

# Spinal Cord and Peripheral Nervous System

John P. Kirkpatrick

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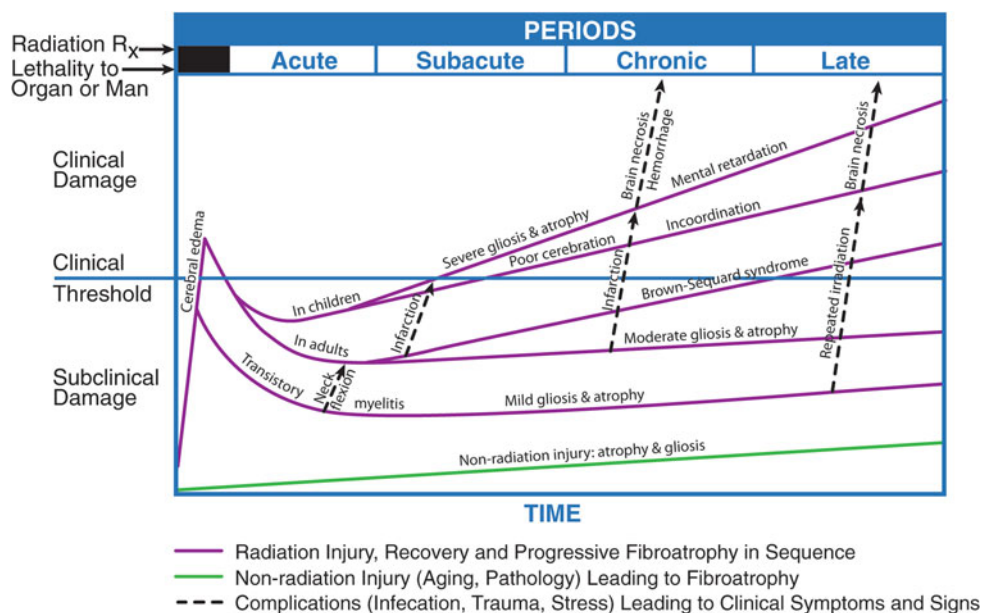
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## Abstract

- Spinal cord and peripheral nerve injury (myelopathy), from radiation therapy can be transient or severe and debilitating, producing pain, paresthesias, sensory deficits, paralysis, Brown-Sequard syndrome, and bowel/bladder incontinence.
- The sympathetic system, the ganglia are located along paired chains on both sides of the vertebral column (the sympathetic trunk), as well as in three major collateral ganglia.
- The principal pathogenesis of injury is established to be due to vascular endothelial damage, glial cell injury, or both.
- Peripheral nerve damage by ionizing radiation has focused on the effect of single, high doses of radiation in animals, simulating the experience of intraoperative radiotherapy. Approximately 15 Gy IORT alone was observed to produce a 50 % reduction in the axon/myelin content.
- Magnetic resonance imaging (MRI) is typically the imaging modality of choice for assessing malignancies involving the spinal cord and brachial plexuses and detecting and diagnosing cord myelopathy.
- The use of various chemotherapy agents during radiotherapy has been shown to increase the radiosensitivity of the spinal cord. Toxicity increases when intrathecal chemotherapy is combined with systemic therapy with CNS irradiation.
- Radiation therapy to the spinal cord and peripheral nerves can induce myelopathy, typically characterized by pain, paralysis, and paresthesias. The risk of myelopathy primarily depends on the total radiation dose and dose per fraction, although the volume irradiated, underlying disease, concurrent therapies, and previous irradiation may also play a role.
- For external beam radiotherapy (EBRT) to the spinal cord in 2 Gy daily fractions, the risk of myelopathy appears low (<0.2 %) at 50 Gy and modest (<10 %) at

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**Fig. 1** Biocontinuum of radiation induced acute, subacute, chronic, and late effects of the CNS (with permission from Rubin and Casarett 1968)



60 Gy, with an approximately 50 % risk of myelopathy at 70 Gy. Due to the severe consequences of myelopathy, clinical dose limits, i.e., shield at 40 Gy, have been used which carry a low (<0.2 %) risk of toxicity.

- The risk of radiation-induced brachial plexopathy is <1 % for a total dose of 50 Gy or less.
- For intraoperative radiotherapy (IORT) to the lumbosacral and brachial plexus, the threshold dose for injury appears to be 15–20 Gy.
- For single-fraction stereotactic radiosurgery to the spine, the risk of radiation-induced myelopathy appears low (well under 5 %) when the maximum point dose to the cord is  $\leq 14$  Gy, though the number of patients is small and the follow-up short at present.

## 1 Introduction

Metastatic vertebral spinal disease is a frequent indication for spinal cord radiotherapy, with an estimated 40% of all cancer patients ultimately developing vertebral body metastases (Klimo et al. 2005). In addition, portions of the spinal cord are often included in radiotherapy fields for treatment of pharyngeal, pulmonary, esophageal, and mediastinal and other malignancies involving the head, and neck, thorax, abdomen, and pelvis. Total nodal irradiation techniques in Hodgkin's disease resulted in radiation myelopathy of a "gap" which was omitted between mantle and para-aortic fields. Likewise, the brachial and lumbosacral plexuses frequently receive high doses of radiation during irradiation of the upper chest wall and pelvis, respectively. Though rare, spinal cord and peripheral nerve injury (myelopathy), from radiation therapy can be severe and

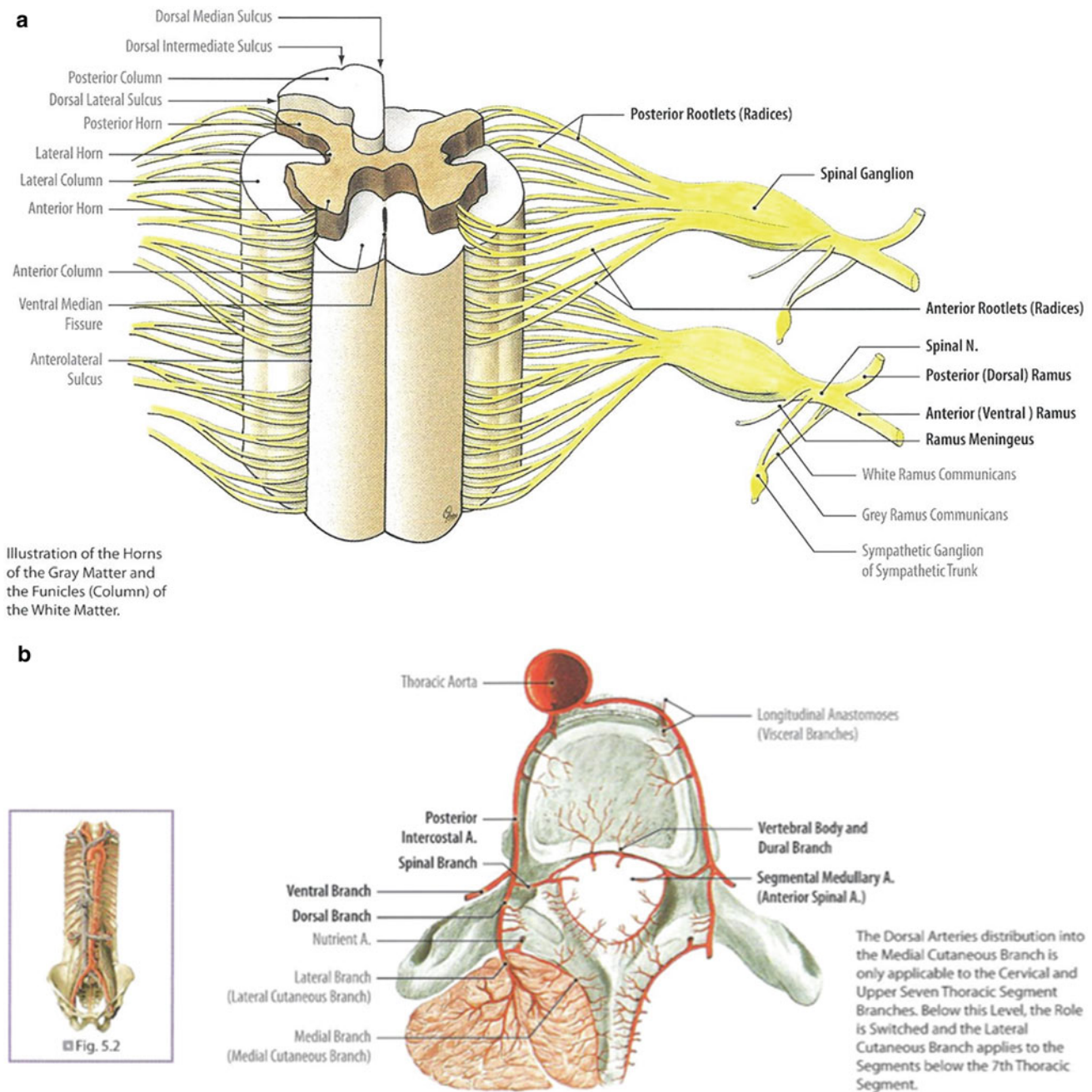
debilitating, producing pain, paresthesias, sensory deficits, paralysis, Brown-Sequard syndrome, and bowel/bladder incontinence (Schultheiss et al. 1995). Biocontinuum of adverse acute and late effects are illustrated in Fig. 1.

## 2 Anatomy and Histology

### 2.1 Anatomy

The spinal cord is considered to be an extension of the central nervous system housed and protected by the vertebral bodies (Fig. 2a). The spinal nerves constitute the peripheral nervous system (PNS) and will be presented sequentially after the spinal cord to provide continuity in discussing the nervous topical headings in this chapter outline.

The spinal cord consists of bundles of motor and sensory tracts, surrounded by the thecal sac, which is, in turn, encased by the spinal canal (Goetz 2003). The spine canal consists of 7 cervical, 12 thoracic, 5 lumbar, and 5 sacro-coccygeal bony vertebrae. Together the spinal canal and cord comprise the spine. While the spinal cord proper extends from the base of skull through the top of the lumbar spine—typically, the level of the first or second lumbar vertebrae in adults versus the second or third lumbar vertebrae in neonates—individual nerves continue down the spinal canal to the level of the pelvis. The conus medullaris is the cone-shaped termination of the caudal cord located in the upper lumbar spinal canal. The cord is tethered to the coccyx caudally by the filum terminale, a continuation of the pia mater. The cauda equina (*L. horse tail*) consists of lumbar and sacral spinal nerve roots traveling inferiorly from the cord prior to emerging from the spine through the intervertebral foramina.



**Fig. 2** **a** Spinal nerves are formed from the motor and sensory fibers coming from the spinal cord. **b** The vascular supply of the spinal cord is shown. **c** Axial image of the spinal cord with different functions linked to different regions is shown. From Nelson et al. with

permission. **d** Dermatomes are shown on the right-hand side of figure **e**, **f**. Schematic diagram of the autonomic nervous system and its chief divisions. **g** Cross-section of peripheral nerve (reproduced with permission from Netter)

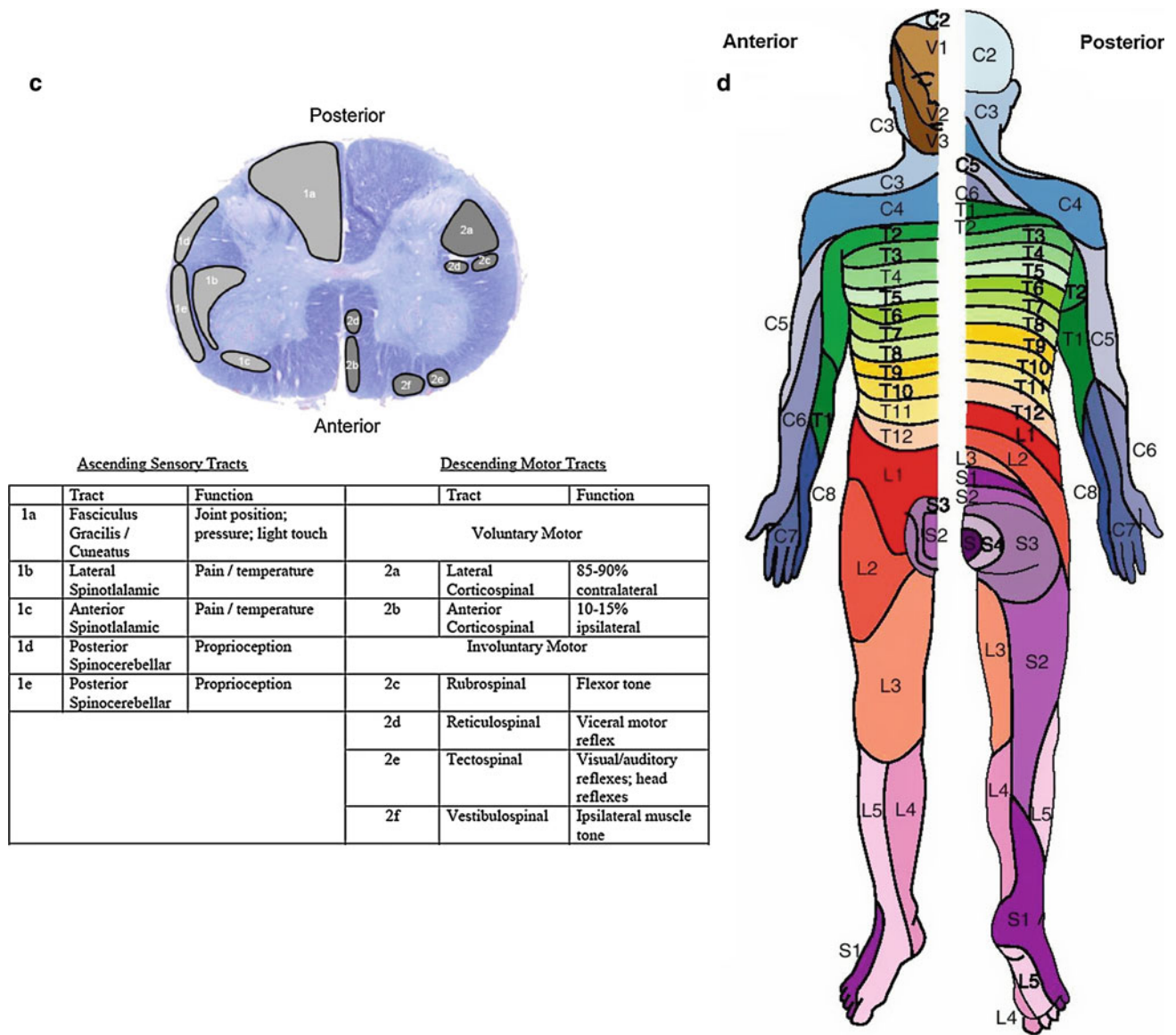
### 2.1.1 Spinal Nerves

The spinal cord is composed of 31 pairs of spinal nerves: 8 cervical (C), 12 thoracic (T), 5 lumbar (L), 5 sacral (S), and 1 coccygeal (Co). The spinal nerves consist of motor and sensory nerve roots, which exit and enter, respectively, the spinal cord at each vertebral level (Fig. 2a). The spinal nerves are named and numbered based on the level at which they emerge from the vertebral canal. C1–7 nerves emerge

above their respective vertebrae, C8 emerges *between* the seventh cervical and first thoracic vertebrae, and the lower thoracic nerves emerge *below* their respective vertebrae.

### 2.1.2 Vascular Anatomy

Vascular anatomy of the spinal cord consists of two arcades of arterioles supplied by the anterior and posterior spinal arteries. Radiation injury to these fine arterioles is often



**Fig. 2** (continued)

suggested as the mechanism for radiation-induced myelopathy rather than a direct effect on the spinal cord parenchymal cells (Fig. 2b).

### 2.1.3 Functional Anatomy

The functional anatomy of the spinal tract of the spinal cord is depicted spatially relating spinal tract function to specific zones in Fig. 2c. Typically, the transaction of the spinal cord is characterized by the “butterfly” appearance of the longitudinal directed spinal axial tracts.

The axial image of the spinal cord reveals central gray matter containing motor neurons, surrounded by white matter made up of well-defined neuronal tracts. Broadly, these are classified as descending motor tracts, carrying either voluntary or involuntary motor signals from the

cortex or brain stem to target muscle groups, and ascending sensory tracts, transmitting signals from peripheral sensory nerves to the brain. There are two principal voluntary motor fiber tracts. The lateral corticospinal tract, located in the posterolateral portion of the white matter, carries 85–90 % of all voluntary motor activity from the contralateral cerebral motor cortex. The anterior corticospinal tract carries the remaining signals, but in an ipsilateral fashion, crossing to control contralateral target muscle groups at the level of action.

The cell body of the ventral (motor) roots is in the anterior horn within the cord parenchyma. The cell bodies of the sensory nerves are located in the dorsal root ganglia. Each dorsal root carries the input from all the structures within the distribution of its corresponding body segment.



**e Sympathetic Nervous System**

Eye:	Dilator Pupillae M.	► Mydriasis
	Tarsal M.	► Elevates and depresses the eyelids and widens the palpebral fissure
	Orbitalis M.	► Protrusion of the bulb
Salivary Glands:		Watery salivary secretion
Vessels (Skin, Mucous Membrane, Brain; in part, Skeletal Muscles, Intestines):		
Arteries	► Vasoconstriction	
Veins	► Vasoconstriction	
Heart:		
Coronary Arteries	► Vasoconstriction	
Myocardium	► Increases heart rate	
	► Increases power of contraction (ionotropic) of the myocardium	
Tracheal & Bronchial Musculature:	► Relaxes	
Gastrointestinal Tract:	► Decreases gland secretion (minor)	
	► Promotes water resorption	
Pancreas (endocrine part):	► Decreases insulin secretion	
Liver:	► Promotes glycogenolysis and gluconeogenesis	
Urinary Bladder:	► Contraction	
Internal Sphincter M.	► Contracts the uterine musculature	
Genitals:	► Contracts the smooth musculature of the seminal vesicle, the prostate, and the ductus deferens	
	► Contracts the smooth muscles in the capsule of the spleen	
Spleen:	► Contracts the smooth muscles in the capsule of the spleen	
Adrenal Gland:	► Secretes adrenalin and noradrenalin	

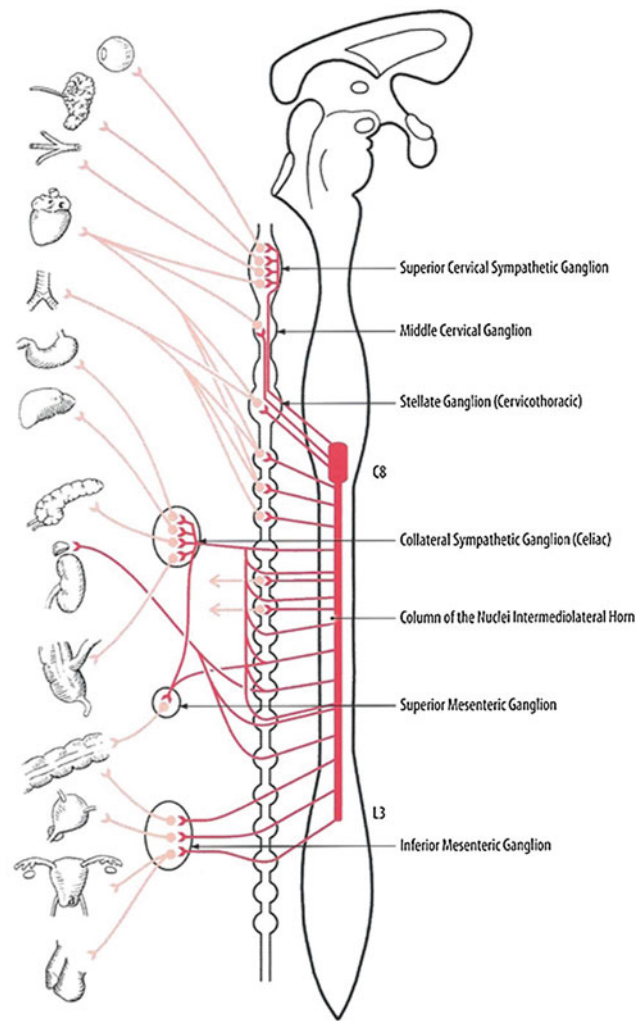
**Fig. 2** (continued)

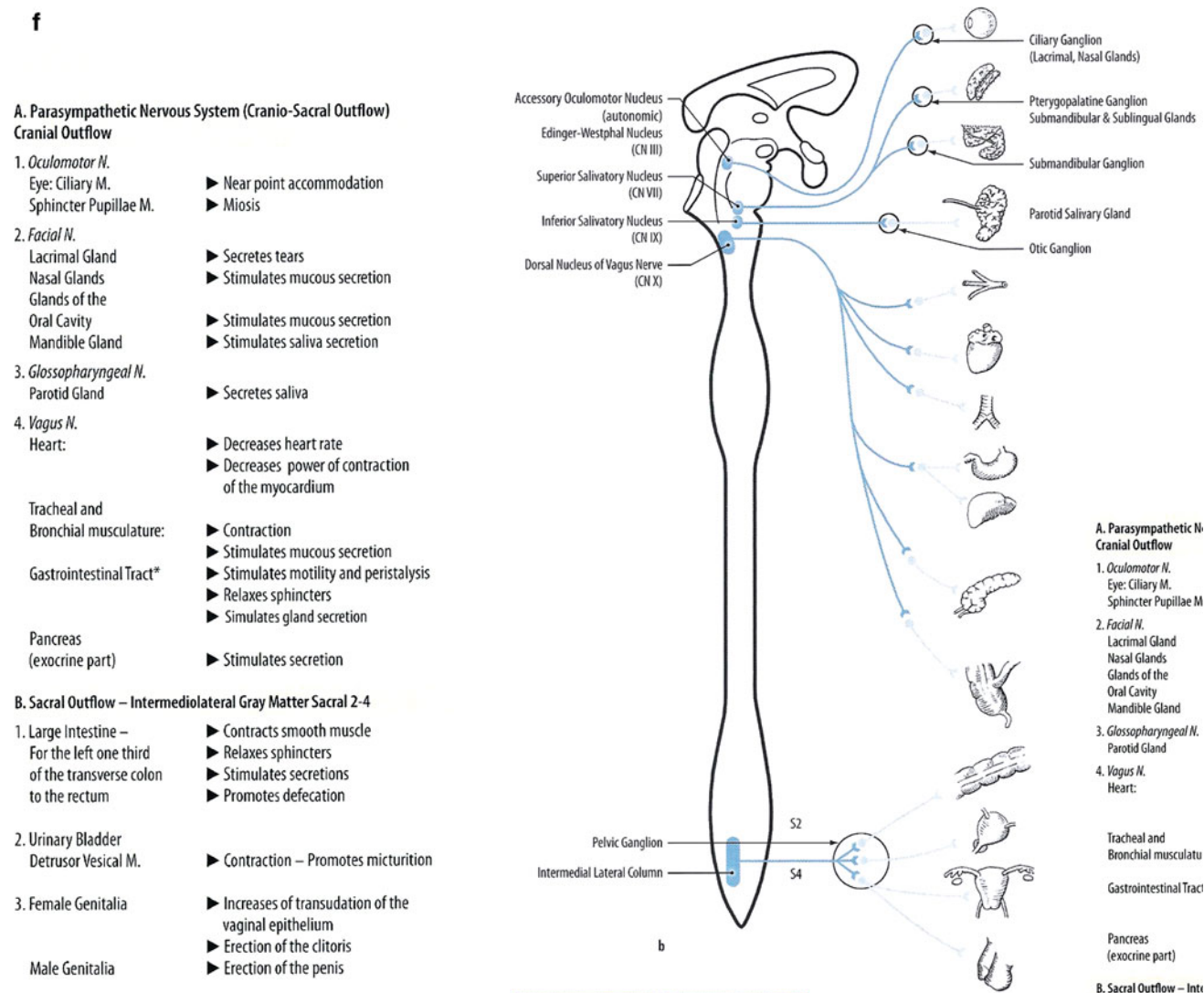
Figure 2d is a dermatomal diagram showing typical sensory distributions. Note that these dermatomes overlap somewhat, dipping as they travel from the spine around the flanks to the chest and abdomen.

The autonomic system is subdivided into the sympathetic, parasympathetic, and enteric systems. In contrast to the somatic nervous systems, signals from the autonomic nervous system to target organs are largely involuntary. These target organs include the hollow viscera, exocrine glands, heart and blood vessels. The sympathetic and parasympathetic divisions provide opposing actions, with the former presiding over emergency responses (the so-called “flight-or-fight” response) and the latter mediating restoration of the body. Though many target organs of the autonomic nervous system are dually innervated, the sympathetic response is generalized, i.e., a variety of organ systems are affected simultaneously, while the actions of the parasympathetic system tend to be more discrete. Figure 2e, f illustrates the

target organs for the sympathetic and parasympathetic divisions. Figure 2g is a cross section of a peripheral nerve.

The anatomy of these two divisions is also different. In the sympathetic system, the ganglia are located along paired chains on both sides of the vertebral column (the sympathetic trunk), as well as in three major collateral ganglia overlying the celiac, superior, and inferior mesenteric arteries. In contrast, the parasympathetic ganglia are located close to or within the target organ. Both systems are under complex control of the central nervous and hormonal systems, particularly the hypothalamus.

The enteric division of the autonomic system controls the functions of the gastrointestinal system along its entire length, including motility, secretion, and absorption. Though its actions are influenced by the sympathetic and parasympathetic divisions and hormonal systems, it essentially functions independently of the central nervous system and the rest of the ANS. The nerves in the enteric system



are organized in two major plexuses—the mesenteric and the submucous plexus—which are distributed circumferentially around gastrointestinal viscera.

## 2.2 Histology

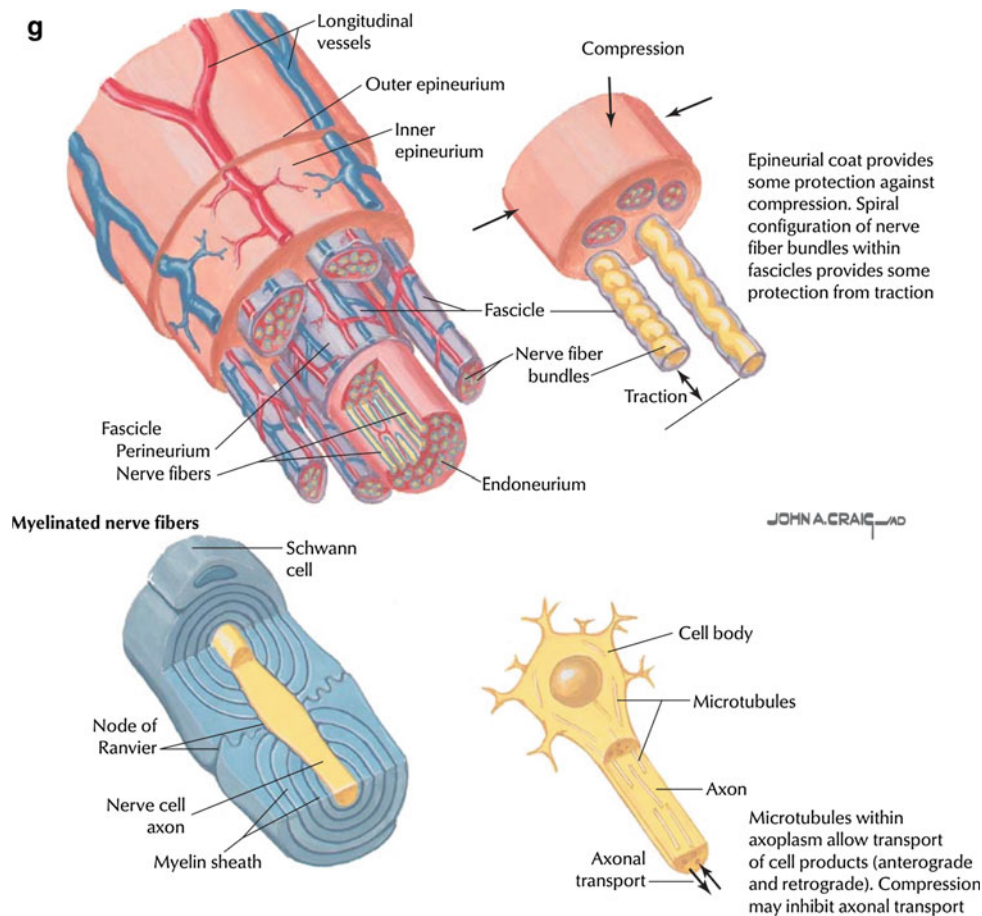
### 2.2.1 Spinal Cord Segment

The spinal cord segment is characterized by the “butterfly contour” which consists of an anterior median fissure and the posterior median sulcus (divide the spinal cord into half). The pia mater, a very thin layer of loose connective tissue, attaches to the surface of the spinal cord. The blood vessels at the entry of the anterior median fissure are branches of the anterior spinal artery and vein, which supply the spinal cord. In the gray matter, the neurons are present in groups, and nerve fibers enter and leave, forming a dense network. The dorsal root fibers enter the posterior horn of the spinal cord

through the posterolateral sulcus, and ventral root fibers leave the spinal cord through the anterolateral sulcus (Fig. 3a).

### 2.2.2 Spinal Horn Neurons

Spinal cord horns consist of motor neurons that are multipolar cells with a large nucleus and prominent nucleolus. Nissl bodies are present in the cell body and dendrites, but not in the axons. Bundles of dendrites extend from the gray matter to the white matter, where the myelinated nerve fibers are seen in cross section. The small nuclei in both gray and white matter belong to the various glial cells, which cannot be classified in H.E.-stained preparations. In addition, blood vessels travel to gray matter, forming the blood–brain barrier with the perivascular feet of astrocytes, which are not visible in this drawing. Figure 3b shows an enlargement of the boxed area in Fig. 3a, showing details of part of the anterior horn and the white matter.



**Fig. 2** (continued)

### 2.2.3 Spinal Ganglion

The spinal ganglion is located on the posterior nerve roots of the spinal cord. It contains the cell bodies of the pseudounipolar primary sensory neurons. The ganglion is enclosed by a dense connective tissue capsule, which divides into trabeculae to provide a framework for the neuronal cells. The neurons of the spinal ganglion are large cells with a large nucleus. Their cell bodies appear round in section and display intense cytoplasmic basophilia. Each ganglion cell body is surrounded by a layer of flat satellite cells, which provide structural and metabolic support to the neurons. Within the ganglion, fascicle of myelinated nerve fibers in both cross and longitudinal sections can be observed. In addition, blood vessels occur throughout the ganglion (Fig. 3c). Peripheral nerve is also shown (Fig. 3d).

## 3 Physiology and Biology

### 3.1 Physiology

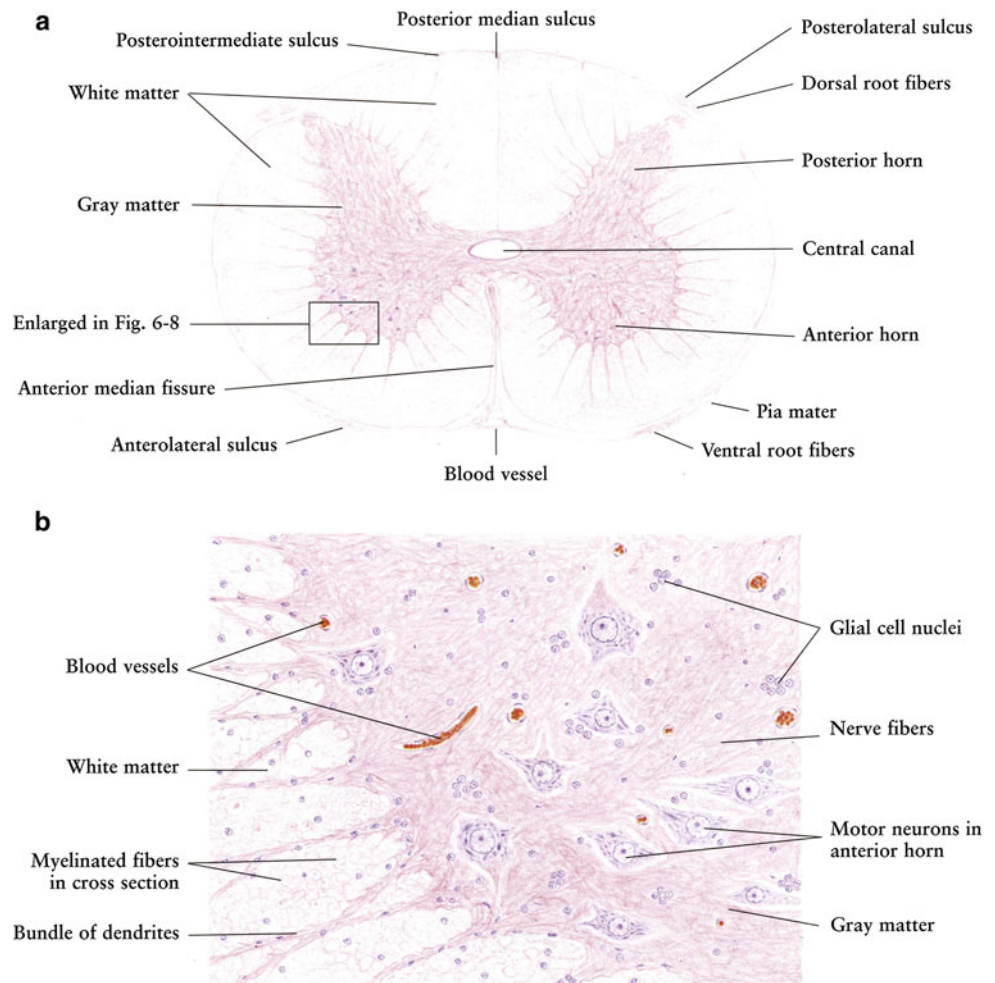
The major neurolinks between the brain and the body is via the spinal cord through the peripheral nervous system via

spinal nerves that branch out to somatic peripheral nerves or the autonomic neurons to vital viscera.

- *Corticospinal* or pyramidal tracts provide the innervation for skeletal muscles, especially the hand. The upper motor neuron connects the brain to the spinal cord (and nerve horns), and the lower motor neurons extend from anterior horn cells via peripheral nerves to muscles.
- *Somesthetic* system provides sensation of pain, temperature, and pressure conveyed from primary somatosensory cortex by the anterolateral spinothalamic and spinoreticular tracts. The spinal lemniscal tracts provide proprioception, vibratory, tactile sensations.
- Cerebellar afferent pathways provide an important role for coordinating movement: posture, movement of head and eyes. Cerebellar efferent pathways coordinate fine, smooth coordinating movement to the proximal and distal portions of limbs.
- Autonomic nervous system instructs visceral, smooth muscle, cardiac muscle, the lung, gastronal tract, the urinary system as well as salivary, lacrimal, sweat glands, the reproductive and sexual activities in addition to the peripheral vascular system. In essence, the vital viscera are regulated via the sympathetic and parasympathetic systems.



**Fig. 3** Histology: **a** spinal cord segments, **b** spinal horn neurons (with permissions from Zhang 1999), **c**, **d** spinal ganglion



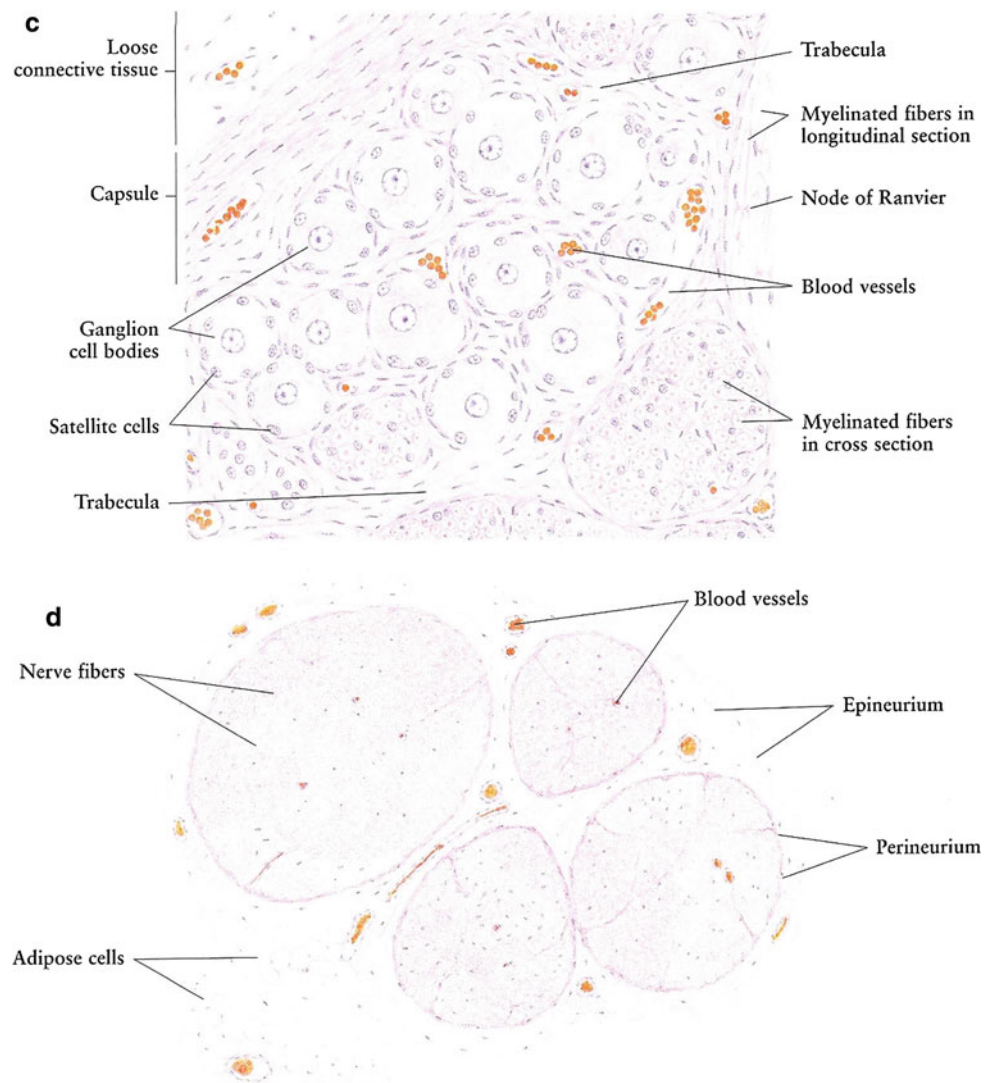
### 3.2 Biology: Small Animal Models

A large number of small-animal studies have been conducted to explore spinal cord tolerance to de novo radiation and re-irradiation, including time-dependent repair of such damage. A number of reports suggest regional differences in radiosensitivity across the spinal cord (Corderre et al. 2006; Phillipens et al. 2007). The clinical endpoint in most of these studies is paralysis, with the spinal cord exhibiting non-specific white matter necrosis pathologically. The principal pathogenesis of injury is generally believed to be due to vascular endothelial damage, glial cell injury, or both (Schultheiss et al. 1995; Corderre et al. 2006). Utilizing precisely focused proton irradiation of the rat spinal cord, Bijl et al. (2002, 2005) demonstrated large regional differences in cord radiosensitivity. There was a rightward shift in the dose response curve from 20.6 Gy (ED50) with full thickness irradiation, compared to 28.9 and 33.4 Gy for lateral cord treatment (wide and narrow geometry, respectively), and 71.9 Gy when only the central portion of the cord was treated. White matter necrosis was observed in all paralyzed rats, with none seen in non-responders. No damage was observed

in central gray matter for doses up to 80 Gy. The differences in central versus peripheral response were attributed to vascular density differences in these regions, with a potential role for differential oligodendrocyte progenitor cell distribution. However, an alternative explanation may be the functional differences in the cord white matter regions irradiated (Nelson et al. 2009), especially given the clinical endpoint of paralysis, which would not be expected if sensory tracts were preferentially irradiated. No similar reports are available in higher order species, making application of these findings to SBRT difficult.

Various small-animal studies support a time-dependent model of repair for radiation damage to the spinal cord (Ang et al. 1983, 1993, 2001; Knowles et al. 1983; Ruifrok et al. 1994; Wong and Hao 1997). For example, Ang et al. (1993) treated the thoracic and cervical spines of 56 Rhesus monkeys to 44 Gy, and then re-irradiated these animals with an additional 57.2 Gy at 1 or 2 years ( $n = 36$ ), or 66 Gy at 2 or 3 years ( $n = 18$ ), yielding total final doses of 101.2 and 110 Gy, respectively. The primary endpoints of this study were lower extremity weakness or balance disturbances at 2.5 years after re-irradiation. Of 45 animals



**Fig. 3** (continued)

evaluated at the completion of the observation period, four developed endpoint symptoms. A re-irradiation tolerance model developed by combining this data with that of a prior study of single dose tolerance in the same animal model resulted in an estimated recovery of 33.6 Gy (76 %), 37.6 Gy (85 %), and 44.6 Gy (101 %) at 1, 2 and 3 years, respectively (Ang et al. 2001). Using conservative assumptions, an overall recovery estimate of 26.8 Gy (61 %) was obtained. In other words, after an initial course of  $\approx 44$  Gy, the cord “forgot” roughly 60 % of this dose  $\approx 2$  years later.

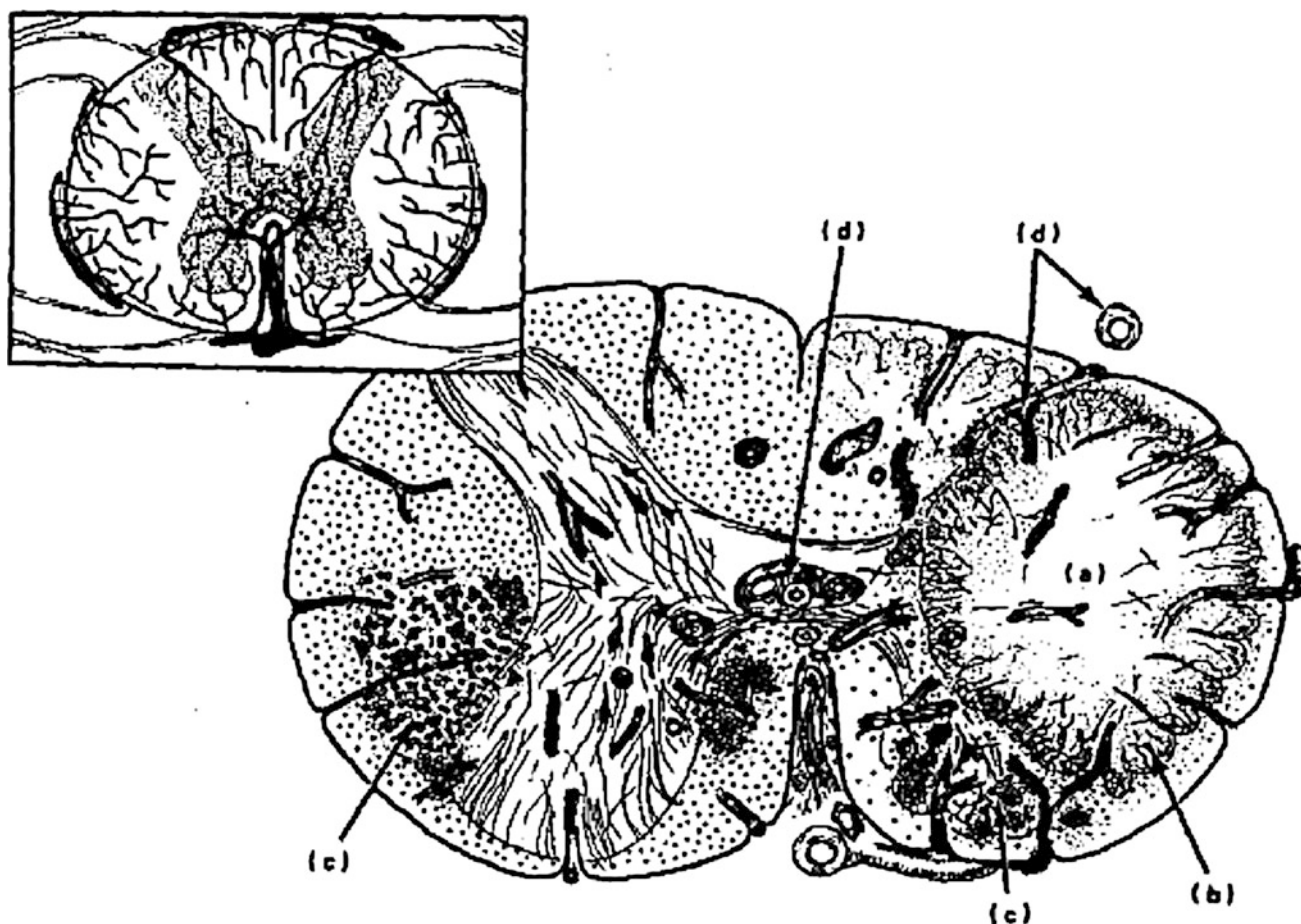
### 3.2.1 Risk Factors

Animal studies suggest that the immature spinal cord is slightly more susceptible to radiation-induced complications and the latent period is shorter (Ang et al. 1983, Ruifrok et al. 1992a, b, 1994). For example, Ruifrok et al. (1992a) found that the 50 % effect dose in 1-week-old rats

was 19.5 Gy versus 21.5 Gy in adult animals ( $p < 0.05$ ). The latency to complications increased from about 2 weeks after irradiation in the 1-week-old rats to 6–8 months in the adults (Ruifrok et al. 1994). While the ultimate white matter changes were the same in these animals independent of age, vasculopathy increased with increasing age at irradiation. While the literature on radiation-induced spinal cord myelopathy is sparse, care should be exercised in irradiating the pediatric spine because of the increased sensitivity of the child’s developing central nervous system and bone to ionizing radiation (Friedman and Constine 2005).

## 4 Pathophysiology

This schematic cross-sectional representation of the spinal cord (Fig. 4) illustrates some of the lesions associated with delayed radiation myelopathy. The typical pathologic



**Fig. 4** **a** Delayed radiation myelopathy: The inset demonstrates the principal arterial distribution with the anterior spinal artery and two posterior spinal arteries giving off circumferential and penetrating branches. The irradiated cord may at any one time present a diversity of effects in various phases of development. The right half of this section shows a large area of necrosis (**a**) through which pass sclerosed branches of the penetrating vessels. The edge of this lesion retains some of the fibrillar ground substance and a few glial cells. Within, but

at the periphery of, the necrosis is a broad zone of “gitter” cells or foamy histiocytes (**b**). There are several moderately well demarcated foci of demyelination (**c**) depicting early stages in the development of necrosis. The vasculature is prominent (**d**), especially on the right side of the cord, owing to intimal and medial thickening and a marked increase in the perivascular connective tissue [with permissions from White, D. C. (133a)]

features for radiation-induced myelopathy are tabulated in Table 1. Laboratory investigations implicate the vascular changes in arterioles as the key underlying etiology.

## 5 Clinical Syndromes

Both transient and irreversible syndromes form the spectrum of radiation injuries to the spinal cord. Transient myelopathy is the most common syndrome, seen 2–4 months following irradiation. Lhermitte’s sign has been described frequently after 40–45 Gy mantle irradiation for Hodgkin’s disease, and it appears as a shock-like sensation along the spine and tingling or pain in the hands from neck flexion or stretching from the arms (160). The mechanism is presumably a transient demyelination induced by a transient vasculopathy.

Very occasionally, rapidly evolving permanent paralysis is seen, possibly resulting from an acute infarction of the cord of the supplying artery being occluded.

Chronic progressive radiation myelitis is rare. Intramedullary vascular damage that progresses to hemorrhagic necrosis or infarction is the likely mechanism, although extensive demyelination that progresses to white matter necrosis is an alternative explanation. Initial symptoms are usually paresthesias and sensory changes, starting 9–15 months following therapy and progressing over the subsequent year. Diagnosis of myelitis rests on supportive information: the lesion must be within the irradiated volume, and recurrent or metastatic tumor must be ruled out. In addition, the cerebrospinal fluid protein levels may be elevated; myelography can demonstrate cord swelling or atrophy, with MRI and CT scan providing additional

**Table 1** Spinal cord changes in radiation myelopathy (Okada 2001)

White matter lesions	Vasculopathies	Glial reaction
1. Demyelination: isolated nerve fibers	1. None	1. Microglia/Macrophages
2. Demyelination: groups of nerve fibers (spongiosis)	2. Increased vascularity	a. morphology
3. “Inactive” malacia	3. Telengectasias	i. rod-shaped
a. spongiosis spheroids		
b. scar	4. Hyaline degeneration and thickening	ii. foam cells
	5. Edema and fibrin exudation	iii. multinucleated
4. “Active” malacia	6. Perivascular fibrosis and inflammation	b. patterns
a. coagulative malacia	7. Vasculitis	i. diffuse
b. liquefactive malacia	8. Fibrinoid necrosis	ii. focal
i. amorphous	9. Thrombosis	iii. perivascular
ii. foam cell fields	10. Hemorrhage	2. Astrocytes
iii. cystic		a. morphology
		i. inconspicuous
		ii. Edematous
		iii. fibrillary
		b. patterns
		i. diffuse
		ii. focal
		iii. perivascular
		3. Gliosis

supportive information. Various clinical endpoints are categorized and graded in the SOMA LENT system (Table 2).

## 5.1 Detection

In the initial evaluation, a detailed history and physical exam, with special attention to neurologic signs and symptoms, should be obtained. These data are essential for establishing a baseline status against which changes in neurologic function can be measured, correlating functional deficits with anatomic lesions identified on imaging (below), and identifying patient factors, such as diabetes, peripheral vascular disease, pre-existing cognitive deficits, social support resources and recent/concurrent medications, that will influence the choice of and response to therapy.

### 5.1.1 Electromyography

Electromyography (EMG) and nerve conduction studies (NCS) are typically performed in tandem to determine the action potential and conduction velocity of nerves, respectively (Falah et al. 2005; Corbo and Balmaceda 2001). EMG/NCS neuropathies can result from a variety of cancer-associated causes besides radiation-induced injury, including chemotherapy, tumor compression/invasion of nerves, surgical changes, and paraneoplastic syndromes. In patients with radiation-induced fibrosis, these electrodiagnostic studies often reveal fibrillations, positive sharp waves, and myokymia (Corbo et al. 2001; Mullins et al. 2007).

While history, physical exam, electrodiagnostic testing, and MRI studies can reveal abnormalities in nerves and associated structures, it is frequently difficult to establish the proximal cause of those abnormalities (Lederman and Wilbourn 1984; Planner et al. 2006). While a study of <sup>18</sup>F-DG PET in breast cancer patients with brachial plexopathy suggested that the lack of hypermetabolic activity was characteristic of radiation-induced plexopathy (Ahmad et al. 1999), several case reports describe hypermetabolic purely radiation-induced lesions associated with transient myelopathy (Chamroonrat et al. 2005; Uchida et al. 2008).

## 5.2 Diagnosis

### 5.2.1 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is typically the imaging modality of choice for assessing malignancies involving the spinal cord and brachial plexuses (Grossman and Yousem 2003). Accurate, precise delineation of the extent and location of tumor in relation to normal tissue structures is necessary to identify target lesions for radiation therapy and quantitatively gauge the response of tumor to radiation therapy. In addition, computed tomography is frequently critical to both plan radiation treatment and provide precise localization and visualization of bony structures and/or fiducial markers for image-guided radiotherapy (Yin et al. 2006). MRI myelopathy can accurately delineate the segment of spinal cord irradiated through degeneration of the axonal tracts distal to injury (Rubin et al. 1994). An example of radiation-associated myelitis is shown in Fig. 5.

## 6 Radiation Tolerance

### 6.1 Dose, Time, Fractionation

The most widely observed clinical dose limits are 45 Gy in 22–25 fractions of 1.8–2.0 Gy, and a TD<sub>5</sub> of 50 Gy has been suggested. However, this TD<sub>5</sub> value is overly conservative. While a 5 % risk might be considered clinically



**Table 2** LENT SOMA for the Spinal Cord

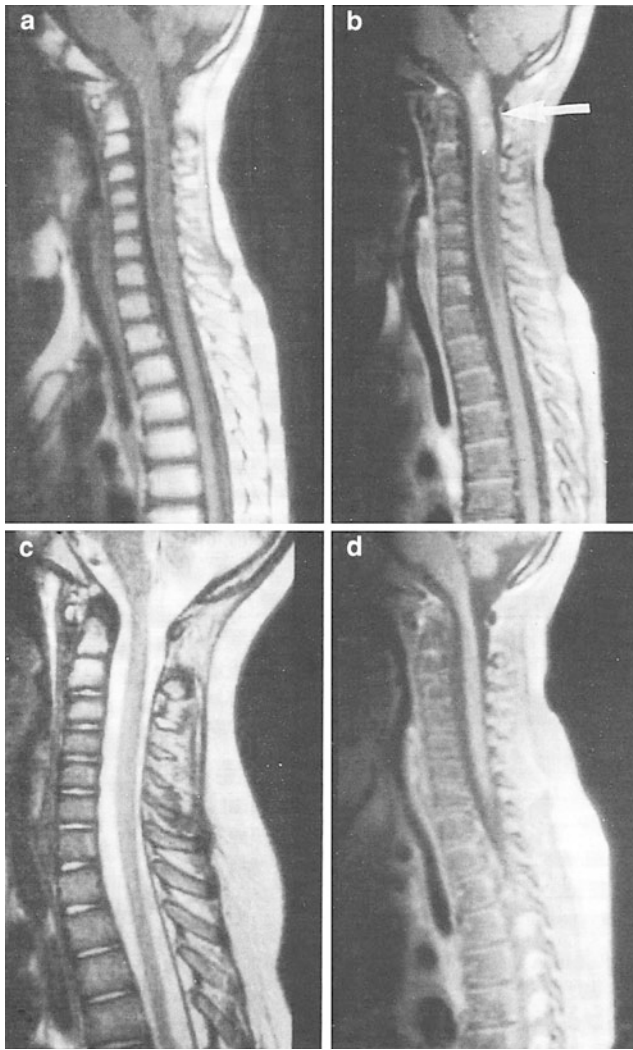
Spinal cord				
	Grade 1	Grade 2	Grade 3	Grade 4
<i>Subjective</i>				
Paresthesias (tingling sensation, shooting pain. Lhermitte's syndrome)	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciation
Sensory (numbness)	Minimal change	Mild unilateral sensory loss; works with some difficulties	Partial unilateral sensory loss; needs assistance for self-care	Total loss of sensation, danger of self-injury
Motor (weakness)	Minor loss of strength	Weakness interfering with normal activities	Persistent weakness preventing basic activities	Paralysis
Sphincter control	Occasional loss	Intermittent loss	Incomplete control	Complete incontinence
<i>Objective</i>				
Neurologic evaluation	Barely detectable decrease in sensation or motor weakness on one side, no effect on function	Easily detectable decrease in sensation or motor weakness on one side disturbs but does not prevent function	Full Brown-Sequard syndrome, loss of sphincter function, prevents function	Complete transection disabling, requiring continuous care
<i>Management</i>				
Pain	Occasional non-narcotic medication	Persistent non-narcotic medication, intermittent low dose steroids	Intermittent high dose steroids	Persistent high dose steroids
Neurologic function	Needs minor adaptation to continue working	Regular physiotherapy	Intensive physiotherapy plus regular supervision	Intensive nursing and/or life support
Incontinence	Occasional use of incontinence pads	Intermittent use of incontinence pads	Regular use of incontinence pads or self-catheterization	Permanent use of pads or catheterization
Analytic MRI	Edema	Localized demyelination	Extensive demyelination	Necrosis
CT	Assessment of swelling, edema, atrophy			
MRS	Assessment of chemical spectra			
PET	Assessment of metabolic activity			
Serum	Assessment of myelin basic protein levels			
CSF	Assessment of total protein and myelin basic protein			

acceptable for other organs, a 5 % risk is clearly unacceptable for the spinal cord given the severe clinical consequences of myelopathy. Thus, the historical  $TD_5$  value was more accurately describing the dose that would yield a clinically acceptable complication rate (closer to  $\approx 1$  per 1,000; i.e., the  $TD_{0.1}$ ).

Published reports of radiation myelopathy rates for 335 and 1,946 patients receiving radiotherapy to the cervical and thoracic spine, respectively, are summarized in Tables 3 and 4. While a few of these patients received relatively high doses/fraction, none were treated using stereotactic techniques to exclude a portion of the circumference of the cord. Note that the dose to the cord is the prescribed dose reported in those studies; typically, dosimetric data were not available

to calculate the true cord dose. The probability of myelopathy was derived from the raw percentage of patients developing myelopathy by correcting for the estimated overall survival as described by Schultheiss (2008).

Using the above data, Schultheiss (1986, 2008) estimated the risk of myelopathy as a function of dose. The 2-Gy equivalent dose using the LQ model with the  $\alpha/\beta$  ratio of 0.87, is calculated for each study (Schultheiss 2008) in Tables 3 and 4. A good fit to the combined cervical and thoracic cord data reportedly was not possible and separate analyses were performed. For the cervical cord data, values of  $D_{50} = 69.4$  Gy and  $\alpha/\beta = 0.87$  Gy were obtained with a Pearson  $\chi^2$  statistic of 2.1 for 5 degrees of freedom, providing a reasonable fit of the model as shown in Fig. 6a.



**Fig. 5** Postradiation changes in the spinal cord: chemoradiation myelitis in 8-year-old girl with history of chemotherapy and radiation for acute lymphocytic leukemia (ALL). One year after the therapy, she developed limb weakness and urinary retention. **a** Sagittal T1-weighted magnetic resonance (MR) image reveals hyperintense marrow and edematous cervical cord. The bone marrow shows signs of radiation changes with increased signal intensity in C1 and C2. **b** Sagittal T1-weighted postgadolinium MR image with fat saturation demonstrates an enhancing mass in the upper cervical cord (arrow). Because there was no evidence of ALL relapse, this was presumed to represent radiation myelitis. **c** Sagittal fast spin echo T2-weighted image 1 year later demonstrated an essentially normal cord. **d** Sagittal T1-weighted postgadolinium MR image with fat saturation shows that the enhancing lesion has resolved (with permission from Braggs et al. 2002)

The 95 % confidence intervals were 66.4–72.6 Gy for  $D_{50}$  and 0.54–1.19 Gy for  $\alpha/\beta$ . At 2-Gy per fraction, the probability of myelopathy is 0.03 % for a total dose of 45 Gy and 0.2 % at 50 Gy. However, the further one gets into the tail of the dose–response function, the more dependent the estimates become on the statistical distribution used to model this function.

Because of the dispersion in the thoracic cord data, a good fit of these data reputedly could not be obtained. As shown in Fig. 6b, most of the thoracic cord data points lie to the right of the dose–response curve for the cervical cord. This suggests that the thoracic cord is less radiation sensitive than the cervical cord. For external beam radiotherapy (EBRT) to the spinal cord in 2 Gy daily fractions, the risk of myelopathy appears low (<0.2 %) at 50 Gy and modest (<10 %) at 60 Gy, with an approximately 50 % risk of myelopathy at 70 Gy, based on the above analysis. Note that earlier “consensus opinions” (Withers et al. 1988; Emami et al. 1991) suggested more conservative guidelines for spinal cord tolerance, likely as a result of the concern for the severe disability resulting from spinal cord damage (Fowler et al. 2000).

There is an increased risk of myelitis following use of a continuous hyperfractionated accelerated radiation treatment (165), suggesting that a 6-h interval between treatments is insufficient to allow for significant repair. Shortening the interval between treatments from 24 h to 6–8 h reduces spinal cord tolerance by 10–15 %. In animal models, the dose rate also influences risk (van der Kogel 166, 167).

## 6.2 Dose/Volume Constraints

A suggested association between dose, volume, and risk of myelopathy is shown in Fig. 6c. The right y-axis indicates the tolerance dose ranges for the  $TD_{5-50}$  for whole organ irradiation. The left axis relates dose to risk for variable volumes irradiated. (Modified from Rubin et al. 1997). The volume effect has been assessed in animal studies.

In recent series of experiments, four different lengths of the rat spinal cord (2, 4, 8, and 20 mm) were irradiated with single doses of protons (150–190 MeV) using paralysis as functional endpoint. A minor increase in tolerance was observed when the irradiated rat cord length was decreased from 20 mm ( $ED_{50} = 20.4$  Gy) to 8 mm ( $ED_{50} = 24.9$  Gy), whereas a large increase in tolerance was observed when the length was further reduced to 4 mm ( $ED_{50} = 53.7$  Gy) and 2 mm ( $ED_{50} = 87.8$  Gy). These results suggest that for small field lengths there may be a volume effect and that tiny overlaps of RT fields in the clinic might be tolerable, but that anything more than a few mm would not be tolerated.

These investigators also addressed the significance of partial volume irradiation and inhomogeneous dose distributions to the cord using a “bath and shower” approach. “Bath” irradiation represents doses to a larger volume that are on both sides of a “shower” irradiation focused on a smaller volume (i.e., a low dose bath with a focal hot spot shower in the middle). For different bath doses, the  $ED_{50}$  for

**Table 3** a. Summary of published reports of cervical spinal cord myelopathy in patients receiving conventional RT (modified from Schultheiss 2008)

Institution	Dose (Gy)	Dose/fraction (Gy)	Cases of myelopathy/total number of patients	Probability of Myelopathy <sup>a</sup>	2-Gy dose equivalent <sup>b</sup>
McCunniff (1989)	60	2	1/12	0.090	60.0
	65	1.63	0/24	0.000	56.6
Abbatucci (1978)	54	3	7/15	0.622	72.8
Atkins (1966)	19	9.5	4/13	0.437	68.6
Marcus (1990)	47.5	1.9	0/211	0.000	45.0
	52.5	1.9	0/22	0.000	49.8
	60	2	2/19	0.118	60.0
Jeremic (1991)	65	1.63	0/19	0.000	56.6

<sup>a</sup> Calculated using the percentage of patients experiencing myelopathy corrected for overall survival as a function of time by the method in Schultheiss (2008)

<sup>b</sup> Calculated using  $\alpha/\beta = 0.87$  Gy

**Table 4** Summary of published reports of thoracic spinal cord myelopathy in patients receiving conventional RT [modified from Schultheiss (2008)]

Institution	Dose (Gy)	Dose/fraction (Gy)	Cases of myelopathy/total number of patients	Probability of Myelopathy <sup>a</sup>	2-Gy dose equivalent <sup>b</sup>
Hazra (1974)	45	3	1/16	0.093	60.7
Choi (1980)	45	3	0/75	0.000	60.7
Abramson (1973)	40	4	4/271	0.063	67.9
Fitzgerald (1982)	40	4	6/45	0.332	67.9
Madden (1979)	40	4	1/43	0.284	67.9
Guthrie (1973)	40	4	0/42	0.000	67.9
Dische (1988)	34.4	5.7	13/145	0.278	78.9
Hatlevoll (1983)	38	3 × 6 Gy + 5 × 4 Gy	8/157	0.196	77.0
	38	3 × 6 Gy + 3 × 4 Gy + 2 × 2 Gy	9/230	0.151	67.4
Eichhorn (1972)	66.2	2.45	8/142	0.256	76.5
Scruggs (1974)	40	5 × 4 Gy + 8 × 2.5 Gy	2/248	0.028	57.4
Macbeth (1996a, b)	18.4	9.2	3/524	0.032	64.5
	39.8	3.06	2/153	0.062	54.5

<sup>a</sup> Calculated using the percentage of patients experiencing myelopathy corrected for overall survival as a function of time by the method in Schultheiss 2008

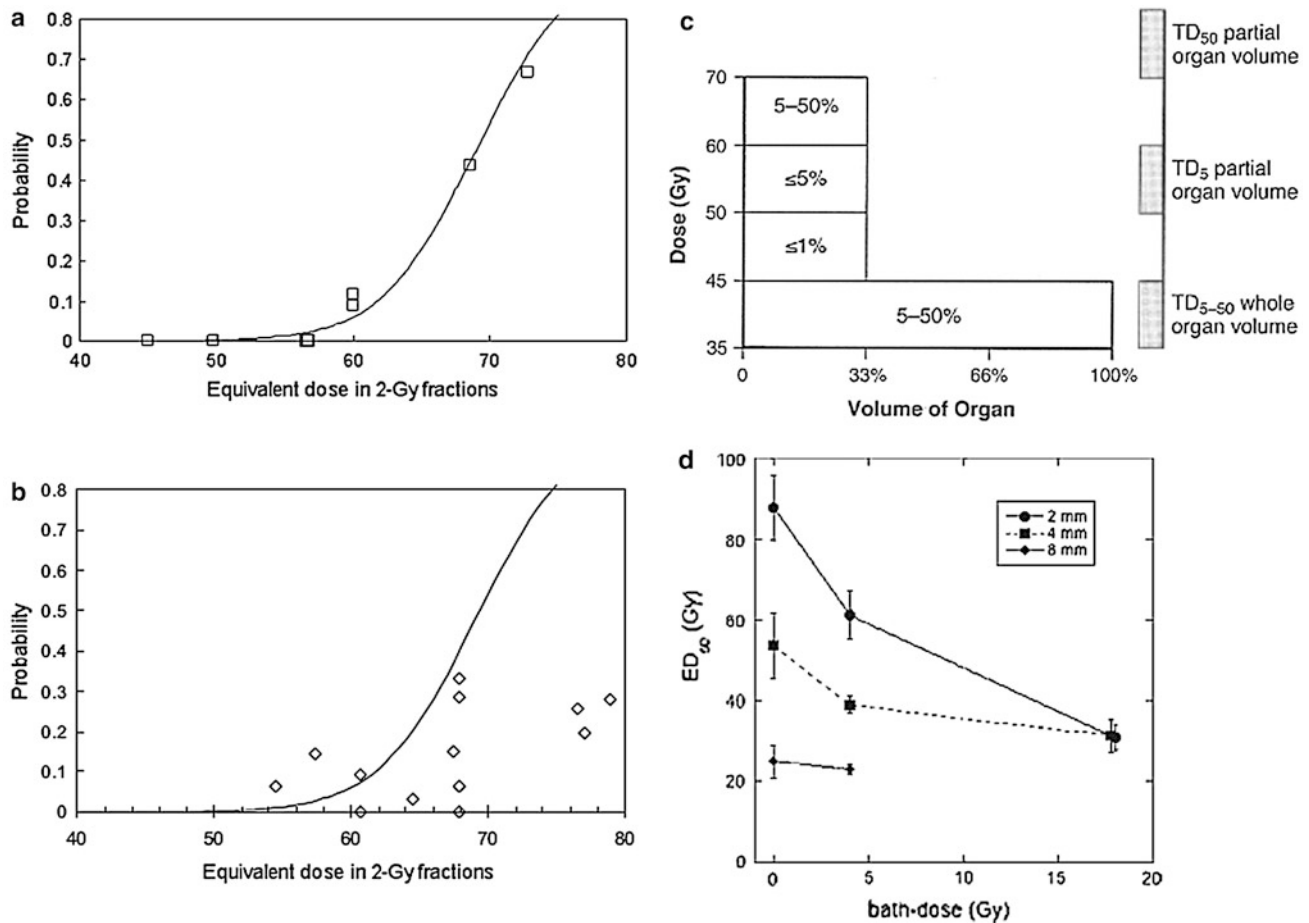
<sup>b</sup> Calculated using  $\alpha/\beta = 0.87$  Gy (18)

spinal cord damage was determined, and compared to the situation with a bath dose of zero (i.e., homogeneous irradiation of the spinal cord to the shower dose). With a bath dose of zero, the ED<sub>50</sub> is relatively high (e.g., >80 Gy for a 2 mm length of cord irradiated). The ED<sub>50</sub> values drop dramatically even at modest bath doses (Fig. 6d). The effect of the bath dose was greatest at smaller size shower doses, and was relatively modest when the shower field lengths increased to 8 mm (Bijl et al. 2002, 2003).

In concert, one interpretation of these data is that there are neighborhood effects that ‘protect/mitigate’ the cord injury, but that these protective effects can extend only a few mm in length. For example, one might hypothesize that

a 2 mm focus of high dose radiation (i.e., shower in the above vernacular) leads to local damage that is “mitigated by the neighborhood” only a mm or two away. As the focus of high dose is enlarged, there is less capability for such mitigation since the distance between the irradiated and non-irradiated tissues is, on average, greater. The bath dose, that is low enough not to cause any evident functional consequences by itself, appears to reduce the ability of the neighboring tissues to provide mitigation. The clinical implications of these data are interesting. Inadvertent overdoses of the cord may occur in the setting of abutting RT fields (e.g., via mis-calculated gaps, or set-up errors). At first blush, the data on the far left-hand side of Fig. 6d might





**Fig. 6** **a** The dose-response function for the myelopathy of the cervical spinal cord and associated data points are from Table 3 (Reprinted with the permission of *International Journal of Radiation Oncology Biology Physics*). **b** The dose-response function for myelopathy of the cervical cord (solid line) and data points for the thoracic spinal cord are derived from Table 4 (Reprinted with the permission of *International Journal of Radiation Oncology Biology*

*Physics*). **c** Radiation tolerance: dose/volume constraints. The right y-axis indicates the tolerance dose ranges for the TD<sub>5-50</sub> for whole organ irradiation. The left axis relates dose to risk for volumes irradiated. (Modified with permissions from Rubin et al. 1997). **d** ED<sub>50</sub> for rats irradiated with protons with various lengths of cord (with permissions from Bijl et al. 2002, 2003)

suggest that tiny regions of overlap (e.g., 1–2 mm) might be tolerable, but that anything more than a few mm would not be tolerated. However, even with very small overlaps of 1–2 mm, the dose to the adjacent spinal cord would largely eliminate this ‘neighborhood mitigation effect.’ Thus, any overlap of abutting fields is likely not tolerable in the clinic.

## 7 Chemotherapy

A variety of chemotherapeutic agents have been implicated to be toxic to the central nervous system. The chemotoxic drugs are similar to those causing encephalopathy (Table 5).

In rats, the use of various chemotherapy agents during radiotherapy has been shown to increase the radiosensitivity of the spinal cord. Administration of intrathecal ara-C

(Ruifrok et al. 1993) or intraperitoneal fludarabine (Grégoire et al. 1995) immediately prior to irradiation of the spinal cord showed an enhanced effect on radiation-induced injury, yielding a dose modifying factor of 1.2–1.3. There are rare reports of radiation myelopathy at relatively low doses in human patients post chemotherapy. Ruckdeschel et al. (1979) found a single case of radiation myelitis in a series of 15 lung cancer patients receiving cyclophosphamide, adriamycin, methotrexate, and procarbazine followed 3 weeks later by ten 300-cGy fractions to the mediastinum and lesion. The maximum dose to the cord was less than 21 Gy (BED  $\approx$  43Gy<sub>2</sub>). Chao et al. (1998) described a case of radiation myelopathy in a patient with non-Hodgkin’s lymphoma initially treated with VACOP-B chemotherapy and autologous bone marrow transplant followed by consolidative radiation to the mediastinum; the upper thoracic spine received a maximum dose of 40.3 Gy in 22 fractions

**Table 5** Antineoplastic drugs associated with cerebral encephalopathy

<i>Antimetabolites</i>
High-dose methotrexate
5-Fluorouracil (with allopurinol)
Cytosine arabinoside (ara-C)
Fludarabine
PALA (N-[phosphonacetyl]-L-asparate)
<i>Alkylating agents</i>
Cisplatin
Ifosfamide
BCNU (carmustine)
Spiromustine
<i>Plant alkaloids</i>
Vincristine (associated with inappropriate antidiuretic hormone secretion)
<i>High-dose regimens used in bone marrow transplantation</i>
Nitrogen mustard
Etoposide
Procarbazine
<i>Miscellaneous</i>
Mitotane
Misonidazole
L-asparaginase
Hexamethylmelamine
Interleukin-2

From Kagan (1993), with permission

(BED  $\approx$  81Gy<sub>2</sub>). Seddon et al. (2005) reported fatal radiation myelopathy in a patient who received 50 Gy to the cervical spinal cord in 30 fractions (BED  $\approx$  92Gy<sub>2</sub>) 4 months after treatment with busulfan and melphalan for a paraspinal Ewing sarcoma. Many of these agents are neurotoxic in their own right (Lee et al. 1986) and caution is advised in their concurrent use during irradiation of the central nervous system (Schultheiss et al. 1995).

## 7.1 Combined Modality

The most recognized example of adverse combined radiation and drug effects involves methotrexate (Fig. 7) (Bleyer 1981; Bernaldez-Rios et al. 1998; Evans et al. 1981). Large doses of methotrexate alone can lead to leukoencephalopathy; however, this complication is seen most often when the drug is given intrathecally and/or in high doses intravenously combined with whole brain irradiation.

It had been assumed that most drugs would not cause CNS late effects because of their inability to cross the blood–brain barrier. However, because radiation alters and increases

capillary permeability, (Rubin et al. 1994) a combined-modality regimen may lead to systemically administered drugs entering the brain (Williams et al. 1993; Qin et al. 1997). In addition, damage to the vascular choroid plexus can affect methotrexate clearance, decreasing turnover, thereby leading to higher drug concentrations. Therefore, combination therapy sequencing for brain neoplasms should be approached with caution (Remsen et al. 1997). For example, a 1998 study employing a combination of high-dose systemic methotrexate with intrathecal methotrexate followed by whole brain irradiation for primary CNS lymphoma has observed a high rate of severe leukoencephalopathy in patients older than 60 years of age (Abrey et al. 1998).

Encephalopathies are induced by both irradiation and chemotherapy and can be acute and chronic. Figure 7a shows a Venn diagram that illustrates the pathophysiology of delayed neurotoxic sequelae seen months to years later associated with CNS irradiation, intrathecal methotrexate, and high-dose intravenous methotrexate, alone or in combination. In Fig. 7b, incidence is greatest for all modes combined. In this Venn diagram, the incidence is very low when either irradiation or chemotherapy is administered alone, but it increases considerably (up to 45 %) when combined. The mechanism is believed to be attributable to alteration of the blood–brain barrier by irradiation, followed by direct entry of methotrexate into the CNS, causing diffuse necrosis and damage.

The increasing use of combined-modality therapy (e.g., the conditioning regimens for bone marrow transplantations) has led to an awareness of risk factors in the pediatric population (Silber et al. 1992; Moore 1995; Smedler et al. 1995). Alertness must be maintained for signs of developmental difficulties, and attempts should be made at all times to minimize the radiation treatment fields in children.

The combination of radiation and chemotherapy is well documented to exacerbate the potency of the toxicity especially if administration of both modalities is combined and different routes of drug delivery occur simultaneously. The classic reference is Bleyer in the treatment of acute lymphocytic leukemia in children.

## 8 Special Topics

### 8.1 Spinal Cord

#### 8.1.1 Hypofractionation

Hypofractionation via radiosurgery is increasingly employed in the treatment of spinal lesions. Though reports of toxicity are rare, the follow-up time is short and patient numbers small. Caution should be observed in specifying the dose, taking special care to limit the dose to the cord by precise immobilization and image guidance. Predictions based on conventional fractionation should not be applied to





**Table 6** Summary of published reports of spinal cord doses and myelopathy in patients receiving stereotactic radiosurgery

Institution (Ref.)	Cases of myelopathy/ total patients	Total dose (Gy)	Dose/fraction (Gy)	Dose to cord (Gy)	BED to cord (Gy <sub>3</sub> )	Proportion of patients previously irradiated to involved segment of spine
Gibbs et al. (2009)	6/1075	12.5–25	5–25	D <sub>max</sub> : 3–28	Range: 24–121 Gy <sub>3</sub>	>55 %
		<b>25</b>	<b>12.5</b>	<b>D<sub>max</sub>: 26.2</b>	<b>D<sub>max</sub>: 141</b>	
		<b>20</b>	<b>12.5</b>	<b>D<sub>max</sub>: 29.9</b>	<b>D<sub>max</sub>: 81</b>	
		<b>21</b>	<b>10.5</b>	<b>D<sub>max</sub>: 19.2</b>	<b>D<sub>max</sub>: 46</b>	
		<b>24</b>	<b>8</b>	<b>D<sub>max</sub>: 13.9</b>	<b>D<sub>max</sub>: 129</b>	
		<b>20</b>	<b>10</b>	<b>D<sub>max</sub>: 10</b>	<b>D<sub>max</sub>: 33</b>	
		<b>20</b>	<b>20</b>	<b>D<sub>max</sub>: 8.5</b>	<b>D<sub>max</sub>: 43</b>	
Ryu et al. (2007)	1/86 <sup>a</sup>	<10–18	<10–18	Mean ± s.d. D <sub>max</sub> : 12.2 ± 2.5 D1: 10.7 ± 2.3 D10: 8.6 ± 2.1 Maximum D <sub>max</sub> : 19.2 D1: 15.8 D10: 13	Mean ± s.d. D <sub>max</sub> : 62 ± 4.6 D1: 49 ± 4.1 D10: 33 ± 3.6 Maximum D <sub>max</sub> : 142 D1: 99 D10: 69	0 %
		18 <sup>b</sup>	18	Mean ± s.d. D <sub>max</sub> : 13.8 ± 2.2 D1: 12.1 ± 1.9 D10: 9.8 ± 1.5	Mean ± s.d. D <sub>max</sub> : 77 ± 3.8 D1: 61 ± 3.1 D10: 42 ± 2.3	
		<b>16</b>	<b>16</b>	<b>D<sub>max</sub>: 14.8</b> <b>D1: 13.0</b> <b>D10: 9.6</b>	<b>D<sub>max</sub>: 88</b> <b>D1: 69</b> <b>D10: 40</b>	
Gwak et al. (2005)	2/9	21–44	3–5	Median D <sub>max</sub> : 32.9 D25: 11.0 Range D <sub>max</sub> : 11–37 D25: 1.2–24	Median D <sub>max</sub> : 106 D25: 21 Range D <sub>max</sub> : 19–172 D25: 1–88	33 %
		<b>30</b>	<b>10</b>	<b>D<sub>max</sub>: 35.2</b> <b>D25: 15.5</b>	<b>D<sub>max</sub>: 172</b> <b>D25: 42</b>	
		<b>33</b>	<b>11</b>	<b>D<sub>max</sub>: 32.9 D25: 24.0</b>	<b>153</b> <b>88</b>	
Benzil et al. (2004)	3/31	Median: 10	Median: 5	Median: 6.0	12	Unknown
		<b>100</b>	<b>50</b>			
		<b>12</b>	<b>12</b>			
		<b>20</b>	<b>5</b>			
Sahgal et al. (2007a, b)	0/38	24	8	Median D <sub>0.1cc</sub> : 10.5 D <sub>1cc</sub> : 7.4	Median D <sub>0.1cc</sub> : 23 D <sub>1cc</sub> : 14	62 %
Sahgal et al. (2007a, b)	0/16	21	7	Median D <sub>max</sub> : 20.9 D <sub>0.1cc</sub> : 16.6 D <sub>1cc</sub> : 13.8 Range D <sub>max</sub> : 4.3–23 D <sub>0.1cc</sub> : 3.4–22 D <sub>1cc</sub> : 2.8–19	Median D <sub>0.1cc</sub> : 61 D <sub>1cc</sub> : 22 Range D <sub>0.1cc</sub> : 7–76 D <sub>1cc</sub> : 6–54	6 %
Chang et al. (2007)	0/63	30 pts: 30 33 pts: 27	30 pts: 6 33 pts: 9	30 pts: <10 33 pts: <9	30 pts: <16.7 33 pts: <18	56 %
Gertzen et al. (2005)	0/50	19	19	Mean D <sub>max</sub> : 10 Range D <sub>max</sub> : 6.5–13	Mean D <sub>max</sub> : 21 Range D <sub>max</sub> : 11–32	96 %
Nelson et al. (2009)	0/32	Median: 18	Median: 7	Mean ± s.d. D <sub>max</sub> : 14.4 ± 2.3 D1: 13.1 ± 2.2 D10: 11.5 ± 2.1 Maximum D <sub>max</sub> : 19.2 D1: 17.4 D10: 15.2	Mean ± s.d. D <sub>max</sub> : 46.0 ± 13.2 D1: 39.0 ± 10.8 D10: 31.2 ± 8.1 Maximum D <sub>max</sub> : 78.3 D1: 59.1 D10: 46.5	58 %

All patients within that institutional series are shown in normal font; myelopathy cases are shown in **bold**

<sup>a</sup> Patients surviving at least 1 year

<sup>b</sup> Results for subset of 39 lesions treated at Henry Ford Hospital with a single 18 Gy fraction

<sup>c</sup> For the NYMC data (51), the cord dose was calculated assuming that the total dose was delivered in two fractions. While the cord dose for the patients developing myelopathy were not given in the paper, the total BED to the tumor for the three patients experiencing myelopathy was 53.3, 60, and ~167 Gy<sub>3</sub> versus < 50Gy<sub>3</sub> for patients without myelopathy

### 8.1.4 Re-irradiation

When considering re-irradiation of the spinal cord, one must consider the prior dose and fraction size, and the time interval between the courses of radiotherapy (Nieder 2005) (also see Sect. 3.2). Table 7 summarizes published reports involving re-irradiation of the spinal cord utilizing both conventional, full-circumference EBRT and SBRT.

Nieder et al. (2005, 2006) developed a risk stratification model for the development of myelopathy following re-irradiation of the spinal cord with conventionally fractionated, full-circumference EBRT, which appears reasonable based on the above data. They estimated a <3 % risk of myelopathy after re-treatment providing that the total BED<sub>2Gy</sub> is less than 135.5 Gy<sub>2</sub> with no course exceeding 98 Gy<sub>2</sub> and that the interval between courses of radiotherapy is greater than 6 months.

The data are sparse for myelopathy when spinal radio-surgery follows conventional EBRT to the spinal cord. Nelson et al. (2009) described the following conservative approach for calculating an acceptable dose for radiosurgery to the spinal cord in the setting of re-irradiation:

1. Assume a spinal cord tolerance of 50 Gy in 2 Gy/fraction (BED = 83.3 Gy<sub>3</sub>), as this dose yields a risk of transverse myelitis <0.2 % (Schultheiss 2008).
2. Calculate the time-discounted prior BED (BED<sub>prior</sub>) to the cord by assuming an  $\alpha/\beta$  ratio of 3 Gy and a dose recovery of 25, 33, and 50 % at 6 months, 1 year, and 2 years (see Sect. 3.2). For example, for a cord previously treated to 35 Gy in 2.5 Gy fractions 1 year previously, the BED<sub>prior</sub> would be 43 Gy<sub>3</sub>, 67 % of 64.2 Gy<sub>3</sub>.
3. Set the maximum tolerable cord dose as the maximum dose to 99 % of the contoured cord volume over the region of treatment as 83.3 Gy<sub>3</sub> - BED<sub>prior</sub>. In the above example, the cord tolerance would be 40 Gy<sub>3</sub>, equivalent to three 5-Gy fractions.

Thus, in the case in which 99 % of the spinal cord over the length of spine treated with SBRT receives 70 % of the prescribed dose, the calculated maximum tolerated prescription dose would be 7.1 in 3 fractions or 9.1 Gy in 2 fractions. Note that the authors cautioned against using the linear-quadratic equation in calculating BED when the dose per fraction exceeded 10 Gy because of a concern for additional vascular damage (Kirkpatrick et al. 2008).

## 8.2 Plexus of Nerves

Plexus of nerves, especially the Brachial Plexus, are at risk for radiation injury. The bulk of clinical data involves irradiation of the brachial plexus in patients undergoing radiation therapy for breast cancer and of the lumbosacral plexus during treatment of pelvic malignancies. Table 8 presents the results of studies on brachial plexopathy in

patients with breast cancer as a function of biologic equivalent dose (BED), calculated using the expression (Hall 2006)  $n \times d \times [1 + d/(\alpha/\beta)]$  where  $n$  is the number of doses,  $d$  is the dose per fraction (Gy), and the  $\alpha/\beta$  ratio is taken as 2 Gy.

There is substantial variation in the depth that the brachial plexus lies below the skin surface, both between individuals and along its course through the upper chest wall. Moreover, different radiation techniques will include a variable amount of the brachial plexus in the treatment field and substantial volumes of the brachial plexus may receive high doses of radiation, particularly when “deep” tangent fields are employed. Nonetheless, the above data suggest that the risks of brachial plexopathy are low (<1 %) when modern techniques of breast irradiation are employed, the total dose is  $\leq 100$  Gy<sub>2</sub> (equivalent to twenty-five 2-Gy daily fractions) and concurrent chemotherapy is not utilized.

## 8.3 Peripheral Nerves Histology and Functional Anatomy

Peripheral nerves, which include spinal nerves and cranial nerves, contain numerous afferent and efferent nerve fibers of the somatic and autonomic nervous systems. In peripheral nerves, each individual axon is seen either enveloped by the myelin sheath (myelinated fibers) formed by Schwann cells, or surrounded by the cytoplasm microscope. Between these nerve fibers is a delicate loose connective tissue, the endoneurium, in close contact with the individual nerve fibers. The nerve fibers are grouped into bundles or fascicles, and covered by the perineurium, a layer of dense connective tissue composed of fibroblasts and collagen fibers. Each peripheral nerve is composed of one or more fascicles of nerve fibers and is surrounded by a layer of loose connective tissue, the epineurium, which extends from the outside and brings the fascicles together. Figure 3d is a rabbit's sciatic nerve in cross section, consisting of four fascicles of nerve fibers. Note that the blood vessels occur both outside and inside the fascicles as well as within the epineurium.

The dermatomal functional anatomy of the peripheral nervous system consists of the somatic and autonomic nervous systems (Fig. 2d). The somatic nervous system comprises the motor neurons, transmitting signals from the CNS to target muscles and glands and sensory neurons which transmit signals from sensory receptors in the body to the CNS. Peripheral nerves contain both sensory and motor neurons, which are composed of a central axon, surrounded by a Schwann cell and embedded in a richly vascularized endoneurium (refer to Fig. 3d). In larger axons, these Schwann cells wrap multiple times around the axon, forming a lipid-rich myelinated insulation. While many peripheral nerves may arise from or travel to specific spinal nerves

**Table 7** Summary of published reports involving re-irradiation of the spinal cord

Reference	Cases of myelopathy/ total patients	Median F/U (months)	BED, initial course, (Gy <sub>3</sub> ) Median (Range)	BED, re- irradiation (Gy <sub>3</sub> ) Median (Range)	Interval between courses (months) Median (Range)	Total BED (Gy <sub>3</sub> ) Median (Range)	2-Gy dose equivalent, $\alpha/\beta = 3$ Gy Median (Range)	2-Gy dose equivalent, $\alpha/\beta = 1$ Gy Median (Range)
Wright et al. (2006)	0/37	8	60 (10–101)	16 5–50	19 (2–125)	79 (21–117)	47 (13–70)	51 (8–100)
Langendijk et al. (2006)	0/34		–	–	–	<100	<60	<60
Grosu (2002), Nieder (2006)	0/15	30	70 (34–83)	50 (38–83)	30 (6–96)	115 (91–166)	69 (54–100)	70 (48–107)
Schiff et al. (1995)	4/54 4	4 <sup>a</sup>	60 All 60	37 73 <sup>b</sup> (29–115)	10 (1–51) 9 (5–21)	97 133 (109–175)	58 80 (65–105)	62 83 (69–89)
Ryu et al. (2000)	0/1	60	75	72	144	147	88	86
Kuo (2002)	0/1	8	75	42	37	117	70	67
Bauman et al. (1996)	0/2	>3–9	(40–56)	(18–35)	(8–20)	(58–91)	(35–57)	(28–51)
Sminia et al. (2002)	0/8		56 (29–78)	42 (36–83)	30 (4–152)	106 (65–159)	64 (39–96)	69 (48–93)
Magrini et al. (1990)	0/5	168	47 (32–47)	55 (33–67)	24 (12–36)	94 (80–113)	57 (48–68)	56 (47–67)
Rades et al. (2005)	0/62	12	29 (29–47)	29 (29–47)	6 (2–40)	69 (59–77)	41 (35–46)	53 (48–57)
Jackson (1987)	0/6	15	All 73	36 (32–39)	15	106 (103–109)	63 (62–65)	66 (64–68)
Wong et al. (1994)	11/-	11	72 (28–96)	42 (14–86)	11 (2–71)	115 (100–138)	69 (60–83)	80 (65–94)
<i>Stereotactic Body Radiotherapy</i>								
Gwak et al. (2005)	1/3 1	24	(60–81) 81	(64–154) 154	(18–120) 18	(145–235) 235	(87–141) 141	(98–179) 179
Case with myelopathy No myelopathy	2		60, 81	64, 90	54, 120	145, 150	87, 90	98, 114

<sup>a</sup> Overall survival<sup>b</sup> One patient received two courses of re-irradiation, one received three courses

directly, the relationship can be more complex when the nerves are arranged in plexuses. The brachial plexus is of particular concern during irradiation of the upper chest wall as it is located in the supraclavicular area and beneath the clavicles. The roots of the brachial plexus are formed by the anterior rami of spinal nerves C5–T1. These roots in turn form trunks that become divisions, then cords, and ultimately terminal nerve branches, innervating the upper extremities and portions of the trunk. While less complex, the lumbosacral plexus plays a similar role in the innervation of the lower extremities. Damage to the plexus can produce a variety of sensory and motor deficits including pain,

neuropathy, motor deficits, and functional disability. Key nerves arising from the brachial and lumbosacral plexuses, along with their associated spinal nerves, muscle groups, and area of cutaneous innervation are shown in Table 9.

## 8.4 Intraoperative Radiotherapy

### 8.4.1 Clinical Intraoperative Radiotherapy

Kinsella et al. (1985) reported on 40 patients receiving 20–25 Gy IORT at the NCI for pelvic or retroperitoneal tumors in which the lumbosacral plexus is in the radiation



**Table 8** Incidence of radiation-induced brachial plexopathy in patients undergoing radiation therapy for breast cancer (after Galecki 2006)

References	Number of patients		Dose (Number of sessions × dose/fraction)	BED (Gy <sub>2</sub> )	Incidence of radiation-induced brachial plexopathy
Stoll and Andrews (1966)	33 84	Breast	55 Gy (12 × 4.58 Gy) 51 Gy (12 × 4.25 Gy)	181 159	73 % 15 %
Notter et al. (1970)	237	Breast	45 Gy in 27 days to 81 Gy in 21 days	85–237	17 %
Basso-Ricci et al. (1980)	490	Breast	60 Gy (30 × 2 Gy) 49 Gy (25 × 1.96 Gy)	120 97	3.3 % 0 %
Salner et al. (1981)	565	Breast	50 Gy (25 × 2 Gy)	100	1.4 %
Barr and Kissin (1987)	250	Breast	51 Gy (15 × 3.4 Gy)	138	2.4 %
Delouche et al. (1987)	117	Breast	60 Gy (30 × 2 Gy)	120	
Powell et al. (1990)	338 111	Breast	46 Gy (15 × 3.1 Gy) versus 54 Gy (27–30 × 2–1.8 Gy)	116 versus 103–108	5.9 versus 1.0 % ( $p = 0.009$ )
Fowble et al. (1991)	697	Breast	50 Gy (25 × 2 Gy)	100	<1 %
Pierce et al. (1992)	330 <sup>a</sup> 787	Breast	50 Gy (25 × 2 Gy)	100	Chemotx: 5.6 % No chemotx: 0.6 %
Olsen et al. (1993)	128	Breast	50 Gy (25 × 2 Gy)	100	14 %
Livsey et al. (2000)	1665	Breast	45 Gy (15 × 3 Gy)	115	Est. < 1 %
Johansson et al. (2000)	71	Breast	57 Gy (17 × 3.35 Gy) <sup>b</sup>	152	63 %
Bajrovic et al. (2004)	140	Breast	52 Gy (20 × 2.6 Gy)	119.6	14 %
START A (2008a)	749 <sup>c</sup> 1487	Breast	50 Gy (25 × 2 Gy) 3941.6 Gy (13 × 3–3.2 Gy)	100 97.5–108.2	0 % 0.1 %
START B (2008b)	1105 <sup>d</sup> 1110	Breast	50 Gy (25 × 2 Gy) 40 Gy (15 × 2.67 Gy)	100 93.3	0 % 0 %

<sup>a</sup> Out of a total of 1,117 patients, 330 received chemotherapy

<sup>b</sup> Two of 3 fields were treated each session, with the brachial plexus receiving 1.8, 3.4, or 5.2 Gy

<sup>c</sup> A total of 122 patients in the 50 Gy group and 196 patients in the hypofractionated group received radiation therapy to regional lymphatics

<sup>d</sup> A total of 79 patients in the 50 Gy group and 82 patients in the 40 Gy group received radiation therapy to the supraclavicular fossa and/or axilla

field. Three other patients with posterior thigh sarcomas underwent IORT which included the sciatic nerve. In most cases, misonidazole was given immediately prior to IORT and an *en bloc* resection of tumor was performed. In addition, about one-half of the patients received 40–45 Gy conventionally fractionated EBRT postoperatively. Patients were typically examined at 2–3-month intervals for 2–5 years following IORT. A total of five patients were found to have clinical signs of peripheral nerve injury within 9 months of IORT (crude rate of 24 %), exhibiting sensory and motor deficits in the ipsilateral lower extremity. Two of these patients lost function in the affected limb, while the others showed “a slow recovery of nerve function over several months”.

Shaw et al. (1990) described potential peripheral nerve damage in 50 patients treated with surgery and 10–25 Gy

IORT followed by 30–68.9 Gy conventionally fractionated EBRT for treatment of pelvic malignancies. Of these patients, 16 (32 %) exhibited, mild-moderate pain, 8 (16 %) mild-moderate motor weakness, and 11 (22 %) mild-moderate sensory deficits. Severe (intractable) pain was observed in three patients (6 %) and severe motor weakness in two patients (4 %). Willett et al. (1991) treated 30 patients with recurrent locally advanced rectal or rectosigmoid cancer with a combination of preoperative radiation therapy (predominantly 50.4 Gy in 1.8 Gy fractions as most were not previously irradiated), followed by surgical resection and IORT (10–20 Gy with the majority receiving 15 Gy). Of these patients, three (10 %) developed sensory and/or motor pelvic neuropathy.

Kubo et al. (2005) reported on seven patients with soft-tissue sarcoma involving the neurovascular bundle treated

**Table 9** Selected named nerves arising from the brachial or lumbosacral plexus and their associated spinal nerves and areas of innervation

Key nerves	Associated spinal nerves	Muscles/Sensory area innervated
<i>Brachial Plexus</i>		
Musculocutaneous n.	C5–C7	Coracobrachialis, brachialis, and biceps brachii/lateral forearm
Axillary n.	C5, C6	<i>Anterior branch:</i> deltoid and portion of overlying skin <i>Posterior branch:</i> teres minor and deltoid muscles/upper lateral arm
Radial n.	C5–T1	Triceps, supinator, anconeus, extensor muscles of the forearm, and brachioradialis/dorsal side of lateral hand, including area between thumb and forefinger
Median nerve	C5–T1	Pronator teres, flexor carpi radialis, palmaris longus, flexor digitorum superficialis, lateral half of flexor digitorum profundus, flexor pollicis longus, pronator quadratus muscles, first and second lumbricals, muscles of the thenar eminence/palmar side of thumb, index, middle, and distal half of ring fingers
Ulnar nerve	C8, T1	Flexor carpi ulnaris, medial 2 bellies of flexor digitorum profundus, most of the small muscles of the hand/medial hand and medial one-and-a-half fingers on palmar side and medial two-and-a-half fingers on the dorsal side
<i>Lumbosacral Plexus</i>		
Iliohypogastric n.	L1	None/lateral gluteal region and above the pubis
Ilioinguinal n.	L1	None/root of the penis and upper part of the scrotum (male), skin covering the mons pubis and labium majus (female)
Genitofemoral n.	L1, L2	<i>Genital Branch:</i> Cremaster muscle/skin of scrotum/labia majora <i>Femoral Branch:</i> Skin on anterior thigh
Dorsal lateral femoral cutaneous n.	L2, L3	None/lateral part of the thigh
Obturator n.	L2–L4	Medial compartment of thigh (external obturator, adductor longus, adductor brevis, adductor magnus, gracilis muscles)/medial aspect of thigh
Femoral n.	L2–L4	Anterior compartment of thigh (quadricep femoris muscles)/anterior aspect of thigh
Sacral Plexus	L4–S4	See below
Superior gluteal n.	L4–S1	Gluteus medius, gluteus minimus, tensor fasciae latae/none
Sciatic n.	L4–S3	<i>Tibial n.:</i> Posterior compartment/posterolateral leg and foot (medial sural cutaneous n. <i>Common fibular n.:</i> Anterior and lateral compartment/anterolateral leg and foot
Inferior gluteal n.	L5–S2	Gluteus maximus/none
Pudendal n.	S2–S4	Bulbospongiosus, deep transverse perineal, ischiocavernosus, sphincter urethrae, superficial transverse perineal muscles/clitoris, penis
Coccygeal n.	S4–Co1	None/perineum

with fractionated high-dose rate (HDR) brachytherapy to the tumor bed. Seven to ten days post surgery, six patients received 50-Gy HDR brachytherapy in 5-Gy twice-daily fractions while one received 30-Gy HDR brachytherapy plus 20-Gy EBRT. No patient developed peripheral neuropathy and nerve conduction velocity was within normal limits in the three patients evaluated.

The above studies suggest a threshold for radiation-induced neuropathy at 15–20 Gy for a single fraction of radiation therapy to a plexus or peripheral nerve delivered intraoperatively.

#### 8.4.2 Experimental IORT

Giese and Kinsella (1991) and Gillette et al. (1995) provide excellent reviews on peripheral nerve injury from radiation. In particular, the former paper provides a comprehensive

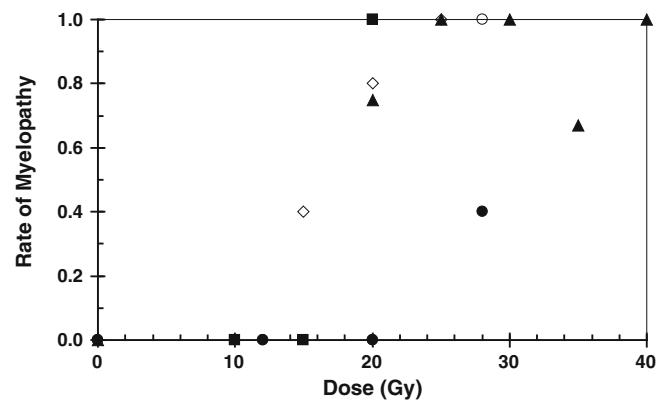
discussion of the early studies. Janzen and Warren (1942) irradiated isolated, intact rat sciatic nerve up to 10,000 roentgen in air and found no neurologic deficits or gross histological changes in neurons after 8 weeks follow-up. As Gillette et al. (1995) and Giese and Kinsella (1991) point out, this may have been an inadequate length of time for injury to have been expressed. In 1959, Lindner irradiated rat sciatic nerves to 30 Gy in 10 fractions, sacrificing these animals at 3–11 months. While no neurologic deficits were observed, approximately one-quarter of the irradiated specimens exhibited nerve degeneration.

Most modern pre-clinical studies of peripheral nerve damage by ionizing radiation have focused on the effect of single, high doses of radiation in animals, simulating the experience of intraoperative radiotherapy. Kinsella et al. (1985) surgically exposed the lumbosacral plexuses and

sciatic nerves of American foxhounds and irradiated these structures in a single fraction ranging from 20–70 Gy. Three additional animals underwent identical surgery and sham irradiation only. At 18 months follow-up, 19 of 21 irradiated animals exhibited motor changes in a hind limb; one of four animals irradiated to 20 Gy and one of three animals treated to 35 Gy showed no clinical indication of radiation-induced nerve damage (Fig. 8). In the animals irradiated to 20–25 Gy—typical doses encountered in clinical IORT—hind limb dysfunction appeared a minimum of 6–7 weeks post radiation. None of the three unirradiated animals showed signs of neuropathy. Kinsella subsequently evaluated the effects of 10, 15 and 20 Gy doses in the same model (Kinsella et al. 1991). At 24 months post IORT, none of the animals receiving 10 or 15 Gy exhibited neurologic deficits, while four of four animals treated to 20 Gy developed unilateral hind limb paresis. At 5 years follow-up, Johnstone et al. (1995) reported an ED<sub>50</sub> of 17.2 Gy with a threshold for peripheral neuropathy of 15 Gy for IORT in this canine model.

LeCouteur et al. (1989) irradiated lumbar nerves in the psoas muscles of beagles irradiated with IORT alone (15–50 Gy), EBRT alone (50–80 Gy at 2–2.67 Gy/fraction) or IORT combined with EBRT (10–42.5 Gy IORT + 50 Gy EBRT at 2 Gy/fraction). The presence of peripheral neuropathy was assessed by neurological exam and by electrophysiology; as the latter study appeared to be somewhat more sensitive for detecting radiation-induced changes, the study primarily focused on the electrophysiological neuropathies. In the IORT alone group, two of five animals receiving 15 Gy, four of five animals receiving 20 Gy and all fifteen animals treated to 25 Gy or higher exhibited abnormal left saphenous nerve dysfunction. An ED<sub>50</sub> of 16.1 Gy was calculated for abnormal electrophysiological function of the left saphenous nerve 2 years post IORT alone. None of the animals treated with EBRT alone showed nerve dysfunction and the outcome for the combined IORT and EBRT group appeared no worse than that for IORT alone. Histological studies of the irradiated tissue 2 years after irradiation revealed both nerve and vascular lesions. Neural damage was characterized by increase in connective tissue in the endoneural, perineural, and epineural spaces, loss of axons and demyelination. Approximately 15 Gy IORT alone was observed to produce a 50 % reduction in the axon/myelin content. At lower doses, IORT alone resulted in hyalinization and necrosis in the media of small arteries and arterioles, while at higher doses small vessel thrombosis and hemorrhage around nerve bundles were observed. An ED<sub>50</sub> of 19.5 Gy was estimated for severe lesions from IORT alone.

In a related study, Vujaskovic et al. (1994) evaluated the neurological and histological impact of 0, 12, 20, and 28 Gy



**Fig. 8** Crude rate of myelopathy as a function of IORT dose in canine models. *Closed symbols* represent observed neurologic deficits (Kinsella 1985▲; Kinsella 1991■; Vujaskovic 1994●) and the *open symbols* EMG abnormalities (LeCouteur 1989◇; Vujaskovic 1994○)

IORT on the left sciatic nerves of beagles. In contrast to the study by LeCouteur, the nerve was separated from the surrounding tissue during irradiation. One year after IORT, statistically significant axon and myelin loss, increases in endoneural, perineural, and epineural connective tissue, and a decrease in small vessels were found in the group of five sciatic nerves treated to 28 Gy, but not in the 15 animals receiving 20 Gy or less. In addition, two of the five animals treated to 28 Gy, but none of the animals treated to lower doses, exhibited severe neurologic deficits over this time. They concluded that the threshold dose for nerve damage in this system lay between 20 and 25 Gy. In a subsequent study combining IORT and hyperthermia, an ED<sub>50</sub> of 22 Gy was estimated for IORT alone for hind limb paresis in the same animal model (Vujaskovic 1996). The addition of hyperthermia reduced ED<sub>50</sub> to 15 Gy and shortened the latency period for the onset of neurologic deficits.

In contrast to the results in dogs, DeVrind et al. (1993) found that isolated rat sciatic nerve was resistant to damage for single IORT doses up to 70 Gy. Note that only a much shorter length of nerve (1–2 cm) was irradiated than in the canine studies (of the order of 10 cm).

In a histopathological study of irradiated tissues obtained at autopsy from 22 patients treated with 20–24 Gy IORT for malignancies of the pancreas, stomach, retroperitoneum, or pelvis, Sindelar et al. (1986) found fibrosis in many of the specimens. Specifically, mild radiation-induced perineural fibrosis was observed in the celiac ganglion in three of four patients treated for unresected pancreatic tumor and in the pelvic nerve plexus for three of five patients treated for resected retroperitoneal sarcoma. The observation that anticoagulants can ameliorate conduction blocks observed in radiation-induced neuropathy and plexopathy suggests a role for reversible ischemia in this injury (Glantz et al. 1994; Soto 2005).

## 9 Prevention and Management

### 9.1 Prevention

*Prevention is essential since radiation myelopathy, once induced, cannot be rectified.* This radiation complication is one of the most dreaded negative outcomes for both patients and radiation oncologists. Although Quantec's thorough review of the available literature indicates that the 'threshold' is at 60 Gy, the generally accepted prescription is to shield to spinal cord at 45–50 Gy, to keep the risk of injury very very low.

It is important to recognize the generally accepted "tolerance" doses; e.g., 5,000 cGy should generally not be exceeded. Prevention is the only satisfactory approach. Abutting fields treated concurrently (e.g., with craniospinal irradiation, and multi-field head and neck treatments) or sequentially (e.g., with treatments to spinal metastases following prior thoracic therapy for lung cancer) need to be checked and rechecked to ascertain that there is no unintended overlap.

### 9.2 Management

In the future, unipotent neuronal embryonal stem cells may become available to regenerate central nervous tissues. This has been demonstrated in brain experimentally by Rubin et al. after administration of supralethal radiation doses. Although corticosteroids have been used, there is no standard approach to achieve restoration of the spinal cord once necrosis has appeared.

## 10 Future Research

In cases where it is appropriate to irradiate only a partial circumference of the cord (as in irradiation of vertebral body lesions) or spare the interior of the cord (epidural disease), dose tolerance may be increased. SBRT, particularly using IMRT techniques, appears well suited for that purpose, as it can be used to deliver concave-shaped RT dose distributions around organs at risk (Nelson 2009). Studies to better understand the importance of the spatial distribution of dose (and hence the utility of partial circumferential sparing) would be useful.

For SBRT of spinal lesions, multi-institutional data needs to be carefully collected over several years' time to better estimate the risk of acute and long-term toxicity. At a minimum, participating institutions should report detailed demographics, current treatment factors (anatomic location of the target lesion, cord volume, number of vertebral

segments involved, number of fractions,  $D_{\max}$ ,  $D_1$ ,  $D_{10}$ ,  $D_{50}$ ,  $D_{0.1cc}$  and  $D_{1cc}$ ), history of concurrent and prior therapies (including the time interval from dose and fractionation of previous radiotherapy to the involved levels) and treatment-related toxicity, particularly neurologic deficits.

Given the low frequency of neurologic deficits in patients receiving spinal radiotherapy, further animal studies designed to understand the relationship between dose, fractionation dose distributions, and time between treatment courses would be useful.

## 11 History and Literature Landmarks

Radiation-induced injury of peripheral nerves was described at the dawn of radiotherapy when unusual "burns" were observed in skin exposed to radium salts or Roentgen rays (Giese and Kinsella 1991). Oudin et al. (1897) presented a "trophoneurotic" hypothesis in which irradiation of cutaneous nerves produced sweat gland and hair follicle atrophy. In 1942, Janzen and Warren found that peripheral nerves were highly radioresistant, though this study has been criticized for short follow-up time (Gillette et al. 1995). A variety of pre-clinical and clinical studies are now available that provide a basis for estimating the effect of conventionally fractionated external beam and single-fraction intraoperative radiotherapy on peripheral nerve tolerance, as described below.

The first published reports of spinal cord myelopathy associated with therapeutic radiation in humans appeared in the 1940s (Ahlbom 1941; Stevenson and Eckhardt 1945; Boden 1948; Greenfield and Stark 1948). Differential responses of the thoracic versus cervical cord have been proposed (Dynes 1960; Kramer 1972), attributed in part based on the greater sensitivity of the former to disruption of vascularity. Conversely, Glanzmann and Aberle (1976) argued that the cervical cord is more sensitive than the thoracic cord. At least some of these differences appear due to differences in technique and fraction, as described by Schultheiss et al. (1995). While radiation-induced spinal cord myelopathy is fortunately rare and analyses of the available data suggest that the risk of myelopathy during conventional external-beam radiotherapy is extremely low at the current dose limits of 45–50 Gy over 5 weeks (Schultheiss 2008).

Utilizing boron neutron capture in animal models, the alpha particles are absorbed by the endothelial cells lining blood vessels without irradiating neuronal tissues in spinal cords. The histopathology is identical to irradiating all of the spinal cord tissues with neutrons. This elegant study clearly provided the histopathologic evidence of vascular-mediated pathogenesis of neural tissue radiation-induced injury.



In stereotactic body radiosurgery, a small lesion is precisely treated with one or a few fractions of radiation at a high dose per fraction. In the spine, successful radiosurgery requires accurate target localization, precise immobilization, image-guidance, and multiple stereotactic beams/arcs to adequately cover the target lesion while minimizing dose to the adjacent cord. While the initial results in a variety of treatment sites, including the lung, liver and spine, appear promising (Timmerman et al. 2007), clinical experience in the spine is relatively limited and the follow-up short (Sagahl et al. 2008; Nelson et al. 2009). Consequently, statements that this is a “safe” treatment modality are somewhat premature, though emerging studies do suggest that the dose limits self-imposed by many practitioners do limit the risk of radiosurgery-induced myelopathy.

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