Chapter IX: Acute Radiation Effects: Organ Specific Organs Dose, and Species Differences:

Section A: CNS (Ionizing Irradiation Effects on the Brain, Spinal Cord, and Peripheral Nervous System)

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Introduction:

Ionizing irradiation effects on the central and peripheral nervous system incorporate the general principles of radiation biology, namely: total dose, dose rate, relative biological effects of the radiation beam, fractionation, and overall time of exposure.

Knowledge of effects of radiation on the nervous system have come from both clinical and basic science reports in published literature.

This chapter will focus on overview of this subject by dividing it into four categories: 1) Total body exposure effects and the central nervous system (CNS) syndrome; 2) Brain irradiation both total and subtotal; 3) Spinal cord irradiation; and 4) Peripheral nerve irradiation.

1) Total Body Exposure Effects and the Central Nervous System:

As described in the Overview Chapter and the Basic Radiobiology Chapter of this web-based textbook, total body irradiation effects with respect to experimental animal models and humans have been characterized in syndromes. That total body dose of irradiation, which can be treated with bone marrow transplantation is defined as the hematopoietic syndrome (In humans, typically 3-4.5 Gy total body dose of x-rays as dose rate of around 2 Gy per minute.), then the gastrointestinal (GI) syndrome (In humans, doses around 4.5 – 10 Gy) and associated with a condition in which bone marrow transplant cannot reverse toxicity and damage largely due to killing of gastrointestinal stem cells, a condition following total body exposure to very high doses (typically above 10 Gy) called the central nervous system (CNS) syndrome. The CNS syndrome, information about which has come largely from nuclear reactor accidents or military exposure, usually presents with immediate nausea, vomiting, seizures, and rapid death usually within one hour.

The etiology of the CNS syndrome has been attributed to brain swelling associated with massive localized and systemic release of inflammatory cytokines. Clinical case reports have suggested that treating patients for the brain swelling episode including: intravenous administration of Mannitol, or other agents designed to keep fluid within the vascular system and prevent brain edema, may provide some symptomatic relief, but are usually ineffective. As will be described in experimental models of total brain irradiation, isolated spinal cord or segmental spinal cord irradiation, tissue swelling mediates local and generalized toxicity. In a setting of a nuclear terrorist event or high dose rate exposure in the case of a nuclear reactor meltdown, concentric rings of isodose curves constructed from the center of the radiation event, usually indicates that patients suffering from seizures or immediate nausea and vomiting, have received doses consistent with the CNS syndrome. There is no known effective treatment.

As related to development of radiation countermeasures, it is also clear that combined injury may result in the CNS syndrome at lower radiation doses. For example, patients presenting with significant body surface area thermal burn, trauma penetrating wounds, bone fracture, and traumatic brain injury, may present with severe nausea, vomiting, and seizures at much lower doses. For triage of radiation casualties, physicians will be tasked with treating the non-

irradiation component of the combined injury first, and may not be aware of the radiation dose sustained by the patient for some time.

In another example, in a patient with penetrating wounds, who has received a total body dose of around 6 – 7 Gy, emergency room physicians may be tasked with controlling hypovolemic shock, intravenous administration of blood products or lactated ringers solution for controlling hemorrhage, may then be aware of the radiation side effects including nausea, vomiting, and seizures attributable to the total CNS response.

As described in the chapter in this textbook on triage of casualties in the setting of a radiation terrorist event, physicians may be tasked with determining which casualties presenting with the same combined injury profile (hemorrhage from penetrating wounds) have received a dose of irradiation that could be effectively treated with bone marrow transplantation (3 Gy) compared to a similar presentation of a patient, who has received a much higher dose and associated with CNS syndrome.

Basic principles of radiation physics may help physicians in either a military or civilian casualty situation, because the presentation of the CNS syndrome will evolve over minutes to an hour, and during that time reports will probably be available as to how close to the center of the radiation each individual was and radiation exposure levels will be available.

2) Brain Irradiation Both Total and Subtotal:

There is much available information and also a high degree of current research interests in the effects of total brain or subtotal brain irradiation. Acute and late effects of ionizing irradiation on the brain have been studied extensively (1-25).

Acute Radiation Effects on the Brain:

Total brain irradiation results in symptoms and signs consistent with basic principles of: total dose, dose rate, volume treated, and fractionation. In a setting of single dose exposure (radiation terrorist event or accidental exposure), the total dose will be significantly modified by beam quality. For example, high linear energy transfer (LET) particle irradiation including: protons, neutrons, and carbon ion irradiation will produce greater levels of symptoms and signs compared to x-rays/gamma rays based on the relative biological effects (RBE). Readers should consult the chapter in this textbook on basic radiobiology principles for detailed explanation of these terms. A clinical radiation oncologist with experience in treating patients with brain tumors, or leukemic infiltrates of the brain, provide a practical experience as to the relative tolerance of whole brain radiation. These reports of induction of seizures by 1 Gy single fraction total brain irradiation at 2 Gy/minute dose rate allow radiation oncologists to modify total brain radiation dose to maximal tolerated levels of 4 Gy of subtotal brain irradiation in the case of the need for emergency treatment.

Emergency treatments in clinical radiation oncology are rare, but include those situations in which a brain tumor increases intracranial pressure by obstructing the cerebrospinal fluid (CSF) circulation through ventricles and aqueducts in the brain. Diagnosis of a brain tumor in the

Emergency Room setting by CAT scan or MRI, will usually result in initial implementation of medical measures first including high dose intravenous cortical steroid therapy to reduce swelling or a radiation oncologist may be called to deliver an emergency treatment. Based on clinical experience, as described above, the lowest possible fraction size used to reduce tumor size reduction to relieve intracranial pressure might be in the range of 3 – 4 Gy with careful attention to avoid as much of the normal tissue as possible, thus delivering subtotal brain irradiation.

Another CNS radiation therapy emergency is that of rapid onset of blindness associated with leukemia cell infiltration of the posterior orbit of the eye and/or optic nerve by leukemia cells. This usually occurs in the pediatric population and can be controlled by small field opposed lateral radiation therapy to doses of 1.8 – 2 Gy. Because of the radiosensitivity of leukemia cells compared to solid tumors, this low dose is practical. Importantly, the relatively small volume of subtotal brain irradiation in this setting reduces the likelihood of normal tissue toxicity.

Late Irradiation Effects On the Brain:

Late effects of total brain irradiation have become a subject of great interest, particularly the discovery that neurocognitive impairment can be a significant event. In the 1960s and 1970s, pediatric patients with leukemia, who were treated with first line chemotherapy, were discovered to present with relapse in the central nervous system. Pioneering studies by Pinkel, et al. at St. Jude Children's Hospital and others, led to the widespread application of total brain irradiation as a routine therapeutic measure for initial treatment of children with leukemia. Doses of 20 Gy at 2 Gy per fraction were delivered by opposed lateral fields, and the incidence of central nervous system relapse after effective induction of a remission chemotherapy, widely reported. Unfortunately, careful follow-up of these children led to discovery of significant neurocognitive impairment. Children treated in the first and second decades of life presented with significant learning disabilities and multiple confirmatory publications (1-13) led to the elimination of CNS prophylaxis in the vast majority of pediatric leukemias. Some patients with B-Cell Leukemia or T-Cell Leukemia, who were at high risk for CNS relapse will still be treated with CNS irradiation, although the lowest possible dose is recommended (13).

CNS irradiation as prophylaxis in adult patients with Small Cell Lung Carcinoma also was and still is recommended as an additional therapy in this subpopulation of patients (3). While Small Cell Lung Cancer is a disease of adulthood, total brain irradiation in these patients has also been associated with neurocognitive deficits in the long-term survivors, assayed at 5 – 10 years after treatment. Given the much higher likelihood of recurrence of this aggressive lung cancer, decisions are usually made to include total brain irradiation (prophylactic irradiation) as part of the treatment program. Whole brain irradiation is usually delivered after completion of induction chemotherapy, although a significant number of patients will elect to forgo this additional treatment once the side effects and risks are explained.

The histopathologic correlates to late effects of whole brain irradiation are subtle. The discovery of neural stem cells (24-25), and the understanding that areas of the brain regenerate actually over time, it became evident that total brain irradiation in the pediatric population was likely to reduce the number of brain stem cells at a much greater frequency than that in adults, however,

adult stem cell destruction by irradiation is considered a mechanism for the late effect. This evidence has indicated that there is an age related radiation sensitivity of the brain. Readers should consult the chapter in this textbook on fetal radiation effects, and particularly recent evidence for inhibition of cell division by irradiation (Ki67 staining of the E13.5 fetal brain) and destruction of brain microvascular endothelial cells (CD31 imaging). The developing fetal brain mouse model has shown a high incidence of irradiation induction of hydrocephalus in rare surviving animals exposed to 3 Gy total body irradiation of the pregnant mother, and a surprising and very interesting therapeutic effect of administration to the mother of the GS-nitroxide drug, JP4-039, at 24 hrs. after irradiation, which significantly improved survival and greatly reduces hydrocephalus.

There are few experimental model systems available to determine the effects of radiation countermeasures against the late sequellae of brain irradiation. Transplantation of neural stem cells (25) has become therapeutic option in specific CNS diseases (Parkinson's Disease, management of post-stroke patients, and in frontotemporal dementia). These clinical trials in other diseases have suggested the possibility of using neural stem cells to ameliorate late side effects of total brain irradiation. Such studies are underway in animal models. The work of John Fike and Charles Lamioli, et al. demonstrated effectiveness of xenotransplant of human fetal neural stem cells into the irradiated rat brain (25).

Amelioration of late radiation effects on the brain has also gained importance with respect to research by the National Aeronautics and Space Administration (NASA). Neurocognitive decline, which is a natural process of aging, has been shown to be accelerated in returning astronauts and clinical trial research models of space irradiation are underway. The readers should refer to the chapter by Jones, Karouia, and Montesinos on space irradiation to understand the potential mechanisms of neurocognitive decline in astronauts exposed to solar proton events, and galactic cosmic irradiation, as well as neutrons within the space vehicle on the central nervous system (14-17). With respect to whole brain radiation toxicity and radiation countermeasures, there is a common concern shared by investigators working for NASA, in radiation counter-terrorism, and in clinical radiation oncology to develop dietary and/or small molecule interventions that can reduce potential late effects in the brain. Research efforts in animal models, predominantly rodents, have led to development of a large number of neurocognitive tests, which can be applied to the study of late radiation effects on the brain.

Effects of Irradiation On Neurocognition:

In mouse and rat models of total body irradiation, neurocognitive defects have been shown to increase in severity over time after irradiation, can be accurately quantitated using the novel methodologies of the Morris Water Maze, Novel Object Recognition, Fear Conditioning, and others. Most of these neurocognitive tests, their use in studies of rodent models of brain damage from a variety of causes, can be obtained from the literature (See chapter on irradiation of fetal mice and (19)). The concept of combined injury also applies with respect to total brain irradiation. Most experience has come from animal models in which the magnitude of the radiation dose sustained and the non-irradiation component of the combined injury can be quantitated. Traumatic brain injury is studied in rodents using a novel technique of removal of the top of the skull (calvarium) and delivering to the top of the cerebrum a precisely measured

controlled cortical impact, which produces localized brain trauma. Delivery of total brain irradiation prior to or after the controlled cortical impact leads to a highly reproducible model of combined injury. Preliminary data have demonstrated that controlled cortical impact increases the measurable toxicity of a given dose of total brain irradiation. A clinical correlate to these studies is the setting of radiotherapy to the brain after surgical removal of a brain tumor. In attempts to minimize the impact of combined injury in this clinical setting is focused on delivering a radiation dose to the site of suspected residual tumor by either brachytherapy – interstitial implantation of radiation sources, or precise delivery of radiation by highly collimated radiation beams (Stereotactic Radiosurgery) reducing the volume of normal tissue treated in a post-operative setting is extremely important to minimize radiation late effects. Analysis of effects of irradiation in such patients requires matched pair analysis of those patients, who received a similar surgery with no irradiation compared to those who received post-operative radiation. Quantitation of neurocognitive effects in such patients is a subject of great interest, and numerous publications document the techniques and neurocognitive tests applied to such patients, as well as methods to analyze the data.

Novel Experimental Models to Study Radiation Effects in the Developing Fetal Brain:

There is a great deal of information on the neuroanatomical development of the brain. Studies in C. elegans, fruit flies, zebra fish, frogs, and other categories of both invertebrates and vertebrates have led to consensus that there are at least three critical cellular elements in the evolution of the brain: radial glial cells, which form the neuronal networks and the complexity of the different phenotypes of cells within the brain, microvascular endothelial cells, which lead neuronal extensions and connections, and the matrix microenvironment of the brain (15-17). As will be described in the section on spinal cord radiation biology, many of these principles also apply to radiation effects on the spinal cord. Elegant studies in the developing rodent brain utilizing new techniques of optogenetics, in which differentiation of neural glial cells to specific lineages results in expression of a fluorochrome protein/levels have allowed neuroscientists to correlate the appearances of specific neuroglial cell lineages with time (19). Matching this data to studies of the radiation sensitivity of the developing mouse fetus in which lower radiation doses results in fetal death by early gestation, higher doses at mid-gestation, and relative radioresistant doses to the near term fetus have led to the conclusion that the most primitive neural stem cells are the most radiosensitive. This conclusion may be complete in that the radiobiology of the microvascular endothelial cells, which also increase in magnitude and complexity with age have not been studied. Finally, the matrix within the developing brain consists of protioglycans, lipids, and complex molecules that construct the microenvironment for development and migration of radial glial cells, and microvascular endothelial cells. Finally, the entire developing brain is continually interacting with blood supply, neurolymph, and communications facilitated by the developing cerebrospinal fluid, which is synthesized in the choroid plexus of the brain, and as development progresses circulates through a system of ventricles and aqueducts, which connect the brain with the spinal cord (17-18).

Early gestation embryos, exposed to irradiation, express radiation damage in the form of spontaneous abortion or termination of pregnancy. However, recent data on low dose rate exposure of early developing fetuses suggests that after doses low enough to facilitate complete gestation and survival, neurocognitive deficits are detected in adult mice. The chapter on fetal

radiation effects describes the complexity of radiation effects on mid-gestation E13.5 total body irradiated fetal mice and indicates radiation effects on endothelial cells (CD31+), all proliferating cells (Ki67+), and the role for immunocytes and reactive cells, many of bone marrow circulatory origin, which interact with the irradiation damaged brain.

The development of radiation protective drugs and radiation mitigators that might be administered to pregnant females in the event of a nuclear terrorist event or radiation accident, must consider radiation effects on the developing brain. Time during which central nervous system develops has been not precise in rodent models, however, the clear evidence of radiation toxicity to the adult brain, where neural stem cells are still active (Gage) adds to the complexity of developing radiation countermeasures, since these would in necessity be administered to adults, young children, the elderly, and potentially pregnant females. As with the development of all new pharmaceuticals, the role of polypharmacy must be considered. A wide range of available pharmaceuticals including dietary supplements and the role of environmental factors indicates that application of radiation countermeasures either in the clinical radiotherapy setting or counter-terrorism setting must account for potential interaction of such countermeasures with pharmaceuticals already in the system of the exposed individual.

3) Spinal Cord Irradiation Effects:

Acute radiation effects on the role of volume, initial studies on single fraction and fractionated irradiation to the spinal cord, role of volume, dose, dose rate, beam quality, and treatment time (26-35).

The role of the spinal cord microenvironment in radiation responses. Recent studies with Amyotrophic Lateral Sclerosis (ALS) model systems including: SOD^{G93A} mice, which are transgenic and contain four copies of the mutant human Superoxide dismutase 1 (SOD1) gene demonstrate that the onset of paralysis of the spinal cord typically will be at 90 days after birth and resulting in significant hind limb paralysis can be ameliorated by total body irradiation and bone marrow transplant.

These studies have great relevance to the use of pharmaceutical agents in radiation countermeasures or medical uses in the irradiated spinal cord. Medical issues involve not only the dose volume relationships of toxicity to spinal cord irradiation, but also anatomy. The radiosensitivity relative to volume treated is greatest in the brainstem than in the cervical spinal cord, thoracic spinal cord, lumbar spinal cord, and finally nerve roots (26-31).

Mammalian spinal cord demonstrates both anatomic and physiological mechanisms of irradiation damage. Basic principles of radiation biology apply, specifically with respect to volume treated, radiation dose, beam quality, fraction size, and overall treatment time. Information on human spinal cord injury comes largely from reports of clinical use of radiation therapy in the first decades of the 20^{th} Century. In the 1920s and 1930s, widespread use of orthovoltage/kilovoltage radiation therapy was developed to shrink the size of masses in the chest and also to treat superficial skin tumors in the neck and chest region. During those decades, radiation was measured as Roentgens in air or ionization of air measured in physical ionization chambers. Therefore, dose to response calculations were based largely on correlation of air – dose with

physical responses of tumors measured by standard diagnostic x-rays. With orthovoltage irradiation, toxicity was initially determined by skin damage, since the back scatter of low energy x-rays produced a significant skin reaction. First reports of irradiation damage to the spinal cord led to a diagnosis of transverse myelitis ( ) a physical destruction of the neurons and vasculature in specific sections of the spinal cord, and proceeded by symptoms and signs of spinal cord damage. Within weeks to months after completion of doses of irradiation, principally to the cervical or thoracic spinal cord, patients presented with reports of "shooting – pains" in the lower extremities, "tingling", and unusual sensory experiences. Motor damage followed shortly, and in autopsy specimens, the spinal cord was noted to have significant volumetric shrinking and specific destruction of neurons and vascular destructions within that segment of spinal cord, which could be matched to the skin changes seen in the same patients. The Lhermitte's Syndrome (25) was reported to describe these first events in radiation spinal cord injury or radiation myelitis.

Animal model experiments were designed to document the role of volume of spinal cord treated, the total dose were correlated to the histopathologic evidence of spinal cord damage. Initial experimental studies by Boden leading up to the elegant studies of Van der Kogel and colleagues (36-42) documented the chronologic events in acute radiation spinal cord damage and anatomic variation in onset of damage and its severity. Based on these clinical observations and animal studies, dose constraints were placed on the spinal cord in the 1950s, and with the advent of Cobalt 60 teletherapy in that decade followed by use of linear accelerators in the 1960s, better physical dosimetry and 3-dimensional treatment planning, dose constraints were modified. Studies in animal models confirmed clinical observations that the most radiation sensitive anatomic areas of the spinal cord were associated with vascular supply density of motor neurons and axonal tracks. Depending on target volume and field size, cervical spinal cord was reported to be the most radiosensitive. Of interest, restral structures including the brainstem and mid-brain displayed the same radiation dose constraints. This observation may be confounded by the field size limitations to mid-brain and brainstem target volumes, whereas cervical spinal cord is often treated in its entirety for patients with head and neck cancers, and tumors in the cervical spine. Depending on volume and fraction size, as well as treatment time, doses of 50 Gy in 5 to 6 weeks are considered a safe limit of radiation treatment plans for patients with mid-brain and brainstem target volumes. Cervical spine doses are kept below 40 Gy, based on rare, but significant clinical reports of spinal cord damage in doses above that level (43-48). Fraction size (dose delivered per day) is the key determinant of acute spinal cord damage and fraction size is at or below 2.0 Gy per day or maximum 10 Gy per 5 day treatment week is routinely recommended.

Less prone to irradiation damage is the thoracic spinal cord followed by the lumbar spinal cord. Nerve roots below the third lumbar vertebrae are more resistant to radiation dose and treatment volume.

Modern radiobiology approaches toward understanding spinal cord damage have been pioneered by the work Van der Kogel and colleagues (36-42). These studies have led to a series of contemporary radiobiologic questions that are yet to be answered, namely the role of neuroglial cell migration to irradiated volumes, the toxicity of nerve stem cells, interaction of vasculature

and microenvironment with neuroglial cells, and most recently, the potential role of bone marrow derived progenitors of microglial cells in the evolution of irradiation damage.

Pioneering Experiments of Van der Kogel:

The animal model systems, segments of rat spinal cord, were irradiated with single fraction size beams, and the evolution of neurofunctional damage was mapped (41). Within a target volume, several millimeter length segments were irradiated to a high dose (X) and segments of the spinal cord superior and inferior to that high dose area received a lower dose (Y). These initial experiments demonstrated that a relatively lower dose delivered to the volume X in that dose delivered to that volume alone, which produced transverse myelitis, could be converted to a pathologic dose by giving a lower dose of radiation to the segments above and below that volume (Y). Depending on the volume of tissue in the adjacent area (Y), transverse myelitis could be induced in the high dose region (X) at a greater frequency as the total volume increased ( ).

These experiments have simplicated the potential role of many variables not previously considered as relevant to spinal cord damage. While there was much interest in the radiobiology community in the mechanism of the phenomenon of the abscopal effect, this mechanism was thought to be restricted to anatomic regions some distant from the irradiated target volume. For example, irradiation of the head and neck region to treat a squamous cell carcinoma of the floor of the mouth, was associated with bone marrow suppression in the lower extremities, both in experimental models and in clinical case reports. This (negative abscopal effect) is still the subject of significant investigation and is thought to be mediated by humoral cytokines released from the irradiated target volume, which have a specific negative regulatory effect on stem cells within the bone marrow. The reverse (positive abscopal effect) in which irradiation of a visible tumor volume in one area of the body has been associated with regression or shrinkage of a tumor volume in a distant site has also been thought to mediated by release of inflammatory cytokines, oxidized phospholipids, DNA breakdown products including nucleosides, but as with the "positive abscopal effect" has been associated with target regions, anatomically distant from the irradiated region.

In the case of the work by Van der Kogel, large volume, low dose irradiation of areas of the spinal cord adjacent to a specific higher dose region, was not called an abscopal effect, but rather an "adjacent volume effect". The mechanism of the observations in these experiments has led to exciting research questions.

Do cells from the brain and spinal cord region superior to a target volume migrate through the spinal cord vascular and/or cerebral spinal fluid to the sites of ionizing irradiation to both induce damage, and provide amelioration of damage? Neuroscientists studying traumatic spinal cord injury and also Amyotrophic Lateral Sclerosis (ALS), as well as Multiple Sclerosis, first documented the role of pro-inflammatory (M1) and anti-inflammatory (M2) microglial cells. These cells arrive at distinct time points at the sites of spinal cord injury including ionizing irradiation damage. There is still a question of whether damaged cells in the irradiated volume of the spinal cord recruit M1 microglial cell progenitors to release inflammatory cytokines at the site of irradiation. Release of TGF-β, IL-1, TNF-α, and other pro-inflammatory mediators has

been documented early in the evolution of localized spinal cord damage. Alternatively, irradiation to the microenvironment surrounding neurons including endothelial cells, stromal cells, and white matter (nerve axons) may elicit and initiate the recruitment of M1 microglial cells. There are many studies in the neuroscience literature that are approaching this sequence of events, and also attempting to define small molecules and cellular therapies to block this first step. The general consensus is that M1, pro-inflammatory microglial cells, either initiate or contribute to spinal cord damage resulting in sensory and motor deficits.

Another question from the Van der Kogel experiment involves the origin of neural stem cells (41), and their potential migration through the spinal cord circulation and/or CSF to the sites of irradiation damage in neural stem cells locally injected into irradiated tissue of the spinal cord and facilitate regeneration of neural connections and recovery of damaged spinal cord segments? Such experiments are being evaluated in animal models of traumatic spinal cord transection and also in new research areas involving administration of matrix compound and grafted biomaterials to stimulate nerve growth across transected areas in the fields of Bio-Engineering and Material Science. However, one difference, which distinguishes radiation damage to the spinal cord, is the role of the irradiation damage to the matrix through which nerve axons and neural stem cells and their progenitors must migrate to such areas of injury.

Yet, another area of investigation is stimulated by the pioneering experiments of Van der Kogel is that involving the microcirculation of the spinal cord (46). The physiology of the brain and spinal cord is still being investigated, but it is clear that compromising the microcirculation in the spinal cord can lead to and certainly exacerbate traumatic injury including that caused by ionizing irradiation. The radiosensitivity of endothelial cells and microvasculature has been studied extensively in skin and epithelial tissues, however, little attention has been directed to the spinal cord circulation.

Patients with tumors such as Giant Cell Tumor arising in the cervical or thoracic vertebrae, and drawing vasculature from the spinal cord have provided an opportunity to study radiation effects on spinal cord vasculature. Particularly, in patients requiring post-operative radiotherapy in which neurosurgical approaches to tumor excision and define thusly, the vasculature supplying the tumor, radiation effects on the target volume have been documented with respect to serial angiography and mapping the effects of irradiation on revascularization of the target volume.

As it relates to the general purpose of this textbook, namely understanding how radiation countermeasures and radiation dosimetry could direct the delivery of therapeutics to casualties from a radiation terrorist event or nuclear reactor accident, total spinal cord irradiation volume would be expected to produce a greater potential for spinal cord damage than partial body irradiation, where higher doses were delivered to one area of spinal cord for protection of other areas. However, because of the adjacent volume effects described in this chapter, careful attention should be delivered to choice of surgical procedures for handling combined injury in areas of the spinal cord and also a caution concerning repair of vascular damage might influence the microcirculation to the spinal cord.

4) Radiobiology of Peripheral Nerves:

Much information has been obtained in the Radiation Oncology literature from the study of acute and long-term outcomes in the management of patients with single nerve tumors, meningiomas, and squamous cell tumors of the nasopharynx and sphenoid sinus in which cranial nerves are involved in the planning target volume. The principles of volume treated, total radiation dose, fraction size, and overall treatment time apply in these settings. The pioneering studies of Flickinger and Lunsford with Gamma Knife Radiosurgery of acoustic neuromas, documented the importance of volume to dose relationships (49-50).

While the general consensus around radiation oncologists is that peripheral nerve is relatively radioresistant compared to spinal cord or brain, there are several situations in which irradiation-induced nerve damage can be clinically quite significant.

Much information on the tolerance of nerve to radiation has come from studies of cranial nerve involvement in the target volume during radiotherapy of tumors of the base of the brain (meningioma, clivus melanoma, metastatic cancer to base of brain, and primary tumors of cranial nerves including acoustic neuroma and situations in which the cranial nerve itself is the target volume such as in stereotactic radiosurgery of trigeminal neuralgia.

Pioneering studies carried out by Radiation Oncologist, John Flickinger, M.D. and Neurosurgeon, L. Dade Lunsford, M.D. at the University of Pittsburgh first demonstrated that tolerance of cranial nerve tissue to Gamma Knife Radiosurgery. Doses of 50 – 70 Gy to millimeter volumes of neural tissue resulted in localized nerve transection, reducing doses and incorporating fractionation for Gamma Knife Radiosurgery in which up to 200 individual Cobalt beams, each directed by a capsule placed within a globe that encircles the head of an immobilized patient focused multiple microbeams on millimeter size lesions within the cranial nerve complex reducing total dose and fractionation resulted in control of nerve sheath tumors (acoustic neuromas) and facilitated specific ablation of regions in the 5^{th} cranial nerve associated with Trigeminal Neuralgia, syndrome of chronic pain. In a recent publication, the role of specific antiseizure and analgesic medications, comparing Tegretol – Carbamazepine with Neurontin, it was reported that patients receiving Neurontin had a decreased overall incidence of irradiation-induced late cranial nerve damage after successful treatment of trigeminal neuralgia (51). These data, which established the safe radiation tolerance for stereotactic radiosurgery of cranial nerve tumors, also emphasized the importance of antiseizure and analgesic medications as radiation mitigators, since these data also represent a report of mitigation of late radiation effects on normal cranial nerves.

Stereotactic radiosurgical approaches to treatment of tumors in cranial nerves, which allow analysis of late radiation effects, would not apply necessarily to radiation countermeasures for radiation terrorism or nuclear reactor accidents in which significant body volumes including total body irradiation might be sustained. Very high doses delivered to small volumes in stereotactic radiosurgery do, however, provide a window of understanding on the tolerance of cranial nerves to ionizing irradiation.

Situations in which cranial nerves are not the therapeutic target, but rather contribute to radiation side effects due to proximity to tumor volume are those associated with radiotherapy of tumors of the base of the brain. Squamous cell carcinoma of the nasopharynx and sphenoid sinus

represent tumor target volumes in close proximity to multiple cranial nerves. The advent of precise magnetic resonance imaging (MRI) to facilitate a precise delineation of squamous cell carcinoma invading nerves and migrating through foramina in the base of the brain by travel along nerve sheaths. Precise MRI imaging, waited to distinguish fatty tissue around nerves, from nerve tissue, and distinguishing both types of cell populations from tumor have facilitated precise delineation of tumor volumes in fractionated radiotherapy. Dose tolerance of cranial nerves, principally branches of the 7^{th} facial cranial nerve, and 5^{th} trigeminal nerve have been reported in the Modern Radiotherapy literature for treatment of head and neck cancers invading the base of the brain.

The mechanism of radiation damage to peripheral nerves is more complex and involves the study of microvasculature, effects of irradiation on myelination by Schwann cells, and the mechanism of radiation fibrosis. Clinical radiotherapy reports of treatment of tumor target volumes involving peripheral nerves emphasizes the importance of combined injury. Soft tissue sarcomas of the extremities represent a radiotherapy treatment knowledge, which often involves treatment of peripheral nerves. Surgical resection of soft tissue sarcomas, which when in proximity to or invade peripheral nerves, provides a challenge to the surgeon to remove as much of the disease as possible and leave minimal disease for post-operative radiotherapy. However, management of patients with multiple recurrent or low intermediate grade soft tissue sarcomas in which multiple surgical procedures proceed referral for post-operative radiation presents a challenge to the radiation oncologist. Healing tissue in multiply operated sites incorporates an escalating level of fibrosis. Radiotherapy of fibrotic tissue containing microscopic residual tumor necessitates doses of 50 Gy or higher. Compromise of the microcirculation through nerve plexus such as in the brachial plexus of patients with soft tissue sarcoma near the axilla makes radiotherapy more difficult. Acute radiation induction of cytokines and inflammatory mediators in the radiation field, produces localized edema. Surgical manipulation of tissues can compromise lymphatic drainage and the result in irradiation-induced edema puts pressure on peripheral nerves causing microcirculatory facets in nerve damage. Many patients requiring radiotherapy of peripheral nerve containing target volumes already have significant circulatory and lymphatic compromise.

Readers should refer to the chapter on irradiation-induced delay in skin wound and bone wound healing (Glowacki, et al.) to gain further insight into the concept of combined injury with respect to peripheral nerves. While nerve tissue itself may be relative radioresistant, as evidenced by data with radiosurgery of cranial nerves as cited above, the application of radiotherapy to peripheral nerve tissue in the post-operative setting represents a true presentation of the combined injury model.

Patients receiving post-operative chest wall radiotherapy after mastectomy for breast cancer are at risk for the late effect of angioedema.

Particularly, if patients have received axillary node dissections as part of total mastectomy, the vascular and lymphatic compromise to the brachial plexus can be significant. In those patients, who have residual breast cancer on the chest wall as identified by microscopic positive deep margins after mastectomy, post-operative radiotherapy may be indicated. The use of Intensity Modulated Radiotherapy (IMRT) has allowed radiation oncologists to decrease the radiation dose to the lateral tangent field near the axilla, however, in the absence of IMRT, the high dose

region in the lateral tangential field may involve the post-operative axillary volume. These patients may suffer exacerbation of arm edema resulting from radiation effects on the already compromised lymphatic system. Patients wear an elastic stocking on the ipsilateral arm to reduce accumulation of fluid, however, angioedema is associated with significant axillary nerve compromise and nerve side effects reported by patients as numbness, tingling, and sensory loss. Some patients report significant pain. These forms of peripheral nerve injury are not direct irradiation effects, but rather combined injury effects in which the induction of edema and late fibrosis by irradiation exacerbates the post-surgical changes. Modern era localized radiotherapy by stereotactic body radiosurgery targets these specific areas of local recurrence or positive margins and keeps irradiation from the post-surgical axilla to minimize edema and associated peripheral nerve damage.

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