocorticoid preparation. Steroid myopathy has been particularly associated with the use of fluorinated glucocorticoids such as dexamethasone. Although the evidence supporting this relationship is not strong, anecdotal reports suggest that weakness that develops during treatment with a fluorinated glucocorticoid may improve when equivalent doses of a nonfluorinated preparation are substituted. Some reports indicate that growth hormone, insulin-like growth factor-1 and amino acid supplementation, may ameliorate the weakness of steroid myopathy.

**Pneumocystis carinii pneumonia** — Pneumocystis carinii pneumonia (PCP) is a life-threatening opportunistic infection that occurs in immunocompromised hosts, including patients with brain tumors treated with glucocorticoids. The risk of symptomatic PCP infection is increased while glucocorticoids are being tapered. Concurrent chemotherapy may be an additional risk factor for the development of PCP.

The mechanism by which glucocorticoids predispose to the development of PCP is poorly understood, but suppression of cellular immunity leading to reactivation of latent infection probably plays a role. Although the hallmark of PCP is fever and dyspnea with or without a prominent dry cough, the presentation can be subtle and nonspecific. Thus, the diagnosis should be considered in any patient developing respiratory symptoms.

Because of the risk of PCP and its associated morbidity and mortality, we suggest PCP prophylaxis in patients who are receiving prolonged (more than six weeks) courses of glucocorticoids, especially as steroid therapy is withdrawn.

**ACUTE TREATMENT OF ELEVATED ICP** — A significant increase in ICP can be a medical emergency, and treatment should be undertaken as expeditiously as possible. Although glucocorticoids are an important component of therapy, additional interventions may be required.

**Spinal cord tumors and metastases**

**INTRODUCTION** — Spinal cord tumors can occur within or adjacent to the spinal cord. They are considered to be intraaxial in location and can be either primary or metastatic. Primary spinal cord tumors account for 2 to 4 percent of all primary central nervous system (CNS) tumors, one-third of which are located in the intramedullary compartment.

Spinal cord tumors are classified according to their anatomic location.

- Intramedullary — Intramedullary tumors arise within the spinal cord itself. Most primary intramedullary tumors are either ependymomas or astrocytomas.
Metastases are being recognized with increasing frequency, primarily because of improvements in imaging modalities.

- Intradural-extramedullary — Tumors arising within the dura but outside the actual spinal cord are termed intradural-extramedullary. The most common tumors in this group are meningiomas and nerve sheath tumors.
- Extradural — Extradural tumors are usually metastatic and most often arise in the vertebral bodies. Metastatic lesions can cause spinal cord compression either by epidural growth that results in extrinsic spinal cord or cauda equina compression or less frequently by intradural invasion.

PRESENTATION

Symptoms — Tumors within or extrinsic to the spinal cord can cause symptoms through disruption of normal neural elements and pathways, producing both local and distal effects. The most frequent local effect is pain that causes nocturnal awakening. Patients often describe this pain as a gnawing and unremitting. The site of this may provide an indication of the anatomic location of the tumor.

Neurologic dysfunction distal to the lesion is due to interruption of ascending and descending spinal cord pathways. The most common sequelae are sensory dysesthesias and muscular weakness, especially of the iliopsoas musculature. Patients often report progressive difficulty in ambulation. Severe distal sensory loss and sphincter dysfunction also may occur. Although neurologic manifestations may begin unilaterally, they can progress to involve both sides of the spinal cord and thereby produce bilateral symptoms and signs.

History — A prior history of cancer may suggest a diagnosis of metastasis to the spinal column, which may cause axial or radiating pain.

Physical examination — A thorough physical examination is necessary to define probable sites of tumor involvement, document preoperative neurologic deficits, and determine progressive neurologic deterioration. An assessment of the patient’s ambulatory status is also necessary since this carries important prognostic significance.

Imaging — Magnetic resonance imaging (MRI) of the spine is currently the diagnostic study of choice, providing excellent delineation of the spinal cord and surrounding structures. Almost all intrinsic spinal cord tumors and metastases enhance with gadolinium.

INTRAMEDULLARY TUMORS — The majority of intramedullary primary spinal cord tumors are gliomas. The major types of glial tumors are ependymomas, astrocytomas, and oligodendrogliomas, and mixtures of these cell types are occasionally seen within a single tumor. Spinal cord gliomas are rare compared to cerebral lesions, probably because of the relative paucity of glial tissue in the spinal cord. Ependymomas comprise approximately 60 to 80 percent of spinal gliomas compared to 3 percent of intracranial gliomas.
Ependymomas — Ependymomas are intramedullary tumors that may be located anywhere along the spinal cord. Approximately one-half occur in the lumbosacral spinal cord or filum terminale; the other 50 percent occur anywhere in the cervical or thoracic spinal cord. Extraneural metastases are uncommon.

Ependymoma — Ependymomas are the most common intramedullary tumors in adults, with a peak age at presentation between 30 and 40 years. They tend occur centrally within the cord, expanding it symmetrically as they grow. The spinal cord may be expanded along several segments, and a tumor-associated cyst (syrinx) is common. These lesions generally enhance intensely on MRI.

Optimal management consists of gross total resection by an experienced surgeon. Although these are infiltrative tumors, a total or near-total resection can frequently be achieved without causing further neurologic deficits. There are no randomized trials that have evaluated the role of adjuvant RT.

There is no proven role for chemotherapy in recurrent or metastatic spinal cord ependymomas.

Myxopapillary ependymoma — Myxopapillary ependymomas are biologically and morphologically distinct from other ependymomas. These tumors most commonly arise in the lumbosacral spinal cord and filum terminale. Myxopapillary ependymomas are slow-growing glial tumors that typically are found in young adults and are more common in males.

Initial management of these tumors consists of laminectomy with attempted surgical resection. These tumors frequently can be totally resected, and many patients are cured following gross total resection. However, some patients recur locally or with leptomeningeal tumor dissemination as much as 20 years after the initial surgery. Subtotal resection may be necessary, particularly in patients with unencapsulated tumors. In such cases, survival may still be prolonged. Multivariate analysis showed a statistically significant decrease in the incidence of recurrence in those receiving high-dose postoperative RT (≥50 Gy).

Anaplastic ependymoma — These high-grade ependymomas have anaplastic features on histological examination (necrosis, mitosis, vascular proliferation, cellular pleomorphism, and overlapping of nuclei). These tumors are relatively uncommon and comprised only 5 percent of spinal ependymomas in one large series. Compared to lower grade ependymomas, anaplastic tumors appear to have a higher recurrence rate and poorer survival.

Astrocytomas — Astrocytomas occur throughout the spinal cord. The pathologic features of spinal astrocytic lesions are predictive of the biologic behavior and clinical course. Approximately one-half of spinal cord astrocytomas are pilocytic and one-half are infiltrative astrocytomas.
Pilocytic astrocytomas are well circumscribed and low grade with nonaggressive clinical behavior.

Diffuse fibrillary astrocytomas of the spinal cord usually appear as nonencapsulated lesions that enhance minimally or heterogeneously on MRI. About one-third are histologically high-grade.

There are no randomized trials defining the optimal approach to the management of these tumors.

Management of ependymomas and astrocytomas — The initial step in the management of a patient with a presumed primary intramedullary spinal cord tumor is resection to the maximum extent possible. A total or near-total resection can frequently be achieved without causing further neurologic deficits.

Given the rarity of spinal cord diffuse fibrillary astrocytomas, there are no randomized trials to guide recommendations for subsequent treatment. Our approach is to use fractionated RT for low-grade tumors that are incompletely resected and for all high-grade tumors. There is no established role of chemotherapy in the initial management of these patients.

Metastases — Intramedullary spinal cord metastases are rare, although the increased use of MRI has resulted in more frequent recognition of such lesions. About one-half of cases are associated with lung cancer. Breast cancer, renal cell carcinoma, lymphoma, and melanoma are other tumor sites that metastasize to the spinal cord.

Intramedullary metastases are usually observed in patients with widespread metastatic disease. The majority of patients also have brain and lung metastases, while leptomeningeal metastases are seen in approximately 25 percent. MRI is generally diagnostic and a CT-myelogram can be useful in patients who cannot undergo MRI.

Management of intramedullary metastases generally consists of fractionated RT, which usually maintains but does not improve the pretreatment level of neurologic function. As with the treatment of brain metastases and epidural spinal cord compression, corticosteroids are used to diminish the effects of radiation-induced edema until RT is completed.

INTRADURAL EXTRAMEDULLARY TUMORS — Both meningiomas and nerve sheath tumors (schwannomas and neurofibromas) can develop in the intradural extramedullary spinal compartment.

Meningioma — Meningiomas can arise from arachnoidal cells anywhere along the neuraxis. They are occasionally found in association with neurofibromatosis. Approximately 90 percent of the tumors occur within the cranial fossa.

Spinal meningiomas most commonly occur within the thoracic spine. The tumors are frequently adherent to the spinal dura, requiring dural resection for complete removal, and also grow along intradural and extradural components of the nerve roots.
Spinal meningiomas are typically slowly growing, invasive lesions and often erode bone. Pathologically, spinal meningiomas demonstrate the same features seen with intracranial lesions.

The usual treatment for spinal meningiomas is resection, and complete resection can often be achieved. The dural origin is generally cauterized and occasionally resected. Thoracic spinal roots may be sacrificed as necessary to obtain a complete resection; cervical and lumbar nerve roots are preserved whenever possible.

Nerve sheath tumors — Nerve sheath tumors constitute about 25 percent of tumors arising in the intradural extramedullary space.

EXTRADURAL PRIMARY TUMORS — The most common tumors arising in the extradural space are metastases. Several uncommon primary tumors can also arise in the extradural space.

Metastases — Metastatic tumor from any primary site can involve the epidural area and can cause epidural spinal cord compression. The three most common primary tumors are prostate cancer, breast cancer, and lung cancer. The clinical features and management of this complication are discussed separately.

Chordomas — Chordomas are rare bone tumors that are locally invasive, frequently recur, and are relatively radioresistance. The tumors are remnants of the primitive notochord and may occur at the skull base (35 percent), cervical, thoracic and lumbar spine (15 percent), and sacral regions (50 percent).

• Surgery and RT — Treatment of chordomas arising in the spine consists of wide local excision when possible. However, many chordomas are not amenable to complete resection.

Sarcomas — Sarcomas arise from mesenchymal elements and may erode into the bony spine. Rarely, they can arise directly from bony elements of the spine. These lesions usually occur in younger patients, and are treated with a multimodality approach that includes surgery, radiotherapy and chemotherapy.

• Bone sarcomas, particularly osteosarcomas, may develop in patients with polyostotic Paget disease (pagetic sarcoma). This is a rare anaplastic malignancy with a peak incidence in the seventh and eighth decades of life. Paget’s osteosarcomas are usually sclerotic lesions, occasionally blastic. Treatment usually consists of vertebrectomy, followed by chemotherapy and radiation. The prognosis of this tumor is poor.
• Chondrosarcoma is a malignant tumor of cartilage in which the matrix is entirely chondroid in nature. The presence of discrete calcified opacities is a radiographic hallmark of these lesions. Chondrosarcomas of the spine are relatively infrequent (5 percent of all spinal tumors). They typically originate in the vertebral body and extend into the adjacent soft tissue and spinal canal.
These tumors have a predilection for the lower thoracic and lumbar regions. Surgery is the primary treatment for chondrosarcomas. RT and chemotherapy play a minor role and are only used in high-grade chondrosarcomas.

- **Leiomyosarcoma** is a malignant mesenchymal tumor composed predominantly of spindle cells that exhibit smooth muscle differentiation. Primary leiomyosarcoma of the bone is extremely rare.
- **Ewing sarcoma** is a small round cell tumor, which can arise in bone or soft tissue.

**Lymphoma** — Lymphomatous involvement of the spine is most often due to metastatic disease but occasionally can represent primary disease. Treatment can include surgery, radiotherapy, and chemotherapy.

**Plasmacytomatas and multiple myeloma** — The spine can be the initial site of involvement for plasma cell neoplasms. Although plasmacytomatas can be solitary, these lesions more commonly are part of a diffuse process.

**Benign lesions** — Benign lesions can arise in the spine and must be differentiated from malignant tumors:

- **Osteoid osteomas** — Osteoid osteomas are small lesions (<2 cm) that typically arise in long bones, although about 10 percent occur in the spine. Conservative management with salicylates is often sufficient.
- **Osteoblastomas** — Osteoblastomas are larger lesions (>2 cm) that also typically occur in young men. Because of their size, these lesions tend to cause neurologic symptoms. Although benign, these lesions tend to recur and generally are managed surgically.
- **Osteochondromas** — Osteochondromas are benign lesions that account for less than 4 percent of spinal tumors. These lesions consist of both healthy bone and a cartilaginous cap. Biologic behavior varies, and surgery should be considered only for lesions producing symptoms. The most important complication is malignant degeneration to a peripheral chondrosarcoma, the risk of which is less than 1 percent.
- **Chondroblastomas** — Chondroblastomas are tumors arising in bone and comprised of immature cartilage; only rarely have these been reported to arise in the spine.
- **Giant-cell tumors** — Giant-cell tumors comprise 4 to 8 percent of all primary bone tumors; up to 10 percent may arise in the spine, particularly in younger individuals. Giant-cell tumors tend to be larger, very vascular, and have a high frequency of recurrence.
- **Vertebral hemangiomas** — Vertebral hemangiomas are nonneoplastic lesions that are composed of thin-walled blood vessels. Typically these are an incidental finding in the spine, and only rarely produce symptoms.
- **Aneurysmal bone cysts** — Aneurysmal bone cysts are nonneoplastic, expansile lesions, which account for up to 15 percent of primary spine tumors. These lesions tend to be locally aggressive with a substantial potential for neurologic compromise. Thus early surgical resection and spinal stabilization is generally required.
SUMMARY AND RECOMMENDATIONS

Tumors affecting the spinal cord can be classified as intramedullary, extramedullary intradural, or extradural. The most common intramedullary tumors include ependymomas, pilocytic astrocytomas, and diffuse fibrillary astrocytomas. Myxopapillary ependymomas constitute a distinct subset of ependymomas that occur almost exclusively in the conus medullaris and filum terminale of the spinal cord.

Maximal surgical resection is the initial step in the management of patients with intramedullary spinal cord tumors. For patients with low or intermediate grade (WHO I or II) intramedullary glial tumors in whom the initial surgery results in a complete resection, we suggest observation rather than adjuvant radiation therapy (RT). For patients in whom complete resection has not been possible (ie, biopsy only or incomplete resection), we suggest postoperative adjuvant RT. Observation may be a reasonable alternative for individual patients based upon a consideration of particular details.

The most common intradural, extramedullary tumors are meningiomas and nerve sheath tumors. The presentation and management of these tumors is discussed separately. The vast majority of tumors occurring in the extradural space are metastases. These tumors are particularly important because of the risk of epidural spinal cord compression. The clinical features and management of this complication are discussed separately.

Neoplastic meningitis

Neoplastic meningitis (NM) is the result of multifocal seeding of the leptomeninges by malignant cells. It occurs in 3% to 8% of all cancer patients and is becoming more common as cancer patients live longer. NM results in significant morbidity, and median survival is short despite therapy. Autopsy studies show that 19% of patients with cancer and neurologic signs and symptoms have evidence of meningeal involvement.

Epidemiology

NM is diagnosed in 4% to 15% of patients with solid tumors (termed carcinomatous meningitis), 5% to 15% of patients with leukemia (leukemic meningitis) and lymphoma (lymphomatous meningitis), and 1% to 2% of patients with primary brain tumors. Autopsy studies show that 19% of patients with cancer and neurologic signs and symptoms have evidence of meningeal involvement. Adenocarcinoma is the most frequent histology, and breast, lung, and melanoma are the most common primary sites to metastasize to the leptomeninges. Although small cell lung cancer and melanoma have the highest rates of spread to the leptomeninges (11% and 20%, respectively) because of the higher incidence of breast cancer (with a 5% rate of spread), the latter accounts for most cases in large series of the disorder. Carcinomas of unknown primary constitute 1% to 7% of all cases of NM. NM usually presents in patients with widely disseminated and progressive systemic cancer (>70%), but it can present after a disease-free interval (20%) and even be the first manifestation of cancer (5%-10%), occasionally in the absence of other evidence of systemic disease.
Pathogenesis
Cancer cells reach the meninges by various routes: (1) hematogenous spread, either through the venous plexus of Batson or by arterial dissemination; (2) direct extension from contiguous tumor deposits; (3) and through centripetal migration from systemic tumors along perineural or perivascular spaces.

Once cancer cells have entered the subarachnoid space, cancer cells are transported by cerebrospinal fluid (CSF) flow, resulting in disseminated and multifocal neuraxis seeding of the leptomeninges. Tumor infiltration is most prominent at the base of brain (specifically the basilar cisterns), the dorsal surface of the spinal cord, and, in particular, the cauda equine. Hydrocephalus or impairment of CSF flow may occur due to ependymal nodules or tumor deposits obstructing CSF outflow, particularly at the level of the fourth ventricle, basal cisterns, cerebral convexity, or spinal subarachnoid space.

Clinical Features
Leptomeningeal carcinomatosis classically presents with multiple clinical manifestations encompassing symptoms and signs in 3 domains of neurologic function:

1. Cerebral hemispheres - dysfunction are headache and mental status changes. Other signs include confusion, dementia, seizures, and hemiparesis
2. Cranial nerves - diplopia is the most common symptom of cranial nerve dysfunction, with cranial nerve VI being the most frequently affected, followed by cranial nerves III and IV. Trigeminal sensory or motor loss, cochlear dysfunction, and optic neuropathy are also common findings.
3. Spinal cord and roots - weakness (lower extremities more often than upper), dermatomal or segmental sensory loss, and pain in the neck, back, or following radicular patterns.

Overall, the finding of multifocal neuraxis disease in a patient with known malignancy is strongly suggestive of neoplastic meningitis.

CSF Examination
The most useful laboratory test in the diagnosis of NM is the CSF examination. Abnormalities include which, though suggestive of NM, are not diagnostic:

- Increased opening pressure (>20 cm of H₂O)
- Increased leukocytes (>4/mm³)
- Elevated protein (>50 mg/dL)
- Decreased glucose (<60 mg/dL)

The presence of malignant cells in the CSF is diagnostic of NM. In patients with positive CSF cytology, up to 45% will be cytologically negative on initial examination. The yield is increased to 80% with a second CSF examination, but little benefit is obtained from repeat lumbar punctures after 2 punctures.
The low sensitivity of CSF cytology makes it difficult not only to diagnose NM but also to assess the response to treatment. Biochemical markers, immunohistochemistry, and molecular biology techniques applied to CSF have been explored in an attempt to find a reliable biologic marker of disease.

Numerous biochemical markers have been evaluated, but, in general, their use has been limited by poor sensitivity and specificity. Particular tumor markers such as CEA (carcinoembryogenic antigen) from adenocarcinomas, and AFP (α-fetoprotein), and β-HCG (β-human chorionic gonadotropin) from testicular cancers and primary extragonadal CNS tumors can be relatively specific for NM when elevated in CSF in the absence of markedly elevated serum levels. Nonspecific tumor markers such as CK-BB (creatine-kinase BB isoenzyme), TPA (tissue polypeptide antigen), β₂ microglobulin, β-glucuronidase, LDH isoenzyme-5, and more recently VEGF (vascular endothelial growth factor) can be strong indirect indicators of NM but none are sensitive enough to improve the cytologic diagnosis. The use of these biochemical markers can be helpful as adjunctive diagnostic tests and, when followed serially, to assess response to treatment. Occasionally, in patients with clinically suspected NM and negative CSF cytology, they may support the diagnosis of NM.

Use of monoclonal antibodies for immunohistochemical analysis in NM does not significantly increase the sensitivity of cytology alone. However, in the case of leukemia and lymphoma, antibodies against surface markers can be used to distinguish between reactive and neoplastic lymphocytes in the CSF.

Cytogenetic studies have also been evaluated in an attempt to improve the diagnostic accuracy of NM. Flow cytometry and DNA single cell cytometry, techniques that measure the chromosomal content of cells, and fluorescent in situ hybridization (FISH) that detects numerical and structural genetic aberrations as a sign of malignancy can give additional diagnostic information but still have a low sensitivity. Polymerase chain reaction (PCR) can establish a correct diagnosis when cytology is inconclusive, but the genetic alteration of the neoplasia must be known for it to be amplified with this technique, and this is generally not the case, particularly in solid tumors.

In cases where there is no manifestation of systemic cancer and CSF examinations remain inconclusive, a meningeal biopsy may be diagnostic. The yield of this test increases if the biopsy is taken from an enhancing region on MRI.

Neuroradiographic Studies
Magnetic resonance imaging with gadolinium enhancement (MR-Gd) is the technique of choice to evaluate patients with suspected leptomeningeal metastasis. Because NM involves the entire neuraxis, imaging of the entire CNS is required in patients considered for further treatment. T1-weighted sequences, with and without contrast, combined with fat suppression T2-weighted sequences, constitute the standard examination.
MRI has been shown to have a higher sensitivity than cranial contrast enhanced computed tomography (CE-CT) in several series and is similar to computed tomographic myelography (CT-M) for the evaluation of the spine but significantly better tolerated.

Any irritation of the leptomeninges will result in their enhancement on MRI, which is seen as a fine signal-intense layer that follows the gyri and superficial sulci. Subependymal involvement of the ventricles often results in ventricular enhancement. Lumbar puncture itself can rarely cause a meningeal reaction, leading to dural-arachnoidal enhancement, so imaging should be obtained preferably prior to the procedure. MR-Gd still has a 30% incidence of false-negative results so that a normal study does not exclude the diagnosis of NM. On the other hand, in cases with a typical clinical presentation, abnormal MR-Gd alone is adequate to establish the diagnosis of NM.

Prognosis
The median survival of untreated patients with NM is 4 to 6 weeks, and death generally occurs due to progressive neurologic dysfunction. Treatment is intended to improve or stabilize the neurologic status, maintain neurologic quality of life, and prolong survival. Fixed neurologic defects are rarely improved with treatment, but progression of neurologic deterioration may be halted in some patients and median survival can be increased to 4-6 months.

Treatment
The evaluation of treatment of NM is complicated by the lack of standard treatments, the difficulty of determining response to treatment given the suboptimal sensitivity of the diagnostic procedures and that most patients will die of systemic disease, and the fact that most studies are small, nonrandomized, and retrospective. However, it is clear that treatment of NM can provide effective palliation and in some cases result in prolonged survival. Treatment requires the combination of surgery, radiation, and chemotherapy.

Supportive Care
Not all patients with NM are candidates for the aggressive treatment. Most authors agree that combined-modality therapy should be offered to patients with life expectancy greater than 3 months and a Karnofsky performance status of greater than 60%. Supportive care should be offered to every patient, regardless of whether they receive NM directed therapy. These therapies include anticonvulsants for seizure control (seen in 10%-15% of patients with NM), adequate analgesia with opioid drugs as needed, as well as antidepressants and anxiolytics if necessary. Corticosteroids have a limited use in NM-related neurologic symptoms but can be useful to treat vasogenic edema associated with intraparenchymal or epidural metastases or for the symptomatic treatment of nausea and vomiting, together with routine antiemetics. Decreased attention and somnolence secondary to whole-brain radiation can be treated with psychostimulants.
Paraneoplastic syndromes

INTRODUCTION — Paraneoplastic neurologic syndromes are a heterogeneous group of neurologic immune mediated disorders that may affect any part of the nervous system from cerebral cortex to neuromuscular junction and muscle.

PATHOGENESIS — The pathogenesis of paraneoplastic neurologic syndromes is not completely understood but, immunologic factors are believed to be important because antibody and T-cell responses against nervous system antigens have been described for many of these disorders. The immunologic response is directed against shared antigens that are expressed by the tumor, but otherwise exclusively expressed by the nervous system. For unknown reasons, the immune system identifies these antigens as foreign and mounts an immune attack against them.

Antibodies can be detected in the serum and cerebrospinal fluid (CSF) of many, but not all, patients with paraneoplastic syndromes and, as will be described for the individual disorders, are highly suggestive of one or a restricted group of syndromes and types of tumors. Antibodies with a direct pathogenic effect have only been found in four disorders of the peripheral nerve or neuromuscular junction. These antibodies are not truly paraneoplastic antibodies, as they can also occur in the non-paraneoplastic setting. These include:

1. P/Q type voltage-gated calcium channel antibodies in the Lambert-Eaton myasthenic syndrome (LEMS)
2. Acetylcholine receptor antibodies in myasthenia gravis
3. Voltage-gated potassium channel antibodies in neuromyotonia
4. Ganglionic acetylcholine receptor antibodies in autonomic neuropathy
5. Recoverin antibodies in carcinoma associated retinopathy

Autoantibodies may also play an important role in other paraneoplastic syndromes such as the stiff person syndrome and dermatomyositis. The role of autoantibodies in the pathogenesis of these disorders is the rationale for the recent use of Rituximab. Although a pathogenic role of paraneoplastic antibodies has not been proven, their presence indicates the paraneoplastic nature of a neurologic disorder, and in many cases, can narrow the search for an occult tumor to a few organs.

INCIDENCE — Paraneoplastic disorders (PND) are more frequent than previously considered, with an incidence that varies with the neurologic syndrome and type of tumor. The more common syndromes are Lambert-Eaton myasthenic syndrome (LEMS), which affects approximately 3 percent of patients with small-cell lung cancer (SCLC), and myasthenia gravis, which affects 15 percent of all patients with thymoma. For other solid tumors, the incidence of paraneoplastic neurologic syndromes is far less than 1 percent in most tumors. Paraneoplastic peripheral neuropathies affect 5 to 15 percent of patients with plasma cell dyscrasias associated with malignant monoclonal gammopathies. More than 50 percent of patients with the rare osteosclerotic form of myeloma develop a predominantly motor paraneoplastic peripheral neuropathy.
Patients with all forms of myeloma, but usually the osteosclerotic type, can develop a severe, symmetric, sensorimotor neuropathy with muscle atrophy in association with the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin).

GENERAL DIAGNOSTIC CONSIDERATIONS — Many paraneoplastic syndromes develop in the early stages of cancer, and the presence of a tumor or tumor recurrence can be difficult to demonstrate.

Diagnostic criteria — These criteria divide patients with suspected paraneoplastic syndromes into "definite" and "possible" categories as follows.

Definite syndromes include:

- A "classical" syndrome and cancer that develops within five years of diagnosis of the neurologic disorder. A classical syndrome is defined as a neurologic syndrome that is frequently associated with cancer. Classical syndromes include encephalomyelitis, limbic encephalitis, subacute cerebellar degeneration, opsoclonus-myoclonus, subacute sensory neuronopathy, chronic gastrointestinal pseudoobstruction, Lambert-Eaton myasthenic syndrome, and dermatomyositis.
- A nonclassical syndrome that resolves or significantly improves after cancer treatment without concomitant immunotherapy, provided that the syndrome is not susceptible to spontaneous remission.
- A nonclassical syndrome with paraneoplastic antibodies and cancer that develops within five years of the diagnosis of the neurologic disorder.
- A neurologic syndrome (classical or not) with "well-characterized" paraneoplastic antibodies and no cancer. These well-characterized antibodies include anti-Hu, CV2, Ri, Ma2, or amphiphysin.

Possible syndromes include:

- A classical syndrome as defined above, no paraneoplastic antibodies, no cancer, but at high risk to have an underlying tumor.
- A neurologic syndrome (classical or not) with partially characterized paraneoplastic antibodies (eg, not the well-characterized antibodies described above) and no cancer.
- A nonclassical syndrome, no paraneoplastic antibodies, and cancer present within two years of diagnosis.

MRI — Neuroimaging can assist in the diagnosis of limbic encephalitis because the medial temporal lobes, the site of major pathology, often show increased signal on FLAIR images and occasionally areas of contrast enhancement. Patients with paraneoplastic cerebellar degeneration may develop signs of atrophy detectable by magnetic resonance imaging (MRI) several months after the onset of symptoms. For most paraneoplastic syndromes, however, neuroimaging studies are normal or nonspecific.

PET — Positron emission tomography of the brain using fluorodeoxyglucose (FDG-PET) will occasionally identify hypermetabolism of the medial temporal lobe(s) in patients with limbic encephalopathy or of the cerebellum in patients with paraneoplastic cerebellar degeneration.
Lumbar puncture — Although detection of paraneoplastic antibodies in the cerebrospinal fluid (CSF) confirms that the disorder is paraneoplastic, in our experience these antibodies are usually present in the serum as well. Exceptions include some patients with anti-Tr antibodies and patients with antibodies to antigens expressed in the cell membrane of neurons of the neuropil of hippocampus. CSF examination can assist in making the diagnosis of paraneoplastic syndromes in two other ways:

- The combination of negative cytology for malignant cells and the absence of meningeal enhancement on MRI can reasonably exclude leptomeningeal carcinomatosis.
- Inflammatory changes (eg, pleocytosis, intrathecal synthesis of IgG, oligoclonal bands) can support the presence of an inflammatory or immune-mediated neurologic disorder.

Electrophysiology — Some paraneoplastic syndromes of the peripheral nervous system are associated with characteristic electrophysiologic findings. These include LEMS, myasthenia gravis, neuromyotonia, and dermatomyositis. However, these findings are also present when the neurologic syndrome is not associated with a tumor. Nevertheless, electrophysiologic findings that confirm the underlying syndrome may still be helpful by directing the search for the neoplasm to specific organs (eg, lung with LEMS, and thymus with myasthenia gravis).

Occult malignancy — While paraneoplastic syndromes are most often diagnosed in the setting of a known malignancy, it is not uncommon for a paraneoplastic disorder develop before a cancer is identified.

The clinical syndrome and identification of certain paraneoplastic antibodies may suggest a specific underlying tumor and direct investigations. In most other instances, the tumor is revealed by computed tomograph (CT) of the chest, abdomen, and pelvis. Whole body fluorodeoxyglucose positron emission tomography (FDG-PET) is useful in demonstrating occult neoplasms or small metastatic lesions. In one case series of 104 patients, sensitivity and specificity of FDG-PET were 80 and 67 percent, compared to 30 and 71 percent for CT. Results from another small study suggest that FDG-PET combined with CT scanning increases sensitivity and accuracy of tumor diagnosis. Additional tests, such as mammogram or ultrasound of the pelvis or testes, are ordered when suggested by the clinical syndrome and identification of certain paraneoplastic antibodies and/or the presence of other risk factors.

TREATMENT OVERVIEW — There are two general approaches to therapy, 1) removal of the antigen source by treatment of the underlying tumors and 2) suppression of the immune response.

Immunosuppression may be beneficial for some conditions, such as the Lambert-Eaton myasthenic syndrome (LEMS) and myasthenia gravis, in which plasma exchange or intravenous immune globulin (IVIG) (eg, 0.4 g/kg daily for five days) is usually effective in suppressing the immune response.
Although most patients with paraneoplastic peripheral neuropathies without paraneoplastic antibodies, there is often evidence of an immune-mediated etiology, such as cerebrospinal fluid (CSF) pleocytosis, increased CSF proteins, or the presence of inflammatory infiltrates on nerve biopsy. For these disorders, and particularly those with predominant demyelinating features, plasmapheresis, IVIG, and immunosuppression may also be effective. In those disorders that are probably antibody-mediated, specific anti-B cell therapy using antibodies such as rituximab could be considered. Case reports and small series describe efficacy of rituximab in pediatric opsoclonus myoclonus, stiff person syndrome, dermatomyositis, anti-Yo positive paraneoplastic cerebellar degeneration, and anti-Hu antibody-associated encephalomyelitis.

For other paraneoplastic neurologic syndromes, there is evidence that prompt oncologic treatment and immunotherapy (immunomodulation, immunosuppression) can be beneficial, especially if instituted during the time of symptom progression rather than after deficits have been fully established. The failure of the neurologic syndrome to respond to treatment may be due to irreversible neuronal damage that occurred before the diagnosis was made and treatment begun.

Since the combination of oncologic and immunosuppressive therapies may have significant toxicity, immunologic treatments should be stratified accordingly. For patients with progressive neurologic symptoms who are receiving chemotherapy, immunosuppression or immunomodulation may include oral or intravenous corticosteroids and intravenous immunoglobulins. Most reports suggest that plasma exchange is rarely effective. Patients with progressive neurologic symptoms who are not receiving chemotherapy should be considered for more aggressive immunosuppression that may include oral or intravenous cyclophosphamide, tacrolimus, or cyclosporine.

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