NEUROMUSCULAR COMPLICATIONS OF RADIATION THERAPY

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ABSTRACT: Neuromuscular late effects of radiation therapy (RT) result from radiation fibrosis (RF) of the treated tissues. The clinical manifestations of this dysfunction have been termed *radiation fibrosis syndrome* (RFS). Any segment of the central and/or peripheral nervous system can be involved, including the brain, spinal cord, nerve roots, plexus, peripheral nerves, and muscles. Often, multiple levels are damaged, resulting in a constellation of findings named for the affected structures (i.e., *radiculo–plexo–neuro–myopathy*). Accurately diagnosing RFS requires the clinician to understand the basics of how radiation is and has been delivered. Key parameters of RT delivery include total dose, dose per fraction, and the radiation field treated. This article describes the basic principles of RT delivery, the pathophysiology of radiation injury, and how to identify and evaluate neuromuscular late effects of radiation in cancer survivors.

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Approximately one-half of the more than 14.5 million cancer survivors in the United States will receive radiation therapy (RT) at some point during the course of their illness.[1,2] RT is used not only with the intention of curing cancer but also palliatively to prolong life and improve quality of life.[3] Despite the therapeutic goals of RT, radiation-induced toxicity can be a major source of impairment and disability for some cancer survivors.[4] This article describes the basic principles of radiotherapy, the pathophysiology of radiation injury to the peripheral nerve, and how to identify and evaluate neuromuscular late effects in cancer survivors.

PRINCIPLES OF RT

A basic understanding of how radiation is delivered is important in identifying and evaluating the potential sequelae that result from it. The primary therapeutic goal of RT is to kill fast-dividing tumor cells while minimizing exposure and, thus, toxicity to normal cells. Radiation, including x-rays, protons, electrons, gamma rays, or photons, may be delivered either externally (external beam radiation therapy) or internally (brachytherapy).[5]

The basic unit used in radiation oncology is the gray (Gy). One Gy is defined as the absorption of 1 joule (J) of radiation energy per 1 kg of matter. It is not uncommon to see patients treated years ago whose RT dosing is expressed in absorbed radiation dose or rads; 1 rad = 0.1 J/kg = 0.01 Gy = 1 cGy. Therefore, a patient whose total dose was 3,600 rads has had RT equivalent to 3,600 cGy or 36 Gy.

Conventional two-dimensional (2D) RT generally uses photons. X-ray imaging is used for treatment planning to position the patient and identify the location of the tumor. Radiation is often but not invariably delivered from anterior-posterior (AP) and posterior-anterior (PA) directions. The radiation beam can be shaped with blocks, but its intensity is not modulated. Care is taken to avoid radiosensitive structures because the amount of radiation must be below the maximal tolerance for the most radiosensitive tissues encompassed by the field. Conventional RT techniques may use a lower dose per fraction and more fractions relative to newer conformal techniques (discussed below). Conventional RT is fast, relatively uncomplicated and inexpensive, and allows for the radiation of large volumes of tissue. Surface hotspots, the inclusion of considerable normal tissue in the radiation field, the inability to spare normal tissue, and the inability to maximize radiation dose to the tumor are all drawbacks to conventional RT. Despite these limitations, conventional RT is still widely and effectively used.

The first reports on the use of conformal radiation techniques are from the late 1980s.[6] Three-dimensional (3D) conformal techniques were developed to overcome some of the limitations of conventional RT.[7] Conformal techniques use 3D imaging such as computed tomography (CT) or MRI to define the tumor and normal tissues.[8] Radiation is delivered from multiple directions and shaped by using Cerrobend blocks, which can be individually molded to the optimal shape, or a multileaf collimator.[8] A multileaf collimator is a

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Abbreviations: 2D, two-dimensional; 3D, three-dimensional; ADL, activity of daily living; AP, anterior/posterior; CIPN, chemotherapy-induced peripheral neuropathy; CMAP, compound muscle action potential; CT, computed tomography; EDX, electrodiagnostic; EMG, electromyography; Gy, gray; HL, Hodgkin lymphoma; HNC, head and neck cancer; IMRT, intensity-modulated radiation therapy; J, joule; MF, mantle field; NCS, nerve conduction study; PA, posterior/anterior; PET, positron emission tomography; PNS, peripheral nervous system; RF, radiation fibrosis; RFS, radiation fibrosis syndrome; RT, radiation therapy; SNAP, sensory nerve action potential

Key words: electrodiagnostic; neuromuscular; peripheral nervous system; radiation; radiation fibrosis

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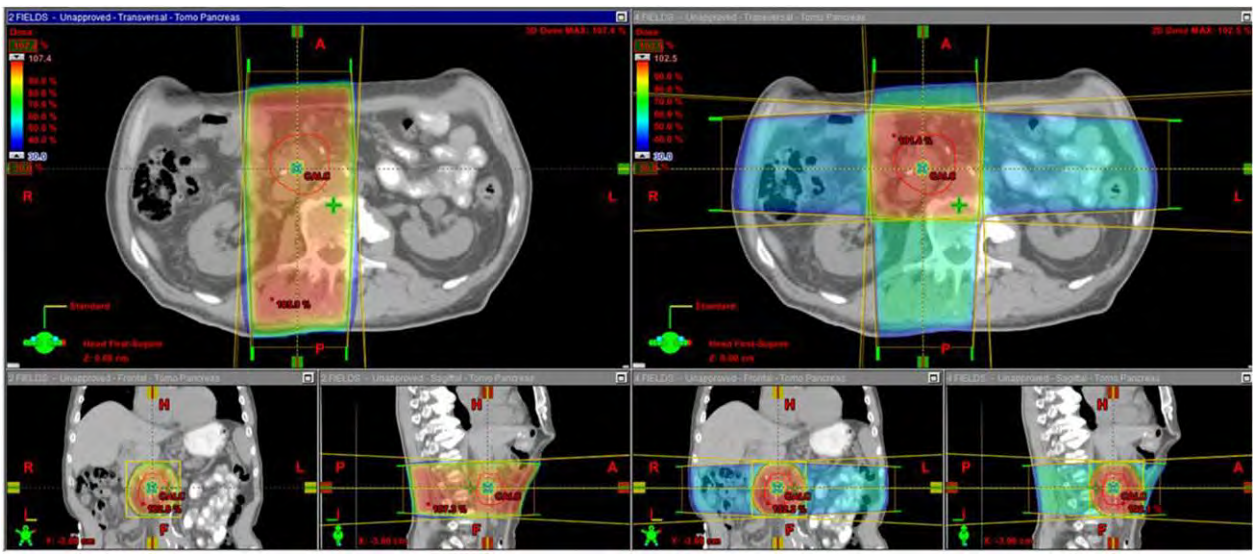

FIGURE 1. Isodose curves are shown for a patient with a pancreatic cancer recurrence in the area of positive margin following a Whipple procedure. Radiation dose is indicated by color, with red being the highest dose and blue the lowest. The target, including allowance for respiratory movement, is outlined in red. The illustration compares an anterior-posterior/posterior-anterior (AP/PA) plan on the left with a three-dimensional (3D) conformal 4-field plan on the right. The dose color wash is set equivalently and shows that, with the AP/PA technique, there is more normal tissue receiving the prescription dose. Conversely, the 3D technique permits more conformal treatment, with less normal tissue outside the target receiving the prescription dose (i.e., high dose). Note that, with the 3D conformal technique, there is much more normal tissue receiving a low and nonzero dose. This low-dose area is called the "integral dose" area. Note also that, with the AP/PA technique, the spinal cord is in the high-dose area, whereas it is not in the high-dose area with the 3D conformal technique. (Image courtesy of Brett Lewis, MD, Radiation Oncology, John Theurer Cancer Center, Hackensack University Medical Center.)

device with individual "leaves" of material, such as tungsten, that can block the path of the particle beam. The leaves can move quickly and independently to form complex patterns. By moving and shaping the beam based on 3D imaging, the target tissue can receive a therapeutic dose of radiation with enhanced sparing of normal tissues relative to conventional RT. Figure 1 illustrates the differences between conventional and 3D conformal RT.

Intensity-modulated radiation therapy (IMRT) is very similar to 3D conformal RT in that it generally uses photons, is planned based on 3D imaging, utilizes radiation beams delivered from multiple directions, and can incorporate a multileaf collimator.[9] The key difference is that in IMRT the beams are divided into a grid-like pattern as "beamlets" as opposed to 1 large beam. Advanced computer software is used determine the optimal pattern of beamlet use with respect to the tumor and normal tissue, thereby modulating the radiation beam. This technique allows very precise control of the radiation and is particularly useful when the tumor is near radiosensitive structures. IMRT is now the most frequently used radiation technique. In head and neck cancers such as those of the nasopharynx, IMRT not only improves local recurrence-free survival but also is associated with a lower incidence of toxicity, such as xerostomia.[10] Treatment planning for IMRT takes longer and is more expensive than conventional or 3D conformal RT.

Stereotactic RT (radiosurgery) also involves the precise delivery of high-dose radiation to a tumor. As with IMRT, stereotactic RT delivers radiation from numerous angles that is focused on the tumor while minimizing radiation dosing to adjacent normal tissues. The primary difference is that stereotactic RT is delivered in few treatments (or fractions, i.e., 1–5).[11] Beam splitting techniques can be incorporated into stereotactic RT, as with IMRT, resulting in very steep dose gradients from the tumor to surrounding normal tissue. Stereotactic radiosurgery is often administered to treat tumors in the lung, prostate, liver, brain, or bone (i.e., CyberKnife).

Although the term *radiosurgery* is often used to describe hypofractionated RT (i.e., 3–5 fractions), stereotactic RT is most commonly used to describe single-fraction RT. Single-fraction RT can deliver very biologically toxic doses with sparing of surrounding tissues. For instance, a single-fraction RT dose for a spine metastasis might be 24 Gy (2,400 cGy) in 1 fraction compared to a standard breast cancer dose of 50 Gy in 25 fractions.[11] Radiosurgery is also commonly employed to treat brain tumors with extreme accuracy (i.e., GammaKnife).[12]

PATHOPHYSIOLOGY OF RADIATION TOXICITY

The pathophysiology of radiation injury to the nerve is not completely understood. Nerve compression by fibrosis of surrounding tissues plays a

Table 1. Normal tissue tolerance to therapeutic radiation.*

Site	TD 5/5 (Gy)† Portion of organ irradiated 1/3	2/3	3/3	TD 50/5 (Gy)‡ Portion of organ irradiated 1/3	2/3	3/3	Complication end point(s)
Neuromuscular							
Brachial plexus	62	61	60	77	76	75	Clinical nerve damage
Brain	60	50	45	75	65	60	Necrosis, infarct
Brain stem	60	53	50	–	–	65	Necrosis, infarct
Cauda equine	No volume effect		60	No volume effect		75	Clinical nerve damage
Optic nerve	No partial volume		50	No partial volume		65	Blindness
Spinal cord	50 (5 cm)	50 (10 cm)	47 (20 cm)	70 (5 cm)	70 (10 cm)	–	Myelitis, necrosis
Musculoskeletal							
Temporomandibular joint	65	60	60	77	72	72	Marked limitation in joint function
Femoral head	–	–	52	–	–	65	Necrosis
Visceral							
Bladder	N/A	80	65	N/A	85	80	Contracture, volume loss
Colon	55	–	45	65	–	55	Obstruction, perforation, fistula, ulceration
Esophagus	60	58	55	72	70	68	Stricture, perforation
Heart	60	45	40	70	55	50	Pericarditis
Kidney	50	30	23	-	40	28	Nephritis
Liver	50	35	30	55	45	40	Liver failure
Lung	45	30	17.5	65	40	24.5	Radiation pneumonitis
Rectum	–	–	60	–	–	80	Severe proctitis, necrosis, fistula
Small intestine	50	–	40	60	–	55	Obstruction, perforation, fistula
Stomach	60	55	50	70	67	65	Ulceration, perforation

-, ; –, negative; Gy, gray; N/A, not assessed.

**Adapted from Emami et al.*[16]

†*TD 5/5 is the average dose that results in a 5% complication risk within 5 years.*

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role as does demyelination and blood vessel injury with subsequent microvascular ischemia.[13,14] The process of radiation-induced nerve injury is characterized by a gradual, stepwise worsening that can progress indefinitely. Three phases of fibrosis have been described.[15] First, there is an initial prefibrotic phase, characterized by endothelial cell dysfunction that is often asymptomatic. Radiation injury is evidenced by signs of chronic nonspecific local inflammation with increased vascular permeability and edema. Endothelial cell dysfunction and vascular thrombosis may result in necrosis of the microvasculature and local ischemia. Second, there follows a constitutive organized phase, wherein the radiated tissue is composed of patchy areas of activated fibroblasts (myofibroblasts) in a disorganized extracellular matrix found adjacent to senescent fibroblasts (fibrocytes) in a dense sclerotic matrix. The combination of damage to the endothelial and connective tissue cells coupled with the action of cytokines results in an immortalized fibrotic process. And, third, there is a late fibroatrophic phase, in which radiated tissue becomes progressively dense due to successive remodeling of the extracellular matrix. The few fibroblasts that remain are encased by a dense extracellular matrix. This last stage may develop and progress years or decades after RT and results in tissues that are poorly vascularized, friable, and fragile. Recurrent inflammation at this late stage can develop in the setting of physical or chemical trauma.

The term radiation fibrosis (RF) is used to describe the insidious, progressive, immortalized, pathologic tissue sclerosis that occurs in response to RT. Radiation fibrosis syndrome (RFS) describes the multiple clinical sequelae that occur as a result of RF.[4] Late effects of radiation can occur in any body tissue including nerve, muscle, bone, fascia, ligament, tendon, skin, and viscera.[4] Table 1 lists the total radiation dose tolerance of various neuromuscular, musculoskeletal, and visceral tissues. The risk, severity, and clinical manifestations of radiation injury depend on a variety of factors that can be directly related to the radiation itself, to concomitant treatments such as surgery or chemotherapy, or to factors intrinsic to the patient, such as diabetes or degenerative diseases (Fig. 2). An understanding of the influence of these factors will assist the clinician in determining whether signs and symptoms are in fact related to radiation and aid in constructing a meaningful, insightful, and clinically relevant evaluation.

FIGURE 2. Common factors contributing to radiation fibrosis syndrome.

Although total dose to a given tissue is generally a major determinant of tissue toxicity, other factors, such as dose per fraction, also play an important role. The risk of brachial plexopathy in breast cancer radiation is illustrative of this point. The standard protocol for breast and chest wall radiation is 50 Gy delivered in 25 fractions of 2 Gy. With this dose and fractionation, the reported risk of brachial plexus injury is <1%.[17] The dose per fraction can safely be increased to between 2.2 and 2.5 Gy as long as the total dose is dropped to between 34 and 40 Gy. If the dose per fraction is increased to between 2.2 and 4.58 Gy and the total dose is increased to between 43.5 and 60 Gy, the risk of brachial plexopathy rises sharply to between 1.7% and 73%.[17]

The size of the radiation field and the amount of normal tissues encompassed by it can vary considerably depending on the disease being treated. The radiation field used to treat a small metastasis, for instance, can be very small (Fig. 1). Conversely, the radiation fields historically used to treat Hodg-

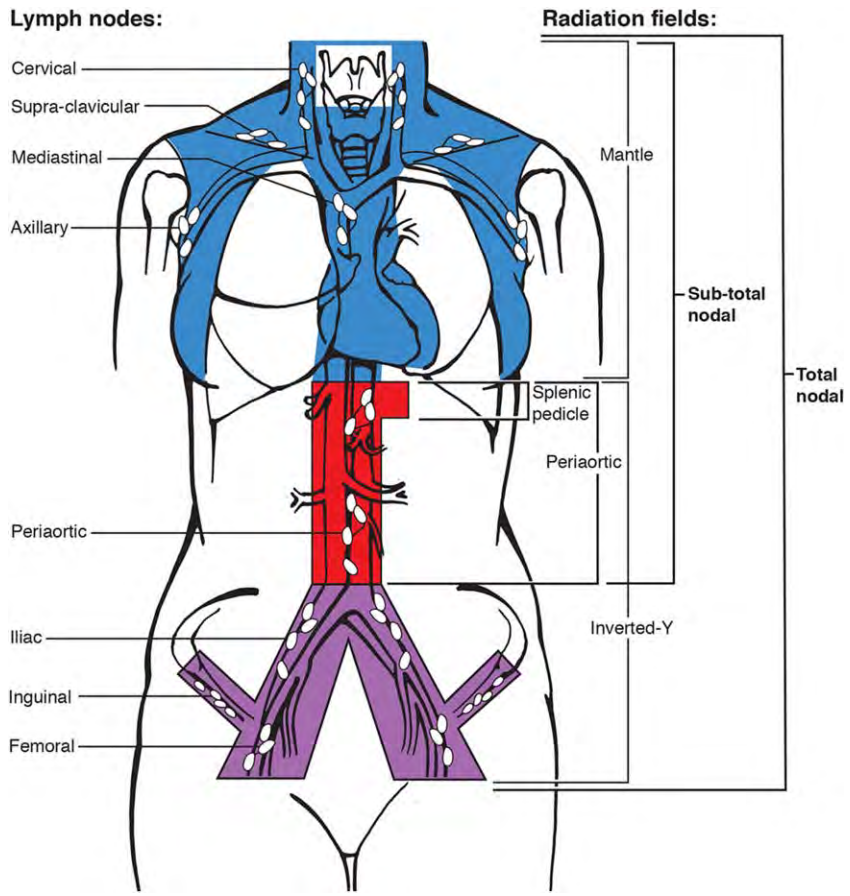

FIGURE 3. Radiation fields historically used to treat Hodgkin lymphoma (HL). The mantle field (MF) includes all the lymph nodes in the neck, chest (exclusive of the lungs), and axillae. Additional fields used to treat HL included the periaortic and ilioinguinal fields that encompass the lymph nodes in those respective regions. When MF radiation was combined with the periaortic and splenic pedicle fields, this was commonly referred to as "subtotal nodal" radiation. When the periaortic and ilioinguinal fields were treated, this was known as "inverted-Y" radiation. If all the fields were radiated, it was referred to as "total nodal" radiation.

Table 2. Incidence of cranial mononeuropathies seen in head and neck cancer.[20]

Cranial nerve		Incidence of mononeuropathy
I	Olfactory	Not assessed
II	Optic	10%
III	Oculomotor	12%
IV	Trochlear	Not assessed
V	Trigeminal	22%
VI	Abducens	8%
VII	Facial	19%
VIII	Vestibulocochlear	Not assessed
IX	Glossopharyngeal	85% with vagus
X	Vagus	85% with glossopharyngeal
XI	Accessory	12%
XII	Hypoglossal	57%

kin lymphoma (HL) can be extensive (Fig. 3) and inclusive of multiple important neuromuscular and visceral structures, including the spinal cord, nerve roots, plexus, peripheral nerves, muscles, heart, blood vessels, lymphatics, lung, etc.[4] The total dose used to treat HL varied significantly but could be as high as 42 Gy or even 46 Gy. As with other malignancies, radiation for HL has evolved significantly and now uses involved-field RT that offers a reduced normal tissue dose and lower secondary cancer risk.[18]

RT is a critical component for the treatment of many head and neck cancers (HNCs). Most contemporary treatment protocols utilize IMRT, with doses ranging from 66 to 74 Gy for gross disease and 50 to 60 Gy for subclinical disease such as lymph nodes in the neck.[19] Fractionation varies but is generally about 2 Gy/fraction. Because of the high total dose and concentration of important structures in the radiation field, HNC survivors treated with radiation are extremely likely to develop neuromuscular and musculoskeletal pain as well as visceral, functional, and other late effects.[4] One study demonstrated that 72 of 328 (22%) HNC patients treated with RT developed cranial mononeuropathies (Table 2).[20] A prospective assessment of 330 HNC survivors treated with radiation found that 12% reported neuropathic symptoms consistent with brachial plexopathy.[21]

NEUROMUSCULAR DYSFUNCTION IN RFS

RF can affect any neural structure, including the brain, spinal cord, nerve root, plexus, peripheral nerve, and muscle. It is possible to injure all or any combination of these structures if they are included in the radiation field. For example, HL survivors treated with mantle field (MF) radiation can manifest damage to the spinal cord, nerve roots, plexuses (cervical and brachial), peripheral nerves (e.g., phrenic, dorsal scapular, spinal accessory), and muscles (e.g., cervical paraspinal, trapezius, scalene, supraspinatus) encompassed by the radiation field (Fig. 4). Such widespread neuromuscular dysfunction is common in HL survivors and has been termed *myelo–radiculo–plexo–neuro–myopathy*.[4] Similarly, an HNC survivor who has received high-dose conformal radiation (IMRT) to their primary tumor and neck may not manifest damage to the spinal cord but can have a radiculo–plexo–neuro–myopathy (Fig. 5).

IDENTIFICATION AND EVALUATION OF NEUROMUSCULAR LATE EFFECTS IN CANCER SURVIVORS

Accurate identification of a neuromuscular disorder as radiation related starts with a comprehensive assessment and understanding of the patient's medical history coupled with a specialized physical examination. Imaging, laboratory evaluation, and electrodiagnostic (EDX) testing can be extremely useful but are not always indicated. As described above, the importance of understanding the key components of the patient's RT, including total dose and dose per fraction, cannot be overstated. Late neuromuscular effects can be related to radiation only if the affected structure either was within or traverses the radiation field. There are tremendous variations in the time to onset and severity of signs and symptoms relative to RT. Some patients will develop signs and symptoms within weeks or months and progress rapidly. Others, even if treated with the same radiation protocol, may not develop RT sequelae for years, if ever.

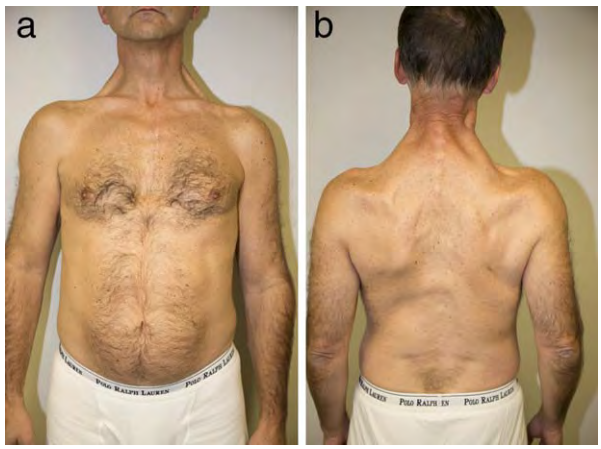

FIGURE 4. (A,B) A 58-year-old man who was diagnosed with HL when he was 15 years old. He underwent an exploratory laparotomy and splenectomy followed by MF radiation (dose unknown due to lost records). He did not receive chemotherapy. He has multiple neuromuscular, musculoskeletal, visceral, and functional late effects of HL treatment including a myelo–radiculo–plexo–neuro–myopathy. Note the marked wasting of the cervical, thoracic, and shoulder girdle muscles with relative preservation of the pectoral muscles which would have been shielded, along with his lung fields, from AP radiation.

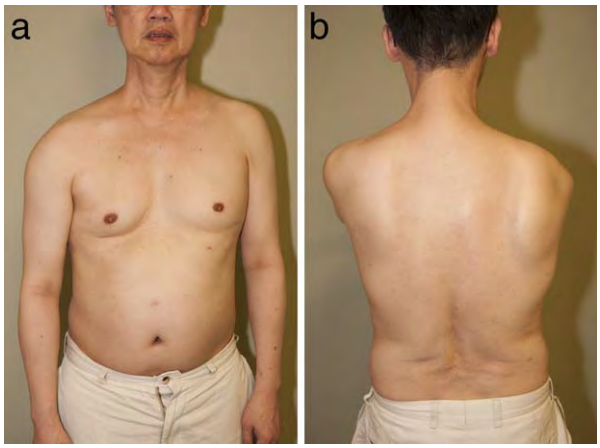

FIGURE 5. (A,B) A 57-year-old man with right-sided nasopharyngeal carcinoma diagnosed 15 years ago and treated with fluorouracil (5-FU) and intensity-modulated radiation therapy (IMRT) 7,020 cGy to the primary tumor and neck lymph nodes. He has electromyography-documented upper cervical radiculopathy, cervical and brachial plexopathy, mononeuropathy of the right spinal accessory nerve, and myopathy in the radiation field. This is termed a *radiculo–plexo–neuro–myopathy*. An IMRT treatment plan spared his spinal cord, and no myelopathy is present clinically. Note atrophy in the right sternocleidomastoid, trapezius, deltoid, and pectoral muscles. The right scapula is laterally winged as a result of trapezius muscle dysfunction. 1 cGy = 0.01 Gray.

Clinically, radiation injury to the nerve can result in pain, sensory dysfunction, or weakness, with subsequent impairment of common functions such as gait and ability to participate in activities of daily living (ADLs). Autonomic dysfunction is also seen and can present in a variety of ways, such as orthostatic hypotension, bowel and bladder change, or sexual dysfunction.

Neuropathic pain is common in RFS and results from damage or dysfunction of affected neural structures such as the nerve roots, plexuses, or peripheral nerves.[22,23] The mechanisms contributing to the generation of neuropathic pain are complex and may involve both centrally and peripherally mediated processes.[24] The generation of ectopic activity in radiation-damaged neural structures is likely a major component of the pathogenesis of pain. Damage to descending modulatory pathways may also be contributory.[25] Because ectopic signals are not generated in a physiologic manner, they can result in severe and intractable pain that is out of proportion to the degree of perceived nerve injury. The etiology of the ectopic signal can be compression, ischemia, or the result of demyelination owing to the underlying pathophysiology of RF; ultimately, axon loss occurs. Ectopic activity resulting from RF can develop in any affected central or peripheral neural structure including the thalamus, ascending spinothalamic tracts of the spinal cord, nerve roots, plexuses, and peripheral nerves. Pre-existing medical or degenerative disorders such as diabetes or spondylosis-related cervical radiculopathy may also affect the peripheral nervous system (PNS). Such nerves may be predisposed to the generation of ectopic pain signals when subjected to RF.[26]

Sensory deficits can be seen in RFS without pain. The primary modalities affected include light touch, pain, temperature, vibration, and position sensation. Sensory deficits can increase the patient's susceptibility to injury and profoundly affect gait, ADLs, and other functions.

Weakness can be caused by damage at any level of the neuromuscular axis, including the brain, spinal cord, peripheral nerve, and muscle. Myelopathy resulting from radiation injury can be "early-delayed," which is almost always reversible, or "late-delayed," which is almost always progressive and permanent.[27] Nerve root damage causes weakness in a myotomal pattern. Multiple nerve roots are often affected, resulting in polyradiculopathy.

Plexopathy can be cervical, brachial, and/or lumbosacral, depending on the radiation field. Differentiating radiation induced from neoplastic plexopathy is a common diagnostic challenge (Table 3).[28] Pain was shown to be a presenting symptom of metastatic brachial plexopathy in 75% of patients in one series; it was also the presenting symptom in 18% of patients with radiation-induced plexopathy.[29] The corollary is that pain was not present in 25% of patients with metastatic brachial plexopathy. The clinician should be careful to supplement their clinical evaluation with imaging, such as MRI with gadolinium or positron emission tomography (PET)/CT, in cases of undiagnosed progressive plexopathy. Serial imaging (i.e., every 3 months) may be appropriate in cases with a high likelihood for a malignant etiology because it is not uncommon for tumor to be the cause of pain even in the setting of an initially negative MRI or PET scan.

The upper brachial plexus and upper cervical nerve roots may be more susceptible to radiation injury in certain clinical situations. Disproportionate radiation effects on the upper plexus may be due to the apical location of the upper plexus in the neck and the long course traversed by its fibers relative to the middle and lower trunk. The upper cervical nerve roots and plexus may be encompassed by the radiation field, whereas the middle and lower plexus structures are excluded in some HNC radiation treatment plans. The pyramidal shape of the thorax and the clavicle may also provide some protection for the middle and lower plexus relative to the upper plexus, although the clinical validity of this phenomenon has not been proven.[28]

Table 3. Clinical findings differentiating neoplastic from radiation-induced plexopathy

Variables	Radiation induced	Cancer
Typical presentation	Weakness, paresthesias	Pain
Pain	Develops late	Develops early and may be severe
Edema	Common	Rare
Plexus involvement		
Brachial	Entire plexus, often upper plexus depending on radiation field	Usually lower plexus
Lumbosacral	Usually bilateral	Lower plexus, usually unilateral
Horner syndrome	Rare	Common
Local tissue necrosis	Common	None
Myokymia on EMG	Common	Rare
Nerve enhancement on MRI	Rare	Present
PET scan	Usually negative	Positive

Mononeuropathies caused by radiation are easily identified when major structures such as the sciatic or femoral nerve are involved in the radiation field.[30] Mononeuropathies may be less obvious when nerves that are not commonly examined or are difficult to examine (i.e., dorsal scapular, suprascapular, long thoracic, or phrenic nerves) are involved. Dysfunction of these nerves can contribute to shoulder dysfunction in many cancer survivors. Bilateral phrenic nerve dysfunction is a known late effect of MF radiation and contributes to respiratory insufficiency in some HL survivors.[31]

Radiation damage to muscle resulting in a focal myopathy has been associated with nemaline rods on histopathological examination.[32] In addition to weakness, myopathic muscles may be more prone to painful spasms, similar in many respects to myofascial pain.[33] The cause of muscle spasm in RFS is likely mediated by several pathologic mechanisms including the myopathy itself, weakness, and fatigability. Additionally, abnormal ectopic activity in the innervating motor nerve can result in a muscle spasm by sending volleys of spontaneous activity to the muscle with resultant contraction.[34] Muscle spasms may not be obvious to the patient because only a subset of muscle fibers may be affected, thus resulting in what is described as vague stiffness or tightness. Muscle spasms combined with direct fibrosis and sclerosis of muscles in the radiation field may result in fixed contractures.[35]

ELECTRODIAGNOSIS IN RFS

EDX evaluation is often useful in patients with RFS to confirm the nature and extent of their PNS dysfunction, exclude competing diagnoses, and assist with prognostication. Designing an EDX study that will accurately and comprehensively assess the full spectrum of the often overlapping neuromuscular disorders in patients with RFS can be extremely challenging. A thorough history and physical examination are instrumental in arriving at a tentative diagnosis and guiding the EDX testing. The examiner should seek to understand all salient details of the patient's cancer history, including when and how it was diagnosed (location and size of the primary tumor), how it was treated (surgery, chemotherapy, radiotherapy), and the patient's present status (no evident disease, local recurrence, metastases).

Knowing the location of the tumor at diagnosis as well as the presence of any residual disease at the time of examination is extremely important for understanding the cause of a patient's past and current neuromuscular disorders. Simply reviewing the radiology reports can be misleading because the radiologist often has not looked for or reported the information required by an EDX consultant. It is not uncommon for tumors to become radiographically undetectable following treatment. Neural structures may have been damaged directly by the tumor (or by RT), but, because of a favorable treatment response, an anatomic source of compression can no longer be identified. The examiner should seek baseline imaging to determine which neural structures may have been compromised.

The types and doses of antineoplastic medications (chemo, hormonal, biologic) should be reviewed, and exposure to neurotoxic agents (i.e., platinum analogues, taxanes, vinca alkaloids) should be identified.[36] Not all patients exposed to neurotoxic chemotherapy will develop chemotherapy-induced peripheral neuropathy (CIPN), and some may develop it at relatively low doses. Medical comorbidities such as diabetes, rheumatic disorders, or degenerative diseases such as cervical spondylosis may increase the patient's susceptibility to developing symptomatic CIPN.[36] It should not be assumed that neuropathic symptoms in a cancer survivor are due to exposure to neurotoxic chemotherapy because other causes such as radiculopathy, plexopathy, mononeuropathy, or other types of peripheral neuropathy are common.[36]

The physical examination should identify muscle atrophy, weakness, and asymmetry (Figs. (4 and 5)). Tattoos used for targeting radiation may be present and are a good indicator of the radiation

field used. The skin may demonstrate atrophy, erythema, hyperpigmentation, hypopigmentation, fibrosis, increased nevi, and other changes. It is common in HNC and HL survivors for shoulder abduction and elbow flexion to be weak, likely because of RF effects on the midcervical nerve roots and upper brachial plexus.[4] Muscles outside the radiation field but innervated by nerves that traverse it are often weak and atrophic (Fig. 5). Reflexes may be absent, depressed, or asymmetric, reflecting damage to peripheral nerve innervation of the muscle/tendon combination under examination. HL survivors treated with MF radiation, and occasionally HNC survivors treated with IMRT, may demonstrate depressed or absent reflexes in the upper extremities as a result of radiation effects on the nerve roots, plexus, and peripheral nerves while simultaneously demonstrating increased lower extremity reflexes and/or clonus owing to radiation effects on the spinal cord.

The type, total dose, fractionation, and fields used to deliver RT will dictate how EDX testing is performed. An optimal study will evaluate all levels of the PNS within or traversing the known radiation field, including the nerve roots, plexuses, peripheral nerves, and muscles. When evaluating a patient with a history of radiation for HL or HNC, nerve conduction studies (NCSs) should include the bilateral median and ulnar motor and sensory nerves as well as at least 1 lower extremity motor and 1 lower extremity sensory nerve. Additional nerves such as the radial motor and sensory or the medial or lateral antebrachial cutaneous nerves should be added as required. This approach will help differentiate radiculopathy from plexopathy and peripheral neuropathy while excluding the presence of competing PNS disorders. The presence of low-amplitude sensory nerve action potentials (SNAPs) in the lower more than the upper extremities is suggestive of a length-dependent polyneuropathy, which is the pattern expected following exposure to taxanes and vinca alkaloid-based chemotherapy as well as a variety of other disorders.[36] Low-amplitude or absent upper extremity SNAPs, with preserved or relatively preserved lower extremity SNAPs, are not consistent with a length-dependent polyneuropathy and may suggest bilateral plexopathy. Alternatively, this unusual pattern may suggest a sensory ganglionopathy (a non–length-dependent form of CIPN) from exposure to platinum-based chemotherapy or from a paraneoplastic disorder.[36] It is common for the upper plexus to be more affected than the lower plexus in HL and HNC survivors. On EDX testing, this usually manifests as abnormalities in the sensory nerves derived from the upper plexus (lateral antebrachial cutaneous, median) being more affected than those from the lower plexus (ulnar, medial antebrachial cutaneous). Compound motor unit action potentials (CMAPs) are often low when severe axonal loss is present. Unfortunately, this finding is not sufficient to differentiate the various disorders (i.e., radiculopathy, plexopathy, mononeuropathy, and myopathy) common in RFS.

Needle electromyography (EMG) is instrumental in identifying PNS disorders resulting from radiation and can help differentiate them from other etiologies. A comprehensive examination generally includes examination of 1 or both upper extremities, multiple proximal muscles, 1 lower extremity, and the paraspinal muscles. Spontaneous activity, motor unit remodeling, and reduced recruitment can be seen in muscles whose neural innervation has traversed the radiation field as well as those inside the field. This is not invariable, however, because the insidious nature of radiotoxicity may produce little sign of active ongoing denervation. It is important to assess muscles in the distribution of different peripheral nerves and roots to distinguish radiculopathy from plexopathy and peripheral neuropathy and so arrive at a clear diagnosis Therefore, NCS findings must be used to arbitrate between PNS disorders to determine whether more than 1 disorder exists.

Needle EMG within the radiation field is challenging because myopathic and neuropathic findings can coexist. CMAPs with low amplitude, short duration, polyphasia, and early recruitment suggesting myopathy are commonly seen within the radiation field.[4] These myopathic changes have been associated with nemaline rods histopathologically.[32] Myopathic motor units may be interspersed with large, long-duration, polyphasic motor units with neurogenic recruitment suggestive of a neuropathic process because neuropathic and myopathic processes can coexist. Although the combination of myopathic and neuropathic motor units within the radiation field is highly suggestive of radiation injury, the relative proportion of neuropathic versus myopathic motor units can vary considerably. Reduced insertional activity can be seen in severely fibrotic muscles. The muscles examined will be dictated by the examiner's understanding of the radiation field and the structures that are encompassed by or traverse it. In addition to a routine root screen, several proximal muscles within the field are generally evaluated. In an HNC survivor, for instance, if clinically indicated, the EDX consultant may examine the trapezius, latissimus dorsi, sternocleidomastoid, scalene, rhomboid, levator scapulae, pectoralis major, serratus anterior, masseter, tongue, cervical paraspinal, and/or thoracic paraspinal muscles to delineate the extent of radiation injury. Although such an extensive

examination is often illuminating, it is not always necessary to determine that damage is consistent with RFS.

Synthesizing the EDX findings into a comprehensive whole is particularly challenging in RFS survivors. Differentiating radiculopathy from plexopathy is based on finding an NCS pattern typical of radiculopathy (low CMAP amplitude with preserved SNAP amplitude) combined with needle EMG findings typical of radiculopathy (spontaneous activity, neurogenic motor unit remodeling in the distribution of 2 or more nerves sharing the same root and/or the appropriate cervical paraspinal muscles). Multiple levels of the neural axis may be affected. If upper extremity CMAP amplitudes are assessed only in the median and ulnar nerves, then only disorders affecting C8, T1, the lower plexus, and the median/ulnar nerve can be evaluated. Testing of more proximal motor nerves and their respective muscles (deltoid, biceps, triceps) may be indicated when asymmetric atrophy is present clinically. Testing should be conducted bilaterally because a 50% or greater side-to-side amplitude difference is suggestive of pathology. The presence of abnormal spontaneous activity and/or neuropathic motor units in the paraspinal muscles, even when intermixed with myopathic motor units, suggests radiculopathy. Mononeuropathy is generally assessed by needle EMG evaluation of proximal muscles such as the trapezius and rhomboids. As with the cervical paraspinals, muscles within the radiation field will often demonstrate both myopathic and neuropathic findings because neuropathic and myopathic processes can coexist.

CONCLUSIONS

Although neuromuscular dysfunction is uncommon following RT for tumors such as breast and prostate cancer, it is expected following the treatment of HNC, HL, and other tumor types in which high doses of radiation in the proximity of key neurologic structures are required. The identification of RFS requires the clinician to be familiar with the basics of radiation delivery. Key factors that contribute to RFS include not only the total dose and dose per fraction but also the radiation field used and the structures encompassed by it. The advanced knowledge of the PNS common to the neuromuscular specialist coupled with attention to the details of radiation treatment will assist the clinician in making accurate and insightful assessments in this challenging population.

I confirm that I have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

REFERENCES

1. Cancer facts & figures 2015. American Cancer Society. Available at http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf. Accessed August 19, 2017.
2. Hauer-Jensen M, Fink LM, Wang J. Radiation injury and the protein C pathway. Crit Care Med 2004;32(Suppl 2):S325–S330.
3. Lutz S. Recent advances in palliative radiotherapy. Curr Opin Support Palliat Care 2012;6(1):77–79.
4. Stubblefield MD. Radiation fibrosis syndrome: neuromuscular and musculoskeletal complications in cancer survivors. PM R 2011;3(11):1041–1054.
5. Camporeale J. Basics of radiation treatment. Clin J Oncol Nurs 2008;12(2):193–195.
6. Aird EG. Radiotherapy today and tomorrow—an introduction to optimisation of conformal radiotherapy. Phys Med Biol 1989;34(10):1345–1348.
7. Bhide SA, Nutting CM. Recent advances in radiotherapy. BMC Med 2010;8:25.
8. Roopashri G, Baig M. Current advances in radiotherapy of head and neck malignancies. J Int Oral Health 2013;5(6):119–123.
9. Nakamura K, Sasaki T, Ohga S, Yoshitake T, Terashima K, Asai K, Matsumoto K, Shioyama Y, Honda H. Recent advances in radiation oncology: intensity-modulated radiotherapy, a clinical perspective. Int J Clin Oncol 2014;19(4):564–569.
10. Peng G, Wang T, Yang KY, Zhang S, Zhang T, Li Q, Han J, Wu G. A prospective, randomized study comparing outcomes and toxicities of intensity-modulated radiotherapy vs. conventional two-dimensional radiotherapy for the treatment of nasopharyngeal carcinoma. Radiother Oncol 2012;104(3):286–293.
11. Laufer I, Rubin DG, Lis E, Cox BW, Stubblefield MD, Yamada Y, Bilsky MH. The NOMS framework: approach to the treatment of spinal metastatic tumors. Oncologist 2013;18(6):744–751.
12. Lin X, DeAngelis LM. Treatment of brain metastases. J Clin Oncol 2015;33(30):3475–3484.
13. Delanian S, Lefaix JL, Pradat PF. Radiation-induced neuropathy in cancer survivors. Radiother Oncol 2012;105(3):273–282.
14. Pradat PF, Delanian S. Late radiation injury to peripheral nerves. Handb Clin Neurol 2013;115:743–758.
15. Delanian S, Lefaix JL. The radiation-induced fibroatrophic process: therapeutic perspective via the antioxidant pathway. Radiother Oncol 2004;73(2):119–131.
16. Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, Shank B, Solin LJ, Wesson M. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991;21(1):109–122.
17. Galecki J, Hicer-Grzenkowicz J, Grudzien-Kowalska M, Michalska T, Zalucki W. Radiation-induced brachial plexopathy and hypofractionated regimens in adjuvant irradiation of patients with breast cancer—a review. Acta Oncol 2006;45(3):280–284.
18. Koh ES, Tran TH, Heydarian M, Sachs RK, Tsang RW, Brenner DJ, Pintilie M, Xu T, Chung J, Paul N, Hodgson DC. A comparison of mantle versus involved-field radiotherapy for Hodgkin's lymphoma: reduction in normal tissue dose and second cancer risk. Radiat Oncol 2007;2:13.
19. Pfister DG, Spencer S, Brizel DM, Burtness B, Busse PM, Caudell JJ, Cmelak AJ, Colevas AD, Dunphy F, Eisele DW, Gilbert J, Gillison ML, Haddad RI, Haughey BH, Hicks WL, Jr. Hitchcock YJ, Jimeno A, Kies MS, Lydiatt WM, Maghami E, Martins R, McCaffrey T, Mell LK, Mittal BB, Pinto HA, Ridge JA, Rodriguez CP, Samant S, Schuller DE, Shah JP, Weber RS, Wolf GT, Worden F, Yom SS, McMillian NR, Hughes M. Head and neck cancers, version 2.2014. Clinical practice guidelines in oncology. J Natl Compr Canc Netw 2014;12(10):1454–1487.
20. Rong X, Tang Y, Chen M, Lu K, Peng Y. Radiation-induced cranial neuropathy in patients with nasopharyngeal carcinoma. A follow-up study. Strahlenther Onkol 2012;188(3):282–286.
21. Chen AM, Hall WH, Li J, Beckett L, Farwell DG, Lau DH, Purdy JA. Brachial plexus-associated neuropathy after high-dose radiation therapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys 2012;84(1):165–169.
22. Levy MH, Chwistek M, Mehta RS. Management of chronic pain in cancer survivors. Cancer J 2008;14(6):401–409.
23. Lema MJ, Foley KM, Hausheer FH. Types and epidemiology of cancer-related neuropathic pain: the intersection of cancer pain and neuropathic pain. Oncologist 2010;15(Suppl 2):3–8.
24. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol 2010;9(8):807–819.
25. Heinricher MM, Tavares I, Leith JL, Lumb BM. Descending control of nociception: specificity, recruitment, and plasticity. Brain Res Rev 2009;60(1):214–225.
26. Campbell JN, Meyer RA. Mechanisms of neuropathic pain. Neuron 2006;52(1):77–92.

27. Giglio P, Gilbert MR. Neurologic complications of cancer and its treatment. Curr Oncol Rep 2010;12(1):50–59.
28. Jaeckle KA. Neurologic manifestations of neoplastic and radiation-induced plexopathies. Semin Neurol 2010;30(3):254–262.
29. Kori SH, Foley KM, Posner JB. Brachial plexus lesions in patients with cancer: 100 cases. Neurology 1981;31(1):45–50.
30. Pradat PF, Bouche P, Delanian S. Sciatic nerve mononeuropathy: an unusual late effect of radiotherapy. Muscle Nerve 2009;40(5):872–874.
31. Avila EK, Goenka A, Fontenla S. Bilateral phrenic nerve dysfunction: a late complication of mantle radiation. J Neurooncol 2011;103(2):393–395.
32. Portlock CS, Boland P, Hays AP, Antonescu CR, Rosenblum MK. Nemaline myopathy: a possible late complication of Hodgkin's disease therapy. Hum Pathol 2003;34(8):816–818.
33. Shah JP, Danoff JV, Desai MJ, Parikh S, Nakamura LY, Phillips TM, Gerber LH. Biochemicals associated with pain and inflammation are elevated in sites near to and remote from active myofascial trigger points. Arch Phys Med Rehabil 2008;89(1):16–23.
34. Miller TM, Layzer RB. Muscle cramps. Muscle Nerve 2005;32(4):431–442.
35. Stubblefield MD, Levine A, Custodio CM, Fitzpatrick T. The role of botulinum toxin type A in the radiation fibrosis syndrome: a preliminary report. Arch Phys Med Rehabil 2008;89(3):417–421.
36. Stubblefield MD, Burstein HJ, Burton AW, Custodio CM, Deng GE, Ho M, Junck L, Morris GS, Paice JA, Tummala S, Von Roenn JH. NCCN task force report: management of neuropathy in cancer. J Natl Compr Canc Netw 2009;7(Suppl 5):S1–S26; quiz S27–S28.
37. Jaeckle KA. Neurological manifestations of neoplastic and radiation-induced plexopathies. Semin Neurol 2004;24(4):385-393.