Despite numerous advances in detection and treatment, cancer remains a major health problem in the United States. One in four deaths in the United States is caused by cancer, and cancer is the leading cause of death in individuals under 85 years of age [1]. However, death rates related to cancer have steadily decreased over the past few decades, and as a result, the number of survivors has exponentially increased. Increasingly, more and more secondary complications caused by cancer and its treatments are being recognized. Neuromuscular complications related to the underlying cancer itself, or caused by associated treatments, such as chemotherapy and radiation therapy, are common but are likely underreported. While neurologic involvement can occur in both the central and peripheral nervous systems at any level, this article focuses on the effects of cancer on the peripheral nervous system.

Using electrodiagnostic studies, neuromuscular abnormalities have been clinically detected in 2.5% to 5.5% of patients with lung or breast cancer, and in 28.5% of patients with various neoplasms [2]. Classification of these abnormalities can be organized either by etiology or by anatomic level. Many etiologies are possible. These include direct compression or infiltration, hematogenous spread, lymphatic spread, meningeal dissemination, or perineural spread. Peripheral nervous system involvement can also be caused by paraneoplastic syndromes, or from common secondary effects related to cancer, such as malnutrition, weight loss, or infection. Acquired neuropathies can result from side effects of the cancer treatments
themselves, including surgery, chemotherapy, radiation therapy, hematopoietic stem cell transplantation, or immunologic therapy. Finally, patients may have pre-existing neurologic conditions, such as diabetic polyneuropathy, that can be exacerbated by cancer or its related treatments. Often, a combination of etiologies can be recognized in individual patients.

Involvement can occur at any level of the peripheral nervous system, including the anterior horn cells, nerve roots, sensory ganglia, brachial or lumbosacral plexus, single or multiple peripheral nerves, neuromuscular junction, and the muscle. Often multiple levels are involved. Neural damage at the cellular level may take place at the cell body, axon, myelin, or a combination of all of the above. The expected clinical findings are dependent on the location of the lesion.

Direct neuromuscular effects of cancer

Radiculopathy

A single or multilevel radiculopathy can result from primary or epidural metastatic tumor extension into the neural foramina (Fig. 1). All tumor types can metastasize to the spine, although the most common primary malignancies that do so include breast, lung, prostate, colon, thyroid, and kidney. Common primary malignant spinal tumors include multiple myeloma, plasmacytoma, and Ewing’s and osteogenic sarcoma. After disc disease and spinal stenosis, tumors involving the spine and spinal cord are the most common causes of radiculopathy [3]. Although a degenerative etiology is more likely to cause symptoms, any patient with a history of cancer who presents with back pain and radicular symptoms and signs on

Fig. 1. Lumbar spine MRI demonstrating epidural disease with cauda equina and left L3 nerve root compression from metastatic prostate cancer (arrows). (A) T2 weighted axial image. (B) T2 weighted sagittal image.
Physical examination warrants imaging, with magnetic resonance imaging (MRI) being the imaging modality of choice. An MRI of the total spine, not solely of the affected area, is subsequently obtained to determine extent of disease in instances where a neoplastic radiculopathy is identified.

**Leptomeningeal metastases**

Leptomeningeal disease is caused by metastatic involvement of the leptomeninges from infiltrating cancer cells. The incidence of leptomeningeal metastasis ranges from 4% to 15% and is felt to be increasing [4]. The most common associated primary cancers are breast, lung, gastric, melanoma, and lymphomas [5]. Of the leukemias, leptomeningeal disease is most commonly seen in acute lymphocytic leukemia [6]. Patients can present with an asymmetric array of symptoms resulting from polyradicular involvement, including focal and radicular pain, areflexia, paresthesias, and lower motor neuron weakness. There may be associated findings of nuchal rigidity, as well as upper motor neuron signs, especially if there is concomitant brain involvement. Cranial nerves are often involved as well, with the oculomotor, facial, and auditory nerves most commonly affected.

MRI with gadolinium of the spine and brain should be performed initially in all suspected cases. Nodular enhancement of the leptomeninges is almost pathognomonic (Fig. 2). The diagnosis is confirmed with the presence of malignant cells on cerebrospinal fluid (CSF) cytology. However, there is a high initial false-negative rate on CSF studies of 40% to 50% [4]. Repeat CSF studies following an initial negative result improves the diagnostic yield to 90% [7]. Electrodiagnostic studies are consistent with a polyradiculopathy; however, underlying findings of an axonal, sensorimotor polyneuropathy, caused by prior chemotherapy treatment, can often be noted and can confuse the issue. Absent F-waves or prolonged F-wave latencies on nerve conduction studies are felt to be an early indicator of nerve root involvement, but are not specific for leptomeningeal disease [8]. Treatment is palliative and involves focal radiation therapy and chemotherapy, either intrathecal or systemic. Overall prognosis is poor and is dependent on multiple factors, including primary tumor type, extent of CSF disease as well as systemic disease, degree of neurologic deficit, and associated medical comorbidities.

**Plexopathy**

Brachial plexopathies from neoplasms are usually the result of metastatic disease, with breast and lung being the most common primary sources [9]. In cancer patients, the frequency of neoplastic brachial plexopathy is 0.43% [10]. If a patient has a history of prior radiation therapy to the axillary or supraclavicular lymph nodes, secondary radiation-induced neoplasms, such as sarcomas, should also be considered. Symptoms include pain,
paresthesias, numbness, and weakness in the distribution of plexus involvement. Metastases can involve any portion of the brachial plexus, but usually involve the lower trunk because of its proximity to axillary lymph nodes and the superior sulcus of the lung. Assessment of T1 fibers with needle electromyography is essential and can help guide further imaging studies [11]. The Pancoast syndrome is a distinct clinical presentation resulting from a superior pulmonary sulcus tumor, presenting with findings of a lower trunk brachial plexopathy and a unilateral Horner’s syndrome [12]. MRI of the brachial plexus is usually diagnostic (Fig. 3).

Neoplastic lumbosacral plexopathies can result from metastatic disease, but are much more likely to be caused by direct extension of local tumor

Fig. 2. Lumbar spine MRI demonstrating leptomeningeal metastasis from breast cancer. (A) T1 weighted sagittal image. (B) T1 weighted sagittal image postadministration of gadolinium. Note the nodular pattern of enhancement (arrows). (C) T2 weighted sagittal image.
or perineural spread [13]. Common tumors involved include colon, gynecologic tumors, lymphomas, and sarcomas. As in brachial plexopathies, neuropathic symptoms will be in the distribution of involvement, and MRI of the lumbosacral plexus is helpful in the diagnosis.

**Neuropathy**

Mononeuropathies most often result from the direct compression or invasion from tumor, such as an isolated radial neuropathy caused by a primary osteogenic sarcoma, or a bone metastasis involving the spiral groove of the humerus. Malignant nerve sheath tumors are rare and usually arise from plexiform neurofibromas [11]. There is a high association with neurofibromatosis type 1. The clinical presentation depends on the individual nerve involved, but severe pain and rapidly growing tumors suggest malignant transformation [14].

Diffuse peripheral nerve infiltration from cancer is rare but has been reported in hematologic malignancies, such as non-Hodgkin’s lymphoma and chronic lymphocytic leukemia [15,16]. Amyloid deposition in primary amyloidosis and multiple myeloma can also result in diffuse polyneuropathy [17].

**Myopathy**

Focal myopathies from tumor involvement are rare, and usually result from direct infiltration from underlying bony metastases or local lymph
node involvement, rather than from hematogenous spread. A more proximal myopathy, associated with macroglossia and muscle pseudohypertrophy, is an uncommon manifestation of primary amyloidosis. Muscle biopsy is diagnostic and demonstrates amyloid deposition surrounding muscle fibers and blood vessels. The selection of muscle to biopsy can be guided by electrodiagnostic findings. Needle electromyography demonstrates myopathic motor unit potentials or a mixture of large and small motor unit potentials, with fibrillation potentials noted primarily in proximal muscles [18].

**Paraneoplastic syndromes**

Neuromuscular paraneoplastic syndromes cause damage to the peripheral nervous system as a result of remote effects from a malignant neoplasm or its metastases [19]. Although rare, it is important to recognize these syndromes. The clinical presentation is usually more rapidly progressive and severe than what would normally be expected in a noncancerous etiology. They often precede the diagnosis of cancer, and early recognition may increase survival. Treatment of the underlying malignancy usually results in improvement of neurologic symptoms. In some disorders, neuronal antigens expressed by the tumor result in an autoimmune response against both the tumor as well as healthy neural tissue, and identification of these markers can help facilitate the diagnosis of a primary tumor. Although some syndromes are associated with an identifiable neuro-oncologic autoantibody, frequently no such marker is detected.

Almost all tumor types have been associated with paraneoplastic syndromes, and any part of the nervous system can be affected. There are, however, certain tumors that have a higher association with paraneoplastic syndromes, with neuroblastoma most often seen in children and small-cell lung cancer most often seen in adults. Paraneoplastic opsoclonus-myoclonus occurs in 2% to 3% of children with neuroblastoma. A small number (1%–3%) of patients with small-cell lung cancer develop Lambert-Eaton myasthenic syndrome (LEMS) or some other paraneoplastic syndrome [20].

*Sensory neuronopathy*

Paraneoplastic sensory neuronopathy or ganglionopathy presents with either an acute or insidious onset of pain and sensory loss. Clinical findings of sensory ataxia and pseudoathetosis are often present at various levels of severity. The findings can be diffuse but are commonly more severe in the upper extremities and may be asymmetric. Motor dysfunction is usually absent; however, sensory neuronopathy can sometimes be seen, along with a more diffuse paraneoplastic neurologic syndrome involving encephalomyelitis, autonomic neuropathy, and motor neuronopathy [19]. A pattern of more severe sensory abnormalities on nerve conduction studies in the upper extremities, compared with the lower extremities, helps distinguish this
entity from a length-dependent sensory neuropathy. The most common associated neoplasm is small-cell lung cancer; however, breast, renal, chondrosarcoma, and lymphoma have also been implicated. The presence of anti-Hu antibodies helps support the diagnosis of paraneoplastic sensory neuronopathy.

**Sensorimotor polyneuropathy**

The diagnosis of a true paraneoplastic distal, symmetric, sensorimotor polyneuropathy is difficult to confirm, as there are many more likely known etiologies that can cause this pattern of involvement, including diabetes mellitus, nutritional deficiencies, and toxic exposure, such as chemotherapy. A subacute, sensorimotor polyneuropathy as a paraneoplastic syndrome is therefore a diagnosis of exclusion. Symptoms include pain, paresthesias, numbness, and weakness in a stocking-glove distribution, along with hyporeflexia. A more rapidly progressive course may be the only distinguishing factor differentiating a paraneoplastic syndrome from an idiopathic or diabetic etiology. Electrodiagnostic findings are consistent with an axonal process. This syndrome has been associated with lung and breast cancer [21].

**Vasculitic neuropathy**

A pattern of clinical and electrophysiologic involvement resembling mononeuritis multiplex may represent a paraneoplastic vasculitic neuropathy. This syndrome has been most commonly reported in association with small-cell lung cancer and lymphoma [22]. Further support for a vasculitis includes an elevated erythrocyte sedimentation rate, and an elevated cerebrospinal fluid protein level. The anti-Hu antibody has also been associated with this syndrome [23]. Biopsy of the sural nerve confirms microvascular involvement. In addition to treating any underlying malignancy, the neuropathic symptoms may also respond to immunosuppressive therapy directed against the vasculitis.

**Lambert-Eaton myasthenic syndrome**

LEMS is a presynaptic disorder of neuromuscular transmission, and is perhaps the best understood paraneoplastic neuromuscular syndrome. Clinically, patients present with fatigue, proximal weakness, hyporeflexia, and autonomic dysfunction. Repetitive strength testing may reveal a “warming-up” phenomenon, where one can display an initial increase in strength with repetition followed by eventual fatigue. Bulbar involvement is rare. LEMS tends to affect adults greater than 40 years of age, and has a male predominance. It can occur independent from cancer, but up to 40% to 60% of cases have been shown to be associated with small-cell lung cancer [9]. LEMS has also been reported to be associated with lymphoma, breast, ovarian, pancreatic, and renal malignancies.
Electrodiagnostic studies are invaluable in the diagnosis of LEMS. Motor responses are reduced in amplitude at baseline. Sensory responses are normal. Repetitive stimulation of motor nerves at low frequency (2 Hz–3 Hz) demonstrates a further decrement in amplitude. Following brief isometric exercise, facilitation occurs and compound muscle action potential amplitudes show at least a 100% increase [24]. This finding is almost pathognomonic for LEMS (see Fig. 3). Antibodies directed against the P/Q-type voltage-gated calcium channels are seen in up to 92% of LEMS patients [9]. Management involves administration of 3, 4 diaminopyridine and treatment of any underlying malignancy.

*Myasthenia gravis*

Myasthenia gravis (MG) is a postsynaptic disorder of neuromuscular transmission and its relationship with benign thymomas is widely recognized. MG occurs in 30% of patients with thymoma, and 15% of patients with MG are found to have thymoma on further radiographic evaluation [21]. Patients present with fatigue and proximal weakness, most notably in ocular and bulbar muscles. Electrodiagnostic studies demonstrate a decremental response in compound muscle potential amplitude with 2-Hz to 3-Hz repetitive stimulation. Unlike LEMS, baseline motor amplitudes are normal in MG, except in severe cases. Immediately following brief exercise, a repair of the decrement is noted. Postactivation exhaustion, with return of the decremental response, is noted 2 to 4 minutes after exercise. Patients under 60 years of age with generalized weakness, or patients with a documented thymoma, are treated via thymectomy [25]. Treatment can also involve the use of cholinesterase inhibitors or immunosuppressive agents.

*Syndromes of neuromuscular hyperactivity*

Hyperactivity syndromes, such as Stiff-person syndrome or neuromyotonia (Isaac’s syndrome), are rare but have been associated with malignancies, including small-cell lung cancer, breast cancer, lymphoma, and invasive thymoma [26–28]. Stiff-person syndrome is a disorder characterized by muscle rigidity and a worsening of symptoms with exposure to certain triggers, such as loud noise or startle. Continuous motor unit activity is noted on needle electromyography, but otherwise electrodiagnostic findings are unremarkable. Antibodies to glutamic acid decarboxylase are present in up to 60% of patients; in some instances there is an association with antibodies against the presynaptic cell membrane protein amphiphysin. Isaac’s syndrome is an autoimmune channelopathy that has been reported in association with Hodgkin’s lymphoma as well as plasmacytoma [29,30]. Antibodies to voltage-gated potassium channels are present in 50% of patients. Continuous motor unit activity is again noted on needle EMG, however unlike Stiff-person syndrome, the symptoms and findings persist during sleep. Neurotonic discharges may also be present.
Myopathy

The findings of a symmetric, proximal myopathy on clinical examination and electrodiagnostic testing can also lead to the discovery of an undiagnosed cancer. Although their classification as a true paraneoplastic syndrome is controversial, polymyositis, and especially dermatomyositis, are associated with an increased incidence of malignancy compared with the general population [31]. Breast, lung, and gynecologic malignancies are most frequently implicated. Paraneoplastic necrotizing myopathy [32] and carcinoid myopathy are syndromes distinct from polymyositis or dermatomyositis. Carcinoid tumors may be associated with a progressive myopathy that has its onset years after the carcinoid syndrome [21].

Motor neuron disease

With regard to motor neuron disease syndromes, as mentioned previously the anti-Hu-associated paraneoplastic encephalomyelitis, sensory neuronopathy, and motor neuropathy syndrome has a strong link with small-cell lung cancer. Subacute motor neuropathy and primary lateral sclerosis have been associated with lymphoma and breast cancer, respectively [33]. There is no known association between cancer and amyotrophic lateral sclerosis; however, in newly diagnosed motor neuron disease a screening for cancer is usually part of the exclusionary diagnostic workup.

Neuropathy associated with plasma cell dyscrasias

Neuropathies associated with paraproteinemias and plasma cell dyscrasias warrant special consideration. Although not considered true paraneoplastic syndromes, there is a high association of neuropathies with these disorders and the presence of monoclonal proteins. These disorders include monoclonal gammopathy of unknown significance (MGUS), Waldenström’s macroglobulinemia, cryoglobulinemia, multiple myeloma, osteosclerotic myeloma, primary amyloidosis, non-Hodgkin’s lymphoma, and the chronic leukemias [34]. Even a diagnosis of MGUS should raise concern, as approximately 20% of these patients will at some point develop a malignant plasma cell disorder. A pattern of mononeuritis multiplex or distal symmetric polyneuropathy can be seen in lymphomas, myelomas, or leukemias, particularly chronic lymphocytic leukemia. Electrodiagnostic studies are usually consistent with an axonal process, although in the case of osteosclerotic myeloma and POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes) syndrome, findings of both axonal loss and multisegmental demyelination can be seen. The electrodiagnostic findings in POEMS syndrome can be similar to those seen in chronic, inflammatory demyelinating polyradiculoneuropathy [35]. The monoclonal gammopathy in these disorders can involve IgM, IgG, or IgA proteins,
and there is some evidence to suggest that the type of paraproteinemia correlates to the clinical and electrophysiologic characteristics of the neuropathy [36].

**Indirect neuromuscular effects of cancer**

Immunocompromised patients are at risk for multiple infections, but with regards to the peripheral nervous system the main pathogen is herpes zoster varicella. Reactivation of herpes zoster, leading to shingles, has been reported to occur in up to 34% of leukemia patients [37], with resulting radicular pain and potential postherpetic neuralgia. Sepsis with multisystem organ failure is a serious complication of cancer and reason for intensive care admission, and in this setting critical illness polyneuropathy and critical illness myopathy are often diagnosed [38]. Other acute weakness syndromes, such as MG, LEMS, and steroid myopathies must be excluded.

Weight loss is a common symptom of malignancy, and there is a higher risk of compression neuropathy, especially the peroneal nerve at the level of the fibular head. This is because the nerve is no longer protected by soft tissue and is more easily compressed against bony structures. A history of habitual leg crossing is sometimes elicited. There may be additional predisposition to injury, given exposure to neurotoxic chemotherapy, to be discussed later in this article. In addition to complications associated with weight loss, malnutrition can be further associated with a neuropathy, secondary to vitamin B$_{12}$ deficiency. Renal failure from myeloma or amyloid involvement can result in a uremic neuropathy. Cachexia and related metabolic proximal myopathies affecting primarily type 2 muscle fibers are also seen.

**Neuromuscular complications of cancer treatments**

**Surgery**

Although uncommon, damage to the peripheral nervous system during the perioperative period can occur in both the cancer and noncancer patient. Because the nature of surgical procedures for the cancer patient is likely to be more complex, it is felt that the likelihood of complications is greater. There are no studies, however, comparing the incidence of unintentional nerve injury in the cancer surgery population to that in the general population. In addition, peripheral nerves are sometimes intentionally sacrificed in the cancer surgery patient to obtain local disease control. The pattern and extent of neurologic involvement following surgery depends on the location of the tumor, patient positioning during surgery, and the patient’s overall preoperative status and propensity to nerve injury [39]. For example, through mechanisms mentioned previously, a cancer patient having undergone a significant amount of weight loss before treatment may be more susceptible to a perioperative peroneal neuropathy at the fibular head,
resulting from positioning following a prolonged surgery and postoperative recovery period.

Perioperative neurapraxic injuries, resulting from compression of peripheral nerves, are well-recognized phenomena. It is felt that these injuries result from the patient’s position during anesthesia or during the immediate postsurgical recovery period [40]. Common sites of injury and associated surgical procedures include brachial plexus injury during thoracotomy or mastectomy, given the abducted position of the involved upper extremity. Abduction of the upper extremity greater than 90 degrees during anesthesia will cause the humeral head to sublux inferiorly, resulting in compression and traction of the brachial plexus. Upon awakening, patients report varying degrees of pain, weakness, and numbness in both the upper and lower trunk distribution. Complete, spontaneous recovery within weeks is common, even in cases of severe plegia. Ulnar neuropathies at the elbow, resulting from arm boards used to secure intravenous lines, and radial neuropathies at the spiral groove, resulting from prolonged time in the lateral decubitus position, are also noted following thoracic surgery.

Compression of the femoral nerve or lumbar plexus can result from traction during pelvic surgery. Patients undergoing hip arthroplasty or acetabular reconstruction are prone to injury, with the peroneal division of the sciatic nerve being the most commonly affected nerve. Injuries to the superior gluteal, obturator, and femoral nerves have also been reported [41]. Cadaveric studies demonstrate that the lithotomy position, with the lower limbs placed in greater than 30 degrees of abduction, causes excessive traction on the obturator nerve. This strain is relieved, however, with concomitant hip flexion [42]. Finally, delayed postoperative hemorrhages and hematomas should be excluded in all patients who develop new neuropathic symptoms 24 to 48 hours after surgery.

There are a few specific neurotmetic surgical injuries that warrant consideration. The spinal accessory nerve is often sacrificed during radical or modified radical neck dissection for head and neck cancers. The branch to the trapezius is usually more affected than the branch innervating the sternocleidomastoid. A resulting drooped shoulder and lateral scapular winging can lead to chronic shoulder pain. During radical or modified radical mastectomy, the intercostal-brachial nerve is frequently damaged, resulting in pain and paresthesias involving the lateral chest wall and medial upper arm, predisposing patients to secondary adhesive capsulitis. Postthoracotomy pain syndrome is caused by sacrifice of the intercostal nerves, may have its onset weeks after surgery, and can persist for years. If there is new pain in the area of surgery, it is important to rule out tumor recurrence invading the chest wall, or thoracic vertebral body metastases causing compressive radiculopathy, before making a diagnosis of delayed postthoracotomy pain syndrome. Damage to lower extremity nerves is uncommon during abdominal or pelvic surgery, unless a tumor has already infiltrated nervous system structures. The rates of unintentional or planned nerve
sacrifice are high in limb-sparing procedures for extremity sarcomas because of the need to achieve adequate tumor-free surgical margins. Electrodiagnostic studies performed immediately after surgery, and 2 to 3 weeks afterward, can help prognosticate neurologic recovery [43]. A thorough discussion of pain syndromes following amputation, including residual limb pain and phantom pain, is beyond the scope of this article.

**Chemotherapy**

Peripheral neuropathy is a common adverse effect of medications in general; however, when these medicines are used to treat life-threatening illnesses, such as cancer, it becomes challenging to balance the potentially functionally limiting side effects with the obvious benefits of chemotherapy. Side effects tend to be dose-dependent, although it is important to recognize pre-existing subclinical neuropathies or a family history of neuropathy, such as in the case of the hereditary sensory and motor neuropathies. The neurotoxic effects of chemotherapy in these patients can occur earlier than expected in the treatment course, and symptoms can be devastating and disabling [44–46]. Although almost all agents have been associated with neuropathies, there are a select number of chemotherapeutics that are especially prone to causing neuropathy. Chemotherapy induced neuropathy generally is characterized by axonal loss via Wallerian degeneration, and presents with a subacute, length-dependent, sensory greater than motor, polyneuropathy. The prognosis for neurologic recovery upon discontinuation of the offending agent is generally favorable, but depends on the severity of symptoms.

Two classes of chemotherapeutic agents in prevalent use are the vinca alkaloids and the taxanes. The vinca alkaloids—such as vincristine, vinblastine, and vinorelbine—are used in the treatment of solid tumors, lymphomas, and leukemias. They are usually given in combination with other chemotherapeutic agents. The mechanism of action with the vinca alkaloids is to arrest dividing cells in metaphase by binding tubulin and preventing its polymerization into microtubules. This is also the proposed mechanism of inducing neuropathy, by inhibiting anterograde and retrograde transport and causing axonal degeneration. Clinical features are those of a distal, symmetric, sensorimotor axonal polyneuropathy, affecting both large and small fibers. Taxanes, such as paclitaxel and docetaxel, are also used to treat solid tumors, such as breast and ovarian cancer. As in the vinca alkaloids, the taxane-induced neuropathy is a length-dependent sensorimotor polyneuropathy resulting from damage to the axonal microtubule system [47]. Similar agents, generally resulting in a length-dependent, axonal neuropathy affecting sensory greater than motor fibers, include thalidomide and bortezomib, both used in the treatment of multiple myeloma.

Etoposide is a lesser used agent but is useful in the treatment of lymphoma, leukemia, small-cell lung cancer, and testicular cancer. As in most drug-induced neuropathies, etoposide is associated with an axonal, distal,
symmetric sensorimotor polyneuropathy. In addition, there have also been reports of an associated severe autonomic neuropathy with orthostatic hypotension and gastroparesis [9].

Platinum based compounds are used in the treatment of solid tumors, such as ovarian, testicular, and bladder cancer. They include agents such as cisplatin, carboplatin, and oxaliplatin. While platinum toxicity can also result in a distal, symmetric, sensorimotor polyneuropathy, there also appears to be preferential damage to the dorsal root ganglia, causing a sensory neuronopathy with clinical features, including sensory ataxia, and upper extremities being more affected than the lower extremities. A “coasting phenomenon” may be noted, where symptoms can progress for months following discontinuation of the platinum compound. Prognosis for recovery in a sensory ganglionopathy is poor.

Cytarabine is used in the treatment of hematologic cancers. There have been reports of severe sensorimotor polyneuropathy, resembling Guillain-Barré syndrome, with high dose administration of cytarabine [48]. Electrophysiologic studies demonstrate a mixed axonal and multifocal demyelinating process.

Hand-foot syndrome is an unusual complication of several chemotherapeutic agents, including 5-flurouracil, capecitabine, doxorubicin, docetaxel, and cytarabine. Clinical features include painful desquamation and discoloration of the palms and soles of the hands and feet. The pain is frequently described as burning in character. Clinical findings include reduced pain and temperature sensation, with preserved reflexes, proprioception, and strength. Electrodagnostic studies are usually normal. Intraepidermal nerve fiber density evaluation demonstrates decreased numbers of small fibers, both proximally and distally, suggestive of a painful small fiber neuropathy [49].

Glucocorticosteroids are perhaps the most frequently used medications in the oncology patient. The primary use of corticosteroids in cancer patients is to control brain and spinal cord edema, but they are also used in the treatment of cancers, such as lymphoma. They are also helpful in treating pain, improving appetite, and managing nausea and vomiting caused by other chemotherapeutic agents. The major neuromuscular complication associated with corticosteroid use is steroid-induced myopathy. Patients present clinically, with proximal weakness and myalgias and without sensory abnormalities. Muscle biopsies demonstrate type 2 muscle fiber atrophy. Needle electromyographic findings are unremarkable. Prolonged, high dose use of corticosteroids can cause steroid-induced diabetes, which can lead to all of the associated secondary complications of diabetes, including peripheral neuropathy.

**Radiation therapy**

Approximately 50% of all cancer patients will undergo radiation therapy at some point during the course of their disease, and radiation therapy is
involved in approximately one quarter of all cancer cures [50]. As patients are living longer following cancer treatments, physicians are becoming more aware of late neuromuscular complications of therapy, especially radiation therapy. Side effects are essentially related to the dose of radiation and the volume of normal tissue that receives radiation [51]. Despite numerous advances with dose-fractionation schedules, beam conformation technology, and the advent of intensity modulated or image guided radiation therapy, it is still necessary to include normal tissue within the treatment field, much like a successful surgery requires adequate negative margins to achieve local disease control.

Radiation causes tissue injury primarily by the induction of apoptosis, a result of free radical-mediated DNA damage. Rapidly dividing cells, such as neoplastic cells, are particularly susceptible. Normal cells are also affected but to a lesser extent. In addition, radiation causes direct and indirect tissue injury that is mediated by a combination of chemokines, cytokines, and other growth factors. This includes activation of the coagulation system, inflammation, epithelial regeneration, and tissue remodeling. Although the exact pathophysiologic mechanism is not entirely understood, it is felt that this damage to the vascular endothelial system, causing abnormal collagen deposition and fibrosis in the perivascular and extracellular matrix, is the primary method resulting in damage to the underlying neuromuscular structures [50].

The clinical effects of radiation on peripheral nerves have been well documented. Any structure in the nervous system, both centrally and peripherally, is susceptible to radiation toxicity, including brain, spinal cord, and the nerve roots. However, the majority of studies and articles examining the phenomenon of radiation-induced damage to the peripheral nervous systems focus on radiation-induced plexopathy, specifically brachial plexopathy.

The primary differential diagnostic concern in a cancer patient with brachial plexopathy is distinguishing between a neoplastic and radiation-induced etiology. Occasionally, the two conditions can coexist. Classically, radiation-induced plexopathy is delayed in onset, pain is less common than in neoplastic plexopathy, and symptoms of weakness and paresthesias are usually progressive [52,53]. There is also more likely to be associated lymphedema in the involved limb. It has been reported that neoplastic plexopathy tends to preferentially affect the lower trunk, and radiation plexopathy the upper portion of the plexus; however, further studies suggest that plexus involvement may be more diffuse and with more overlap in both etiologies than previously suspected [54]. The presence of myokymic discharges and fasciculation potentials strongly suggests a radiation-induced contribution to plexus injury [53]. However, the absence of myokymic discharges does not exclude radiation damage. Even in the setting of classic EMG findings, follow-up imaging of the brachial plexus with MRI is indicated to exclude a concomitant compressive or infiltrating lesion, which could be...
caused by local recurrence, new metastases, or radiation-induced secondary tumors, such as sarcomas.

Originally thought to be relatively radioresistant, it is becoming more apparent that skeletal muscle is also susceptible to late onset effects of radiation therapy. The direct effect of radiation on muscle results in fibrosis and contracture [55]. There have been multiple reports of a late dropped head syndrome in patients who have received mantle field radiation therapy in the distant past as part of their treatment for Hodgkin’s lymphoma [56,57]. Clinical features include slowly progressive atrophy of neck and shoulder girdle musculature. Neck flexor and extensor muscles are markedly weak, with remarkably preserved motor function in the shoulder girdle and upper extremities. Affected muscles have a firm, fibrotic character on palpation. The head tends to be in a forward-flexed position, with a secondary kyphotic spinal posture caused by anterior cervical muscle contracture. Secondary musculoskeletal complications related to impaired posture, such as rotator cuff impingement syndromes, are seen. Needle electromyography demonstrates low amplitude, short duration, polyphasic motor unit potentials in affected muscles, with normal or decreased insertional activity and rare, if any, fibrillation potentials. There may additionally be findings of a concomitant brachial plexopathy [58]. Creatinine kinase levels and inflammatory markers are normal. Muscle biopsy in one patient demonstrated nemaline rod depositions in affected muscles, while biopsy results from unaffected muscles was normal [56].

Trismus is a special myopathic condition where the muscles of mastication, especially the masseter and pterygoids, are affected by radiation therapy used in the treatment of head and neck cancers [59]. Patients present with contractures of affected muscles, with progressive loss of interincisal opening. Pain may or may not be present. Jaw contractures can create difficulties with eating, and malnutrition complications may occur. Oral hygiene is also compromised, which can also be complicated by xerostomia, another common side effect of radiation therapy.

The incidence of radiation-induced secondary tumors is directly proportional to the radiation dose, and inversely proportional to the patient age at which the radiation is administered [60]. Distinguishing between local recurrence, primary metastases, and new tumor types has obvious implications in prognosis and treatment options. Their neuromuscular effects, like other tumors, are dependent on their location in proximity to the peripheral nervous system, and could also result in indirect neurologic effects and associated paraneoplastic syndromes. Secondary tumors include bone and soft tissue sarcomas, leukemias, melanomas, and thyroid cancers.

Hematopoietic stem cell transplant

Hematopoietic stem cell transplantation is performed as part of the treatment for hematologic malignancies, such as leukemias, lymphomas, and
multiple myeloma, as well as for select solid tumors and nonmalignant diseases. These patients will frequently receive additional chemotherapy or radiation therapy as part of their treatment regimen, and are susceptible to related neurotoxic effects, as described earlier. Common neurotoxic chemotherapeutic agents used in the setting of stem cell transplantation include cisplatin, paclitaxel, docetaxel, etoposide, thalidomide, and cytarabine. The chronic immunosuppressed state of these patients also makes them more prone to opportunistic infections and secondary peripheral neuropathies, such as herpes varicella zoster. Metabolic derangements, such as steroid-induced diabetes and malabsorption syndromes, are also common following transplantation, and can likewise result in secondary peripheral nervous system dysfunction.

Chronic graft-versus-host disease (GVHD) is the primary late-term complication associated with transplant. The graft, containing immunologically competent cells, reacts to host tissue antigens and performs an autoimmune response against the transplant recipient. Forty percent of patients having survived more than 100 days after transplant will develop GVHD [61]. There is a high association with chronic GVHD and autoimmune neuromuscular disorders, including inflammatory myopathies, myasthenia gravis, and both acute and chronic polyneuropathies.

Polymyositis, and to a lesser degree, dermatomyositis, are well recognized but uncommon complications of chronic GVHD. The incidence of polymyositis in the GVHD population is greater than that of the general population [62]. The clinical presentation, electrodiagnostic findings, and pathologic findings in GVHD-associated polymyositis are identical to idiopathic polymyositis. Differentiating an inflammatory myopathy from a steroid-induced myopathy is of obvious clinical importance.

MG in the setting of chronic GVHD usually develops between 2 and 5 years after transplantation, during tapering of immunosuppressive drug therapy [63]. Clinically and electrophysiologically, the findings are similar to typical autoimmune MG. Treatment regimens are likewise similar with equal efficacy. Acetylcholine receptor antibodies may or may not be present. There has not been a reported association with thymoma in patients with GVHD-associated MG.

Autoimmune neuropathies have also been associated with GVHD, and can present as either a distal symmetric sensorimotor polyneuropathy with characteristic electrodiagnostic findings, or as a syndrome with features similar to Guillain-Barré syndrome [64,65].

Summary

With numerous advancements in early detection and multimodal therapy, cancer has become a chronic disease. As the number of cancer survivors continue to increase, physiatrists and other neuromuscular disease specialists are more likely to encounter individuals with residual impairments,
disabilities, or handicaps resulting from cancer or related treatments. The cancer patient is especially prone to injury directed at the peripheral nervous system at multiple levels. Tumors can directly compress or infiltrate vital nervous system structures, or can cause severe neuromuscular disorders through a paraneoplastic process. Immunocompromised cancer patients are susceptible to indirect neurologic insult through secondary mechanisms, such as infection or metabolic disorders. Cancer treatments themselves, including surgery, chemotherapy, radiation therapy, and hematopoietic stem cell transplant, can result in devastating neuromuscular complications. Recognition of associated neuromuscular complications of cancer and cancer treatments can be challenging because of the wide, multifactorial array of potential etiologies, but recognizing them is important in designing specific, individualized rehabilitation treatments to the oncologic patient and survivor.

References